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Revised Date: 22-Mar-2017

Clinical Protocol CA209040

A Phase 1/2, Dose-escalation, Open-label Study of Nivolumab or Nivolumab in Combination with Other Agents in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis

[redacted]

Study Director / Central Medical Monitor

[redacted]

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04c	22-Mar-2017	Incorporates Amendment 18
Amendment 18	22-Mar-2017	[redacted]
Administrative Letter 08	23-Feb-2017	Change of Medical Monitor
Revised Protocol 04b	26-Oct-2016	Incorporates Administrative Letter 06, and Amendment 17
Amendment 17	26-Oct-2016	[redacted]
Administrative Letter 06	24-Jun-2016	Change of Medical Monitor
Revised Protocol 04a	01-Jun-2016	Incorporates Amendment 12
Amendment 12	01-Jun-2016	[redacted]
Revised Protocol 04	31-Jul-2015	Incorporates Administrative Letter 03, Administrative Letter 04, and Amendment 08
Amendment 08	31-Jul-2015	Changes include addition of two new treatment arms to the study: [redacted] 2. nivolumab plus ipilimumab combination, as well as other minor clarifications and edits
Administrative Letter 04	15-Jul-2015	Update the pharmacokinetic sampling schedule for subjects in the expansion cohorts.
Administrative Letter 03	28-Apr-2015	The FDA issued a new IND number for the indication of hepatocellular carcinoma for nivolumab.
Revised Protocol 03	29-Oct-2014	Incorporates Amendment 04
Amendment 04	29-Oct-2014	[redacted]
Administrative Letter 02	15-Apr-2014	Change in Study Director/Medical Monitor
Administrative Letter 01	15-Oct-2013	Change in Study Director/Medical Monitor
Revised Protocol 02	06-Sep-2013	Changes include updated text for antiviral medications for HCV and

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Document	Date of Issue	Summary of Change
Amendment 03	06-Sep-2013	[redacted]
Revised Protocol 01	18-Mar-2013	Incorporates Amendment 02.
Amendment 02	18-Mar-2013	[redacted]
Original Protocol	25-May-2012	Not applicable

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SYNOPSIS

Clinical Protocol CA209040

Protocol Title: A Phase 1/2, Dose-escalation, Open-label Study of Nivolumab or Nivolumab in Combination with Other Agents in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

[redacted]

In the Nivolumab plus Ipilimumab Combination Cohort: Subjects will be randomized 1:1:1 to receive

- Arm A--nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week
- Arm B--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3week x 4, followed by nivolumab 240 mg IV q2week
- Arm C--nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6week.

[redacted]

All subjects upon activation of amendment 8 are to be treated until toxicity or disease progression. Treatment may continue beyond progression under protocol defined conditions (see Section 4.2.5).

[redacted]

Study Phase: 1/2

Research Hypothesis:

[redacted]

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In the Nivolumab plus Ipilimumab Combination Cohort, treatment with nivolumab plus ipilimumab will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who are previously treated with sorafenib. In addition, the purpose of the cohort is to evaluate the safety profile of the combination in subjects with advanced HCC who have been previously treated with sorafenib.

[redacted]

Objective(s):

Primary Objective:

[redacted]

- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To establish the safety and tolerability of nivolumab plus ipilimumab in subjects with advanced HCC.
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

[redacted]

Secondary Objectives:

- [redacted]
  - [redacted]
  - [redacted]

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[redacted]

- **Nivolumab plus Ipilimumab Combination Cohort**
  - To assess antitumor activities (TTP and PFS) based on results of BICR and/or Investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab plus ipilimumab.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

[redacted]

Exploratory Objectives:

[redacted]

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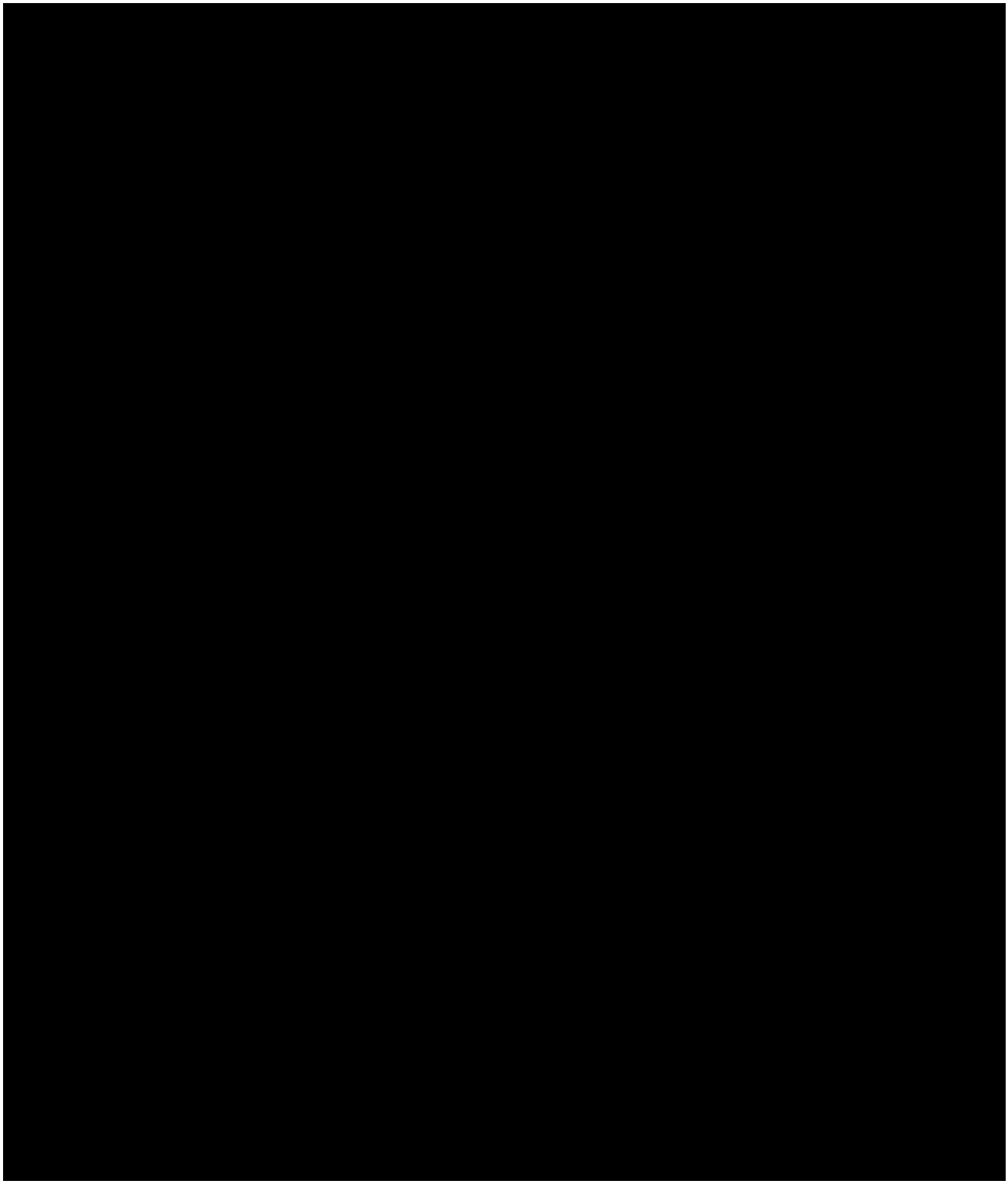

- **Nivolumab plus Ipilimumab Combination Cohort**
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.

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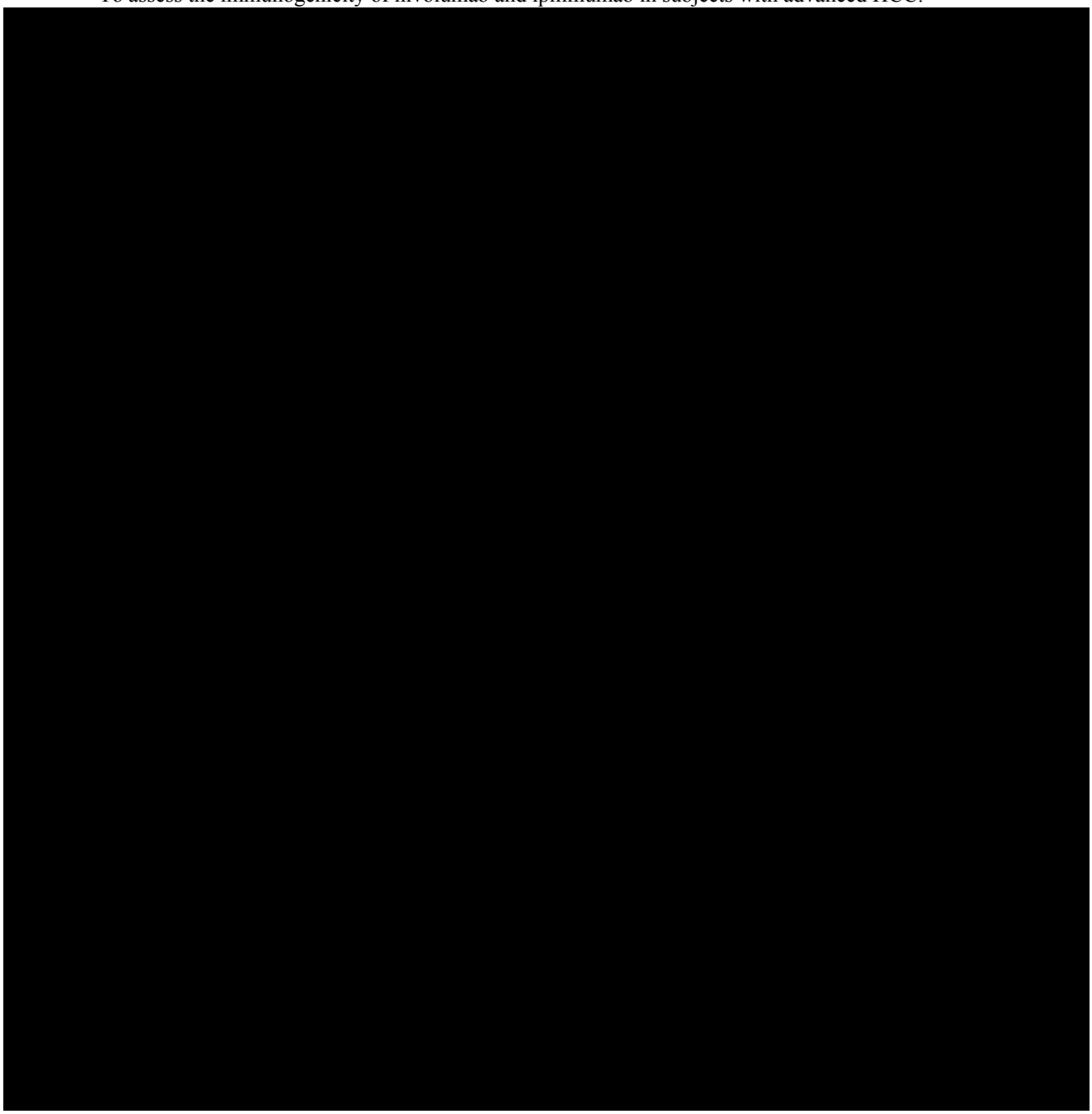
- To describe the effects of nivolumab plus ipilimumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
- To investigate the pharmacodynamic activity of nivolumab plus ipilimumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
- To assess the relationship between nivolumab plus ipilimumab exposure and measures of hepatic dysfunction.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
- To characterize the pharmacokinetics of nivolumab and ipilimumab in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.



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Study Design:

The **Nivolumab and Ipilimumab Combination Cohort** will consist of up to 120 subjects. Uninfected, HCV-infected, or HBV-infected subjects with advanced HCC and previous treatment with sorafenib will be randomized 1:1:1 into 3 different dose arms:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm C--nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week until toxicity or disease progression (n = 40).

A 2-stage design will be employed for each of the 3 dose arms. Twelve subjects in each dose arm will undergo a safety and tolerability assessment at Week 13 (or prior to Week 13 if discontinued). The safety evaluation (Section 3.1.4) will be conducted independently for each dose cohort based on criteria described in Discontinuation Criteria (Sections 4.1.18 for nivolumab and 4.2 for ipilimumab). No additional subjects will be enrolled until the safety evaluation at Week 13 occurs. After completion of Stage 1, enrollment in Stage 2 of the subsequent 28 subjects can occur in each dose arm and is contingent upon the results of the safety evaluation.

- [redacted]

[redacted]

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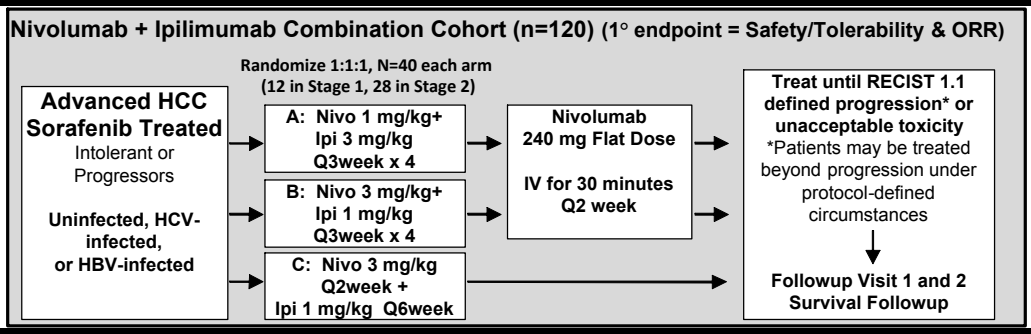

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Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). It is recognized that there may be delayed responses following disease progression with nivolumab and other agents in this class. In these cases, subjects may continue treatment provided that they experience no clinical deterioration. These subjects will continue to be evaluated by RECIST 1.1.

Duration of Study: The study is expected to accrue over a period of approximately 5 years. The study will end when survival follow-up collection has concluded. The last visit will be defined as the latest survival visit included in the final analysis of OS (ie. the latest subject death, loss to follow up, or withdrawal of consent).

Number of Subjects: Approximately [redacted] Nivolumab plus Ipilimumab Combination Cohort (120 subjects), [redacted]

Study Population: The study population will include men and women age 18 or older with advanced HCC. Advanced HCC is HCC not appropriate for management with curative intent by surgery or local therapeutic measures. All subjects must have measurable disease at baseline.

Statistical Considerations:

Sample Size Determination

[redacted]

Nivolumab plus Ipilimumab Combination Cohort: The sample size of each arm is decided based on safety and efficacy considerations. An initial total of 36 subjects will be randomized 1:1:1 (n = 12) into one of three arms within stage 1 to assess safety and tolerability. An additional 28 subjects will be enrolled into each arm that remains open within stage 2 to further establish efficacy and safety. With sufficient follow up for a total of 40 subjects in an arm, this will allow a stable estimate of ORR, adequate safety follow up, as well as information on duration of response. The maximum width of the exact 2-sided 95% confidence interval (CI) is 31.8% when the ORR is in the

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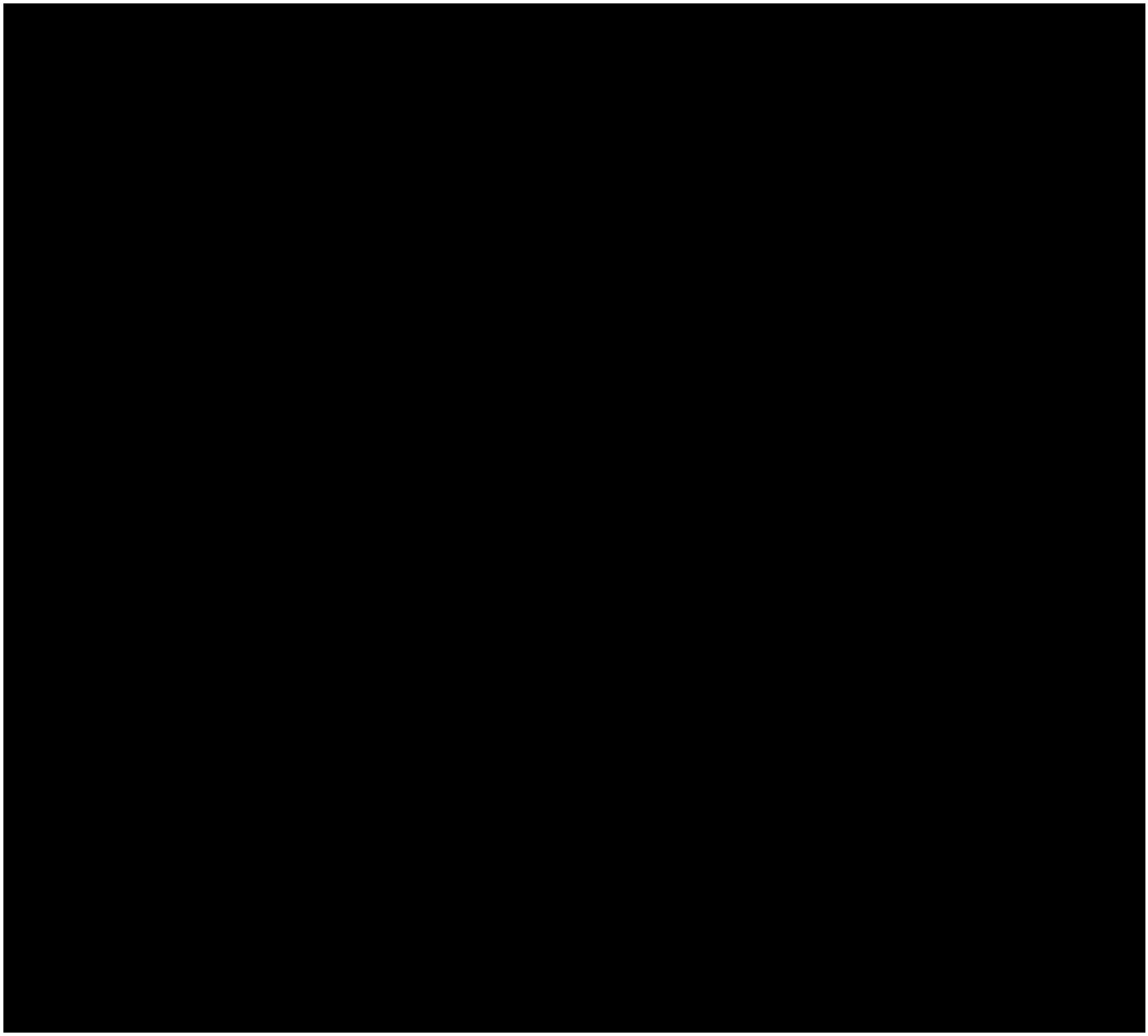
20% to 40% range. Table 2 summarizes the exact 95% CIs and 90% lower bound for a sample size of 40 per arm when observed ORRs are 20% to 40%, respectively.

Table 2: Observed ORR with Exact 95% CI and 90% Lower Bound

Observed ORR	Exact 95% CI	90% Lower Bound
20%	(9.1%, 35.7%)	12.0%
25%	(12.7%, 41.2%)	16.2%
30%	(16.6%, 46.5%)	20.5%
35%	(20.6%, 51.7%)	24.9%
40%	(24.9%, 56.7%)	29.4%



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Primary Endpoint

[redacted]

Nivolumab plus Ipilimumab Combination Cohort

- The primary objective is safety and tolerability of nivolumab plus ipilimumab as evaluated by the following endpoints:
  - Incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, and deaths.
  - Incidence of clinical laboratory test abnormalities.
- ORR, as assessed by Investigators under RECIST 1.1 criteria, is the co-primary endpoint. It is defined as the proportion of all treated subjects whose BOR is CR or PR. For a BOR of CR or PR, the initial response assessment must have been confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

[redacted]

Secondary Endpoints

The secondary efficacy endpoints for assessing antitumor activities include objective response rate (ORR) (Dose Escalation Phase only), CR rate, disease control rate (DCR), duration of response (DOR), TTR (time to response), TTP (time to progression), TTP Rate and PFS (progression free survival), all of which are based on BICR or Investigator assessed response evaluation according to RECIST 1.1. These endpoints, as well as OS (overall survival) and OSR (overall survival rate), will be applied to all cohorts for treatment groups [redacted] as treated (for all other cohorts). Definitions of the above secondary efficacy endpoints are available in Section 8.3.2.

[redacted]

Exploratory Endpoint(s)

Exploratory endpoints include, but are not limited to, BOR or ORR based on BICR assessed response evaluation according to mRECIST for HCC, AFP summary statistics, viral load, EQ-5D and FACT-Hep summary statistics. Detailed descriptions of the above exploratory endpoints are seen in Section 8.3.3.

Analyses

Only safety analysis and primary efficacy endpoint analysis are described below. Please refer to Section 8 for complete descriptions of statistical analyses.

Safety Analysis

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment arm. Adverse events, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v.4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v.4.0 criteria.

Primary Endpoint of ORR in the [redacted] Nivolumab plus Ipilimumab Combination Cohort [redacted]

ORR, as determined based on Investigator assessed tumor response according to RECIST 1.1, is the primary efficacy endpoint. Comparison of ORRs in all randomized subjects will be carried out using a two-sided Cochran-

Mantel-Haenszel (CMH) test stratified by the stratification factors. An associated odds ratio and 95% CI will be calculated. Additionally, ORRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each treatment arm.

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1. INTRODUCTION AND STUDY RATIONALE

Programmed Cell Death-1 (PD-1; CD279) is a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). It is a 55 kD type I transmembrane protein that is a member of the CD28 family of T-cell costimulatory receptors, which also includes cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Inducible COStimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[1] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). PD-1 is primarily expressed on activated T, B, and myeloid cells.[2] Its ligands, PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[3,4] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[5,6]

Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis.[7,8,9] The emergence of autoimmunity is dependent upon the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[10,11,12] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response.[13,14,15,16,17,18]

In humans, PD-L1 is constitutively expressed on macrophage-lineage cells, activated T cells, lung, vascular endothelial cells, and placental syncitiotrophoblasts.[19] Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[20,21,22,23,24,25,26] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[27] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[28] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression.[29] In multivariate analysis, high expression of PD-L1

in melanoma is an independent predictor of vertical growth of primary melanomas and of worse outcome.[30]

BMS-936558 (nivolumab) is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of `both proliferation and IFN-γ release in the MLR.[31] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner.

1.1 Study Rationale

1.1.1 Rationale for Nivolumab in Hepatocellular Carcinoma

Expression of PD-L1 by malignant tumor cells and by other cells in the tumor microenvironment including infiltrating T cells, dendritic cells, and monocytes, has the potential to interact with tumor specific T cells that express PD-1. The interaction of PD 1 on tumor specific cytotoxic T cells with its ligands PD-L1 and PD-L2 causes a decrease in the ability of these cells to proliferate and exert cytotoxic effects, increases their apoptotic rate and alters the functional characteristics of the cells to produce a tolerogenic phenotype. This study will evaluate the effects of PD-1 blockade by nivolumab in subjects with hepatocellular carcinoma (HCC).

There is a strong preclinical rationale for blocking PD-1 signaling in HCC. Lymphocyte homeostasis is closely regulated by the differential effects of cytokines and an array of cell surface signaling molecules that exert opposing actions on T cell proliferation.[32,33,34] One of the primary molecules responsible for T cell expansion in response to antigenic stimulation is CD28. The interaction of CD28 on the T cell with B7.1 or B7.2 on the antigen presenting cell stimulates T cell proliferation and survival through increased expression of bcl2 family members, increased production of IL-2 and decreases the threshold of T cell receptors required for activation.[35] CD28 ligation also increases production of interferon gamma.[36] By necessity a mechanism for elimination of antigen stimulated T cells is required following control of the antigenic challenge to maintain the viability of the host. One important regulator of T cell contraction following antigen stimulation is CTLA4.[37] CTLA4 expression on T cells is increased following antigen stimulation and has an affinity for B7.1 and B7.2 that is 10-fold greater than CD28. Upon control of an antigenic challenge CTLA4 preferentially interacts with the antigen presenting cell to inhibit proliferation of T cells and helps to effect the contraction of the expanded T cell population. Mice that are deficient in CTLA4 die within one month of birth due to massive organ infiltration with lymphocytes as a result of the lack of this inhibitory signaling pathway.[38] A second member of this family of molecules that regulates T cell contraction is PD-1 and like CTLA4 its expression is increased following antigen stimulation.

Following most viral infections the host is capable of eliciting an effective innate and adaptive immune response to eliminate the virus and prevent reinfection. However, both in animals and

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man there are examples of viral infections that are not eliminated following infection but instead a chronic viral infection is established. Examples include lymphocytic choriomeningitis virus (LCMV) in mice and hepatitis B and C in man. In chronic LCMV infection, antigen specific CD8 T cells demonstrate increased expression of PD-1.[39] These T cells have been termed "exhausted" due to their inability to control the infecting virus. Administration of an antibody that prevents PD-1 interaction with its ligands restores the ability of the cells to eliminate the virus infection.

PD-L1 is expressed in tumor biopsies from subjects with HCC. There is some controversy over the cell type that expresses PD-L1 and variability may exist between subjects with different stages of disease, etiologic factors associated with HCC, or immunologic response of the host to the tumor.[40,41,42,43] Hepatocytes and hepatoma cell lines express PD-L1 and its expression is increased by interferon gamma exposure.[44] This implies that the malignant cell may be the source of PD-L1 expression in some tumors but its expression has variably been observed on the malignant cells in patient samples. Some reports identify the hepatoma cells as PD-L1 positive whereas others show them to be negative for its expression. Instead, PD-L1 is observed on the mononuclear cells at the periphery of the malignant cells, potentially acting as a barrier for entry of PD-1 positive T cells. As in renal cell carcinoma and melanoma, expression of PD-L1 in the tumor is associated with an adverse outcome.[45,46] In a study of 265 subjects with HCC, the median disease free survival (DFS) was 14.9 for PD-L1-positive subjects but was not reached for PD-L1-negative subjects. Overall survival (OS) was also worse in subjects with PD-L1 positive tumors, 29.6 months versus 59.4 months.

Hepatocellular carcinoma is diagnosed in more than 500,000 people globally and is the fifth most common cancer in men and seventh in women.[47] There is an uneven distribution of HCC throughout the world with a higher incidence in Asia and Africa. This is related primarily to the differential rates of hepatitis B infection throughout the world and hepatitis B infection is found as a predisposing feature in about 50% of cases. In the United States about 20,000 cases of HCC are diagnosed per year and the incidence is predicted to increase by 81% by 2020. Risk factors for initiation of HCC are related to liver injury and repair particularly in association with liver cirrhosis. Viral infection or other inflammatory insults to the liver account for most cases of HCC. The risk factors for the development of HCC in hepatitis B carriers is highest in Asian men older than 40, Asian women over the age of 50, and in those with liver cirrhosis or a family history of HCC. In subjects with chronic hepatitis B infection but without cirrhosis, HCC is dependent upon viral genotype, replication and the presence of inflammation. Most other cases of HCC are associated with liver cirrhosis due to a variety of agents that damage the liver. Hepatitis C infection is found as the underlying etiology in about 25% of cases and is increasing significantly in the United States. Virtually any cause of liver damage that leads to cirrhosis can predispose to HCC. The most common associated disorders include alcohol-induced liver disease, fatty liver disease, aflatoxin exposure, primary biliary cirrhosis, or genetic predisposition to liver damage including hemochromatosis, alpha-1 antitrypsin deficiency or Wilson's disease.

Advances in the treatment of HCC have been related to improved disease control due to early detection. Early detection permits a curative surgical approach or use of local therapies such as radiofrequency ablation or cryotherapy as a curative option for management. Unfortunately up to 70% of subjects will recur. Liver transplantation is another curative treatment for HCC.

HCC is diagnosed at an advanced stage in more than 80% of subjects thus precluding potentially curative treatment approaches. The prognosis of advanced HCC largely depends not only on the characteristics of the tumor but also on the severity of the underlying chronic hepatic disease, as well as the patient's general condition.[48,49,50] Although chemotherapy has demonstrated activity against HCC, the current standard of care for subjects with advanced HCC is sorafenib.[51] A randomized double-blind, placebo-controlled trial of sorafenib administered at a dose of 400 mg twice daily showed a 2.8 month improvement in median overall survival from 7.9 months to 10.7 months (hazard ratio (HR) in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $P < 0.001$). The median time to radiologic progression was also improved in the sorafenib group from 2.8 months to 5.5 months. There was however no significant difference in median time to symptomatic progression in those treated with sorafenib. Following sorafenib progression there is currently no standard of care agents that demonstrate a survival advantage.

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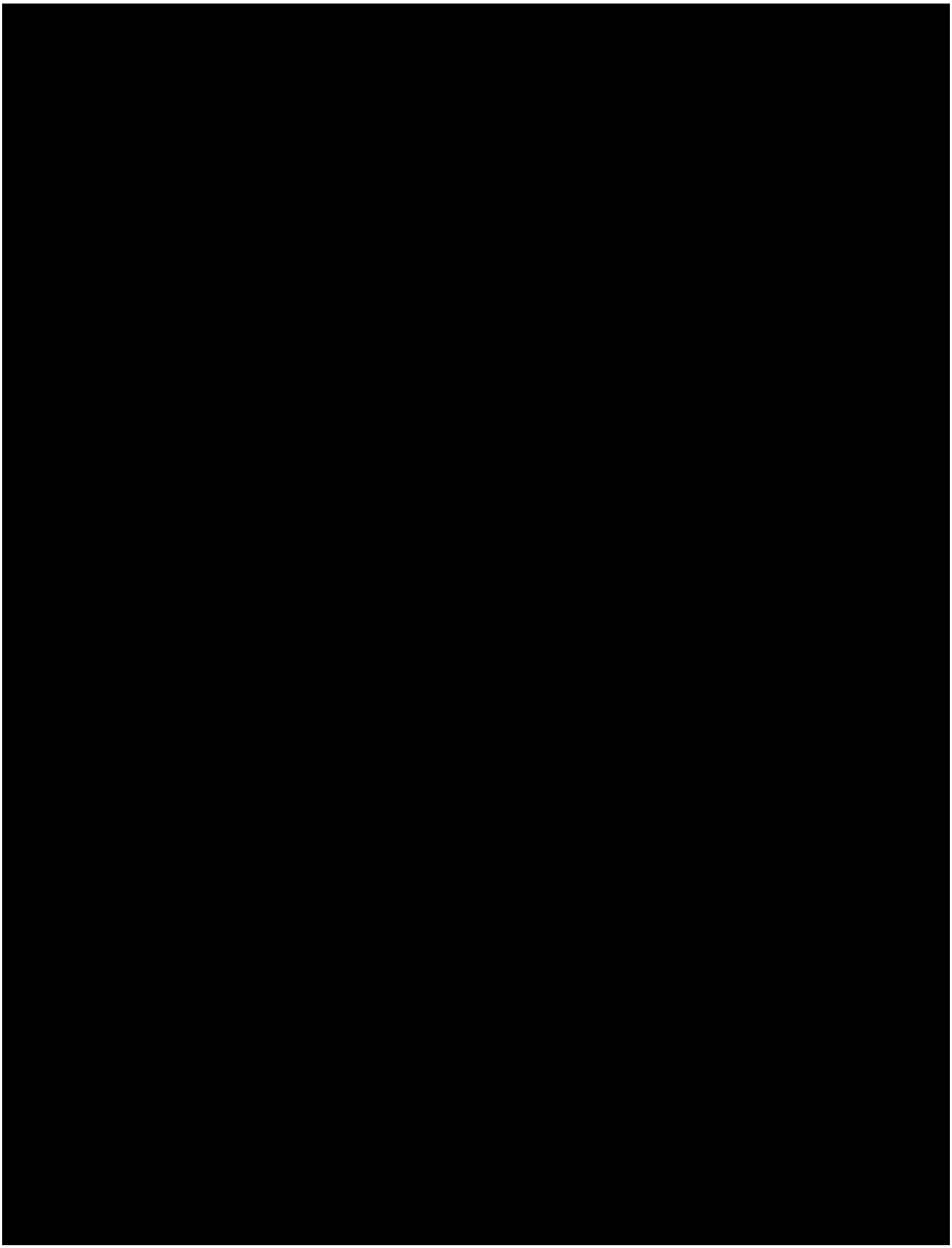

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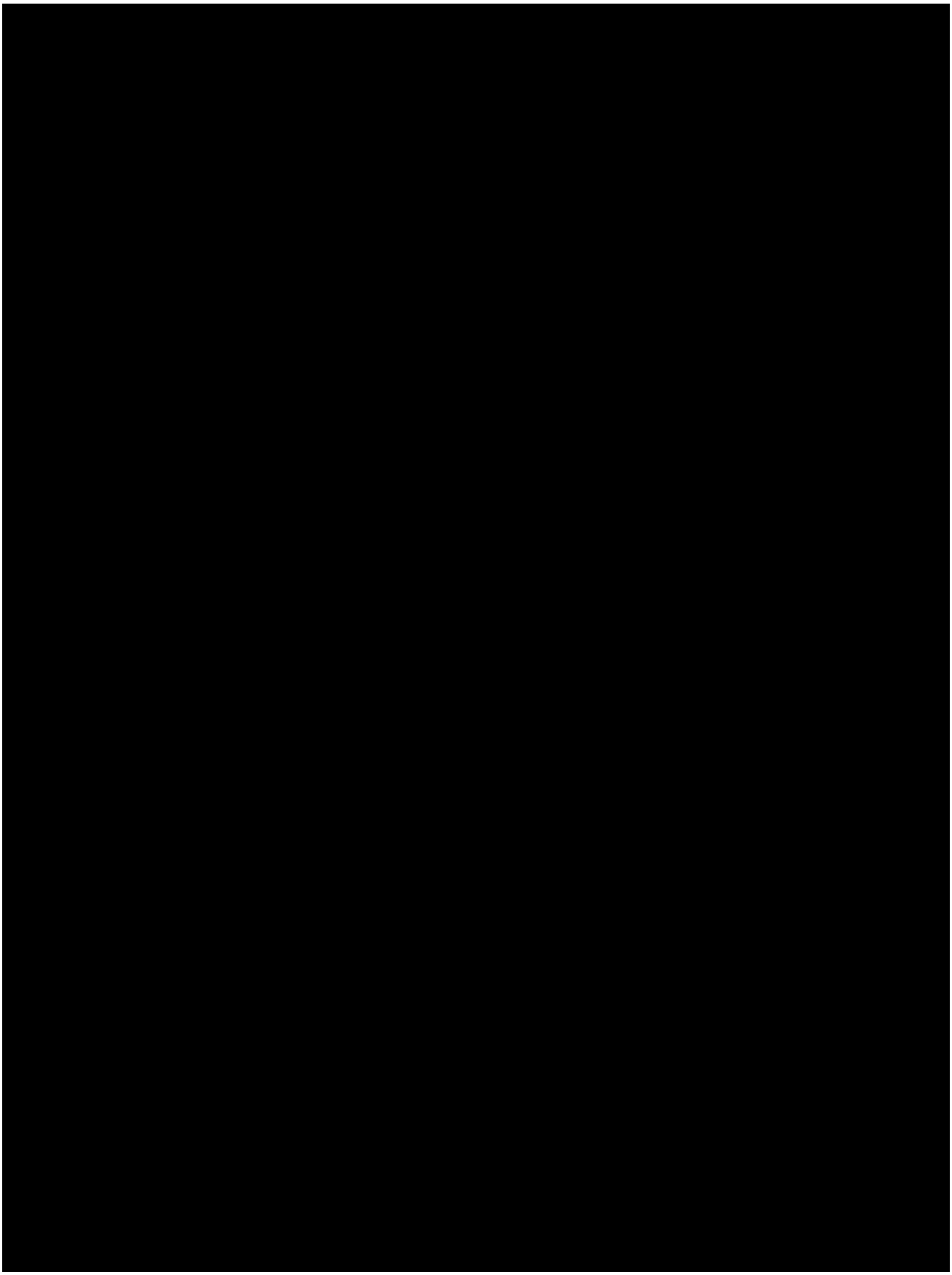

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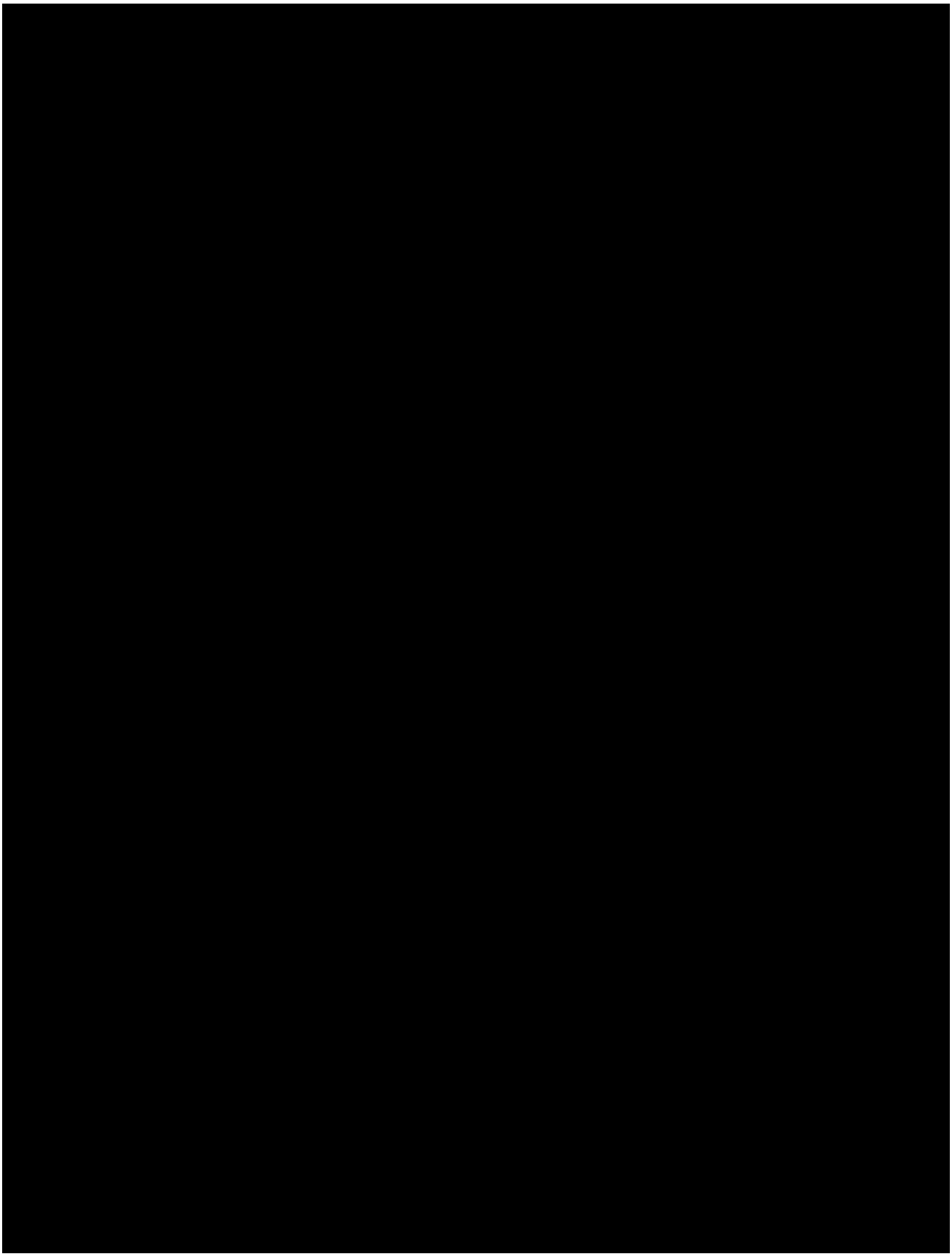

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1.1.8 Rationale for Nivolumab plus Ipilimumab Combination Cohort

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Programmed death 1 (PD-1) receptor and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) are two important cellular targets that play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.[70]

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma [Yervoy® Prescribing Information, 2011] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[71,72] Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous non small cell lung cancer (NSCLC) and radiotherapy for hormone resistant prostate cancer.

Phase 3 studies are ongoing in NSCLC, small cell lung cancer (SCLC), and prostate carcinoma.[73]

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Preliminary data in subjects with advanced HCC support the continued development of Immuno-Oncology (IO) agents in this tumor type. In a Phase 2, non-controlled, open-label, multicenter trial, tremelimumab, a monoclonal antibody that blocks CTLA-4, was administered at a dose of 15 mg/kg IV every 90 days in 20 subjects with advanced HCC and chronic HCV.[74] In terms of antitumor responses, this pilot study in HCV-HCC subjects treated with a CTLA-4 blocking antibody, reported a partial response rate (PR) of 17.6%, a disease control rate (DCR) of 76.4%, and a time to progression of 6.48 months, which compares favorably with sorafenib data as outlined above in Section 1.1.3. A rise in serum transaminases was observed after the first dose in more than half of the subjects. Five of 20 subjects (25%) experienced a Grade 3 or higher elevation in ALT. However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses. An HCC clinical trial is currently on-going for tremelimumab in combination with chemoembolization or ablation.[75]

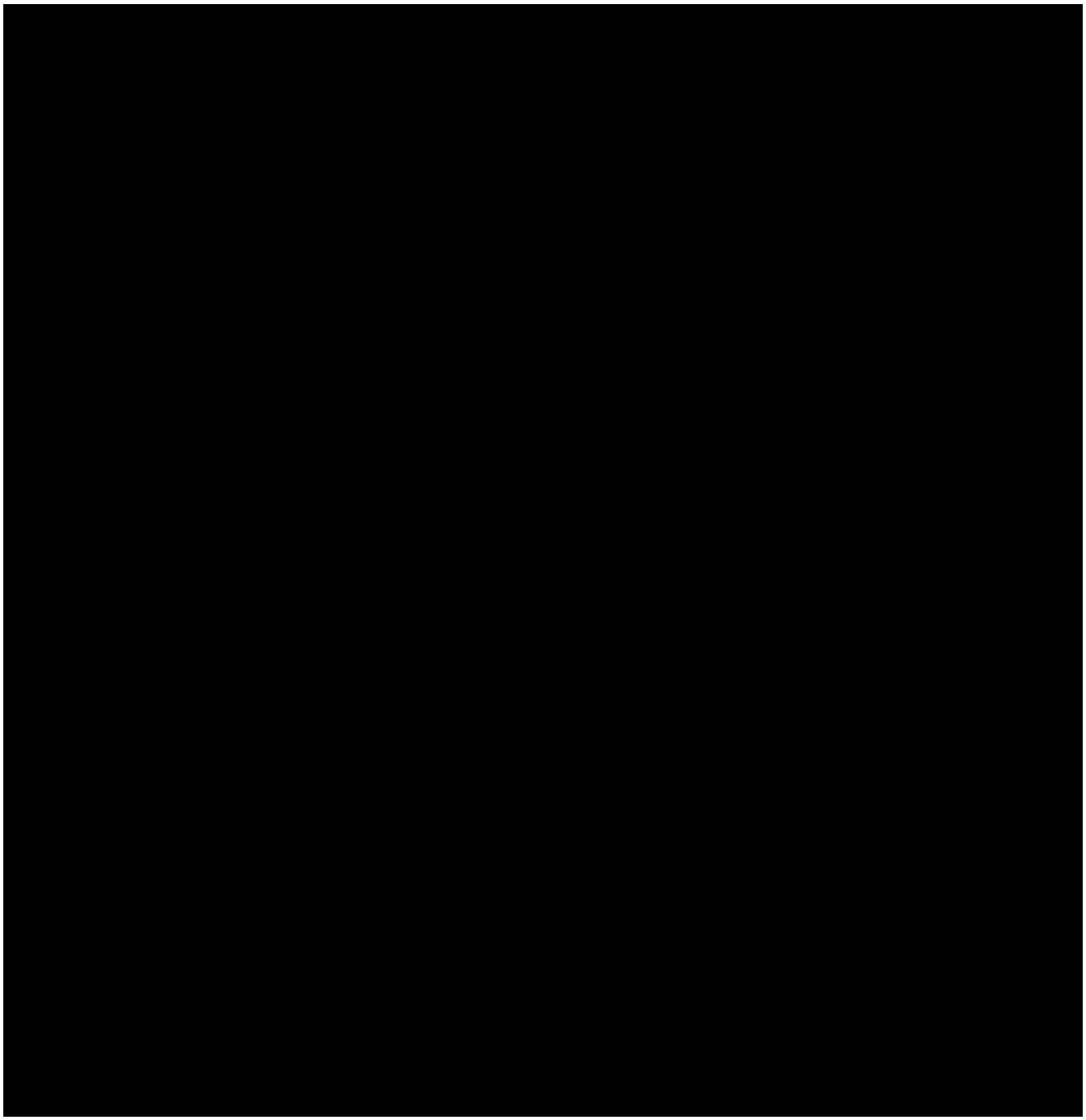
In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[63]

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of an additive to synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. In a Phase 1 study of the combination of nivolumab plus ipilimumab in advanced melanoma (CA209004), there was a 41% response rate, including a 17% complete response rate (CR).[76] A randomized Phase 2 study (CA209069) comparing nivolumab plus ipilimumab versus ipilimumab showed an objective response rate of 61%, including a 22% complete response rate, in previously untreated, advanced melanoma subjects with BRAF wild-type mutation status, versus 11 % for ipilimumab alone.[77] In addition, the combination regimen decreased the risk of melanoma progression or death compared to ipilimumab alone by 60%.

In a Phase 3 trial of combined nivolumab and ipilimumab or monotherapy in untreated melanoma (CA209067), nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone. The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; $P < 0.001$), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; $P < 0.001$). In subjects with PD-L1–negative tumors, the combination of PD-1 and

CTLA-4 blockade was more effective than either agent alone.[78] Additional efficacy and safety results demonstrating the potential for a combination IO approach are outlined in Sections 1.4.4 and 1.4.5.

Taken together, the preliminary monotherapy data of CTLA4 and PD-1 pathway inhibition in HCC demonstrate antitumor activity and manageable safety profiles. Given the increased efficacy observed with combination approaches in other tumor types, nivolumab plus ipilimumab may offer subjects with advanced HCC, who have been previously treated with sorafenib and have no other approved treatment options, the potential for benefit.



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[redacted]

1.1.10 Rationale for Objective Response Rate as Primary Endpoint in [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted]

[redacted]

Objective Response Rate (ORR) as estimated by RECIST 1.1 is the primary endpoint for [redacted] the Nivolumab plus Ipilimumab Combination Cohort, [redacted]

The primary analysis of ORR will be performed at least 6 months after the last patient first dose date. Six months follow-up is thought to be sufficient to characterize durable clinical benefit because in the dose escalation cohorts of CA209040, the majority of responses to nivolumab occurred early (by Week 12) in 7 of 8 subjects; the median duration of response (DOR) was approximately 12 months; and in 1L trials with sorafenib the median time to progression is usually < 4 months. This will allow sufficient follow up for ORR to have a stable estimate, adequate safety follow up, as well as information on duration of response in the [redacted] Nivolumab plus Ipilimumab Combination

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Cohort, [redacted] Furthermore, in advanced HCC subjects who received a systemic multikinase inhibitor, brivanib (BRISK-PS), ORR has been shown to be an independent predictor of OS with median OS of 16.4 months in brivanib responders vs 8.3 months for brivanib non-responders (hazard ratio 0.28; 95% CI 0.14 - 0.55, P < 0.01).[91]

[redacted]

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[redacted]

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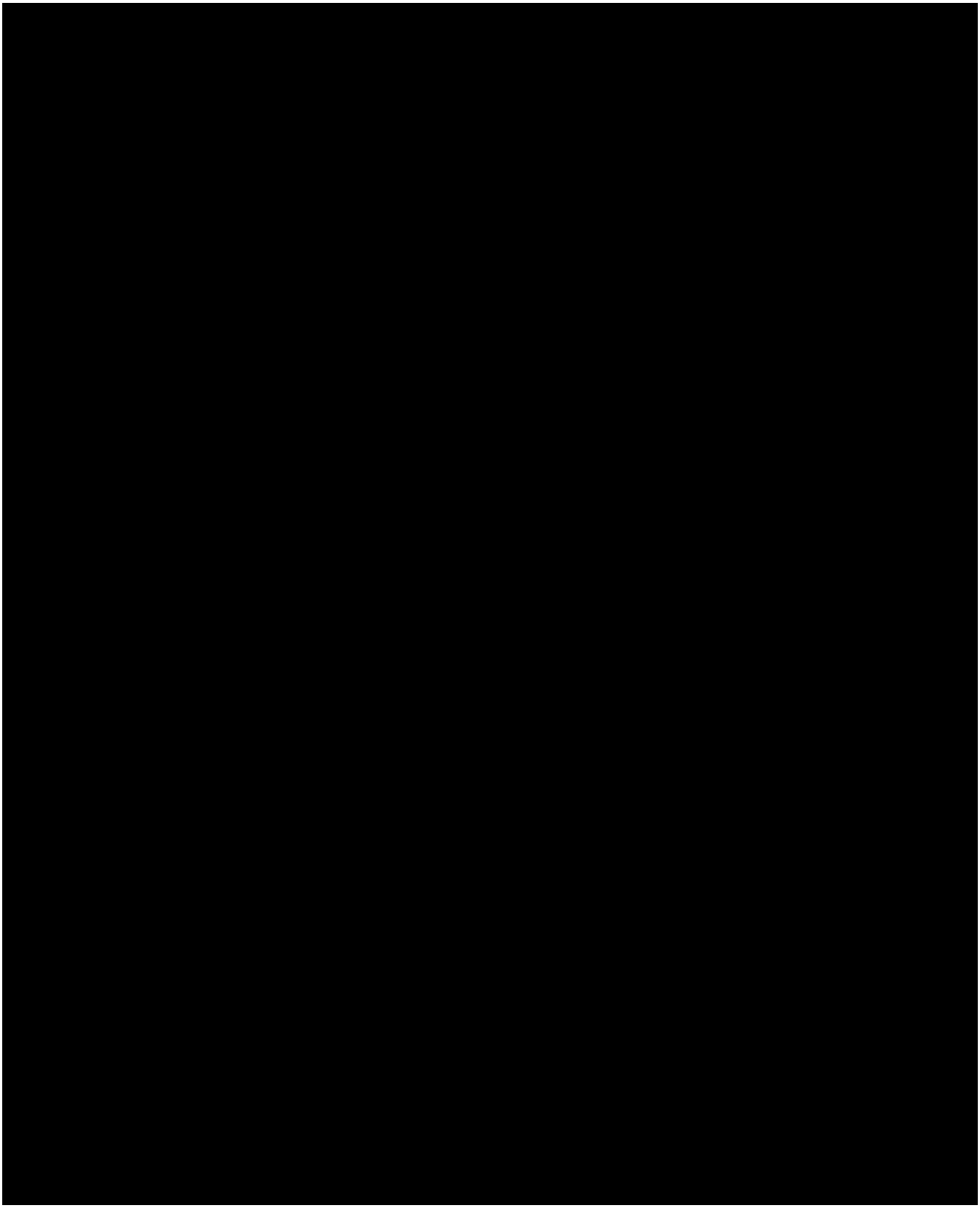

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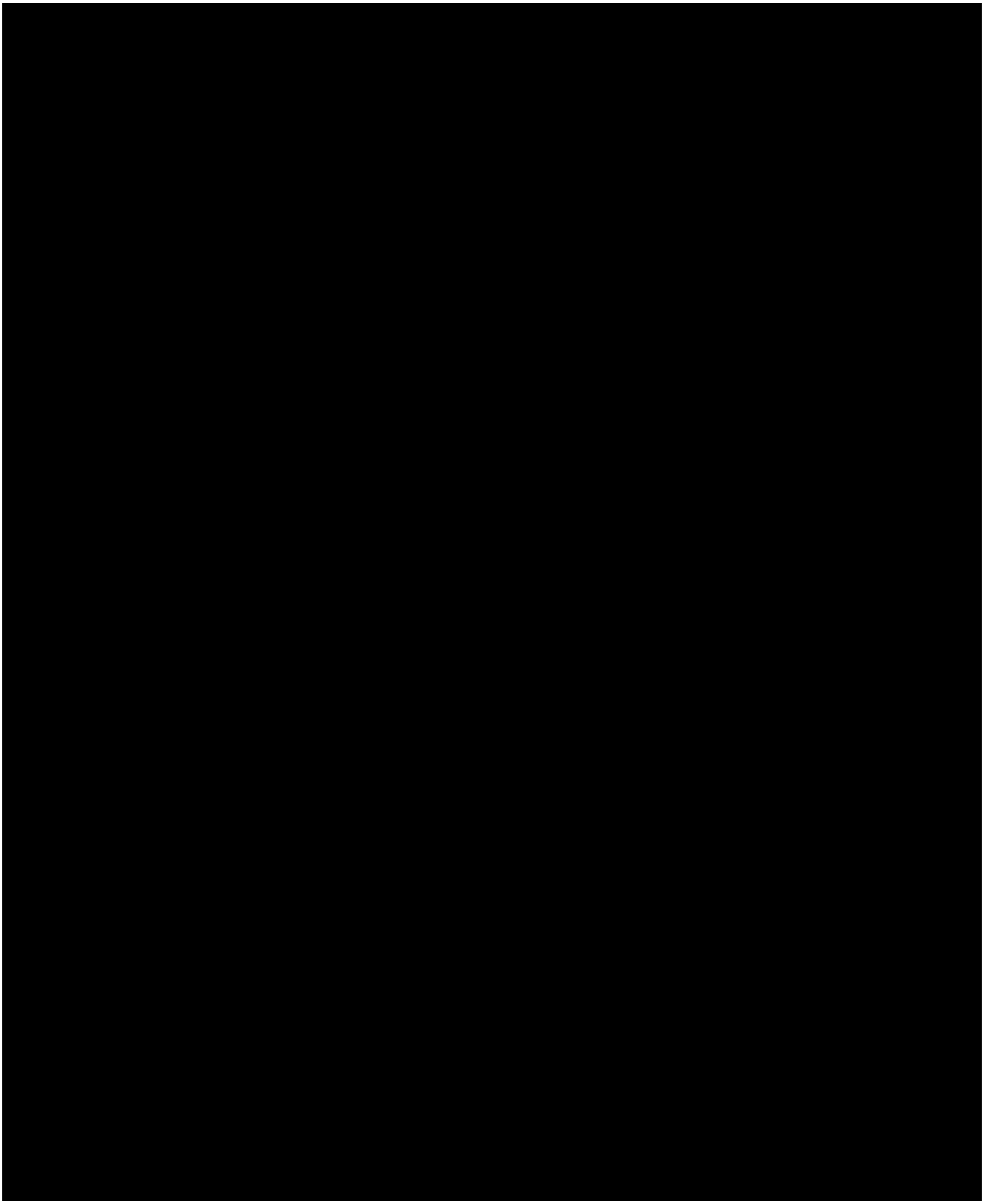

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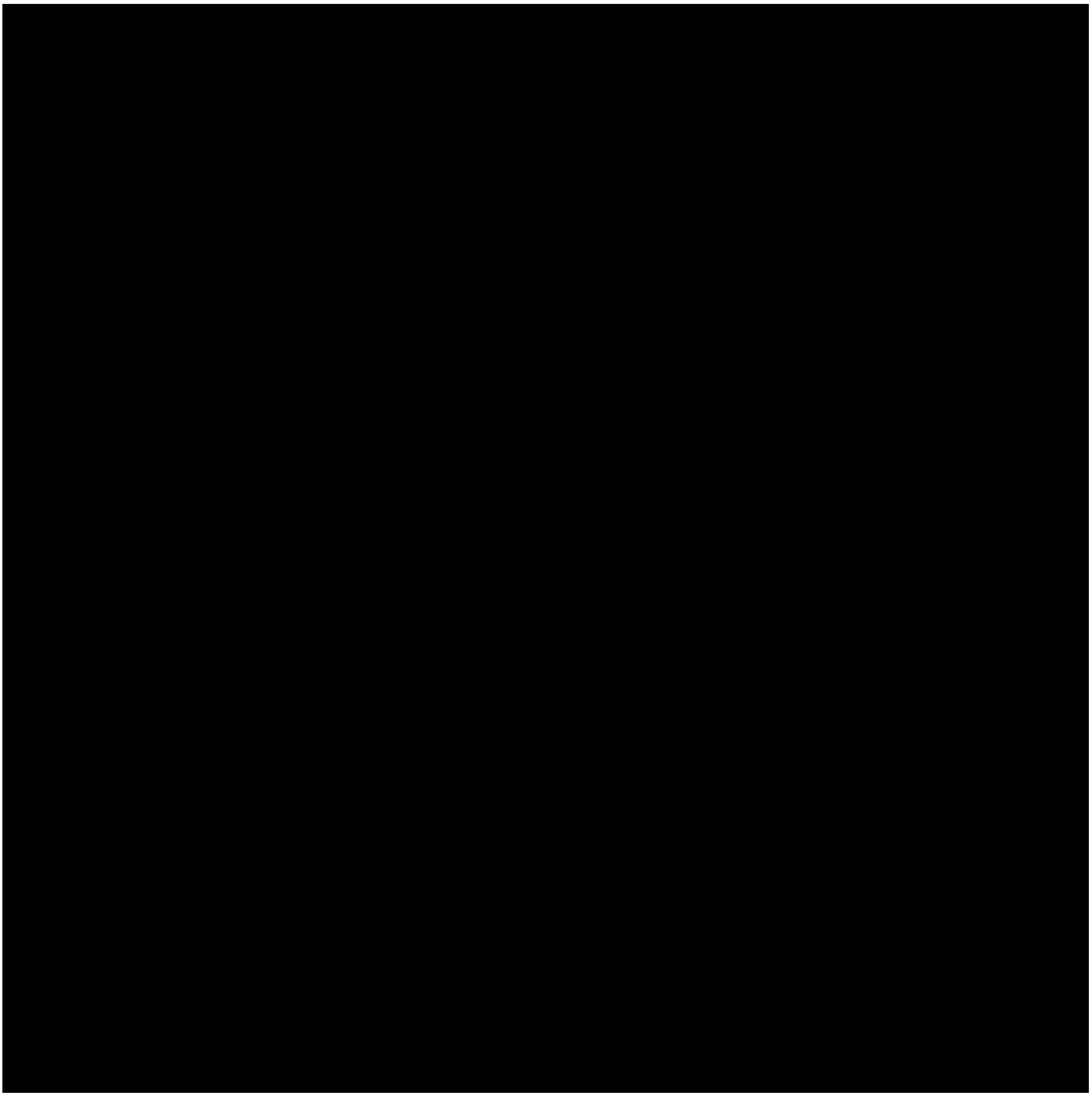

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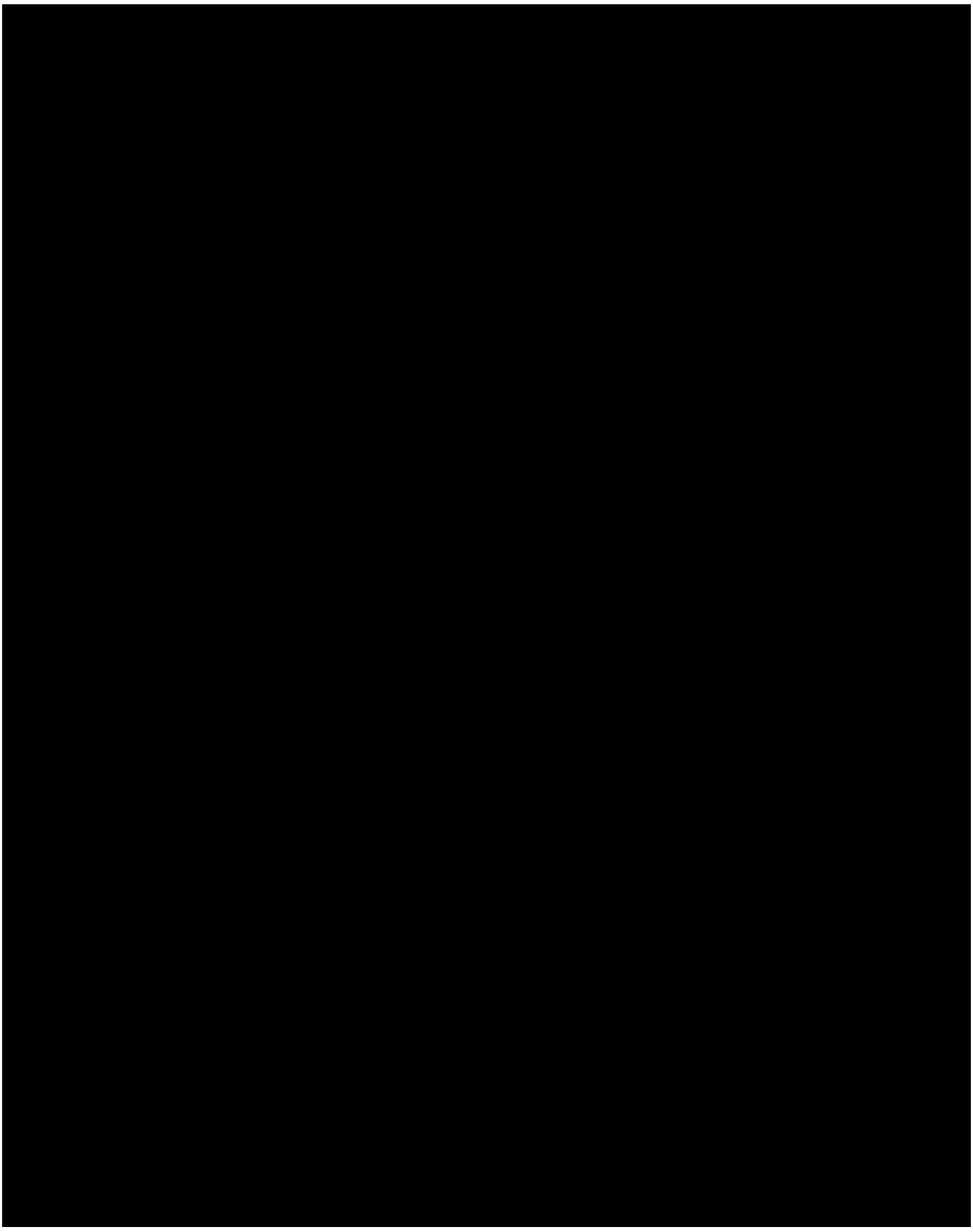

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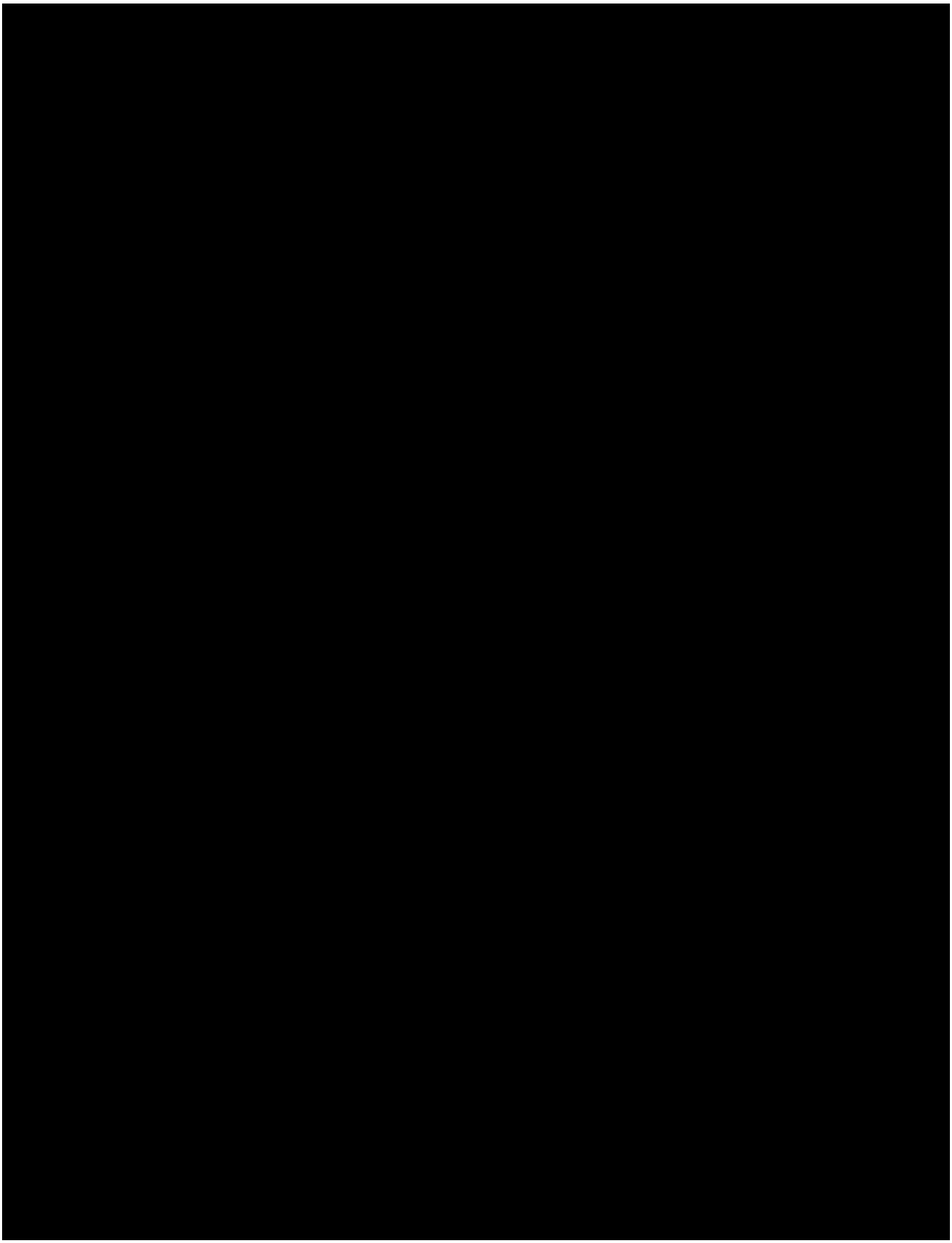

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[redacted]

1.2 Research Hypothesis

[redacted]

In the Nivolumab plus Ipilimumab Combination Cohort, treatment with nivolumab plus ipilimumab will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who are previously treated with sorafenib. In addition, the purpose of the cohort is to evaluate the safety profile of the combination in subjects with advanced HCC who have been previously treated with sorafenib.

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objectives

- [redacted]

[redacted]

- **<u>Nivolumab plus Ipilimumab Combination Cohort</u>**:
  - To establish the safety and tolerability of nivolumab plus ipilimumab in subjects with advanced HCC.
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

[redacted]

1.3.2 Secondary Objectives

[redacted]

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- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To assess antitumor activities (TTP and PFS) based on results of BICR and/or investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab plus ipilimumab.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

[redacted]

1.3.3 Exploratory Objectives

[redacted]

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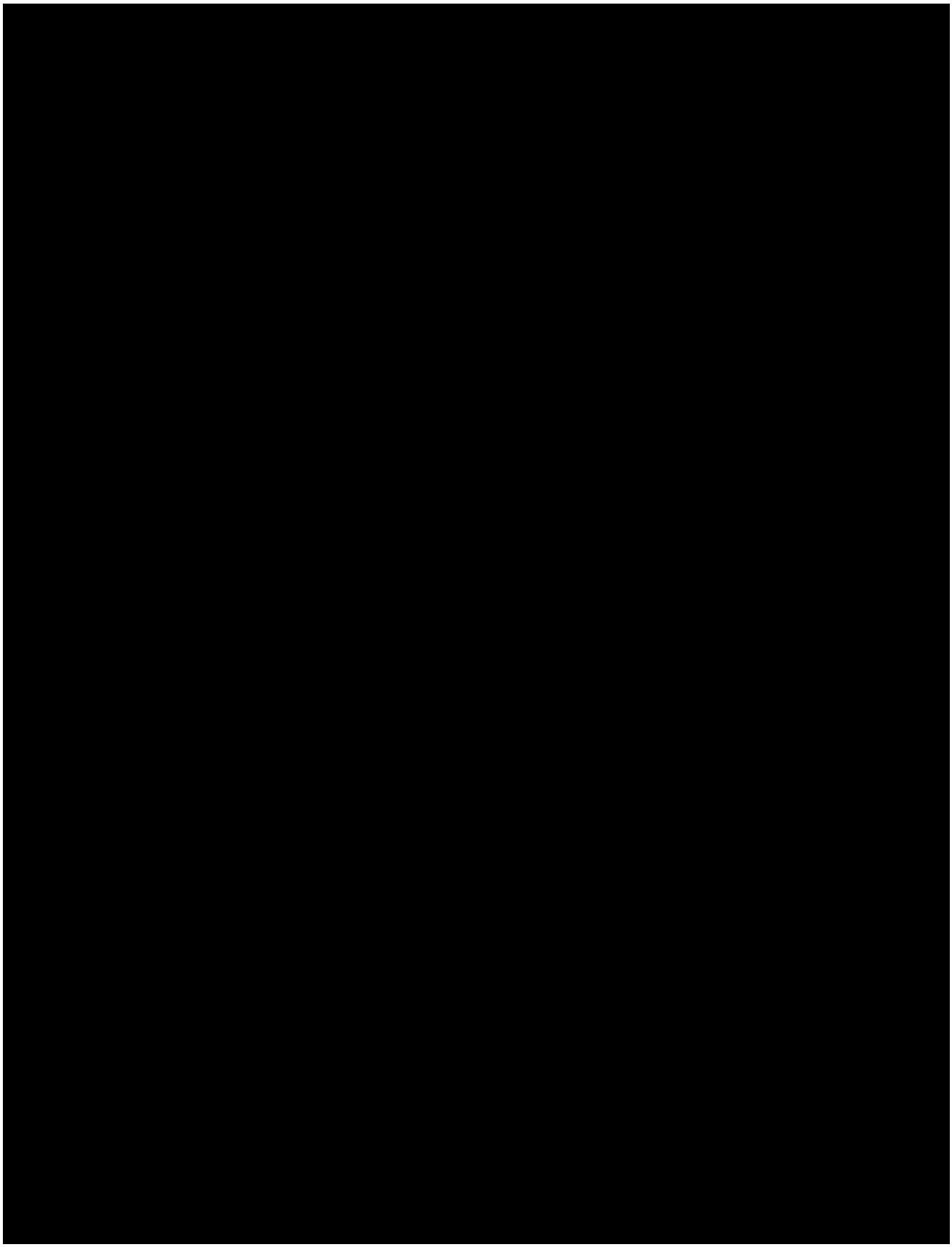

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- [redacted]

- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
  - To investigate the pharmacodynamic activity of nivolumab plus ipilimumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To assess the relationship between nivolumab plus ipilimumab exposure and measures of hepatic dysfunction.
  - To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
  - To characterize the pharmacokinetics of nivolumab and ipilimumab in subjects with advanced HCC.
  - To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.

[redacted]

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1.4 Product Development Background

A summary of the nonclinical pharmacology, toxicology, pharmaceutical and metabolism data is provided in this section. Additional information can be found in the Investigator Brochures for nivolumab[101], ipilimumab[102], [redacted]. The clinical pharmacokinetics of nivolumab and ipilimumab is described below; the clinical pharmacokinetics of cabozantinib is described in Section 1.5.6.

1.4.1 Pharmacology

1.4.1.1 Nonclinical Pharmacology

Nivolumab is an IgG4 antibody which binds to PD-1 (CD279) with nanomolar affinity and shows a high degree of specificity for PD-1, blocking binding of PD-1 to PD-L1 and PD-L2. nivolumab binds to human PD-1 and not to other members of the CD28 family, such as ICOS, CTLA-4 or BTLA.

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1.4.1.2 Metabolism and Excretion

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no tissue distribution studies with nivolumab have been conducted in animals. However, the low volume of distribution in cynomolgus monkeys (0.046 to 0.060 L/kg) indicates that there is little extravascular distribution of the drug.

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals no metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies (mAbs) is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes. In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no mass balance studies with nivolumab have been conducted in animals.

1.4.1.3 Clinical Pharmacokinetics of Nivolumab

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

1.4.1.4 Clinical Pharmacokinetics of Ipilimumab

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the 3 mg/kg and 10 mg/kg doses administered as a 1.5 h IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and was determined to be linear and time invariant in the dose range of 0.3 mg/kg to 10 mg/kg. The mean CL (± standard deviation [SD]) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean steady-state volume of distribution (Vss) (± SD) value was 5.75 ± 1.69 L. The terminal T-HALF determined from PPK analysis was 15.4 days. CL of ipilimumab in subjects with mild and moderate hepatic impairment was similar to that of subjects with normal hepatic function. PK within Japanese

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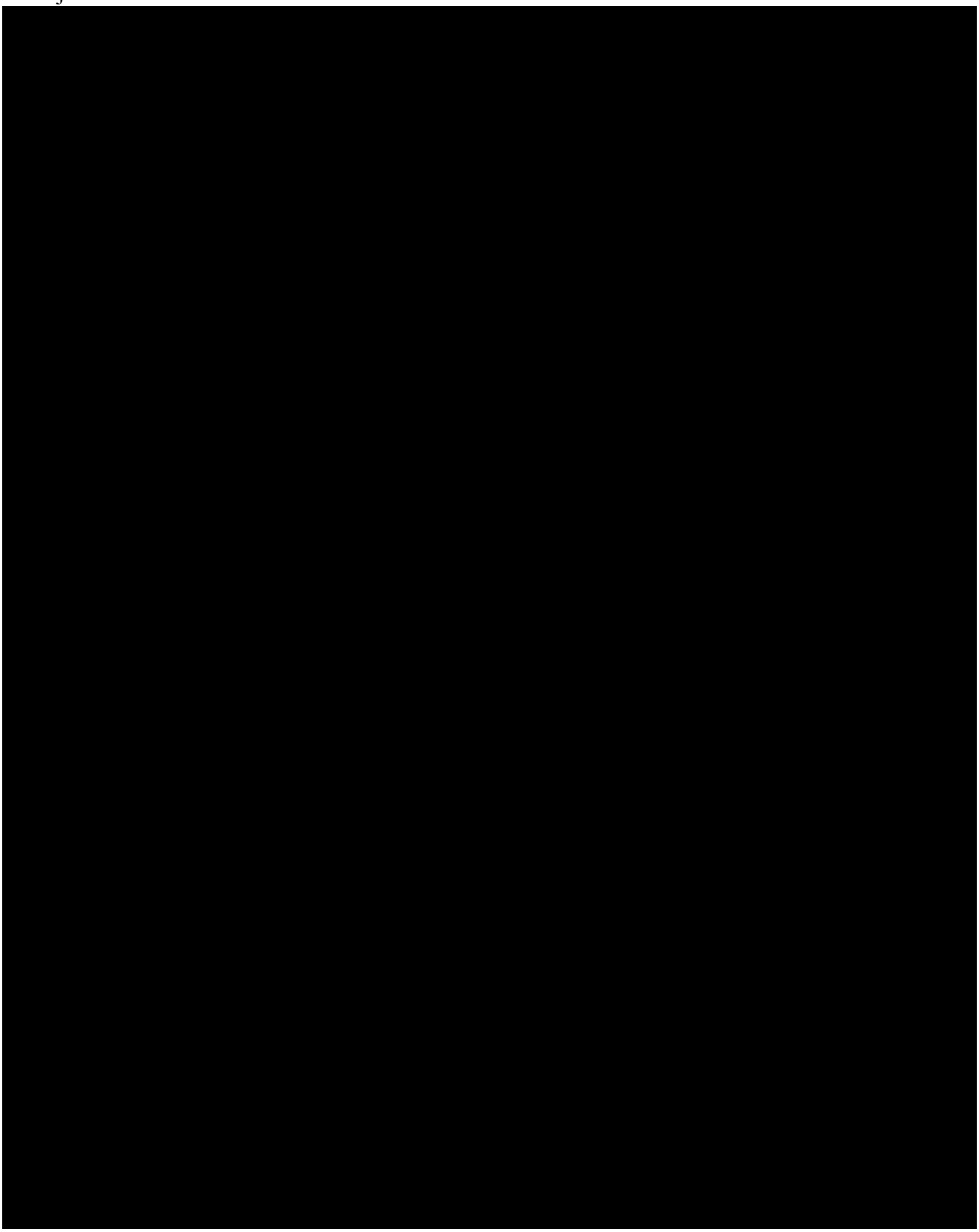
subjects is comparable and consistent with previous PK results reported within non-Japanese subjects.



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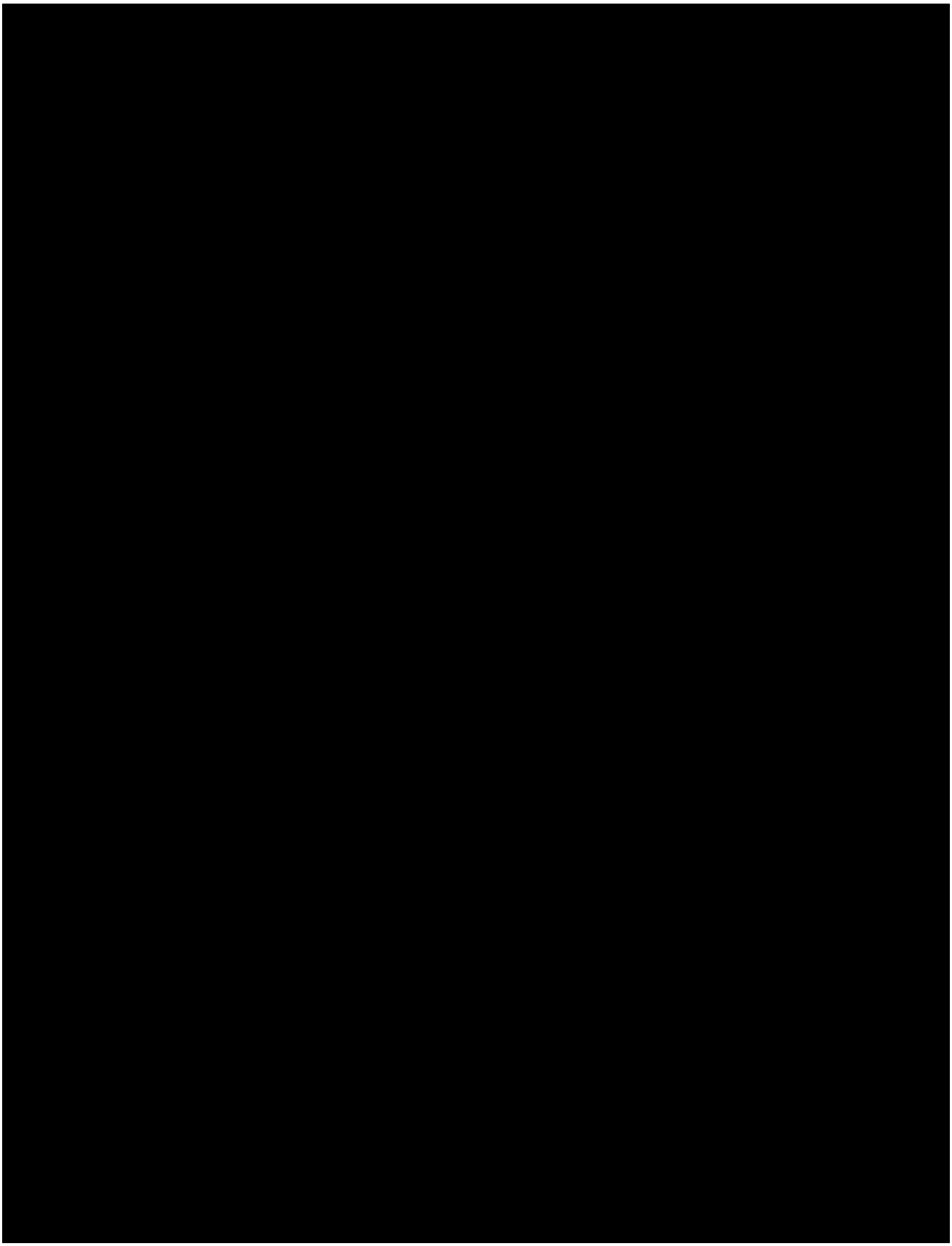

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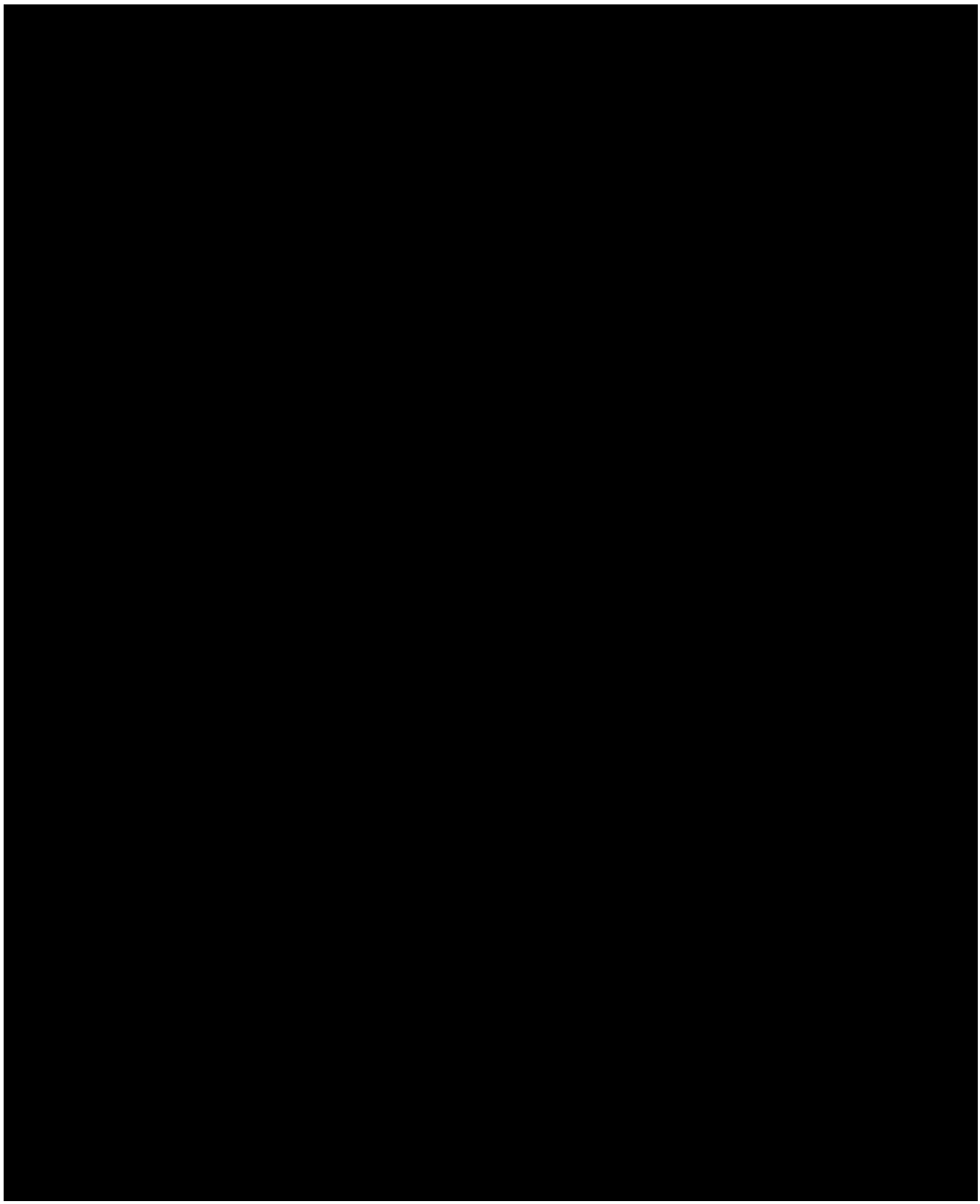

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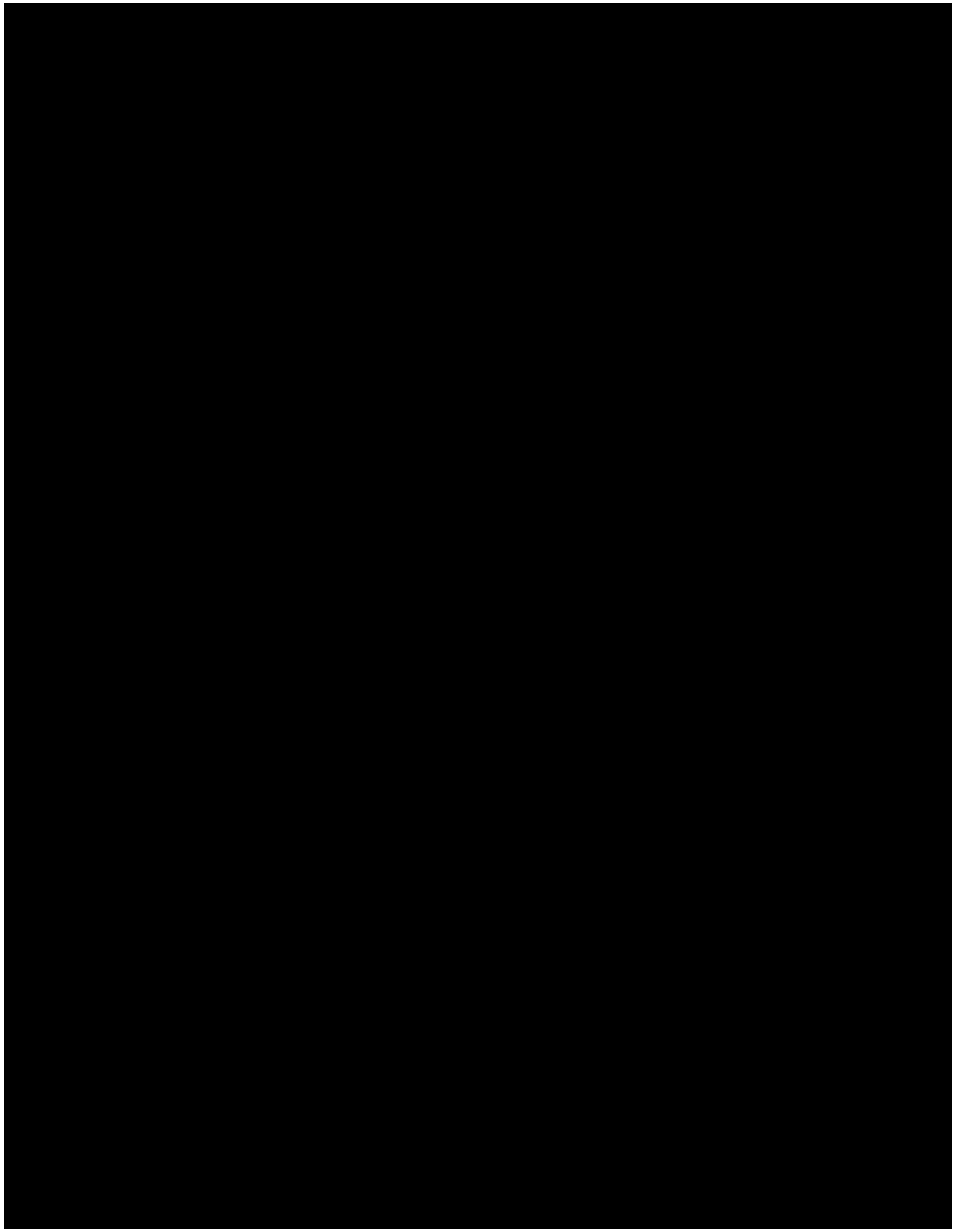

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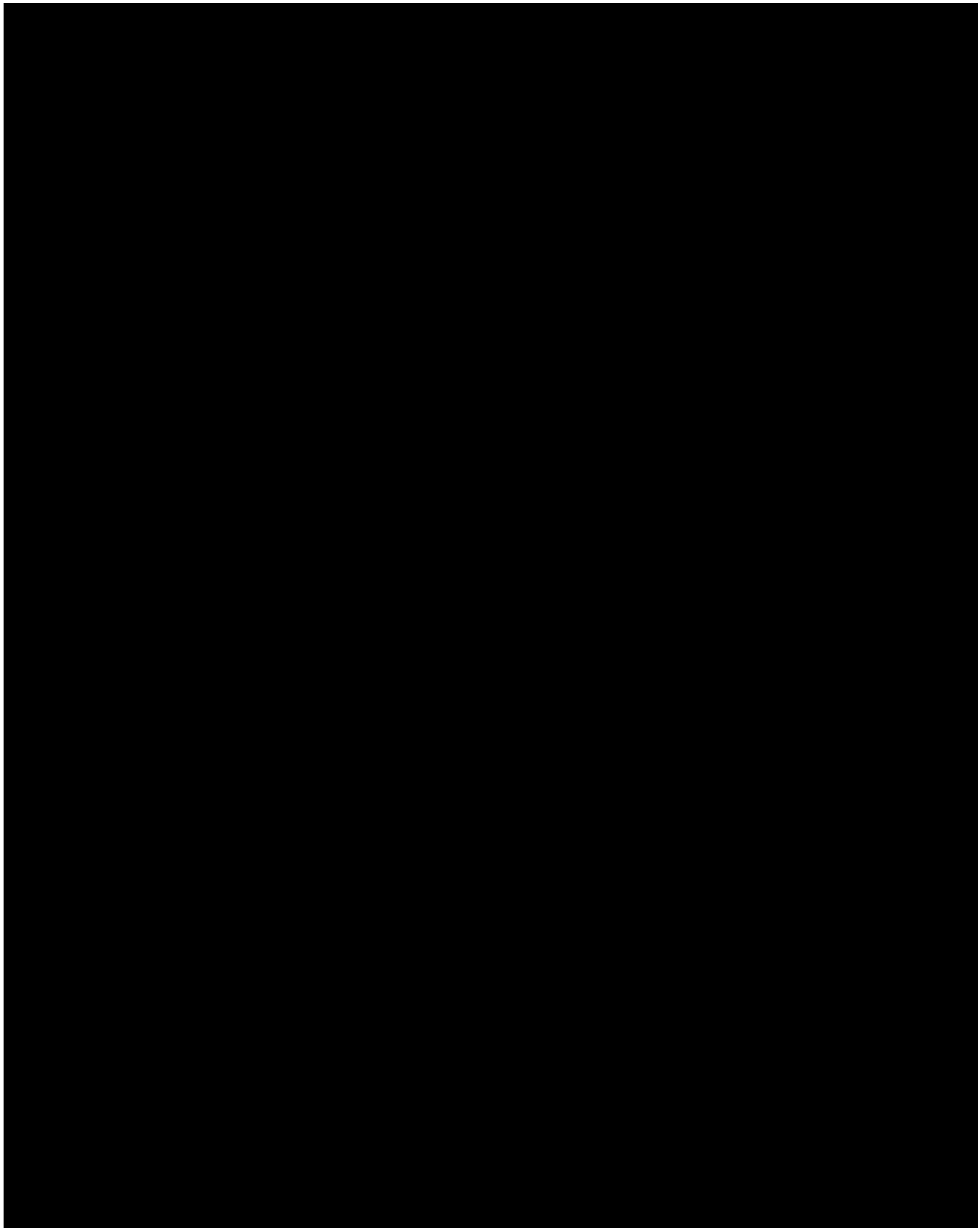

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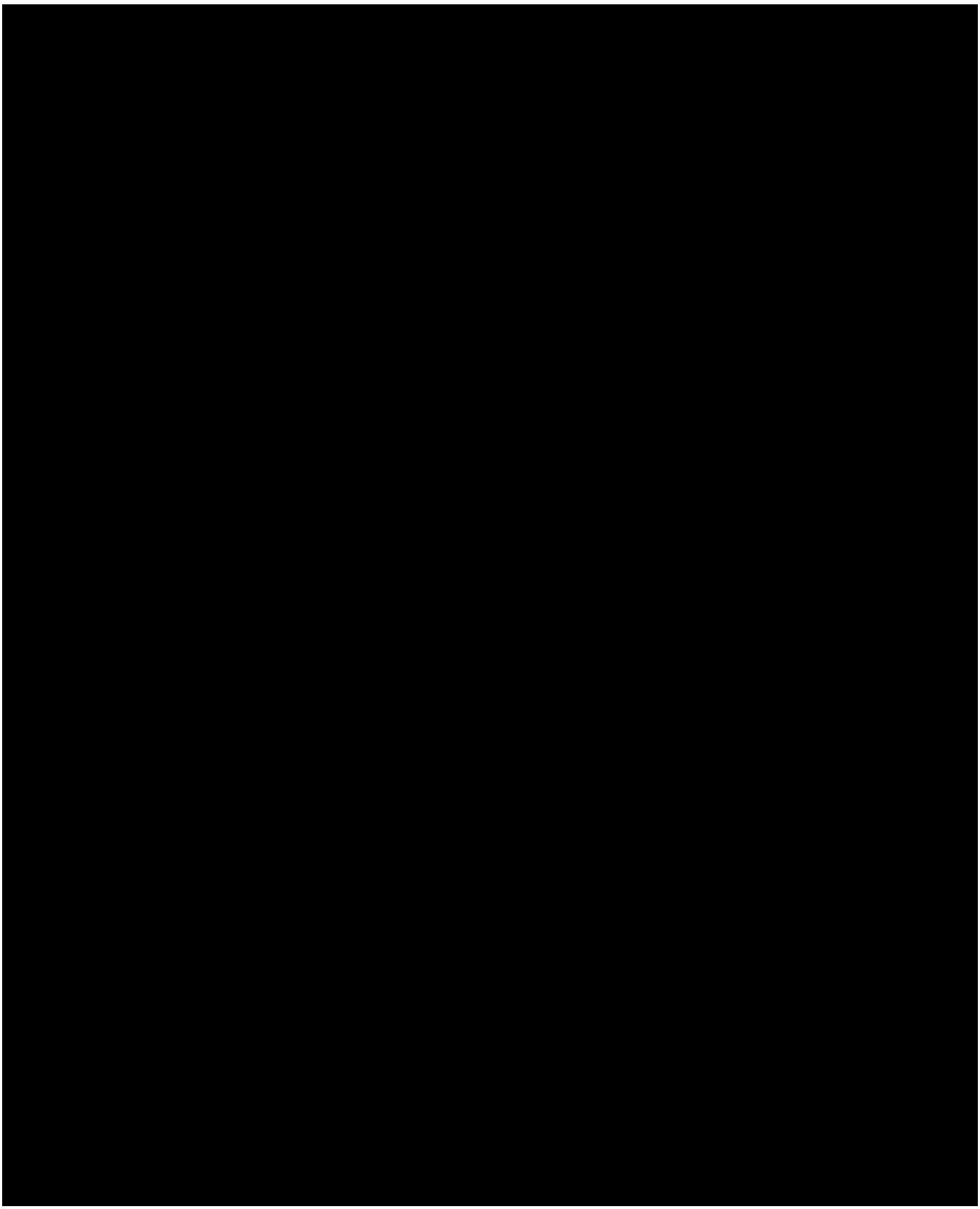

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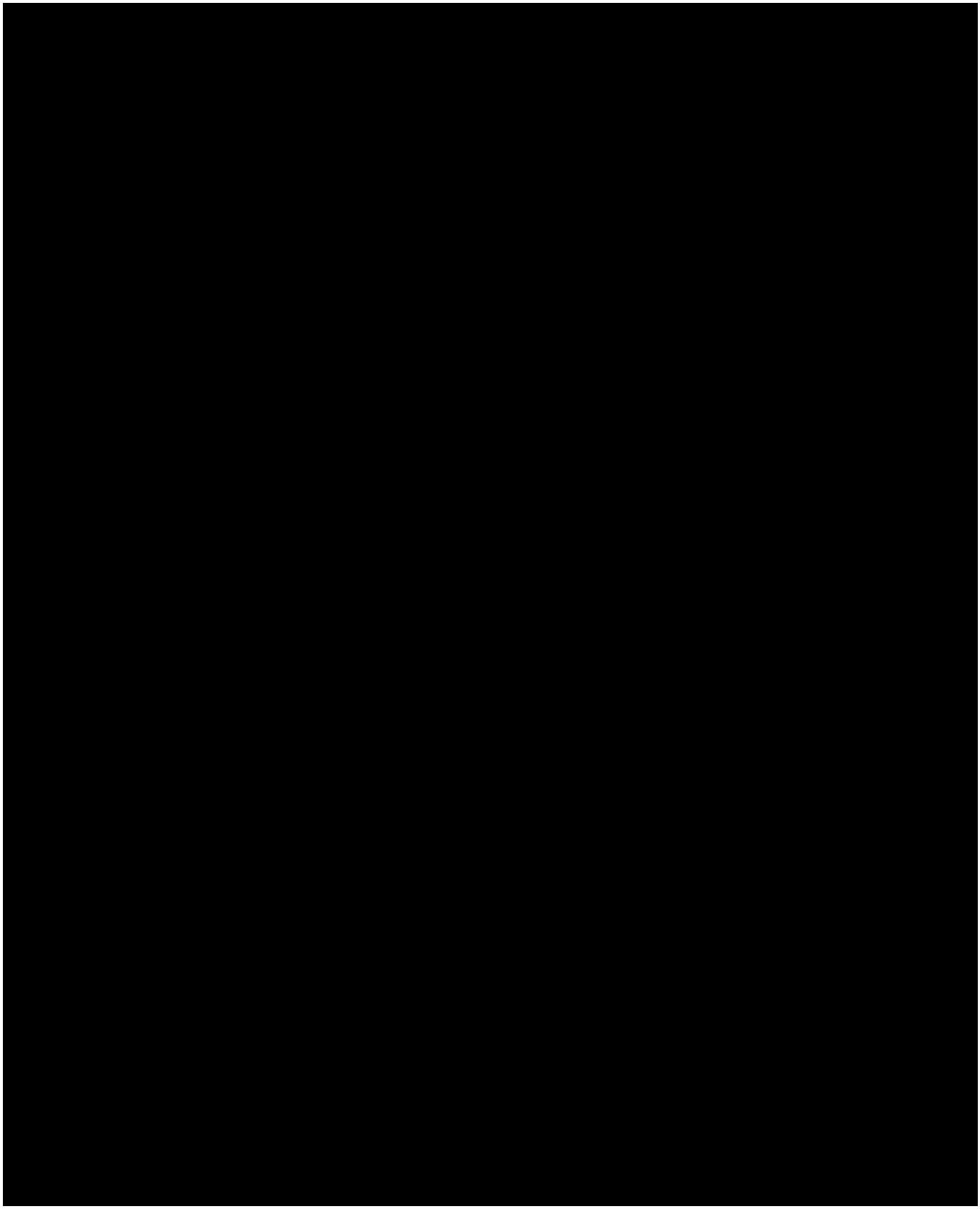

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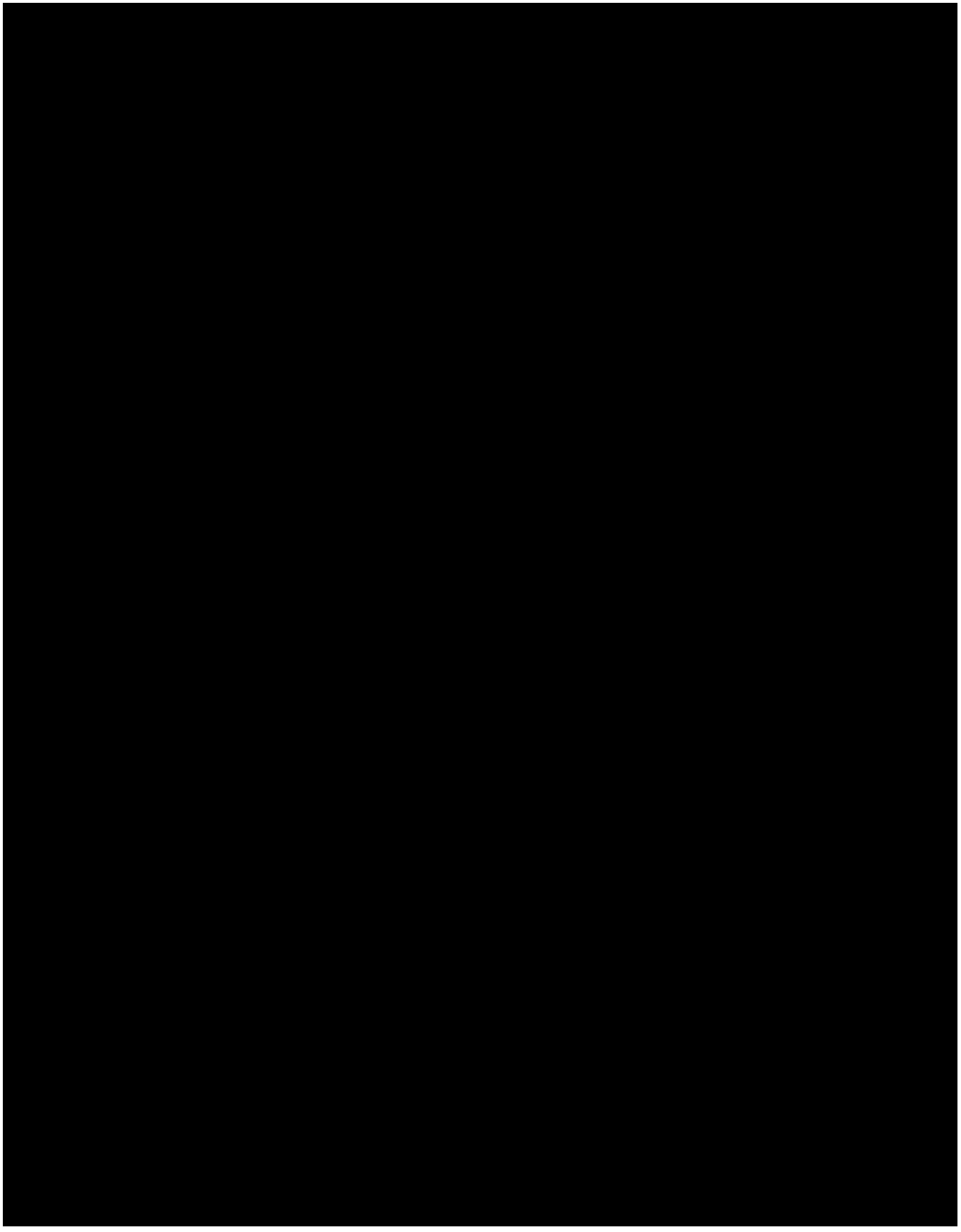

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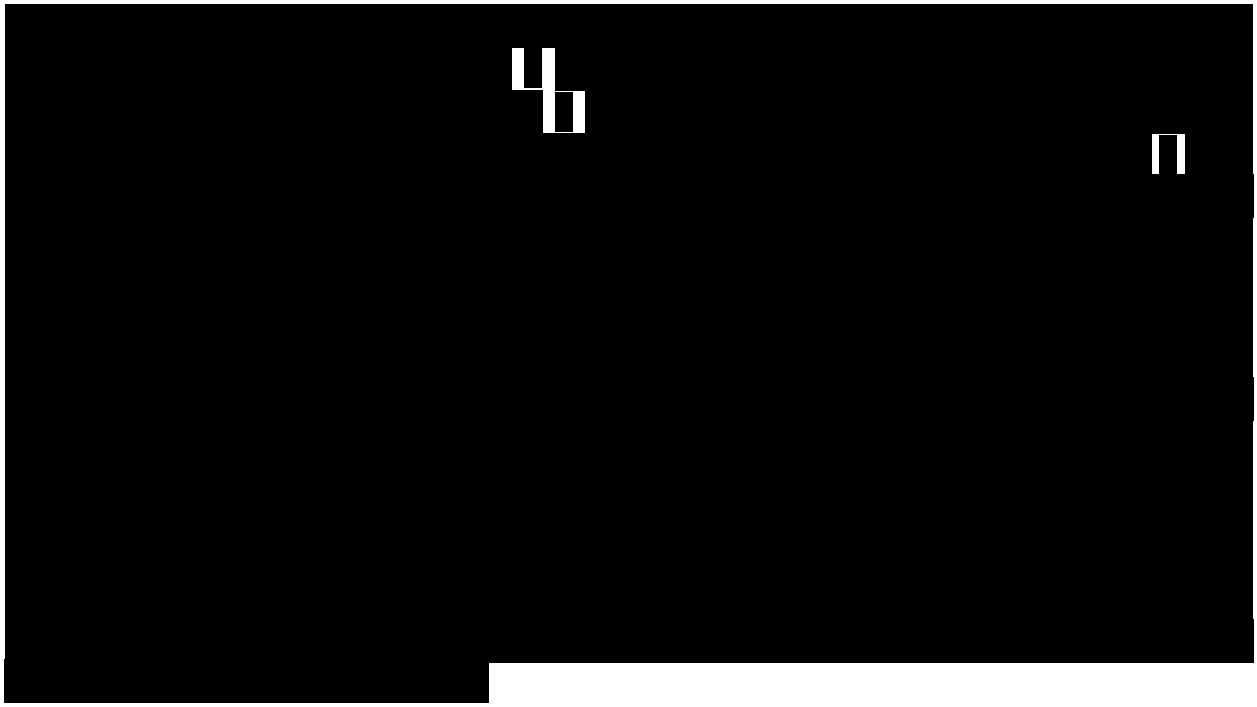

1.4.8 Treatment Experiences with Other Immune Checkpoint Inhibitors in Subjects with Chronic Hepatitis

In addition to the safety profile of nivolumab in subjects with chronic HCV as described in Section 1.4.7 above, there have been a few recent reports of other immune checkpoint inhibitors administered to oncology subjects with chronic hepatitis.

In a Phase 2, non-controlled, open-label, multicenter trial, tremelimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), was administered at a dose of 15 mg/kg IV every 90 days was been administered to 20 subjects with HCC and chronic HCV.[119] A total of 46 treatment doses were administered, and 13 subjects received at least 2 doses. Overall, there was a significant antiviral effect with a median reduction in HCV RNA of 0.76 log at Day 120 (P = 0.11) and 2.1 log at Day 210 (P = 0.017), and 3 subjects demonstrated a transient complete viral response during follow-up. A rise in serum transaminases was observed after the first dose in more than half of the subjects. Five of 20 subjects (25%) experienced a Grade 3 or higher elevation in ALT. However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses.

Since FDA approval of ipilimumab (anti-CTLA-4 mAb) for subjects with metastatic melanoma in 2011, there have been recent case reports that highlight ipilimumab 3 mg/kg can be administered IV every three weeks safely to subjects with metastatic melanoma and chronic HCV (n = 2)[120] or chronic HBV (n = 1).[121] In the subject with metastatic melanoma and chronic hepatitis B, antiviral therapy with tenofovir was initiated to mitigate the potential risk of immune-mediated hepatotoxicity given the high frequency of HBV-infected hepatocytes in subjects with chronic HBV. HBV DNA levels were reduced from 2950 IU/mL to 41 IU/mL

with tenofovir prior to administration of ipilimumab, and the subject completed treatment without any hepatic events or change in LFTs.

In addition to the case report of ipilimumab administration to a single subject with melanoma and HBV as described above, a recent case series of 9 melanoma subjects (4 with chronic HCV and 5 with chronic HBV) has recently been published. Seven subjects had no changes in LFTs during the ipilimumab treatment cycles, 1 subject who had a Grade 2 AST/ALT subsequently normalized by Cycle 4; and 1 HCV-infected subject who had a Grade 1 AST/ALT at baseline developed a Grade 2 AST/Grade 3 ALT after Cycle 3. In summary, these data indicate that ipilimumab can be well tolerated without significant hepatotoxicity in subjects with chronic HCV or HBV.

Similar to the approach previously described[120] and reflective of guidance from an independent HBV/HCC expert panel (as discussed below in Section 1.4.10), subjects in the current study CA209040 are required to have a low HBV DNA level <100 IU/mL and be on antiviral therapy prior to administration of nivolumab to lower HBV viral load and reduce the risk of hepatotoxicity in the setting of nivolumab administration.

Taken together, the treatment experiences of nivolumab in subjects with chronic HCV (Section 1.4.7) and the treatment experiences of tremelimumab or ipilimumab in subjects with chronic hepatitis (Section 1.4.8) add to the growing safety profile of immune checkpoint inhibitors and suggest that nivolumab in virally-infected HCC subjects will be adequately tolerated. Specifically:

- Nivolumab in single ascending doses in chronic HCV is well tolerated with an acceptable safety profile.
- High grade transaminitis may occur with immune checkpoint inhibitors (tremelimumab) in subjects with chronic HCV+/- HCC; however, to date, these elevations are transient, without decline in hepatic synthetic function or hyperbilirubinemia, resolve spontaneously, and do not preclude repeat dosing.
- The safety profile of immune checkpoint inhibitors in the setting of chronic HCV or HBV is evolving; however, based on recent case reports with ipilimumab, immune checkpoint inhibitors can be given safely to subjects with chronic HCV or HBV.

As a result of this additional safety information, the CA209040 study team recommended in a previous amendment that the HBV arm initiate dosing at 0.1 mg/kg independent of the uninfected or HCV-infected arms (see study design Figure 3.1-1). For additional risk mitigation, a sentinel dosing paradigm was utilized in the first HBV cohort of 0.1 mg/kg; therefore, two weeks separated the first nivolumab dose for each subject in the 0.1 mg/kg cohort. However, in subsequent dose panels, a sentinel dosing strategy was not utilized. In addition, dose escalation in the HBV-HCC group was not planned to exceed the MTD in the other two arms of the study.

1.4.9 Definitions for Sorafenib Intolerance and Progression

[redacted]

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- [redacted]

[redacted]

In the Nivolumab plus Ipilimumab Combination Cohort [redacted], 'sorafenib intolerance' is defined as:

- CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (eg to 400 mg once daily)
- ≥ CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (eg to 400 mg once daily).
- Requires a minimum of 14 days of sorafenib exposure (not necessarily consecutive).

In the Nivolumab plus Ipilimumab Combination Cohort [redacted], subjects who failed sorafenib, ie 'sorafenib progressors' are defined as:

- Documented radiographic progression during or after sorafenib therapy.

A decision on temporary or permanent sorafenib treatment interruption or sorafenib-dose reduction should have been based on the recommendations outlined in the sorafenib product label. Supportive therapies for sorafenib-related adverse events should have been administered according to institutional standards and may include but are not limited to treatments listed in the sorafenib product label:

- Dermatologic Toxicities: topical therapies for symptomatic relief
- Hypertension: institution of anti-hypertensive therapy
- Gastrointestinal Toxicities: with a minimal risk of severe nausea, vomiting, and diarrhea, supportive treatment may follow institutional standards.

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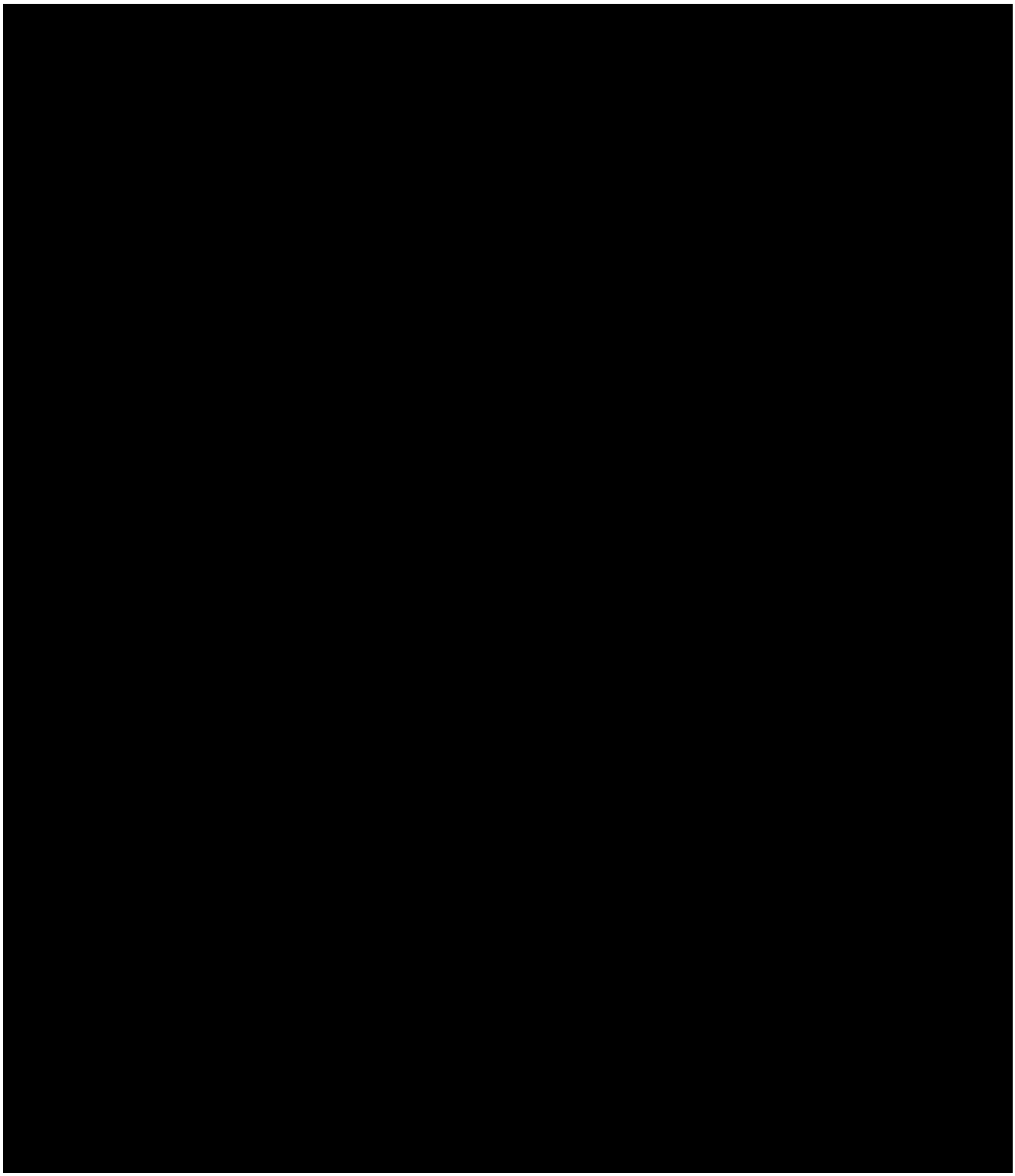
Episodes of sorafenib-related toxicity (onset/end), supportive care measures, length of temporary sorafenib discontinuation and sorafenib dose reduction will be documented in the medical history section of the CRFs. If both disease progression and intolerance are observed at study entry, disease progression will be regarded as the entry criterion.



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1.4.12 Rationale for Nivolumab Flat Dosing in [redacted] Nivolumab plus Ipilimumab Combination Cohort (Post Induction in Arms A and B)

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1,544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate 100 virtual trials, each consisting of two arms, nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1,000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to subjects with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W. Given the lower body weight in

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Japanese subjects (median: 58.4 kg),[122] the exposures following 240 mg Q2W in the range of 50 to 70 kg were also simulated, and they are predicted to be approximately 16.8% greater when compared to the 3 mg/kg, 80 kg reference group.

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC.

Consistent with the nivolumab program and other tumor types, no MTD has been established in the dose escalation phase for the HCC cohorts. In addition, safety has been established up to 10 mg/kg in the uninfected-HCC cohort, and a similar safety profile has been observed regardless of HCC etiology at doses up to 3 mg/kg. As of 12-Mar-2015, 47 subjects had been treated in CA209040 as discussed in Section 1.4.6. In addition, as of 30-June-2015, 3 HBV-infected HCC subjects have received at least 3 doses of 3 mg/kg nivolumab q2 week. No DLT has been observed in the HBV cohort at 3 mg/kg, and the safety profile remains similar across each etiology and dose level. Given similar safety findings across the 3 uninfected, HCV-infected, and HBV-infected subjects in the Dose Escalation Phase, and similar PK observed from preliminary data in HCC, a flat dosing of 240 mg will be administered to all subjects in who will receive nivolumab monotherapy in the [redacted] Nivolumab plus Ipilimumab Combination Cohort.

[redacted]

1.4.14 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[125]

The combination of nivolumab and ipilimumab was evaluated in **CA209004** (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Antitumor activity was observed in 5 different combination cohorts: nivolumab 0.3 mg/kg and ipilimumab 3 mg/kg (Cohort 1, n = 14), nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 2, n = 17), nivolumab 3 mg/kg and ipilimumab 1 mg/kg (Cohort 2a, n = 16), nivolumab 3 mg/kg and ipilimumab 3 mg/kg (Cohort 3, n = 6), and nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 8, n = 41). From this study, it has been found that the 3 mg/kg nivolumab and 3 mg/kg ipilimumab combination regimen exceeded the maximum tolerated dose. Even though the drug-related discontinuation rates in combination cohorts were approximately 26 - 27%, the ORR in these cohorts were still higher compared to nivolumab monotherapy (42% - 44% versus 36%).

Additional studies have demonstrated the potential for IO combinations to improve antitumor responses across the nivolumab program.[101] An ORR of 62 - 65% has been observed in advanced melanoma (CA209067 and CA209069, N = 407) with a combination regimen of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3week x 4. In RCC subjects (CA209016), both nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 21) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 23) showed antitumor activity with an ORR of 38%-40%. In NSCLC subjects (CA209012), both combination regimens demonstrated a favorable efficacy profile with a response rate of 20% and a median OS of 11m for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg,

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and a response rate of 13% and median OS of 19.8 m for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg.

In summary, nivolumab and ipilimumab combinations have shown additive or synergistic activities across the tumor types investigated. To further improve the tolerability profile, other combination dosing regimens were also explored in the nivolumab development program. Less frequent dosing of ipilimumab at 1 mg/kg q6week when given with nivolumab 3 mg/kg q2week was found to have a similar discontinuation rate to that observed in nivolumab monotherapy (11% vs 10%) in preliminary data from CA209012.

Based on these data, the following three dose arms will be evaluated in CA209040:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q2 weeks;
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q 2weeks;
- Arm C--nivolumab 3 mg/kg q 2weeks + ipilimumab 1 mg/kg q 6weeks.

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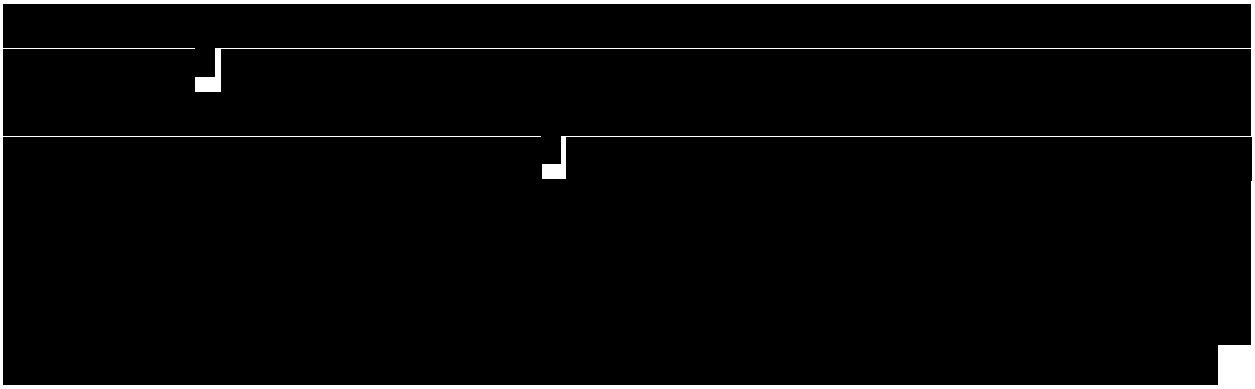

1.4.16 Rationale for Shorter Infusion Times With 240 mg Flat Dose Nivolumab and Ipilimumab

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile.

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60 minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both).

However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration:

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.
- Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90 minute infusion in large phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

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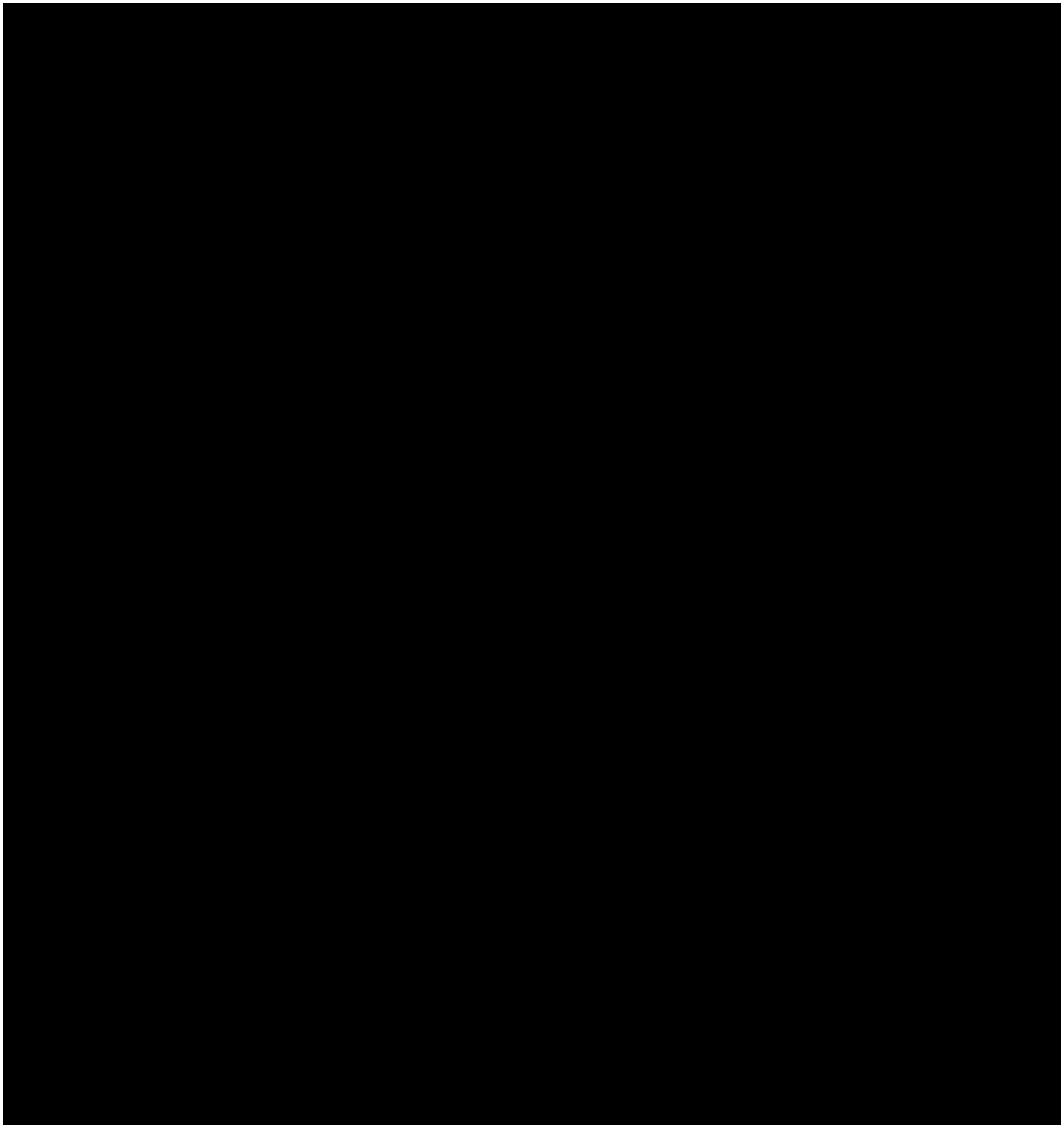
Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.



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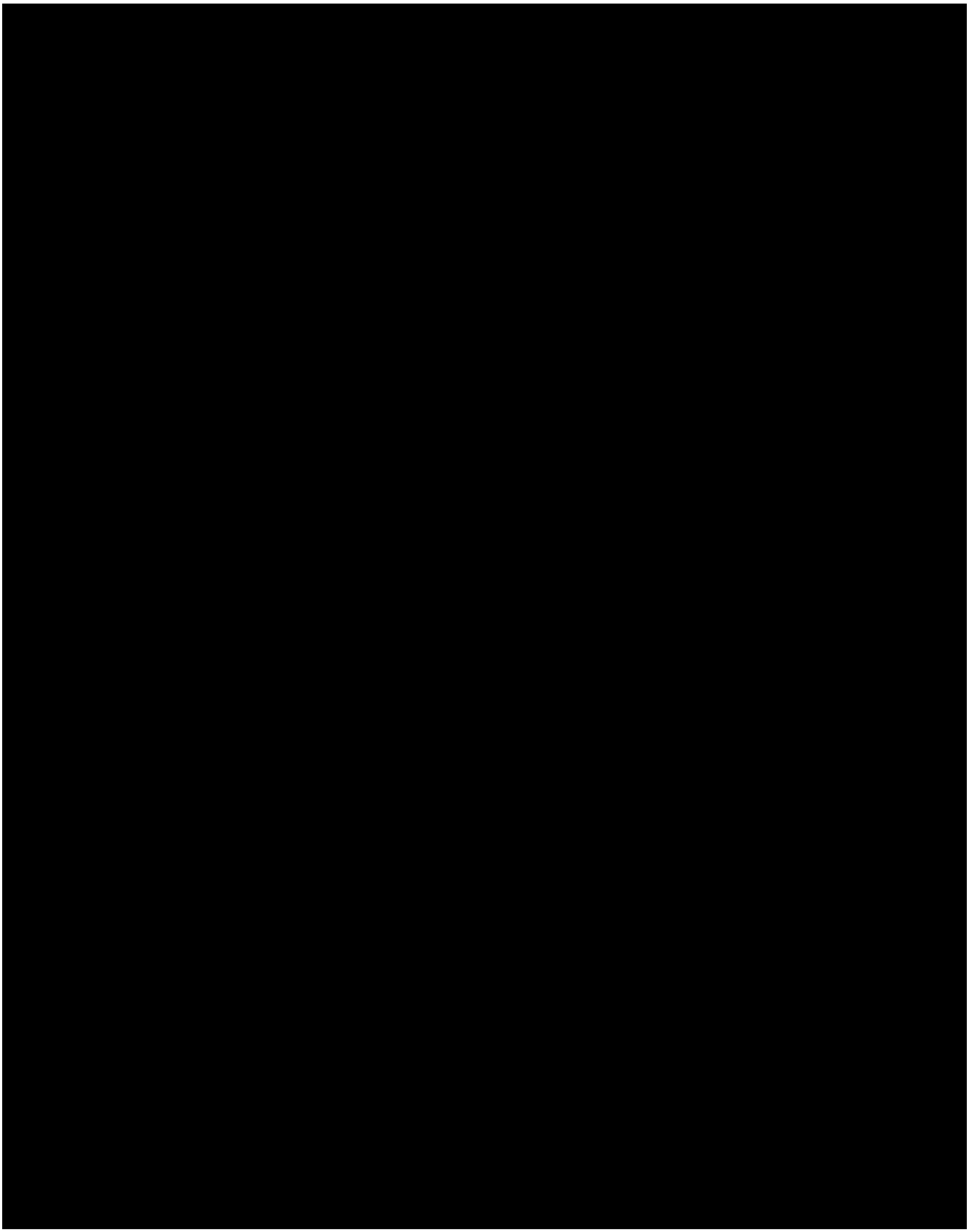

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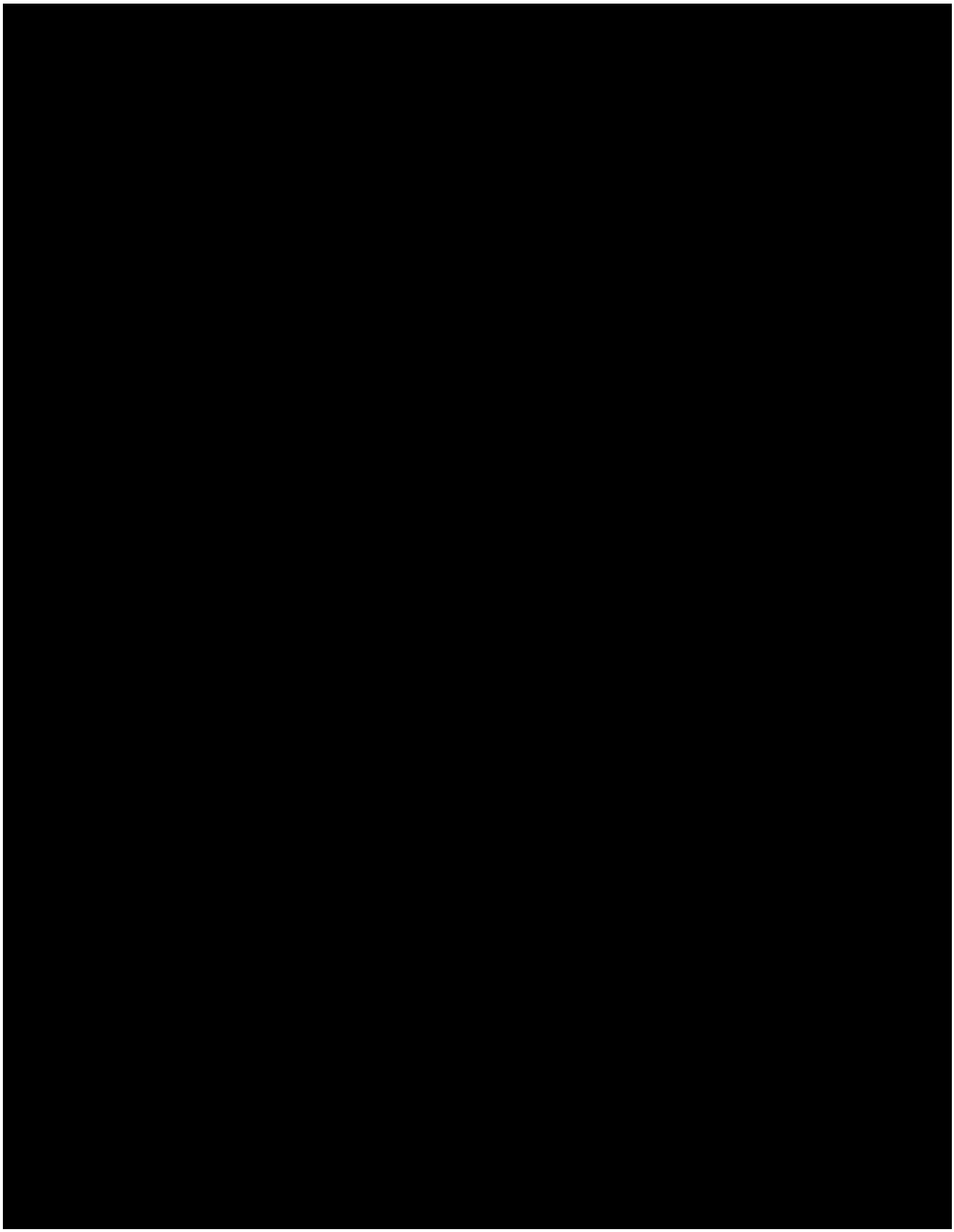

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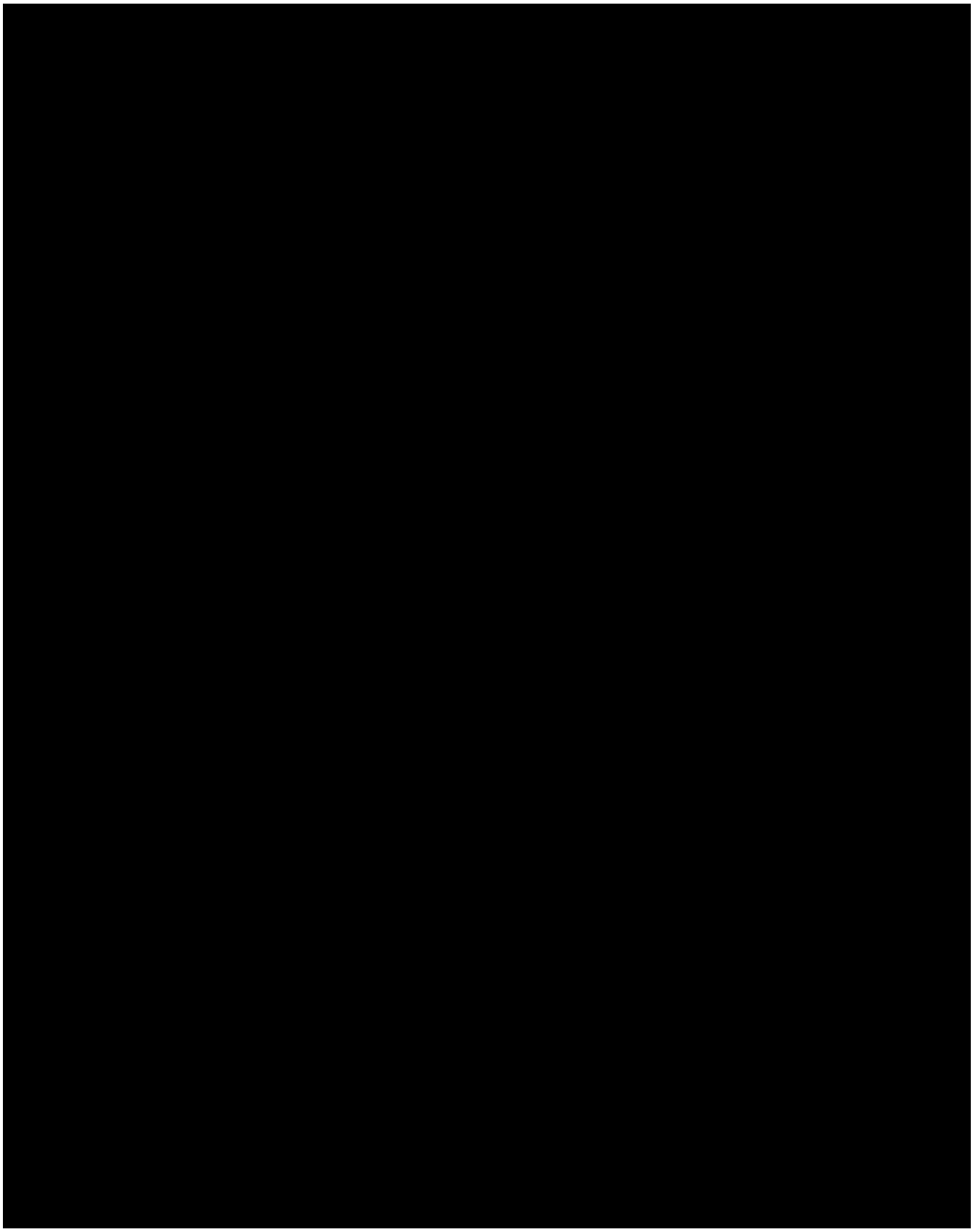

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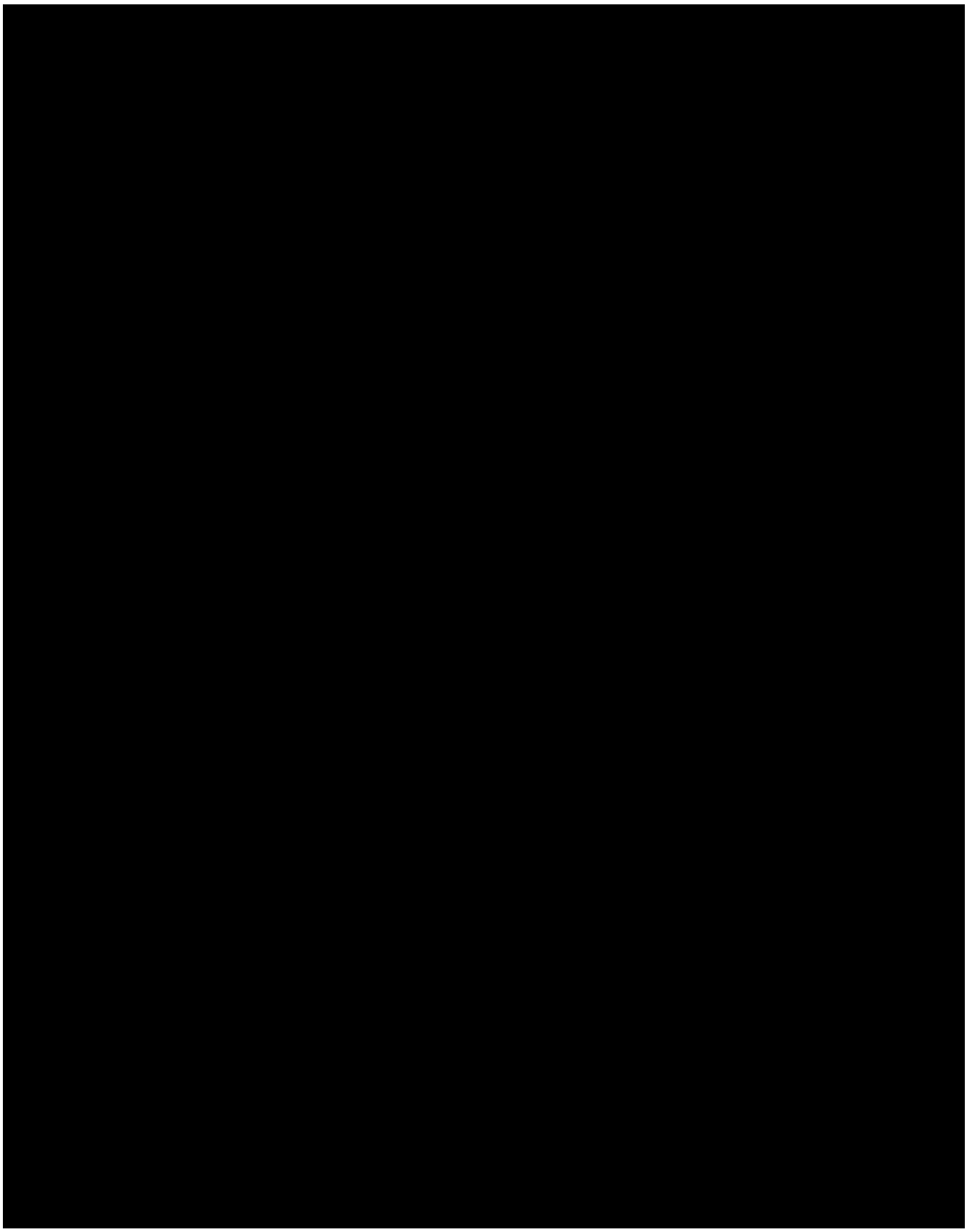

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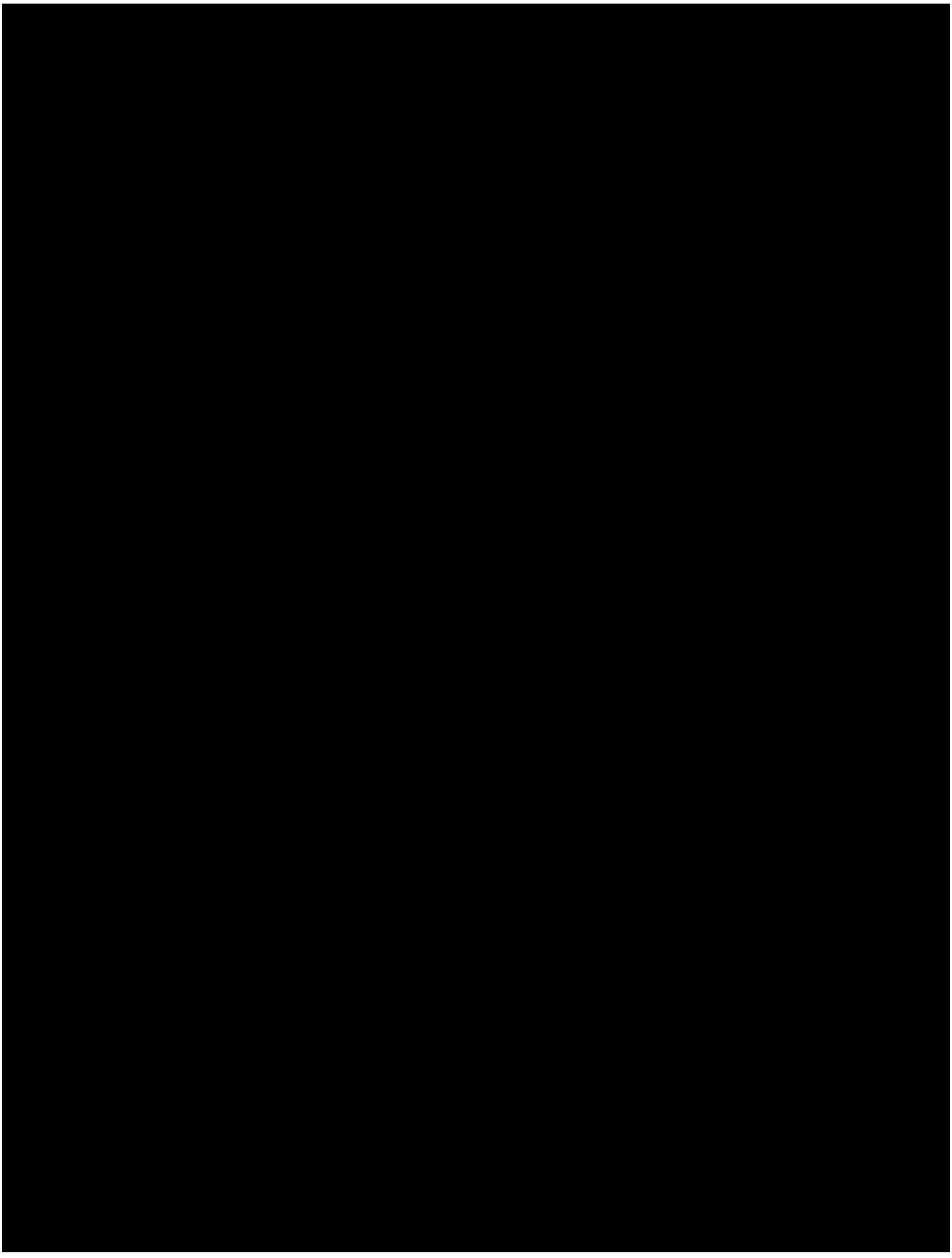

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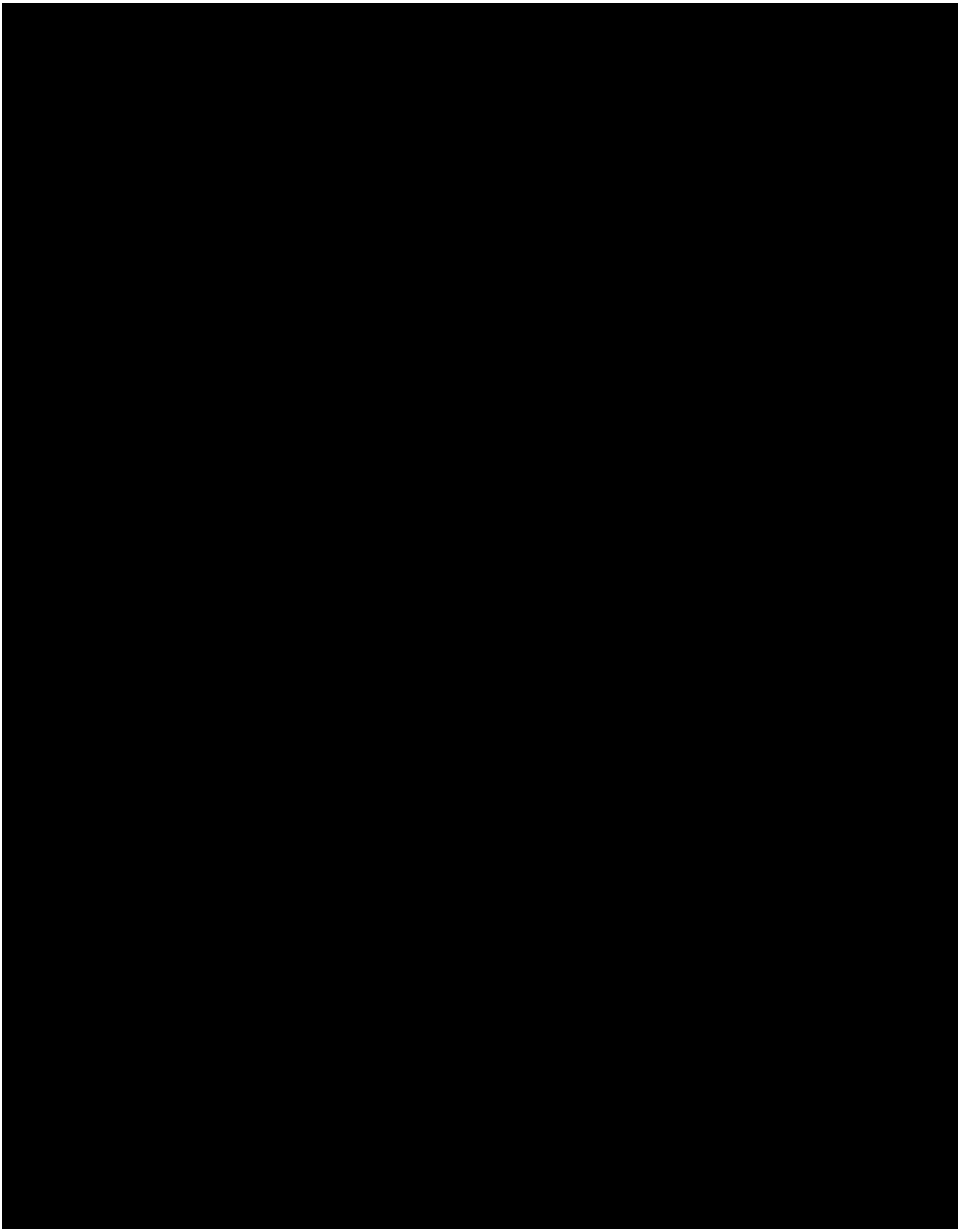

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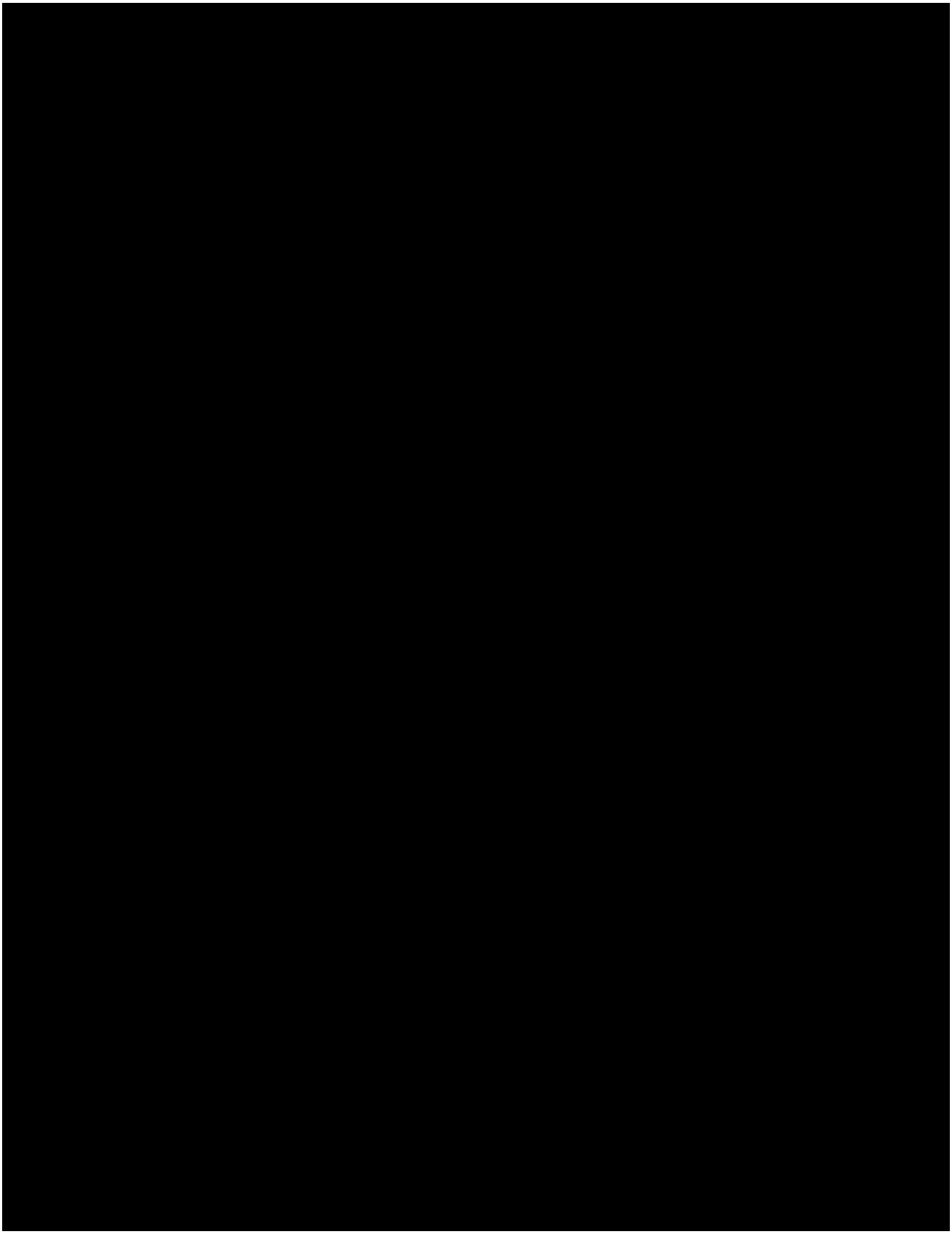

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[redacted]

2. ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

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This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie , Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator,

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should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

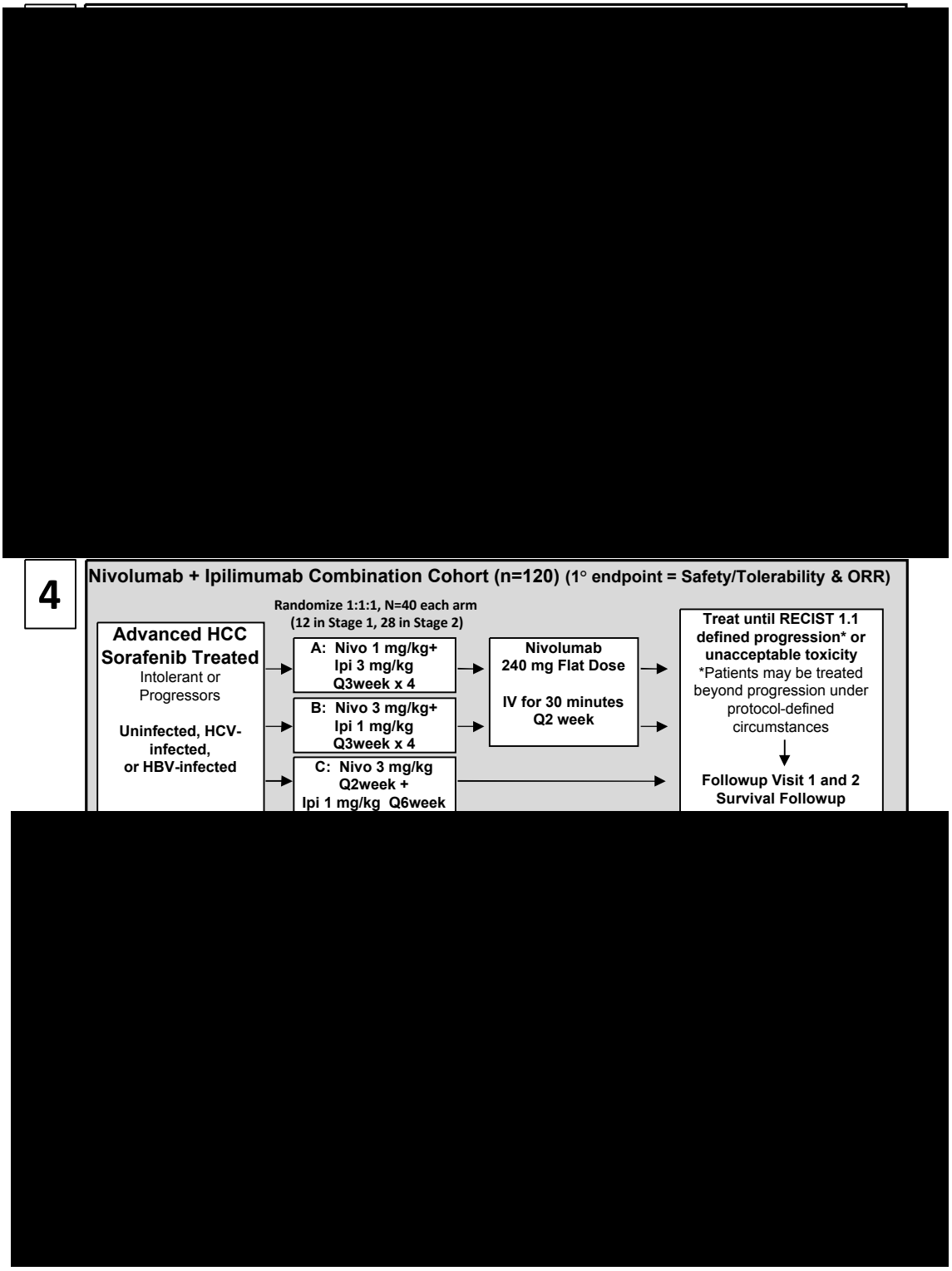
3. INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a phase 1/2, dose-escalation, open-label, non-comparative study of nivolumab or nivolumab in combination with ipilimumab in advanced hepatocellular carcinoma subjects with or without chronic viral hepatitis; [redacted]

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design of CA209040 and Cohorts 1 - 6



[redacted]

Upon activation of Amendment 8, [redacted] the Nivolumab and Ipilimumab Combination Cohort will begin accrual of up to 120 subjects. Uninfected, HCV-infected, or HBV-infected subjects with advanced HCC and previous treatment with sorafenib will be randomized 1:1:1 into 3 different dose arms:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm C--nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week until toxicity or disease progression (n = 40).

Since the use of nivolumab and ipilimumab has not been previously studied in subjects with advanced HCC, a 2 stage design will be employed for each of the 3 dose arms. In Stage 1, 12 subjects will be enrolled in each dose arm, and will undergo a safety and tolerability

assessment at Week 13 (or prior to Week 13 if discontinued) prior to enrollment of any additional subjects.

The safety evaluation (Section 3.1.4) will be conducted independently for each dose arm in Stage 1 based on criteria described in Discontinuation Criteria (Sections 4.2.4). No additional subjects will be enrolled until the safety evaluation at Week 13 occurs. Enrollment of the first 12 subjects in each dose cohort will be limited to select sites. After completion of Stage 1, enrollment in Stage 2 of the subsequent 28 subjects can occur in each dose arm and is contingent upon the results of the safety evaluation.

3.1.1 Treatment Flow

The study will consist of 4 phases: Screening, Treatment, Follow-up and Survival Follow-up.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF)
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analysis. For subbjects in the [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted] central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to subject randomization.

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Treatment Phase:

Study Treatment(s):

Subjects will receive study treatment as described in Sections 3.1 and 4.1

However, upon activation of Amendment 8, all subjects will continue to receive study treatment(s) until:

1. RECIST 1.1-defined radiographic progression, OR
2. Clinical deterioration (Section 3.1.4) suggesting that no further benefit from treatment is likely, OR
3. Unacceptable toxicity, OR
4. Any other criteria for discontinuation of study therapy as outlined in Section 3.1.3.1 (Dose Limiting Toxicity in the Dose Escalation Phase) or Section 3.5 (Discontinuation of Subjects from Treatment).

Treatment may continue beyond progression under protocol defined conditions. Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until progression is both confirmed and found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans or other tumor evaluations. Additional details on treatment beyond progression are located in Sections 4.2.5

Tumor Assessments:

All subjects [redacted] will undergo tumor assessments at every q6 week (± 2 days) for the first 48 weeks, and then q12 week (± 1 week) thereafter until radiographic progression or treatment is discontinued (whichever occurs later). [redacted] Imaging assessments should be performed regardless of dose delay or missed doses in all cohorts.

[redacted]

Follow Up Phase:

Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

Subjects who discontinue study drug for reasons other than radiographic progression or who continue treatment beyond progression will continue to have tumor assessments (if clinically

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feasible) according to the schedule in Table 5.1-9 and Table 5.1-10 and until progression or treatment discontinuation for subjects being treated beyond progression.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study drug.

Survival Follow Up Phase:

Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit (please refer to Section 3.6.

3.1.2 Duration of Study

The study is expected to accrue over a period of approximately 5 years. The study will end when survival follow-up collection has concluded. The last visit will be defined as the latest survival visit included in the final analysis of OS (ie. the latest subject death, loss to follow up, or withdrawal of consent). Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up collection has concluded.

[redacted]

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3.1.4 Safety Evaluation of Stage 1 of the Nivolumab plus Ipilimumab Combination Cohort

A total of 36 subjects will be randomized 1:1:1 (n=12) into one of the following 3 dose arms in Stage 1:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3week x 4 (Week 1, 4, 7, and 10) followed by nivolumab 240 mg q2week (beginning at Week 13)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3 week x 4 (Week 1, 4, 7, and 10) followed by nivolumab 240 mg q2week (beginning at Week 13)
- Arm C--nivolumab 3 mg/kg q2 week (Week 1, 3, 5, 7, 9, 11, 13, etc) + ipilimumab 1 mg/kg q6week (Week 1, 7, 13, etc).

After enrollment of 36 subjects in Stage 1, no additional subjects will be enrolled until completion of the safety evaluation. Safety and tolerability will be determined when subjects reach week 13, or have been discontinued prior to this time point. However, tolerability beyond four doses may also be taken into consideration. All subjects will continue to be followed for safety, progression, and overall survival after discontinuation of study medication. The criteria used to advance to Stage 2 will be based on drug related adverse events leading to permanent

discontinuation in the safety lead-in cohort (Stage 1, n = 12 per dose arm) (listed in Section 4.2.4.1 for nivolumab and 4.2.4.2 for ipilimumab) and include the following:

- If no more than one-third of the subjects in a given treatment arm permanently discontinue study medication prior to Week 13 due to treatment related adverse events, then this dose cohort will be deemed as tolerable and enrollment of an additional 28 subjects may proceed (Stage 2).
- If more than one-third of subjects in a treatment arm permanently discontinue study medication prior to Week 13 due to treatment-related adverse events, then the safety, tolerability, and efficacy of that treatment arm will be reviewed by the Sponsor and investigators prior to randomizing any additional subjects. A decision will be made by the sponsor whether to continue enrollment of an additional 28 subjects (Stage 2).

3.1.5 Evaluation of Risk/Benefit for a Cohort that does not meet Tolerability Criteria in the Nivolumab plus Ipilimumab Combination

In the event that more than 4 of 12 subjects (one-third) per dose arm in Stage 1 require permanent discontinuation due to treatment related adverse events prior to completion of the safety lead-in, the sponsor will review the risk/benefit profile from each cohort and determine whether or not to advance. In this event, the Sponsor will review all available data from Arms A, B, and C, and recommend continuation, modification or termination of a cohort. The rationale for further evaluation is that the most frequent severe drug-related AEs for the combination of nivolumab and ipilimumab have been asymptomatic and reversible (ie, LFTs and lipase laboratory changes) and there is preliminary evidence of deep and durable responses in advanced melanoma (CA209004, CA209067, and CA209069) despite these events. In particular, any assessment of the risk/benefit of a cohort not meeting tolerability will be triggered if the following criteria are met:

- A majority of subjects in the cohort have at least stable disease or a partial tumor response.
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela.
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws.

If a decision is made to continue with a cohort because of a favorable risk/benefit profile (ie. non fatal AEs in subjects with at least stable disease or a partial tumor response) and despite meeting the ‘not tolerable’ criteria above, then the EC/IRBs must be notified.

Informed Consent forms updated, and discussion of the risk/benefit must be documented with all current and future subjects who are randomized to this regimen.

[redacted]

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3.1.7 Stopping Rules for Clinical Deterioration

Clinical deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - Pathologic bone fracture in the region of cancer involvement
  - Cancer related surgery to bone
  - Spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system metastases or ≥ Grade 3 encephalopathy
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject.

For subjects discontinuing treatment because of global deterioration of health status without objective evidence of disease progression at that time, progression should be reported as "symptomatic deterioration". Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

3.2 Post Study Access Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be provided via an extension of the

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study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. No exceptions will be granted.

For entry into the study, the following criteria MUST be met.

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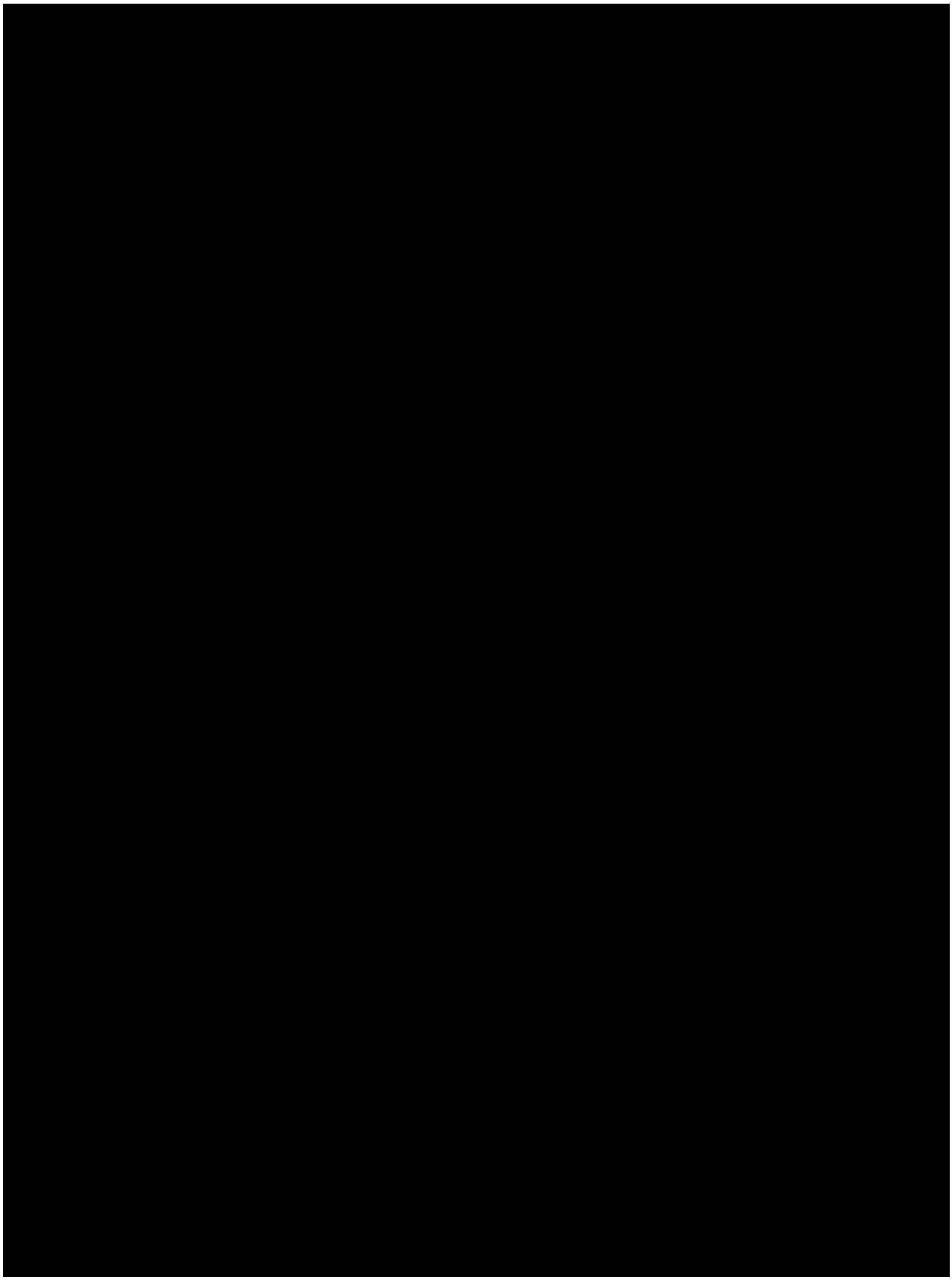

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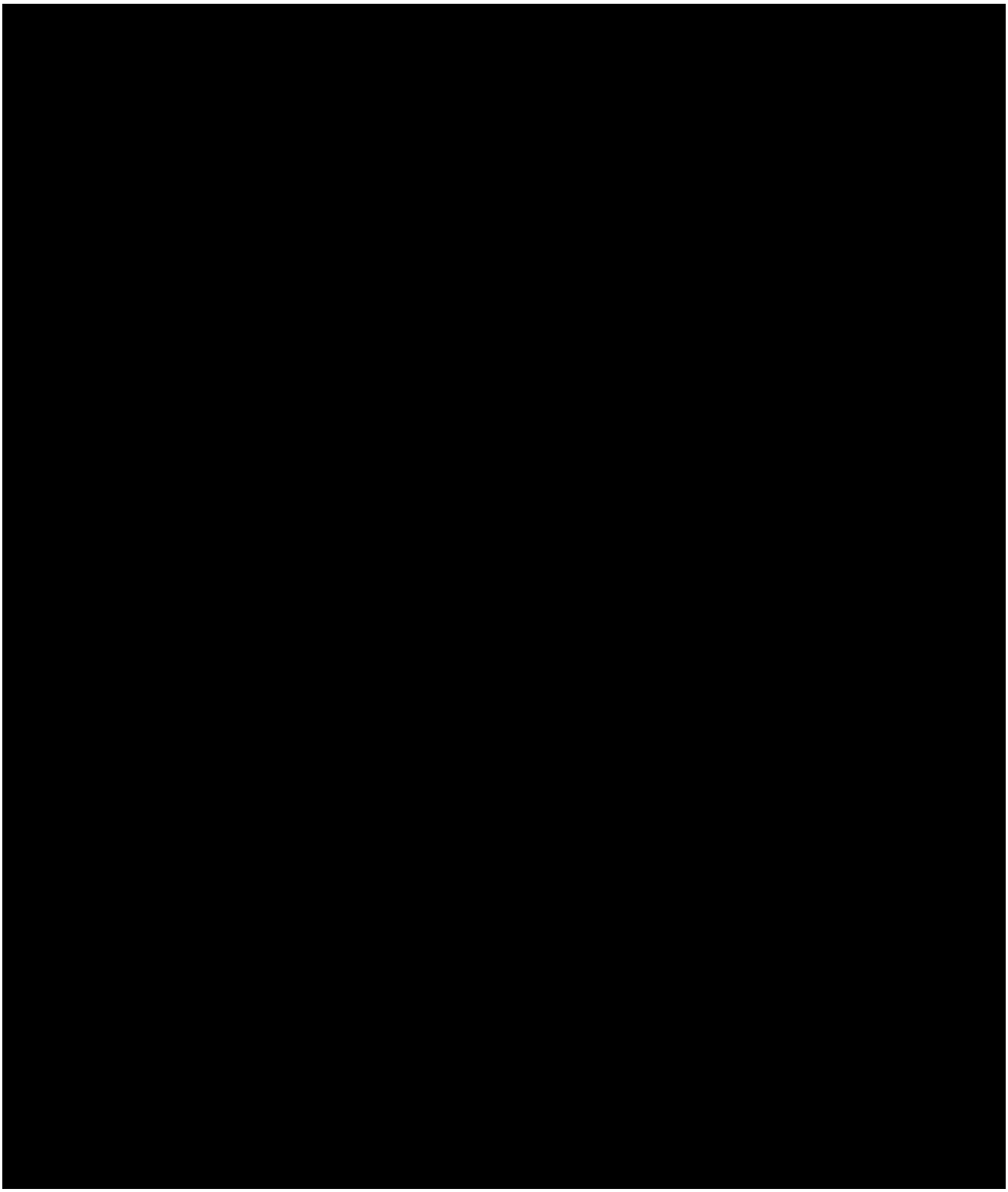

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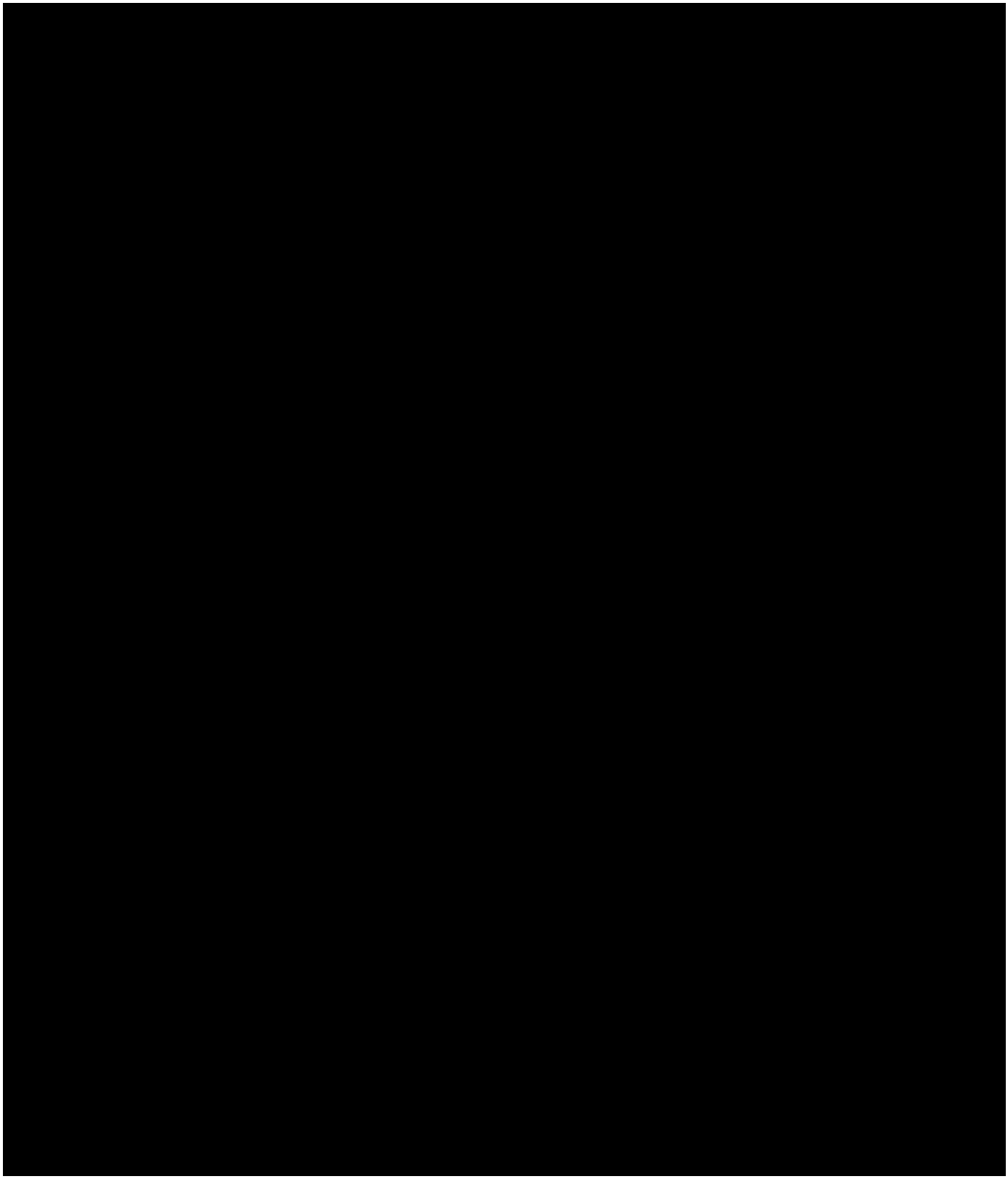

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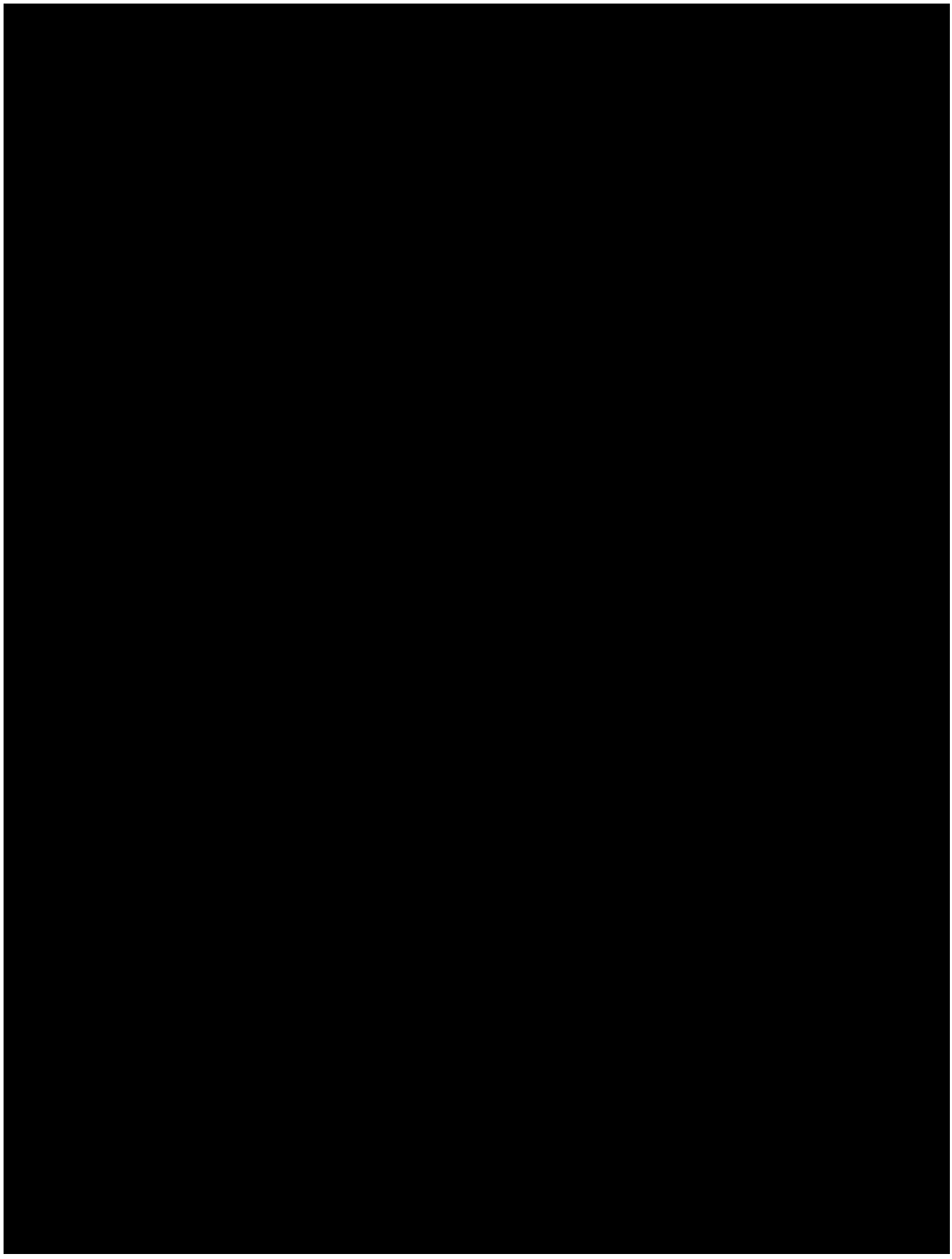

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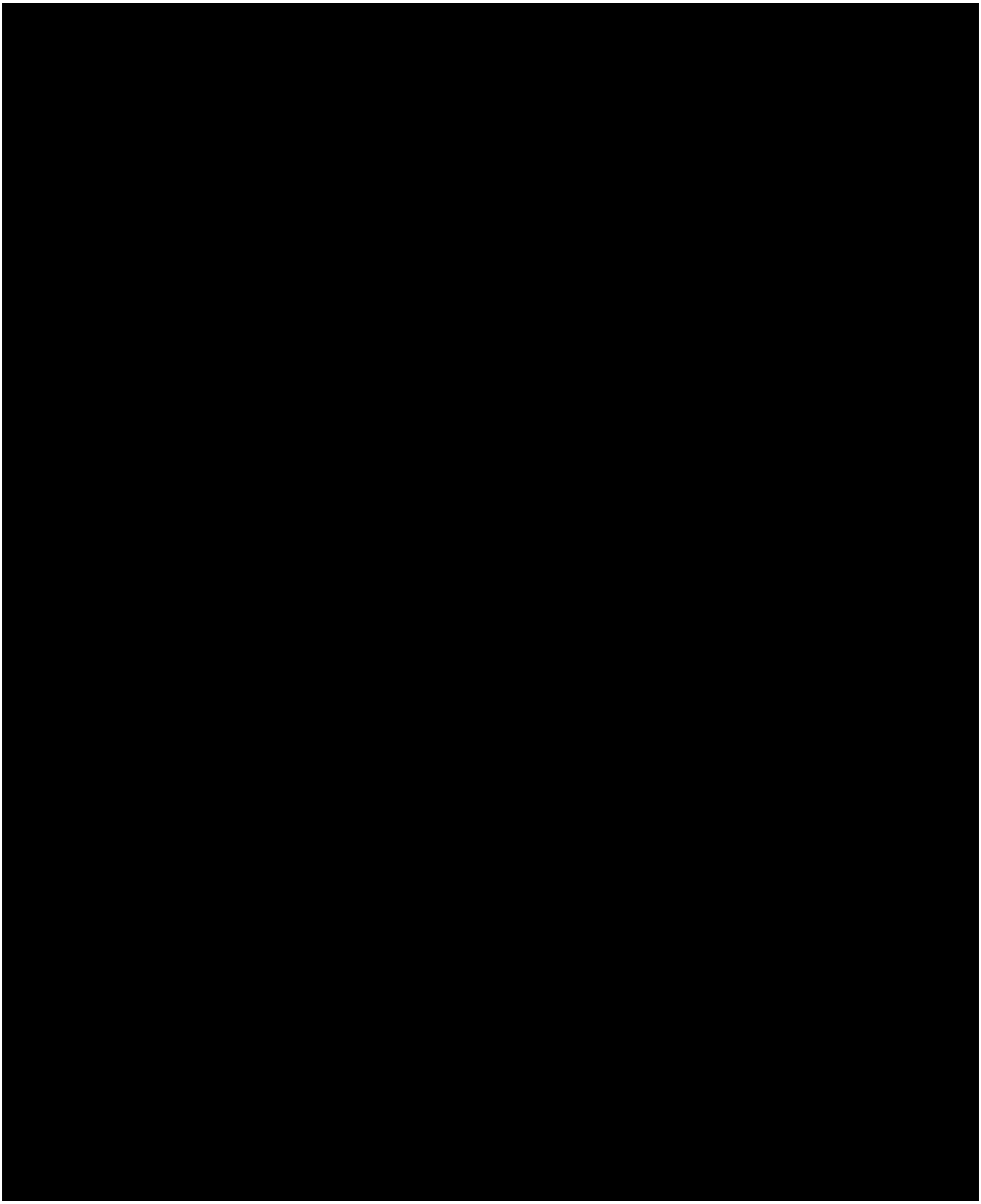

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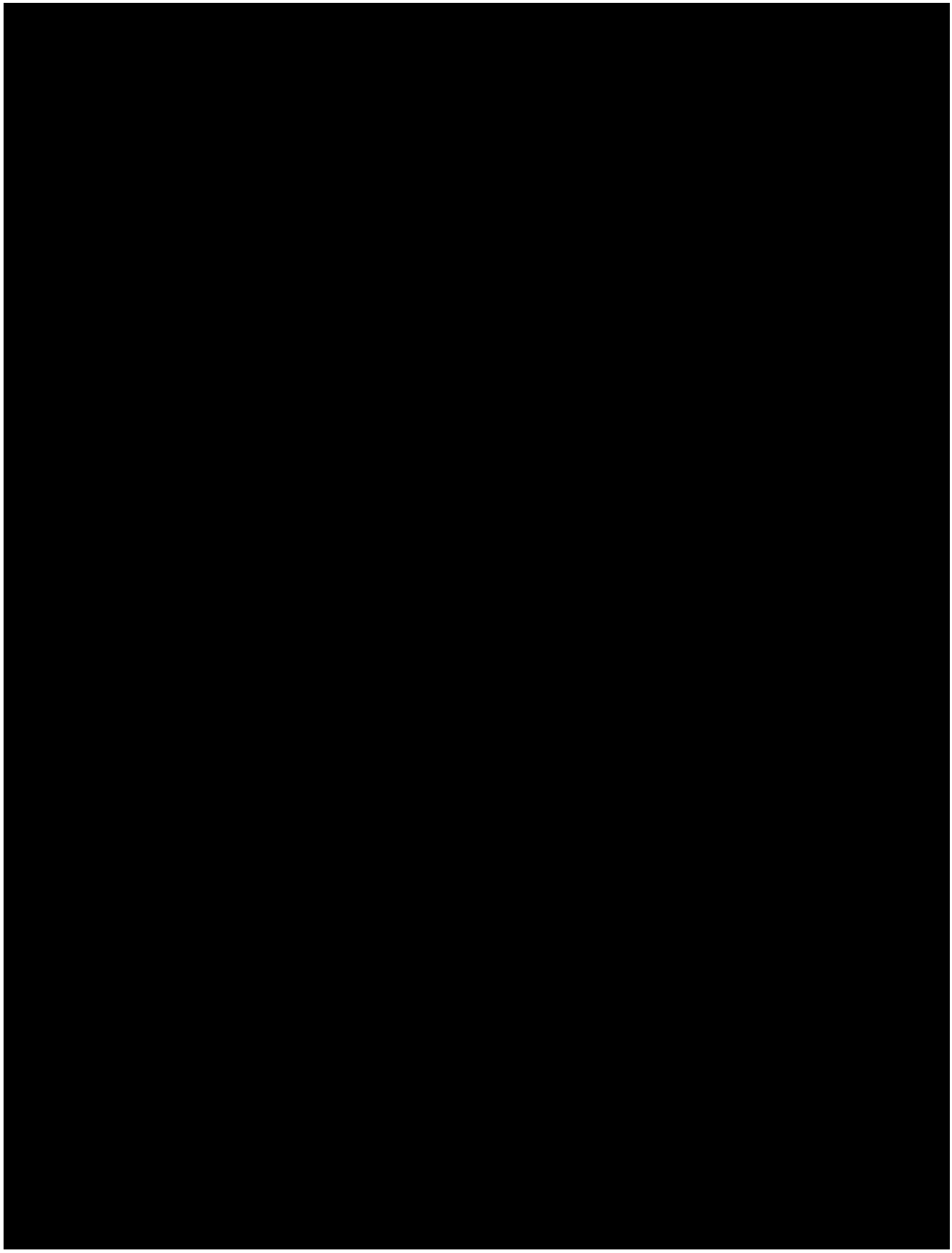

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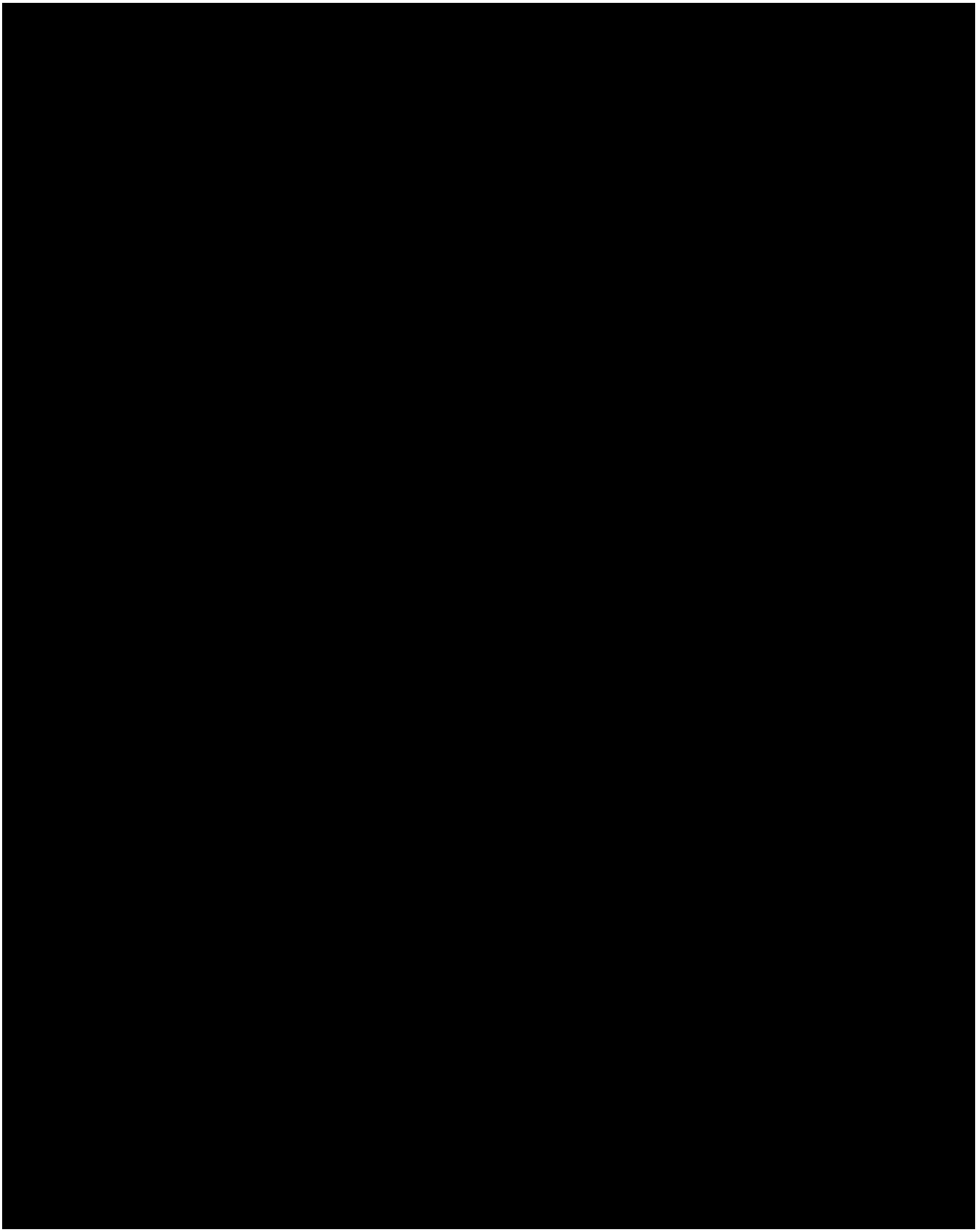

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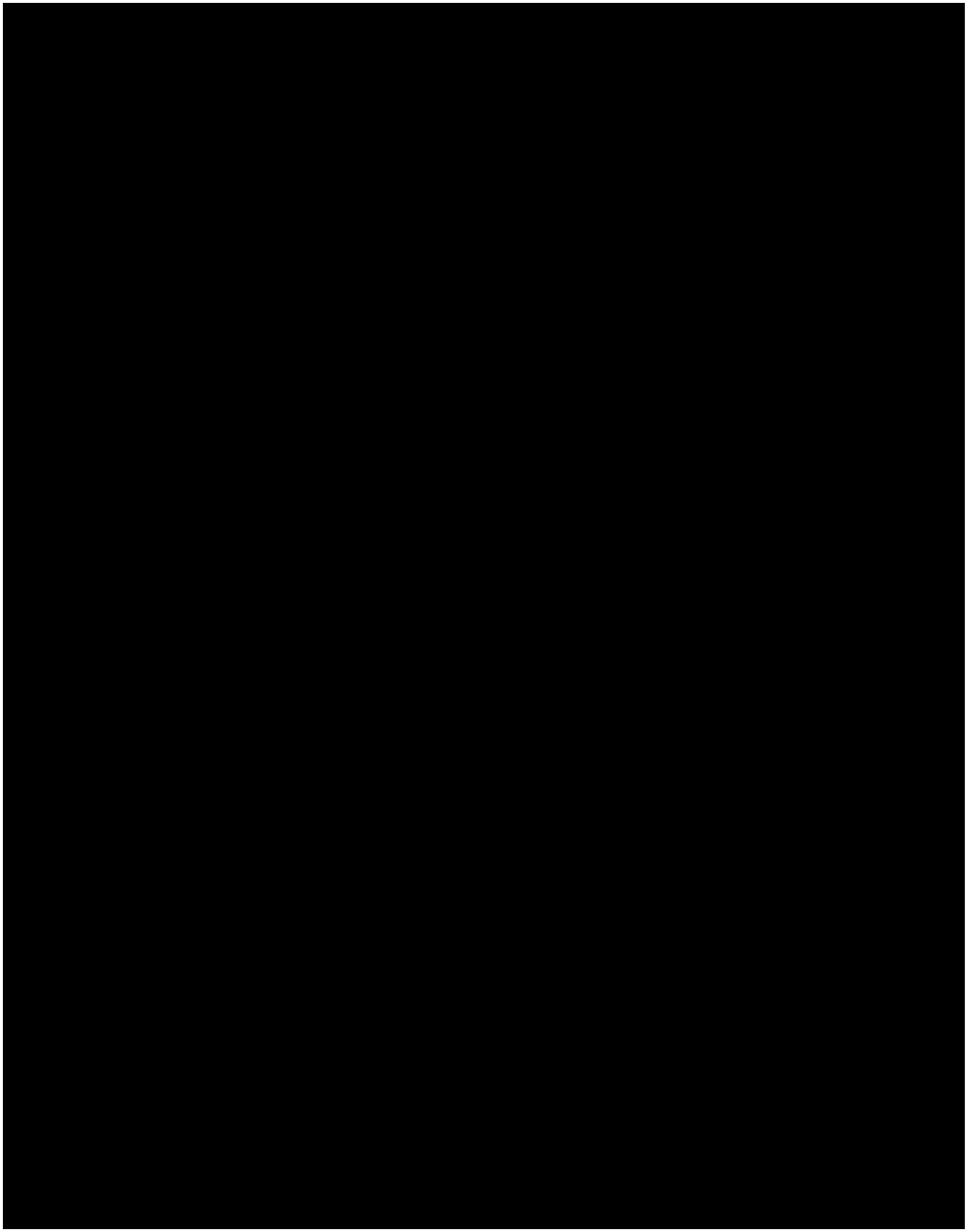

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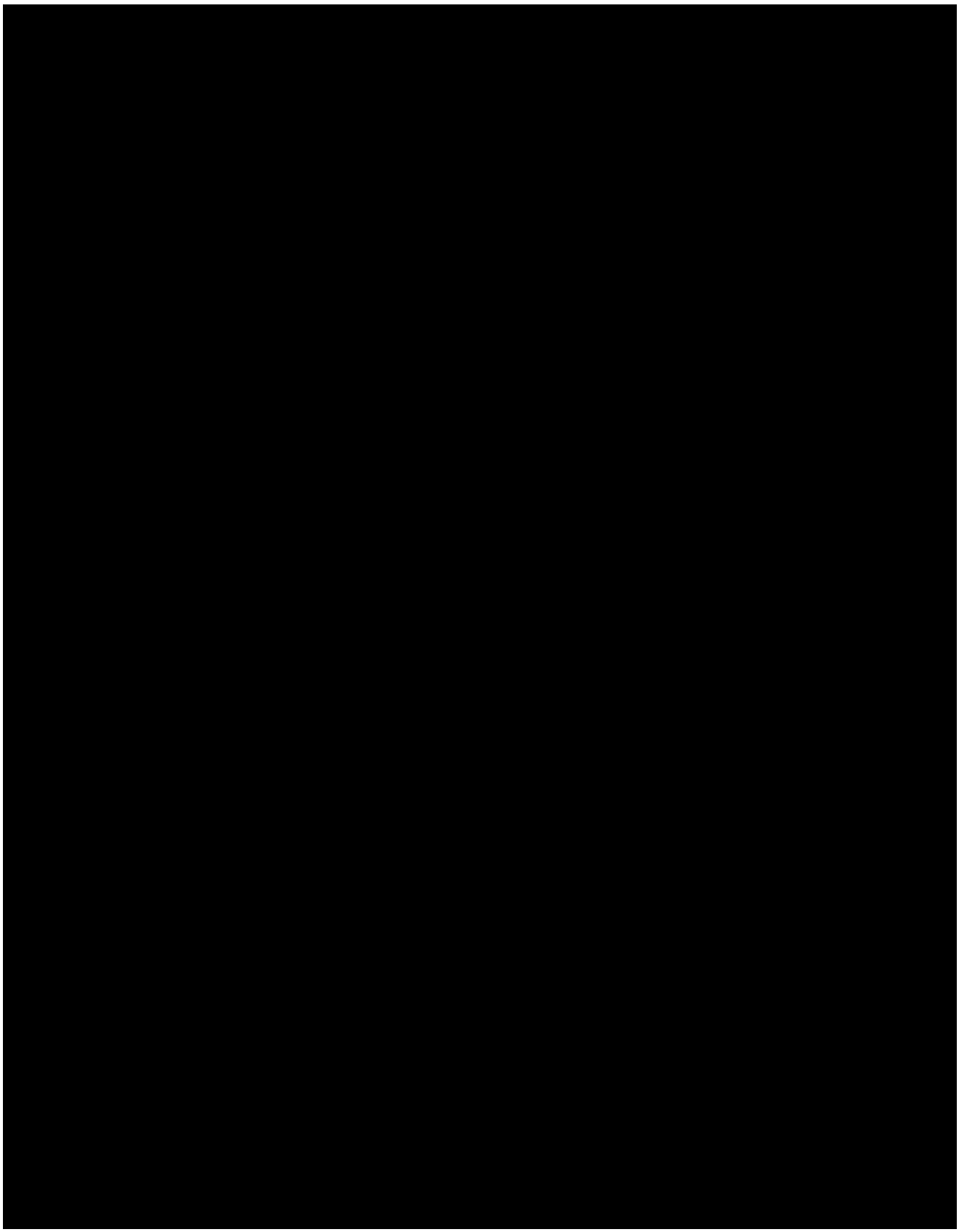

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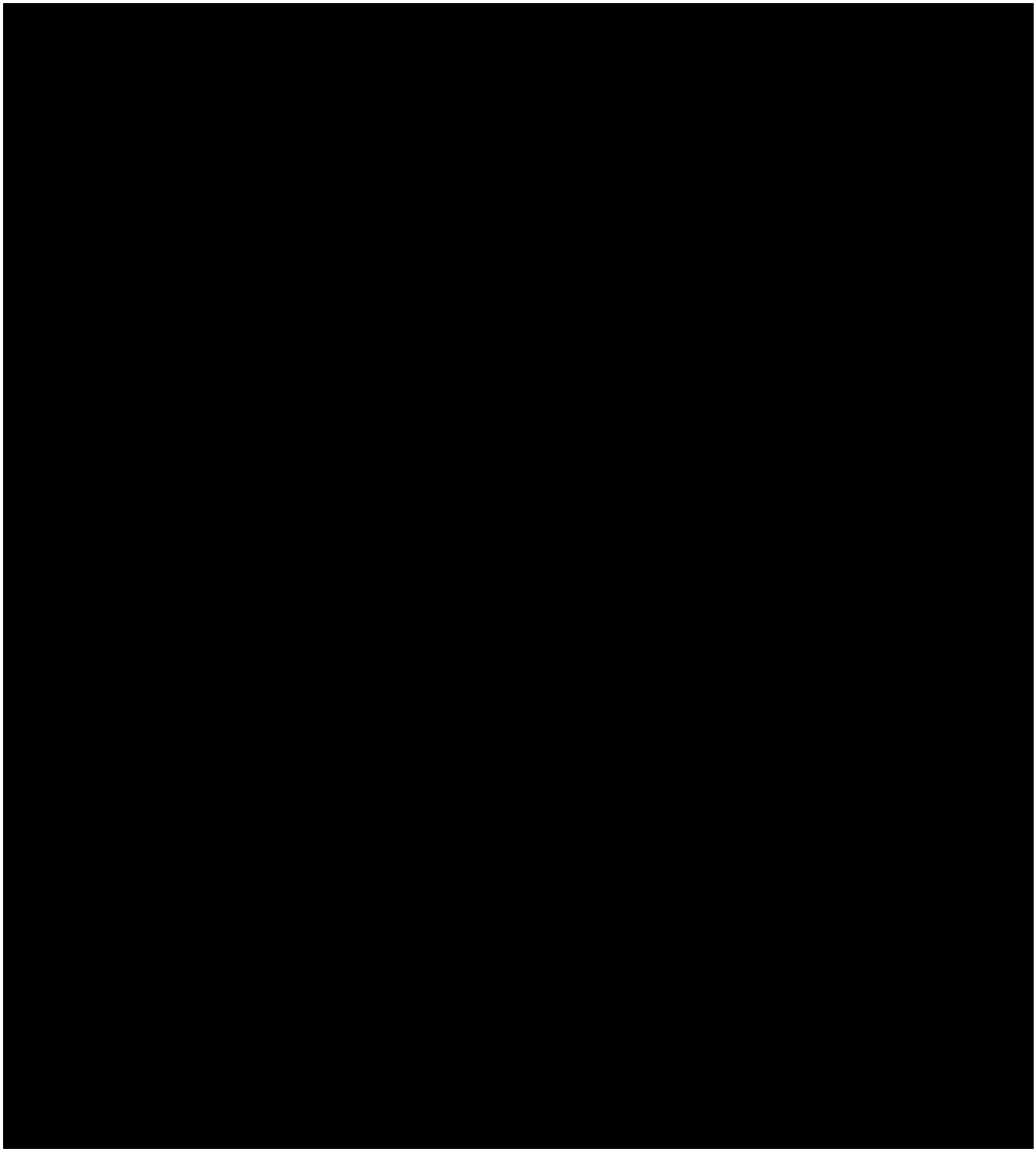

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3.3.3 Nivolumab plus Ipilimumab Combination Cohort

3.3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

c) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented and inclusion/exclusion criteria reassessed.

2. Target Population

a) Subjects with advanced hepatocellular carcinoma

i) Disease not eligible for surgical and/or locoregional therapies

ii) Documented radiographic progression during or after sorafenib therapy or sorafenib intolerance as defined in Section 1.4.9.

b) Histologic confirmation of hepatocellular carcinoma.

i) Subjects with only a radiologic diagnosis of HCC may be enrolled for screening in the study but histological confirmation is mandatory prior to the start of study therapy.

ii) Evaluable tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition) must be received by the central vendor (1 block or 15 unstained slides) for correlative studies prior to randomizing a study subject. If archived samples are not available, subjects must consent to a pre-treatment fresh biopsy as a condition of protocol participation. (Note: Fine needle aspiration (FNA) and bone metastases samples are not acceptable for submission).

c) At least one RECIST 1.1 measurable untreated lesion. All subjects must have at least one previously untreated, unidimensionally measurable lesion by contrast-enhanced spiral computed tomography (CT) ≥ 10 mm or contrast enhanced dynamic magnetic resonance imaging (MRI) scan ≥ 10 mm (malignant lymph nodes must be ≥ 15 mm on short axis).

i) The lesion can be accurately measured uni-dimensionally according to RECIST 1.1 criteria

ii) The lesion has not been previously treated with surgery, radiotherapy, and/or locoregional therapy (eg: radiofrequency ablation [RFA], percutaneous ethanol [PEI] or acetic acid injection [PAI], cryoablation, high-intensity focused ultrasound [HIFU], transarterial chemoembolization [TACE], transarterial embolization [TAI], etc.)

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d) Locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Grade ≤ 1.

e) Cirrhotic status of Child-Pugh Class A (A5 or A6) (Appendix 3)

f) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 4)

g) Subjects are eligible to enroll if they have non-viral-HCC or if they have HBV-, or HCV-HCC, defined as follows:

   i) Chronic HBV infection as evidenced by detectable HBV surface antigen or HBV DNA. Subjects with chronic HBV infection must be on antiviral therapy and have HBV DNA < 100 IU/mL.

   ii) Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody.

h) Screening laboratory values must meet the following criteria, without continuous supportive treatment such as growth factor administration, blood transfusion, coagulation factors and/or platelet transfusion, or albumin transfusion, and should be obtained within 14 days prior to randomization)

   i) Adequate hematologic function:

      (1) WBC ≥ 2000/μL

      (2) Neutrophils ≥ 1500/μL

      (3) Platelets ≥ 60 x 10^3/μL

      (4) Hemoglobin ≥ 8.5 g/dL

   ii) Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or Prothrombin time (PT) ≤ 6 seconds above control.

   iii) Adequate hepatic function with serum albumin ≥ 2.8 g/dL, total bilirubin < 3 mg/dL, and AST and ALT ≤ 5 times the institutional upper limits of normal Adequate renal function with a creatinine clearance > 40 mL/min (Cockcroft-Gault formula)

3. Age and Reproductive Status

a) Males and Females, age 18 or older

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.}

e) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

f) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with study drug and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.}.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

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3.3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC

b) Prior liver transplant

c) No history of hepatic encephalopathy

d) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control

e) Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 3 months

f) Active brain metastases or leptomeningeal metastases. Subjects with treated brain metastases are eligible if the following criteria are fulfilled:

i) The brain lesions have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to the first dose of study drug administration. (If an MRI is contraindicated, a CT scan is acceptable after discussion with the study Medical Monitor.)

ii) There is no requirement for immunosuppressive doses of corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

iii) The case is discussed with the study Medical Monitor

1) **Medical History and Concurrent Diseases**

a) Infections:

i) Active co-infection with

(1) Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR

(2) Hepatitis D infection in subjects with hepatitis B

ii) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

iii) Active bacterial or fungal infections requiring systemic treatment within 7 days prior to study entry.

b) Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.

c) Prior organ allograft or allogeneic bone marrow transplantation

d) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

e) Subjects with any active, known, or suspected autoimmune disease.

i) Subjects with vitiligo, type 1 diabetes mellitus, resolved childhood asthma or atopy are permitted to enroll.

ii) Subjects with suspected autoimmune thyroid disorders may be enrolled if they are currently euthyroid or with residual hypothyroidism requiring only hormone replacement.

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f) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

g) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg/day prednisone equivalents are permitted in the absence of active autoimmmune disease.

h) Any serious or uncontrolled medical disorder that in the opinion of the investigator may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

2) **Prior and Current Therapies**

a) Prior treatment with an anti-PD1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

b) Prior participation in a BMS nivolumab or ipilimumab study.

c) Radiotherapy within 2 weeks prior to study drug administration and no additional radiotherapy for the same lesion is planned.

d) Treatment with any chemotherapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment, with the exception of sorafenib which requires a 14 day washout period.

3) **Physical and Laboratory Test Findings**

a) Positive pregnancy test

4) **Allergies and Adverse Drug Reaction**

a) Known or suspected allergy to nivolumab or ipilimumab or study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

5) **Sex and Reproductive Status**

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6) **Other Exclusion Criteria**

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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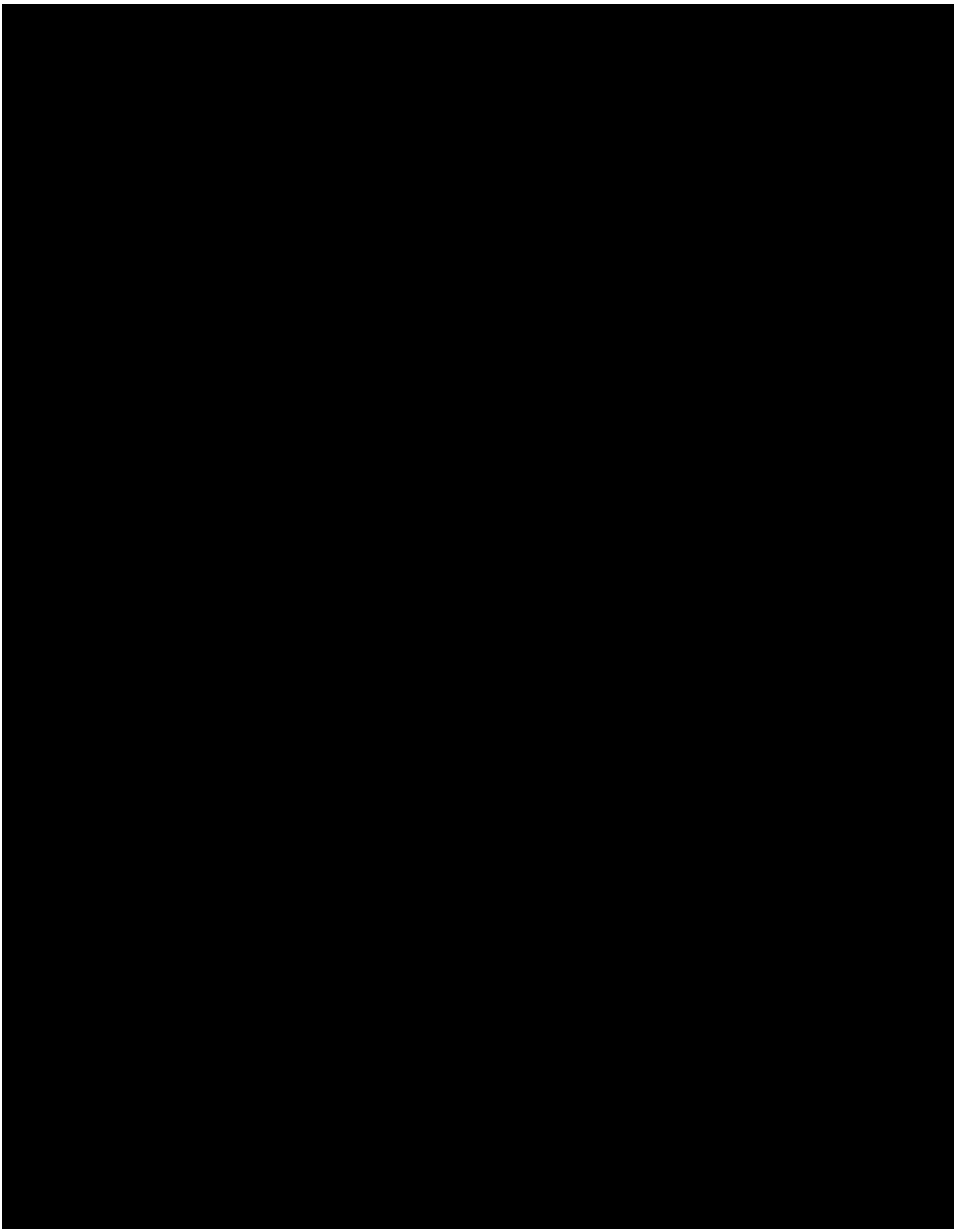

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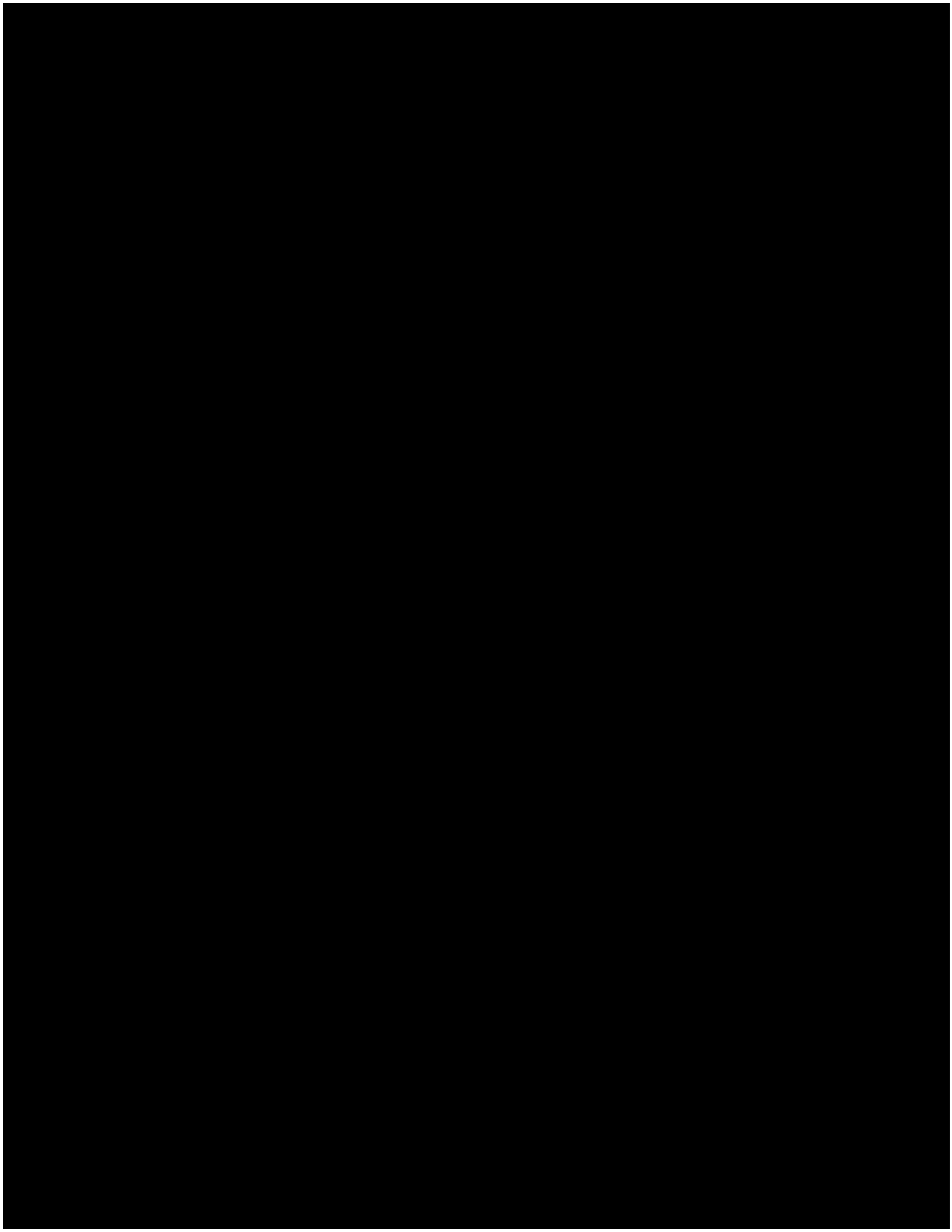

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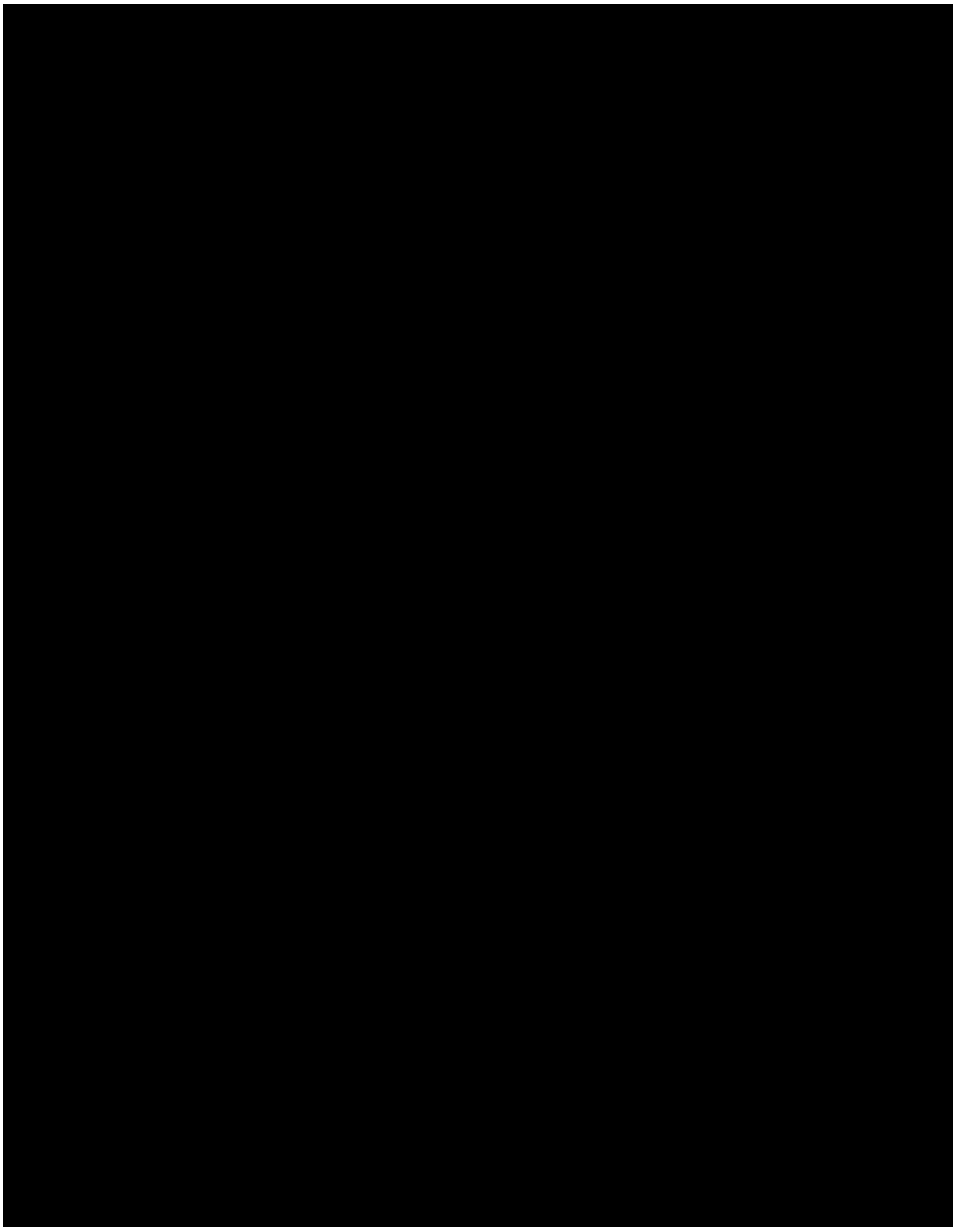

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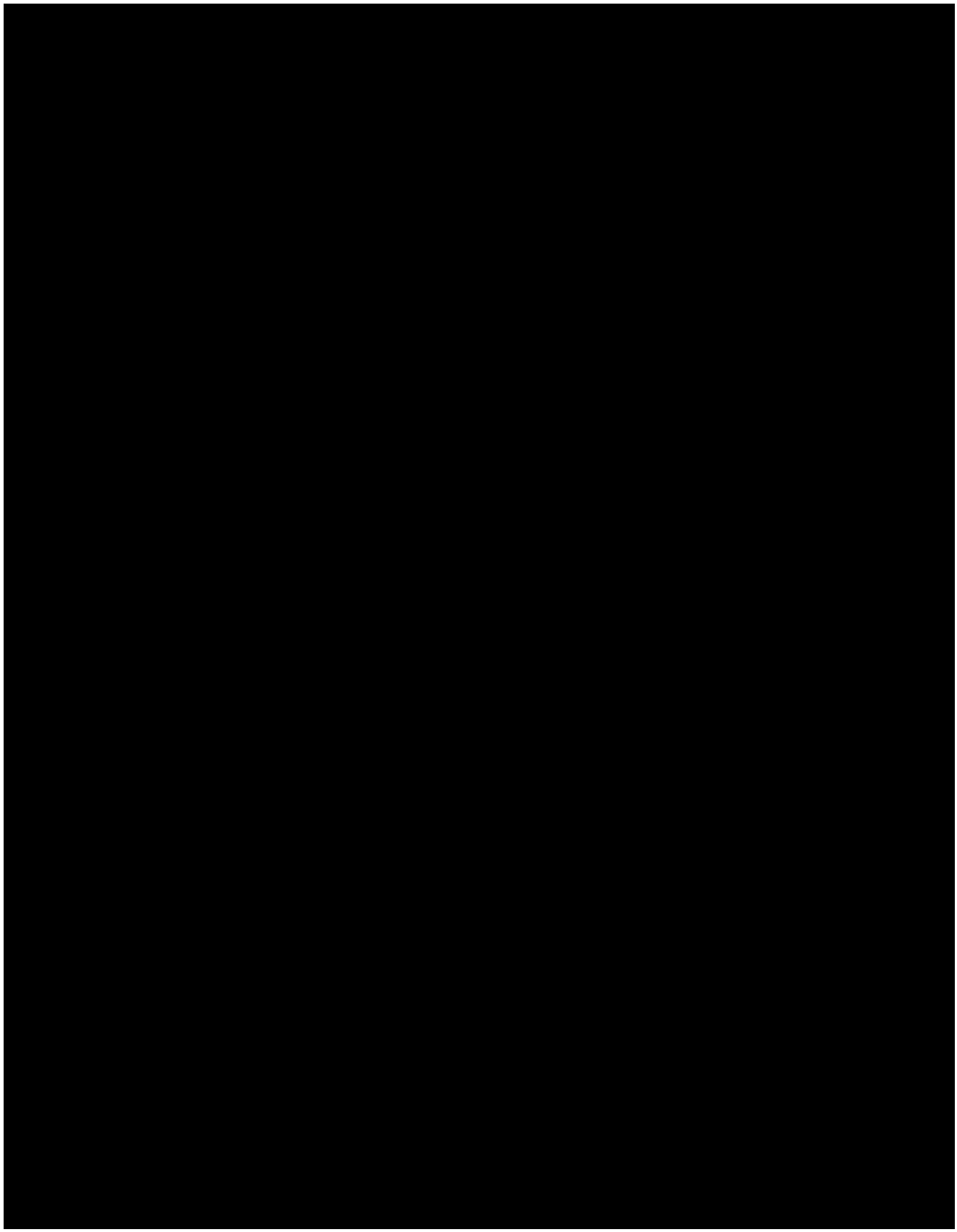

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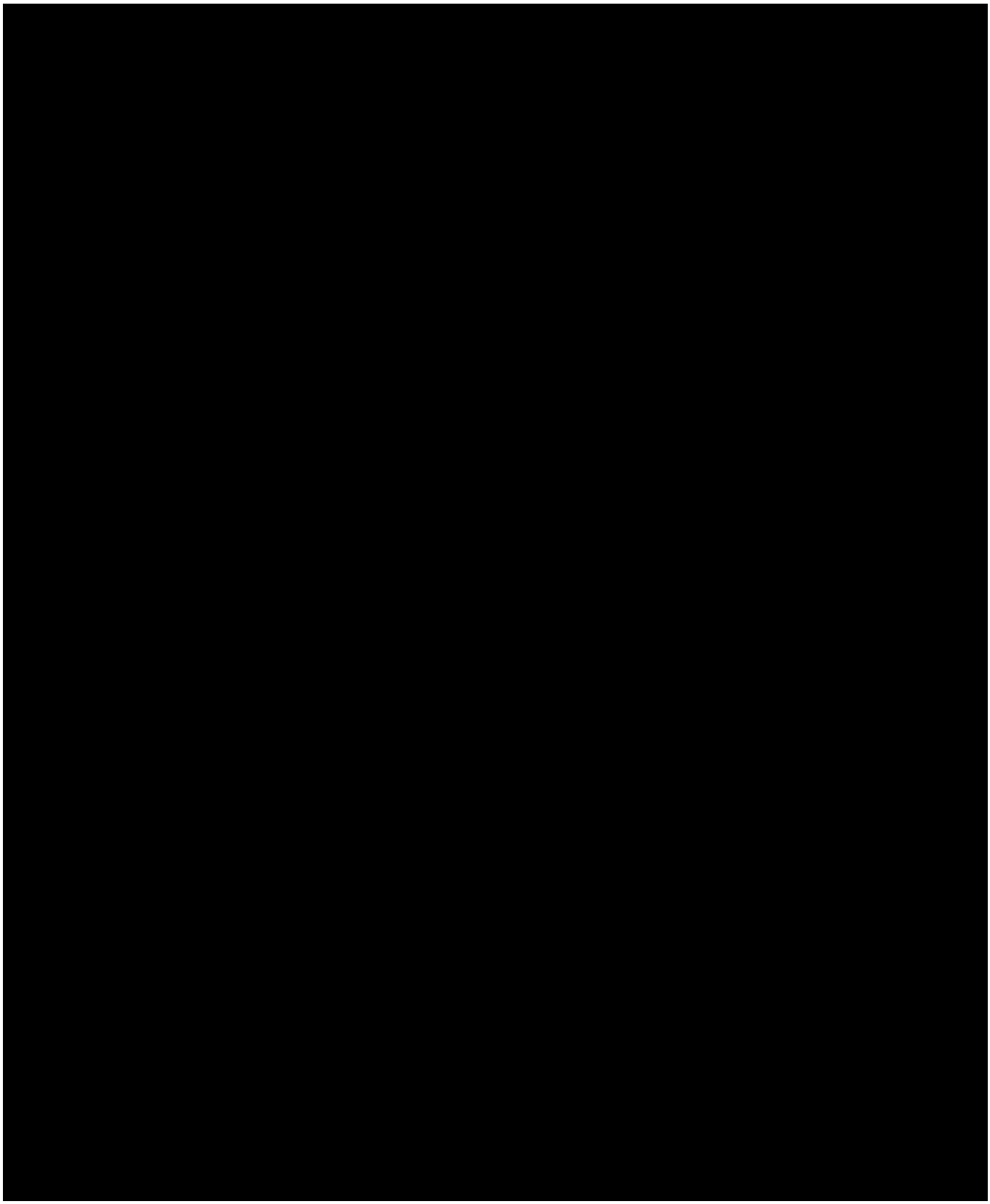

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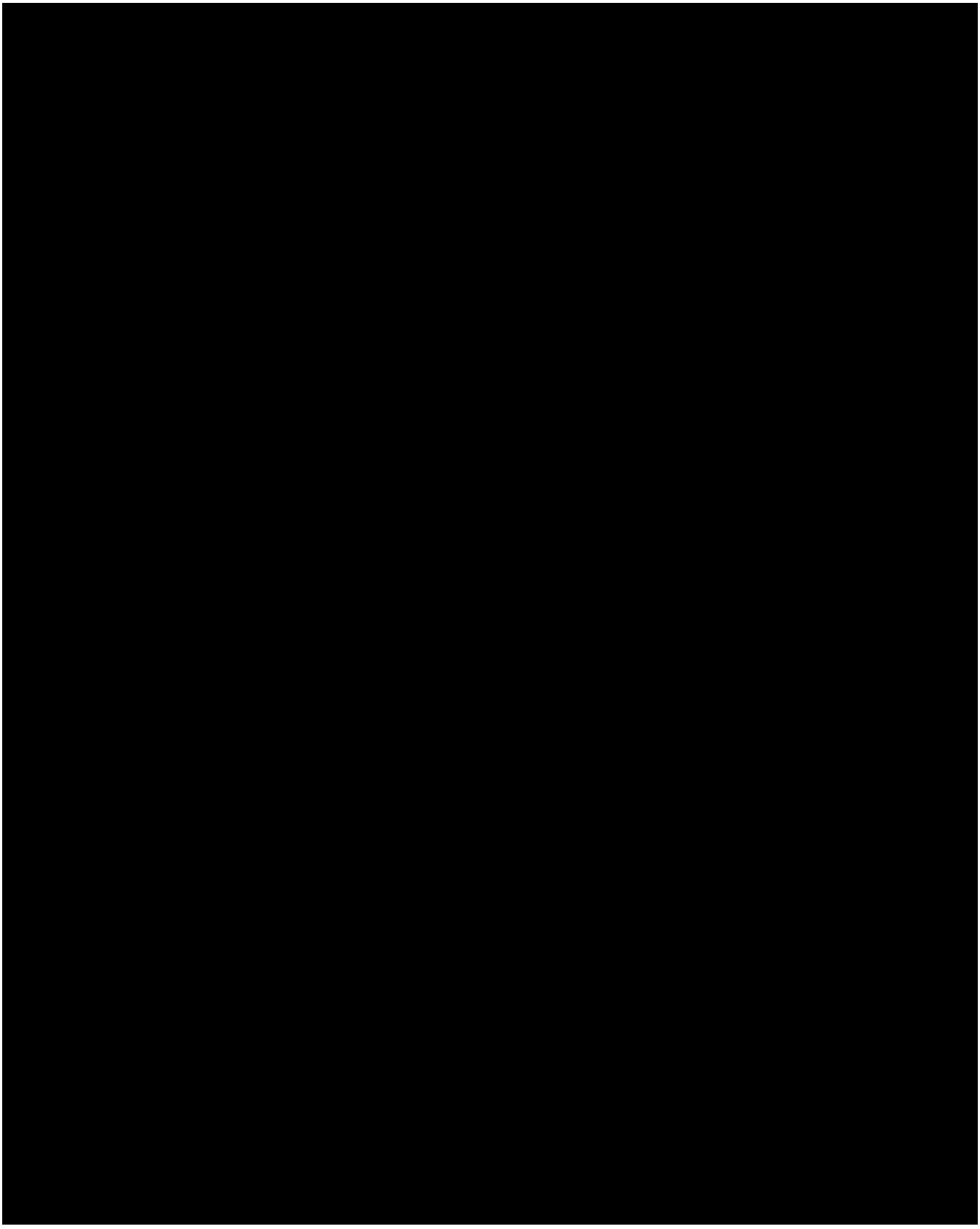

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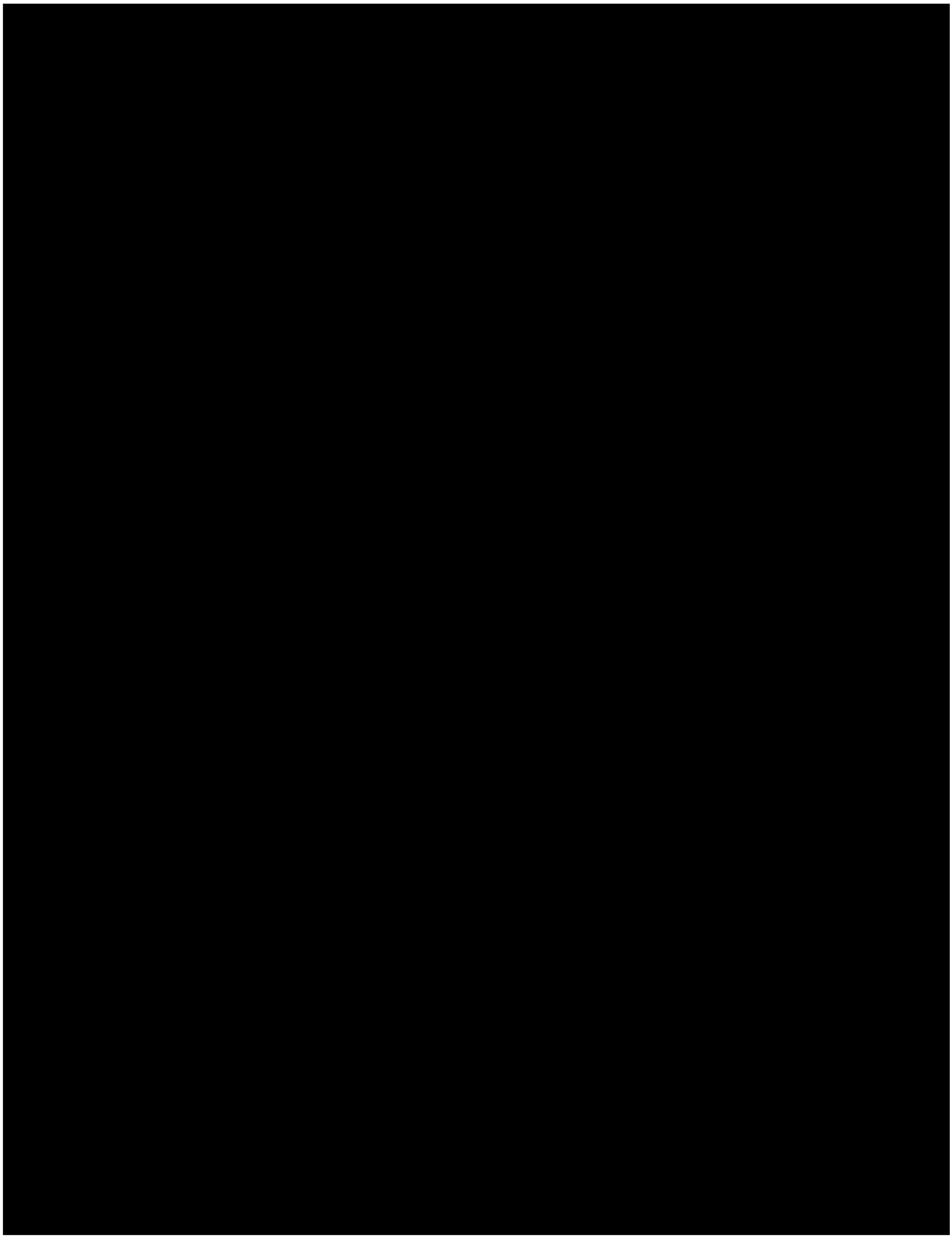

3.3.6 Women of Childbearing Potential

A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout periods below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40mIU/ml at any time during the washout period, the woman can be considered post menopausal.

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

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3.4 Concomitant Treatments

3.4.1 Prohibited Treatments

- Locoregional therapy for HCC
- Concurrent antineoplastic therapy, such as chemotherapy, molecular targeted therapy, hormonal therapy, immunotherapy, botanical formulations with an approved indication for cancer treatment (eg traditional Chinese medicines), radiation therapy (except for palliative local therapy described in Section 3.4.1
- Investigational agents for the treatment of cancer
- For subjects receiving nivolumab, systemic steroids > 10 mg within 14 days of dosing (with a few exceptions eg, steroids for adrenal insufficiency, steroids if taken as part of prophylaxis for CT prep [Section 3.4.2])
- Concurrent immunosuppressive agents (except to treat a drug-related adverse event).
- [redacted]

3.4.2 Other Restrictions and Precautions

- Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive doses (eg, prednisone > 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (eg, prednisone 10 mg/day) are permitted in the context of treating adverse events. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Hormone replacement therapy - subjects may continue to receive hormonal replacement therapy if initiated prior to randomization.
- Bisphosphonates and RANK-L inhibitors
  - For subjects receiving nivolumab or nivolumab plus ipilimumab, these are allowed for bone metastases
  - [redacted]
- [redacted]

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- It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.3 Palliative Local Therapy

Palliative local therapy for clinically symptomatic tumor sites (eg bone pain) including palliative (limited-field) radiation and palliative surgical resection may be considered if the following criteria are met:

- The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 4.2.5).
- The lesion for palliative local therapy is a non-target lesion
- The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record.

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- Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy. In addition, sites must request an Independent Review of Progression from the third party radiology vendor prior to the initiation of palliative local therapy. However, the initiation of palliative local therapy need not be delayed to await the assessment by the Independent Review of Progression.
- Palliative therapy must be clearly documented in the source records and electronic case report form. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events.

3.4.4 Treatment of HBV Virological Breakthrough and Ongoing HCV

Subjects will have ongoing assessments of HBV DNA throughout the course of the study. If a subject has an increase in HBV DNA, then virologic breakthrough should be considered. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a subject has documented virologic breakthrough due to antiviral resistance (defined as a > 1 log IU/mL increase in HBV DNA), then this should be managed based on standardized regional guidelines and treatment with nivolumab monotherapy or nivolumab plus ipilimumab temporarily held. In the absence of a dose-limiting toxicity, or hepatic decompensation, the subject may resume treatment with nivolumab monotherapy or nivolumab plus ipilimumab once virologic control is re-established (HBV DNA < 100 IU/mL), provided both the PI and BMS medical monitor assess the benefit-risk ratio to be in the best interest of the subject. If the subject meets the protocol defined criteria for hepatic dose limiting toxicity in the setting of HBV virologic breakthrough, then resumption of nivolumab monotherapy or nivolumab plus ipilimumab can be reconsidered on a case-by-case basis once the hepatic AE has reversed and virologic control is re-established, if the subject has evidence of a clinical response and both the PI and BMS medical monitor assess the benefit-risk ratio to be in the best interest of the subject.

For any subject who continues to be HCV RNA positive after receiving nivolumab, current guidelines for management of chronic HCV infection, including those from AASLD, EASL, or APASL may be consulted. Initiation of direct acting antivirals (DAAs) for HCV is allowed at the discretion of the investigator after discussion with the BMS medical monitor.

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3.6 Post Study Drug Study Follow-up

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all *randomized* subjects outside of the protocol defined window (Table 5.1-9 and Table 5.1-10). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.7 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as

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to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.8 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a BMS-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4. TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Five or ten nivolumab 10 mL vials will be packaged within a carton. The vials are not subject or treatment group specific.

[redacted]

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[redacted]

In the Nivolumab + Ipilimumab Combination Cohort, subjects will be randomized 1:1:1 to receive:

- Arm A--nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm B--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm C--nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6week until toxicity or disease progression
- In the Child Pugh B Cohort, approximately 50 subjects will receive 240 mg nivolumab IV q2 weeks over 30 minutes.

[redacted]

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4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: nivolumab, [redacted] ipilimumab [redacted]

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational product(s) is/are: medications used to treat nivolumab or ipilimumab infusion reactions (please see Section 4.5). These medications will not be provided by BMS.

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4.1.3 Handling and Dispensing

Table 4.1.3-1: Study Treatment Dose and Schedule

Cohort	Arm	Study treatment	Dose Level(s) and Formulation	Frequency of Administration	Route of Administration
[redacted]					
Nivolumab + Ipilimumab Combination	A	Nivolumab	1 mg/kg for 4 doses than 240 mg	Every 3 weeks for 4 doses than every 2 weeks	IV
		Ipilimumab	3 mg/kg (4 doses only)	Every 3 weeks (4 doses only)	IV
	B	Nivolumab	3 mg/kg for 4 doses than 240 mg	Every 3 weeks for 4 doses than every 2 weeks	IV
		Ipilimumab	1 mg/kg (4 doses only)	Every 3 weeks (4 doses only)	IV
	C	Nivolumab	3 mg/kg	Every 2 weeks	IV
		Ipilimumab	1 mg/kg	Every 6 weeks	IV
[redacted]					

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4.1.3.1 Nivolumab and Ipilimumab Dose and Schedule

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

The sites are responsible for procuring IV bags, diluent, and in-line filters.

For details on prepared drug storage and administration of nivolumab and ipilimumab, please refer to the current Investigator Brochures. Details regarding mixing and concentrations of the doses will be detailed in the pharmacy binder.

The unblinded pharmacist will obtain treatment assignment by IVRS and prepare unblinded drug.

Nivolumab is to be administered as a 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or dextrose solution.

In the Nivolumab plus Ipilimumab Combination Cohort Cohort and the Cabozantinib Combination Cohort triplet Arm, ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the infusion. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion.

Nivolumab weight based dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose.

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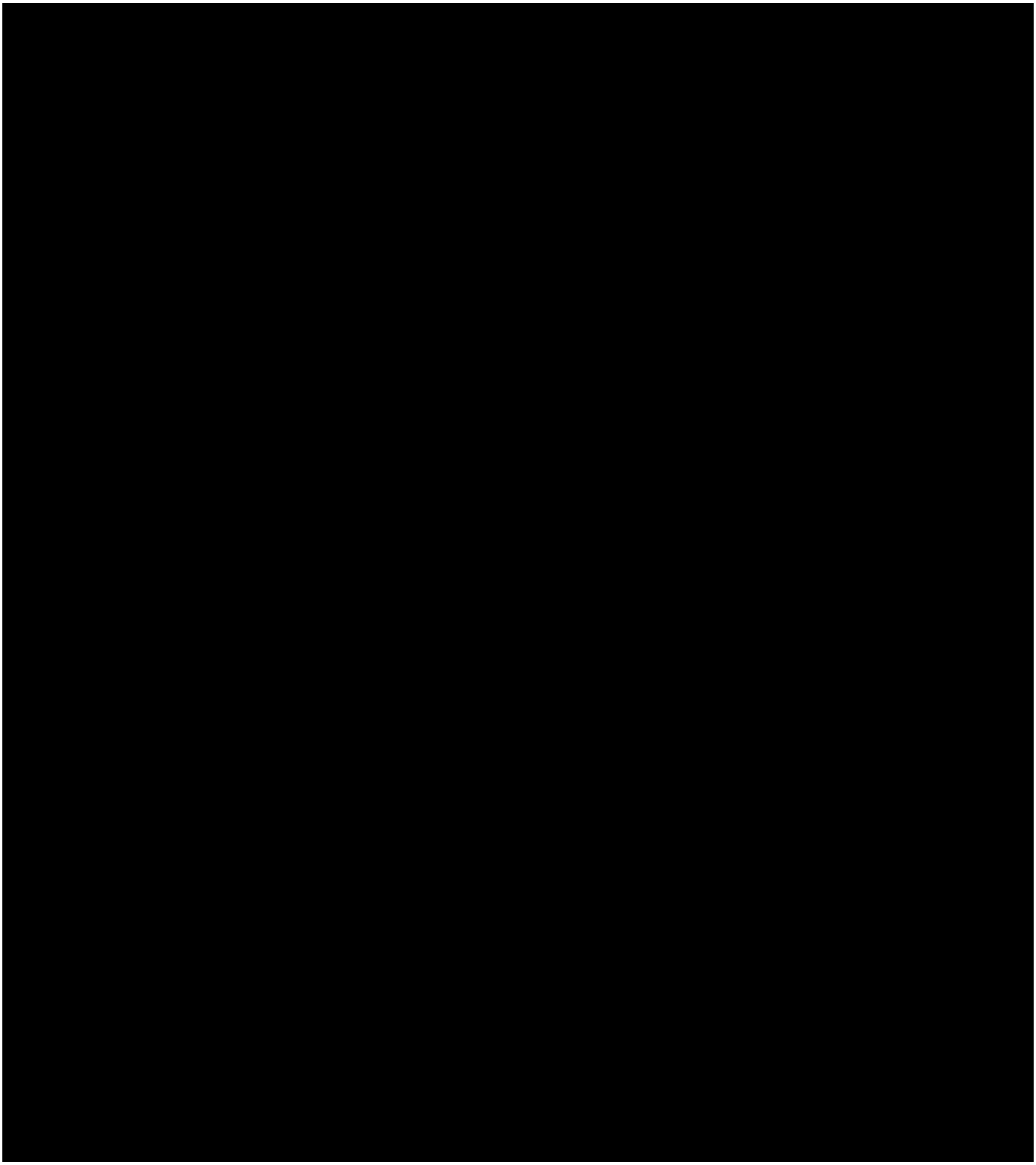

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4.2 Dosage Modification

4.2.1 Dose Delay Criteria

4.2.1.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents, such as nivolumab and ipilimamab, are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic (see protocol specific updates in Section 4.2.1.4)
- Endocrinopathies
- Skin
- Neurological

The above algorithms are found in Appendix 1 of this protocol.

[redacted]

Subjects who require dose delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met (see Section 4.2.3).

[redacted]

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[redacted]

4.2.1.3 Nivolumab and Ipilimumab Dose Delay Criteria for Nivolumab plus Ipilimumab Combination Cohort [redacted]

Dose delay criteria apply for all drug-related adverse events. Treatment delay up to 6 weeks (42 days) from the last dose of nivolumab and ipilimumab are allowable in Arms A and B (Nivo Ipi Combination Cohort) vs 12 weeks (84 days) from the last dose of nivolumab and ipilimumab in Arm C (Nivo Ipi Combination Cohort) [redacted]

- Study drug administration should be delayed for the following:
- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, asymptomatic amylase or lipase, AST, or ALT:
  - Grade 3 lymphopenia does not require dose delay.
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
  - If a subject has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity (2-grade shift).
  - If a subject has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity (2-grade shift).
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for drug-related increase in AST or ALT at 2x baseline value or when AST or ALT is 8x ULN (whichever is lower).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants interrupting the dose of study medication.

Subjects who require delay of nivolumab and ipilimumab should be re-evaluated weekly or more frequently if clinically indicated. It is recommended to monitor elevations in AST or ALT approximately every 3 days till levels peak or begin to decline. Nivolumab dosing can be resumed when re-treatment criteria are met.

Tumor assessments for all subjects should continue as per protocol even if study drug dosing is delayed.

Subjects receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. Refer to Section 4.2.3.2 Criteria to Resume Ipilimumab Dosing for further details.

In subjects in the Nivolumab plus Ipilimumab Cohort (arm C) [redacted] receiving ipilimumab 1 mg/kg q6week:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 7-day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 7-day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.

- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.2.4.2 (Ipilimumab Dose Discontinuation).

[redacted]

Subjects who require dose delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met (see Section 4.2.3).

[redacted]

4.2.1.4 *Protocol-Specific Recommendation for Management of Hepatic Events in Nivolumab or Nivolumab plus Ipilimumab Subjects*

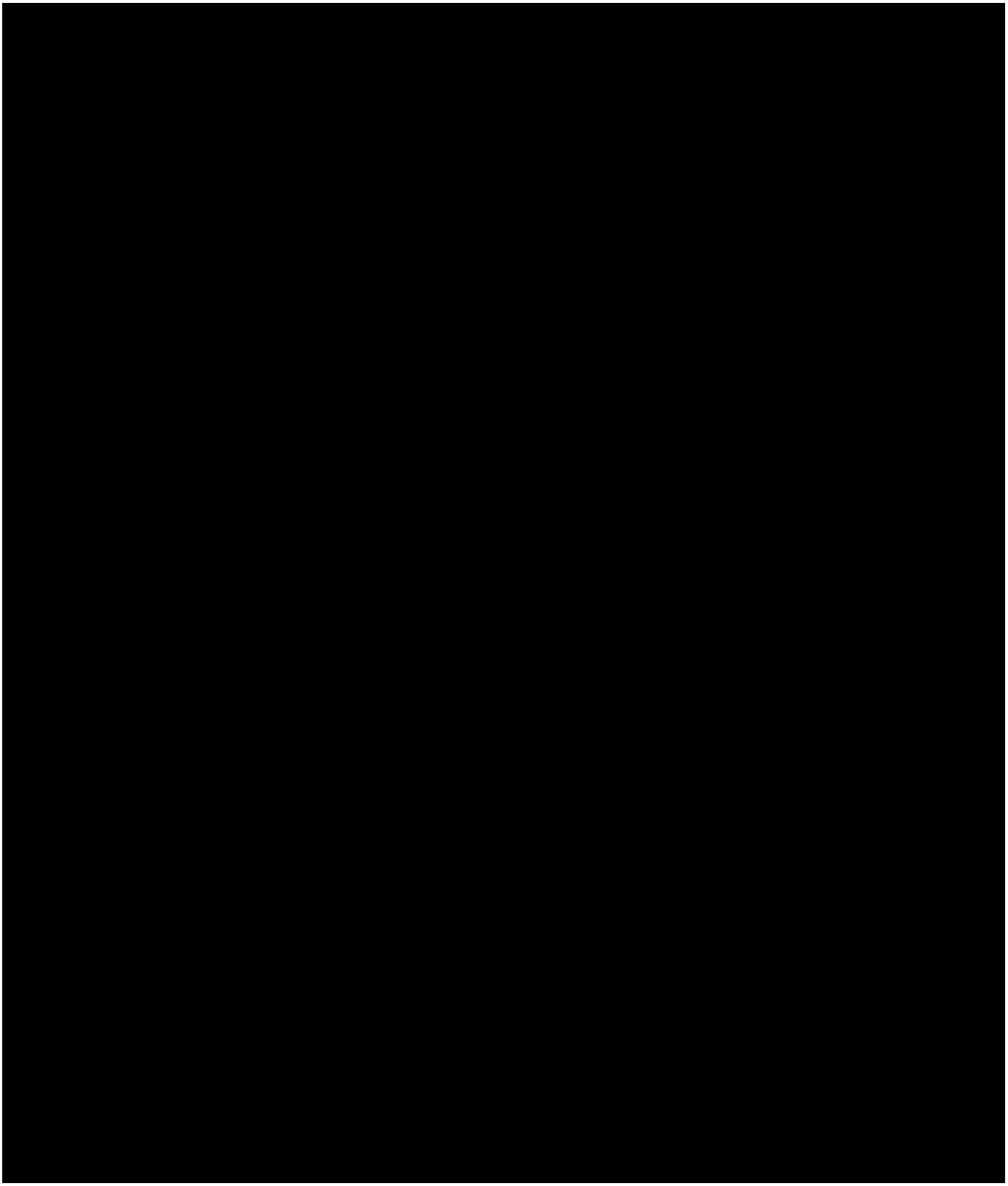
The nivolumab program has developed a standardized algorithm for the management of hepatic events based on cumulative data across the program in subjects with normal hepatic function. Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3x ULN; therefore, only subjects with normal to grade 1 LFTs have been enrolled.

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA209040, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range. This requires a protocol-specific approach for the management of hepatic events, outlined as follows:

- Dose delay criteria for hepatic events are outlined in Sections 4.2.1.2 and 4.2.1.3. If AST or ALT levels do not improve with a dose delay of 3 - 5 days or if the levels worsen, initiate steroid therapy at 0.5 - 2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1 - 2 mg/kg/day methylprednisolone or oral equivalent.
- For all subjects initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3 - 5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Sections 4.2.3.1 and 4.2.3.2, nivolumab and ipilimumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent

discontinuation are reached (Sections). The BMS Medical Monitor must be consulted prior to resuming nivolumab for all subjects who required steroid intervention.



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[redacted]

4.2.2 Dose Reductions and Escalations

4.2.2.1 Dose Reduction and Escalation for Nivolumab or Ipilimumab

Nivolumab or ipilimumab dose reduction and intrasubject dose escalation are not permitted in this study.

[redacted]

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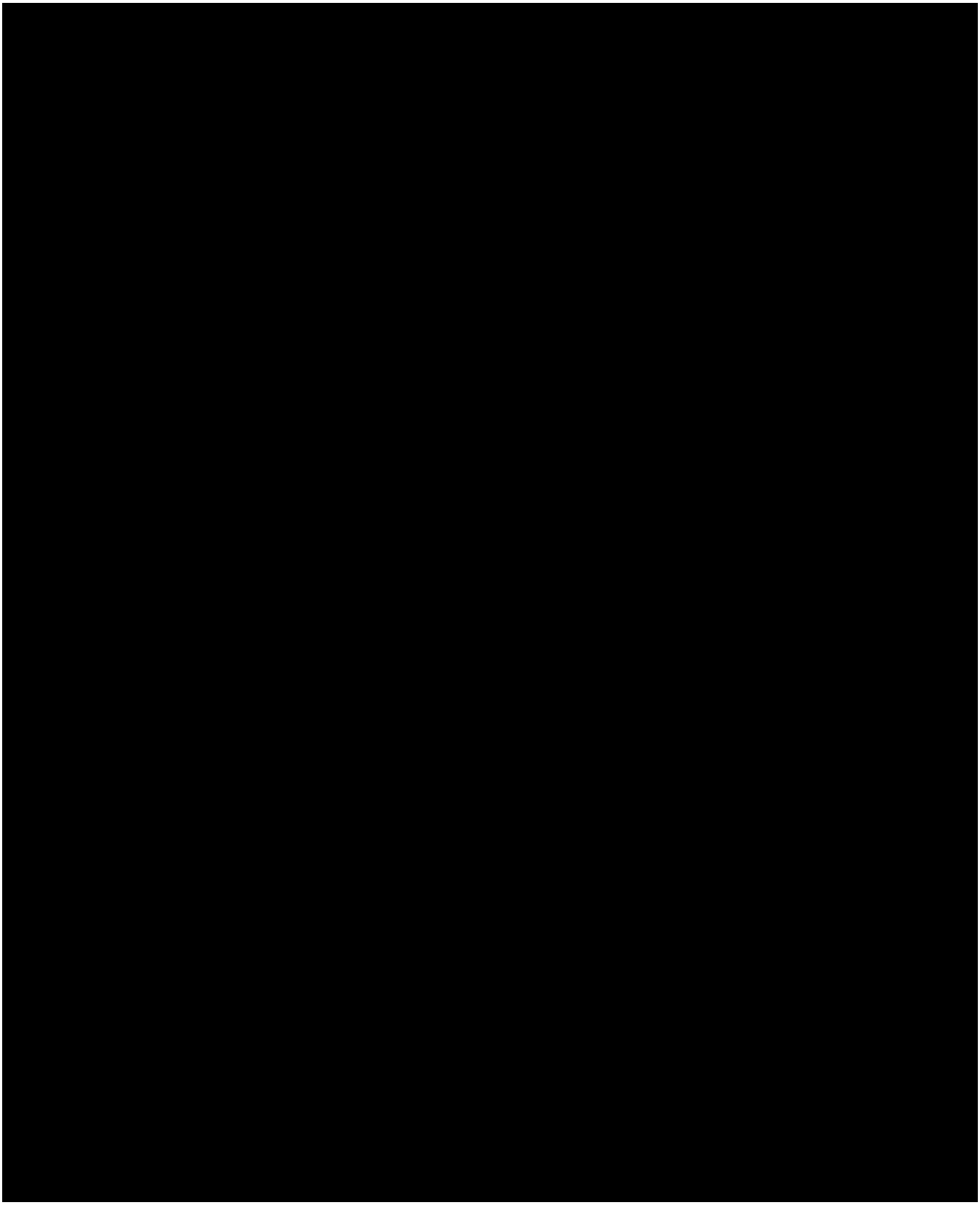

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4.2.3 Criteria to Resume Treatment

4.2.3.1 Criteria to Resume Treatment with Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1 and after discussion with BMS Medical Monitor.
- Subjects with AST, ALT or bilirubin values meeting discontinuation parameters (Section 4.2.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

Resuming treatment after a delay of up to 6 weeks from the previous dose is permitted with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the last dose, the BMS Medical Monitor must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.
- Dosing delays > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

4.2.3.2 Criteria to Resume Treatment with Ipilimumab

Subjects may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

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- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1 and after discussion with BMS Medical Monitor.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ± 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for >12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.2.4.2.

In subjects in the Arm C of the Nivolumab plus Ipilimumab Combination Cohort and Triplet Arm of the Cabozantinib Combination cohort receiving ipilimumab q6week:

- Ipilimumab may not be resumed sooner than 6 weeks (± 7 days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 7-day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

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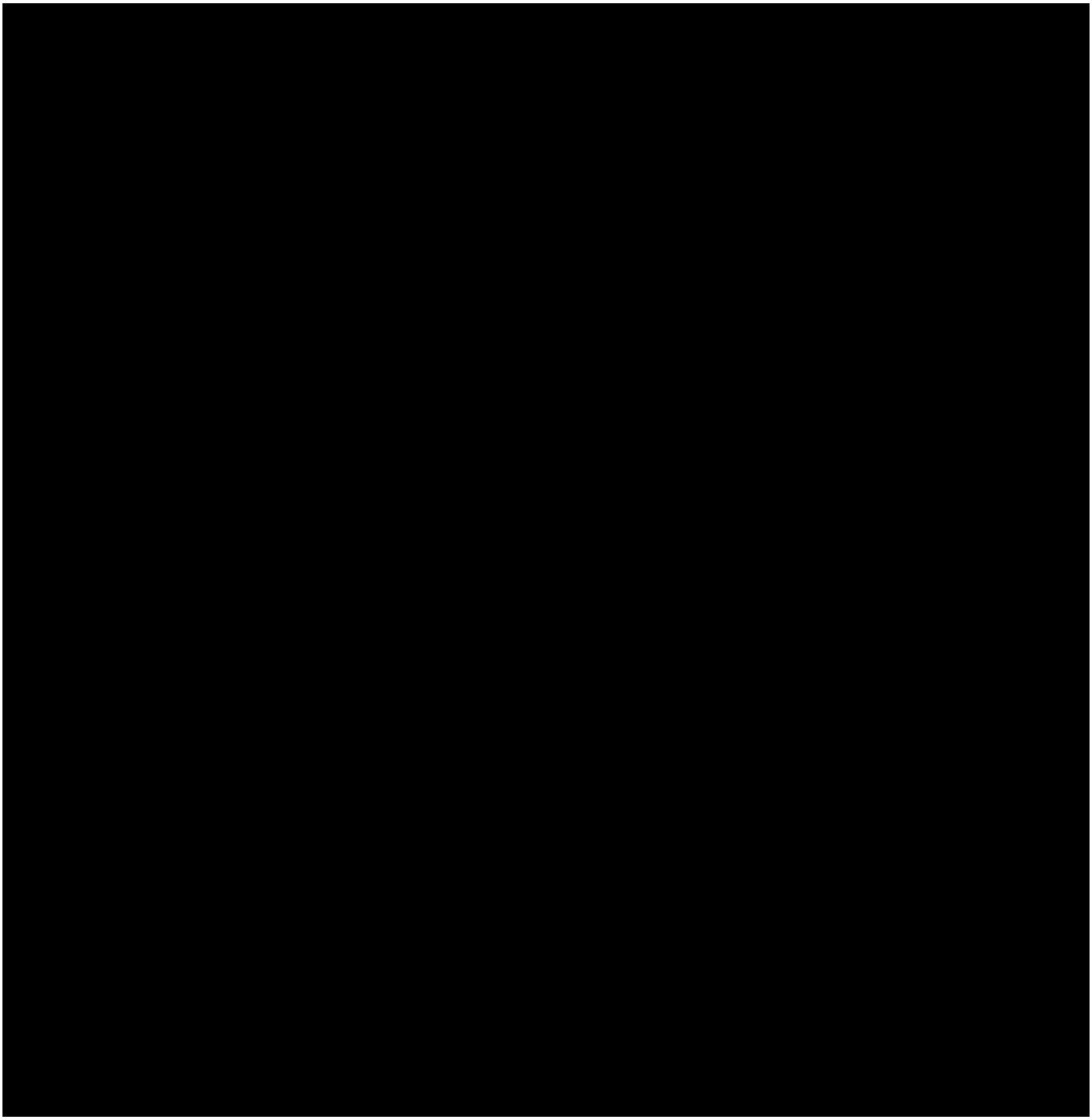

4.2.4 Discontinuation from Study Treatment

4.2.4.1 Nivolumab Permanent Dose Discontinuation Due to Adverse Event(s)

Nivolumab administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 drug-related uveitis, eye pain, or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment

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- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 10 x ULN for > 2 weeks,
      - AST or ALT > 15 x ULN irrespective of duration,
      - T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
      - Concurrent AST or ALT > 3 x ULN and T. bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin
- Any drug-related Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - For Grade 4 endocrinopathy adverse events such as hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively
- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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- [redacted]

For subjects in the Nivolumab plus Ipilimumab Combination Cohort [redacted]:

- Assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab.
- If the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the subject meets criteria to resume nivolumab treatment (specified in Section 4.2.3.1).
- The relationship to ipilimumab should be well documented in the source documents.
- BMS medical monitor needs to be contacted prior to resuming nivolumab.
- If a subject in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.2.4.2 Ipilimumab Permanent Dose Discontinuation Due to Adverse Event(s)

Ipilimumab administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 drug-related uveitis, eye pain, or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction
- Any other Grade 3 non-skin, drug-related adverse events with the following exceptions for laboratory abnormalities, Grade 3 nausea and vomiting, Grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution)
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 10 x ULN for > 2 weeks,
    - AST or ALT > 15 x ULN irrespective of duration,
    - T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
    - Concurrent AST or ALT > 3 x ULN and T. bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin
- Any drug-related Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia

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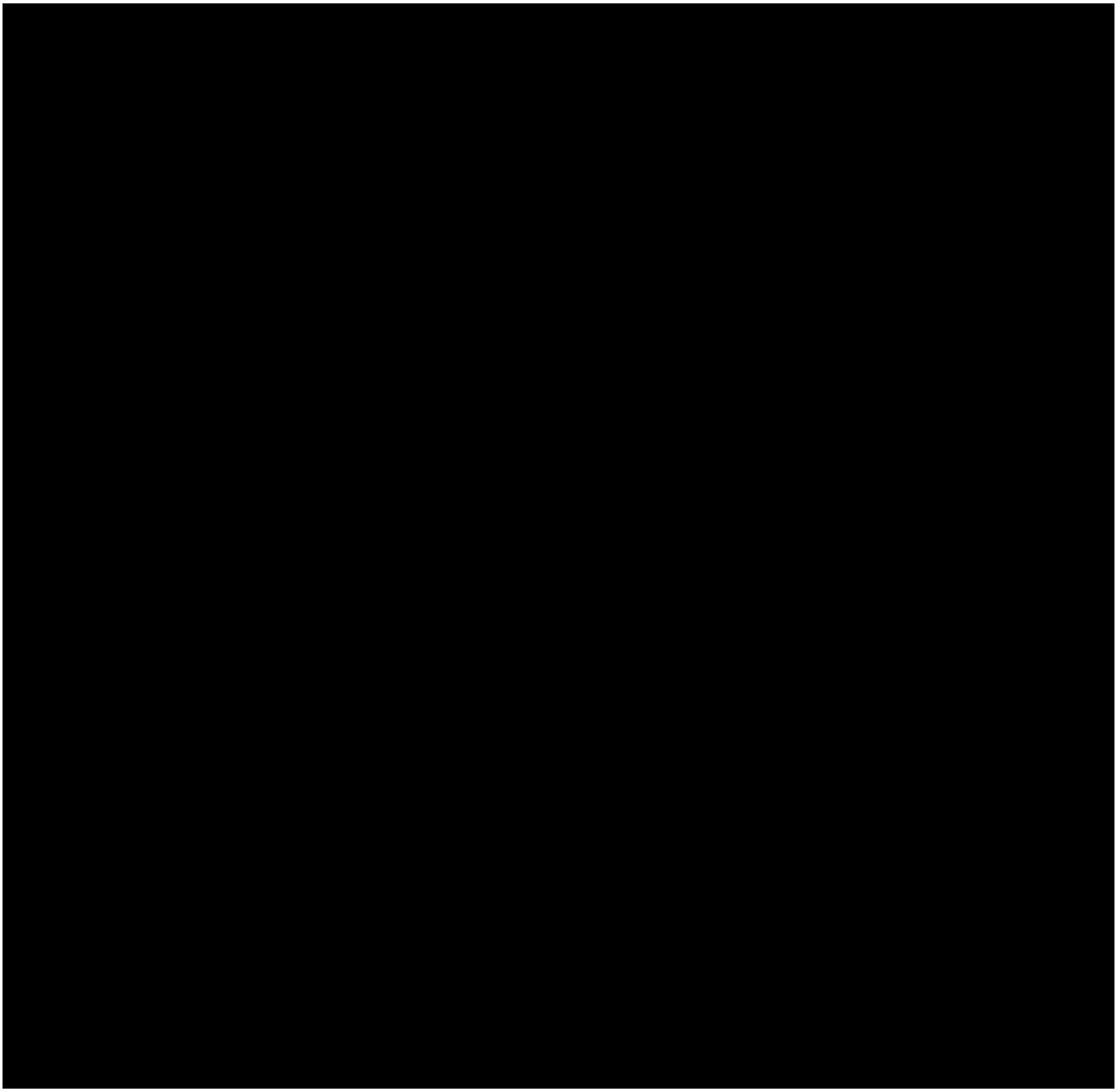
- Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug related reasons may be allowed if approved by the BMS medical monitor. Prior to reinitiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing. Dose limiting toxicity as defined in Section 3.1.3.1.

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a subject in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

[redacted]



4.2.5 Treatment Beyond Progression

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop disease progression by conventional response criteria before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in the Phase 1 study of nivolumab, CA209003, and confirmed in multiple Phase 3 studies [redacted]. Two hypotheses explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of

clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent.

[redacted]

Therefore, subjects regardless of the cohorts, will be allowed to continue study treatment after an initial investigator-assessed RECIST 1.1 (Appendix 2) defined progression as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Subject is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving any additional dose of study treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

These criteria aim to ensure the risk/benefit for continuing treatment will continue to favor the subjects. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records.

If the decision is taken to continue study treatment treatment beyond progression, the subject will remain on the trial and continue to be treated and monitored according to the Time and Events Schedule in [redacted] Table 5.1-7 (Nivolumab plus Ipilimumab Combination Cohort), [redacted]

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden SLD from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase

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in short axis to at least 15 mm). Nivolumab treatment should be discontinued permanently upon documentation of further progression.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For subjects discontinuing treatment because of global deterioration of health status without objective evidence of disease progression at that time, progression should be reported as "symptomatic deterioration". Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

4.3 Method of Assigning Subject Identification

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The exact procedure for using the IVRS will be detailed in a separate document.

4.4 Selection and Timing of Dose for Each Subject

[redacted]

In the Nivolumab plus Ipilimumab Combination Cohort, subjects will be randomized 1:1:1 to receive:

- Arm A--Nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm B--Nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm C--Nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6 week until toxicity or disease progression.

[redacted]

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- [redacted]

4.5 Treatment of Nivolumab or Ipilimumab Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 allergic reaction/hypersensitivity. Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, these reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated with acetaminophen and diphenhydramine for future treatments.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours)

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be

administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject’s medical record and eCRF.
Study treatment compliance will be periodically monitored by drug accountability (including review of dosing diary cards, as applicable). Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

4.8 Destruction and Return of Study Drug

4.8.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

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On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

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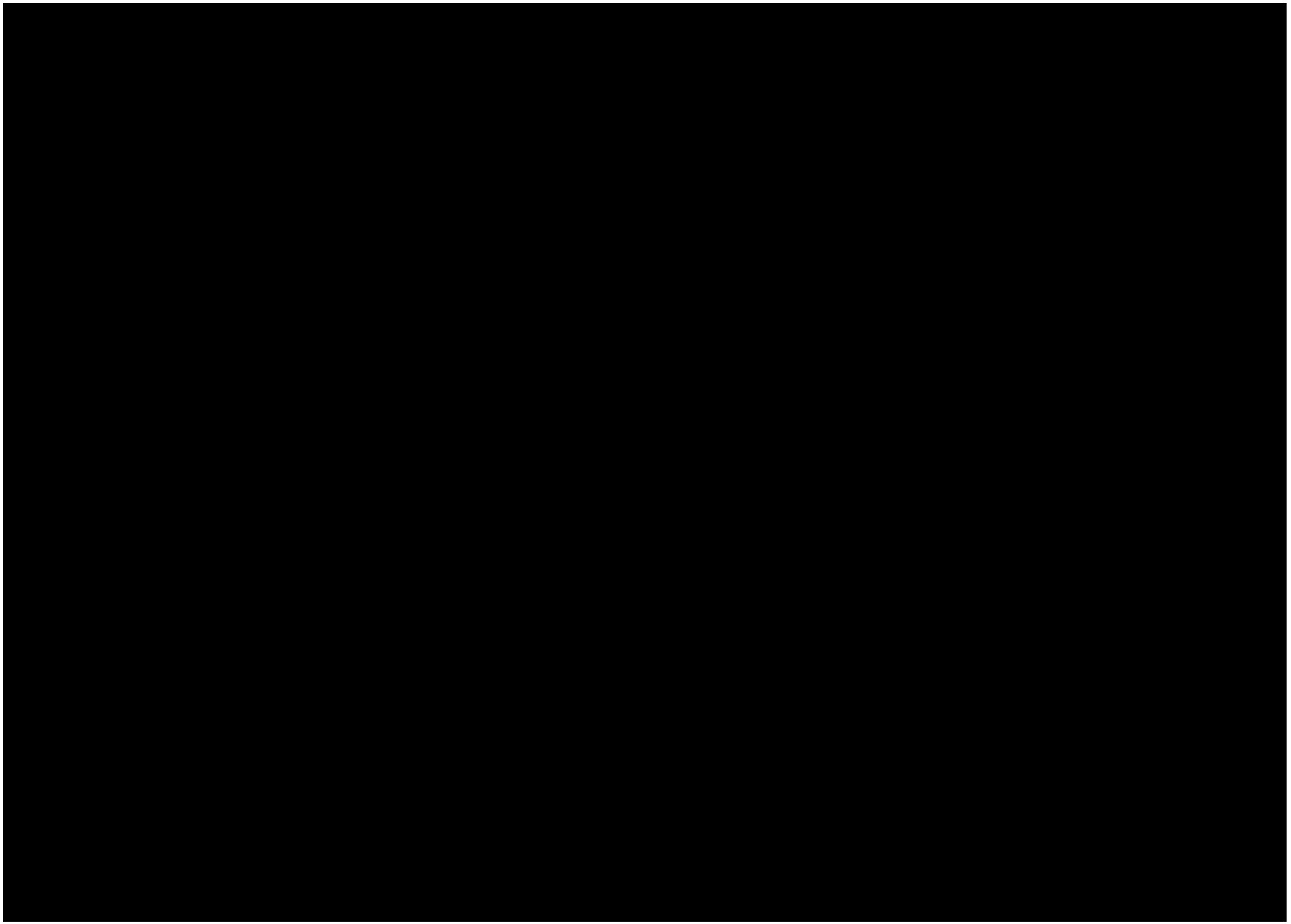

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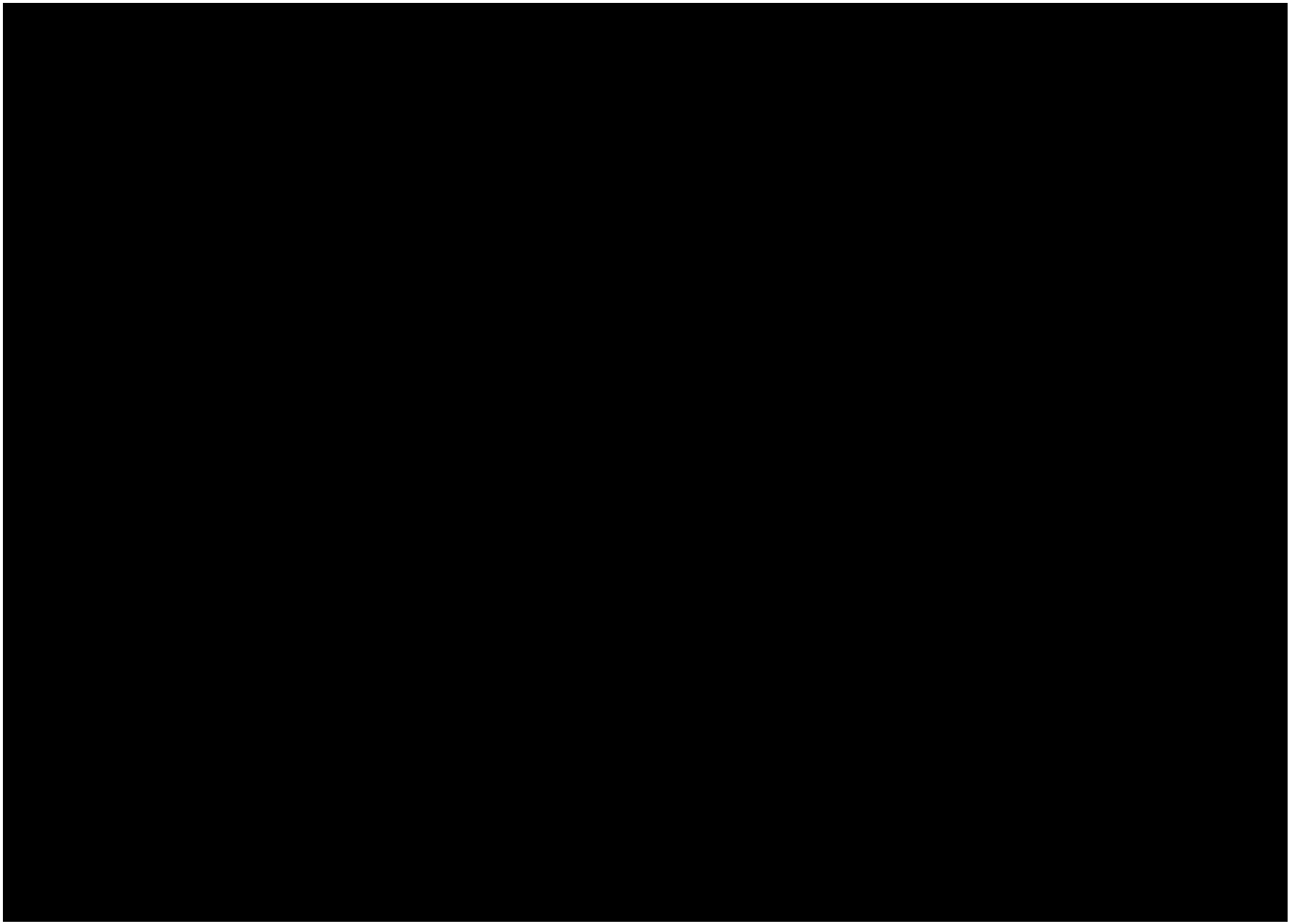

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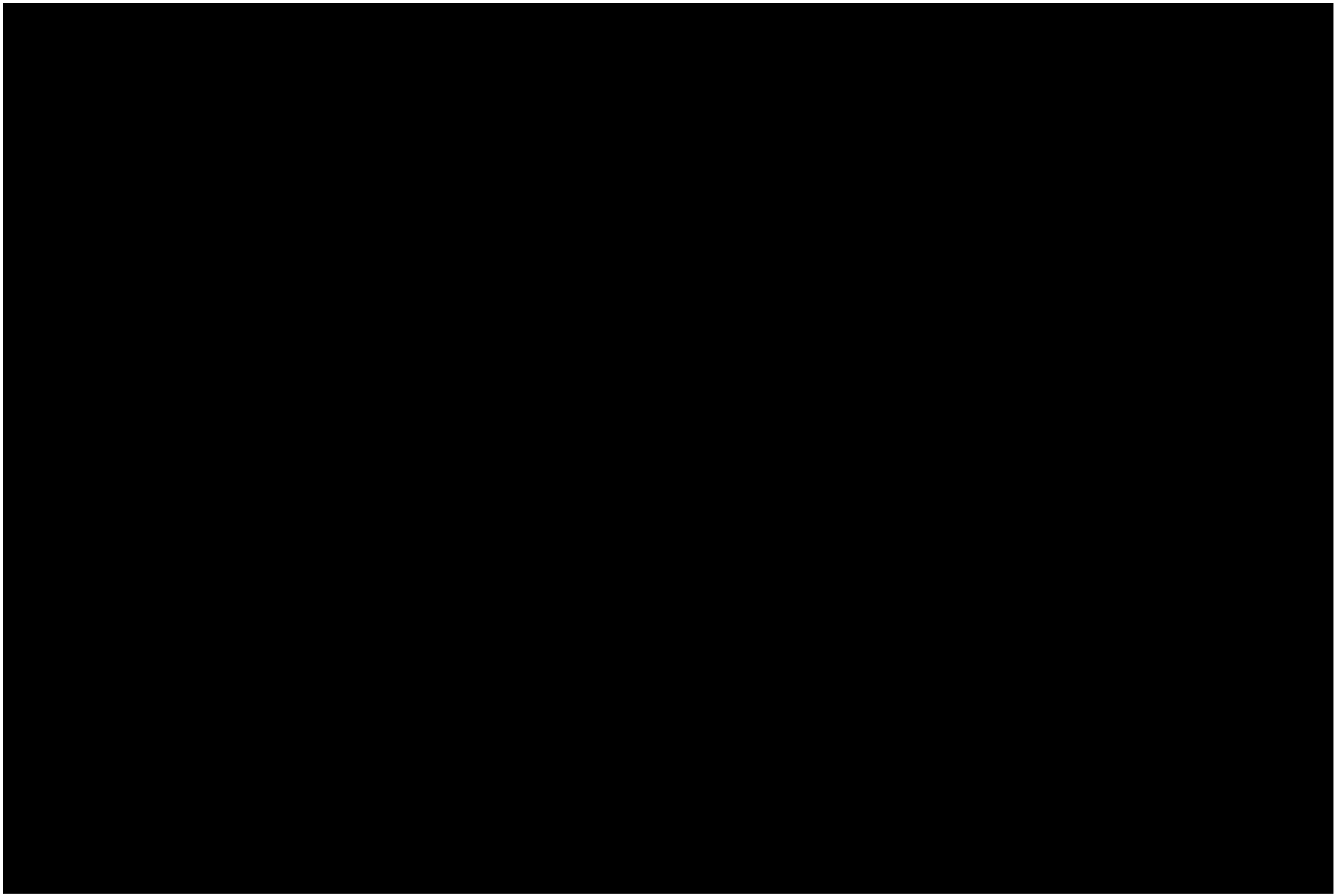

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Table 5.1-3:	**Screening Procedural Outline for Nivolumab plus Ipilimumab Combination Cohort, [redacted]**	
Procedure	**Pre-Treatment Visit (Baseline)**	**Notes**
Eligibility Assessments		
Informed Consent	X	Original informed consent in screening for protocol participation. Study allows for re-enrollment of a subject that has discontinued the study as an enrollment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	Assessed during screening period and (re-enrollment if applicable).
Medical History	X	
Child-Pugh Score	X	Child Pugh A5 or A6 for subjects in the Nivolumab plus Ipilimumab Combination Cohort and Cabozantinib Combination Cohort; Child Pugh B7 to B8 for subjects in the Child Pugh B Cohort
Safety Assessments		
Physical examination	X	[redacted] prior to first dose
Physical Measurements	X	Height and Weight. [redacted] prior to first dose
ECOG Assessment	X	
Vital Signs	X	Including BP, HR, temperature, respiratory rate. Obtain vital signs at the screening visit and [redacted] prior to first dose.
Assessment of Signs and Symptoms	X	[redacted] prior to first dose
Concomitant Medication Collection	X	[redacted] prior to first dose
12 lead ECG	X	[redacted] prior to first dose
Laboratory Tests	X	Within [redacted] prior to randomization to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), Alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase, Glucose, TSH, Free T4, Free T3. Tests will be performed locally. For Cabozantinib Combination Cohort: phosphorus will also be tested.

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Table 5.1-3:	**Screening Procedural Outline for Nivolumab plus Ipilimumab Combination Cohort, [redacted]**	
Procedure	**Pre-Treatment Visit (Baseline)**	**Notes**
Serology for Hep B, Hep C, Hep D	X	HepB surface antigen, HepB surface antibody, Hep B Core antibody, HepB DNA Viral load (PCR) Hep C viral load (PCR) and Hep C Ab, Hep D antibody For chronic HBV subjects in the Child Pugh B Cohort and Cabozantinib Combination cohort, qHBsAg, qHBeAg, and HBeAb. Serology testing to be completed at the Central Laboratory. Local laboratory Hep D result can be used to assess subject eligibility if central laboratory result not available in time. For Child Pugh B Cohort and Cabozantinib Combination Cohort, local laboratory HBV or/and HCV results can be used to assess subject eligibility if central laboratory result not available in time.
Pregnancy test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within [redacted] of first dose of study therapy
SNP/ HLA Sample	X	
Urinary analysis	X	For Cabozantinib Combination Cohort only: urine protocol/creatinine ratio, UPCR must be calculated. If UPCR ≥ 1.0, obtain [redacted] urine protein to check subject eligibility.
Coagulation profile	X	Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead
Efficacy Assessments		
Baseline tumor imaging assessment	X	• CT or MRI of the chest, abdomen and pelvis with IV contrast, including required tri-phasic evaluation of the liver. • MRI is acceptable if CT is contraindicated. • Modality (CT or MRI) used at baseline should be used across all imaging timepoints, if possible. • Bone scan is required if clinically indicated. • MRI brain for subjects with a history of brain metastasis.

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Table 5.1-3:	**Screening Procedural Outline for Nivolumab plus Ipilimumab Combination Cohort, [redacted]**	
Procedure	**Pre-Treatment Visit (Baseline)**	**Notes**
		Baseline tumor imaging assessment should be performed [redacted] prior to first dose.
Other Assessments		
Tumor tissue sample (biopsy)	X	A formalin-fixed, paraffin-embedded tumor tissue (FFPET) block (preferred) or a minimum of 15 unstained slides of tumor tissue (archival or recent) for biomarker evaluation will be obtained prior to subject randomization/treatment assignment. Central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to subject randomization/treatment assignment. The tissue submitted will be assessed for quality with an H &E stain (100 tumor cells) and only those subjects who have meet tissue quality thresholds can be randomized. Subjects whose tissue fails the initial quality assessment can be screen failed and re-enrolled if they consent/agree to a new biopsy.
Clinical Drug Supplies		
Register subject in IVRS	X	A call must be made to the IVRS to register subject after signing informed consent. Central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to subject randomization/treatment assignment.

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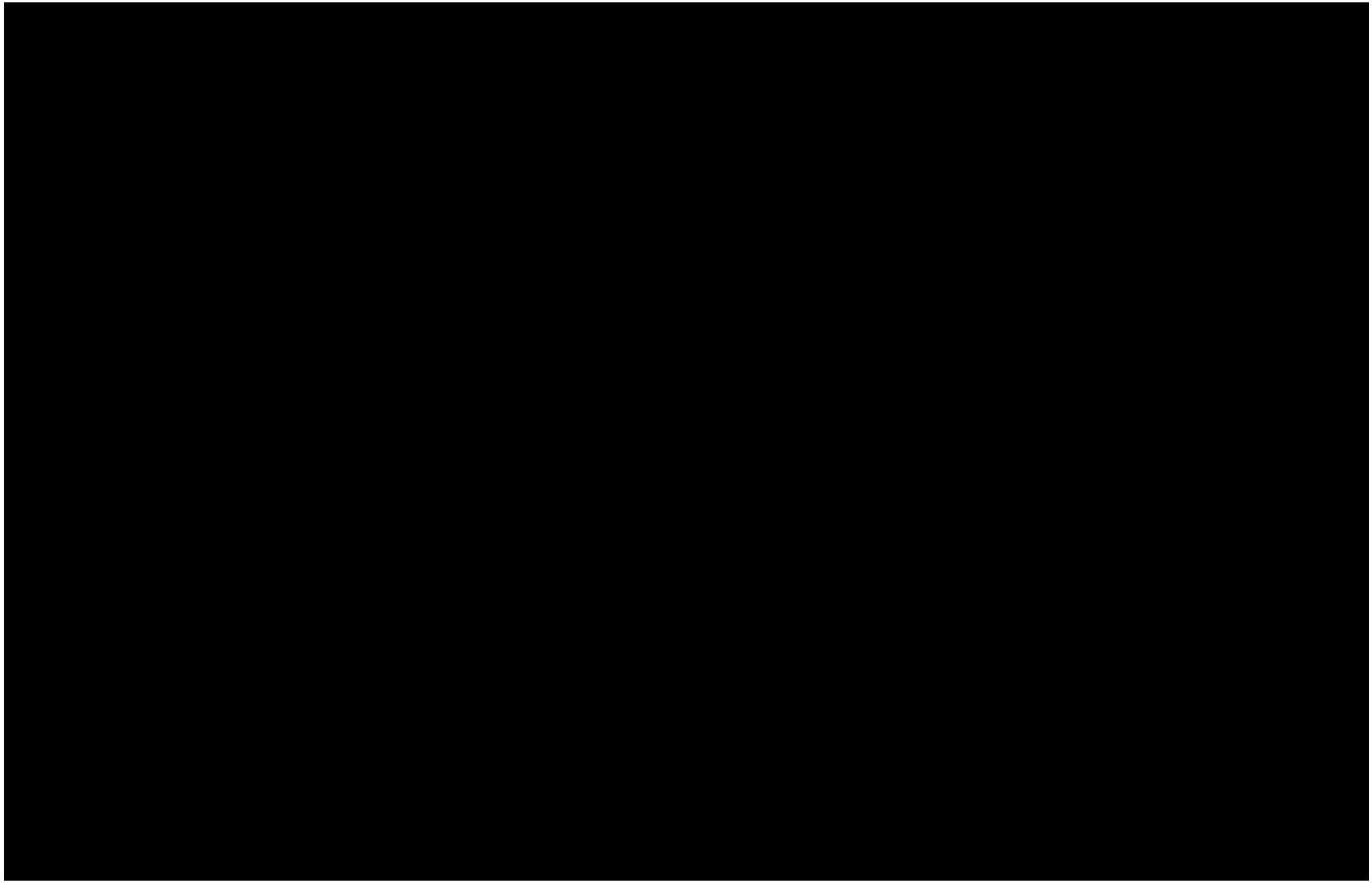

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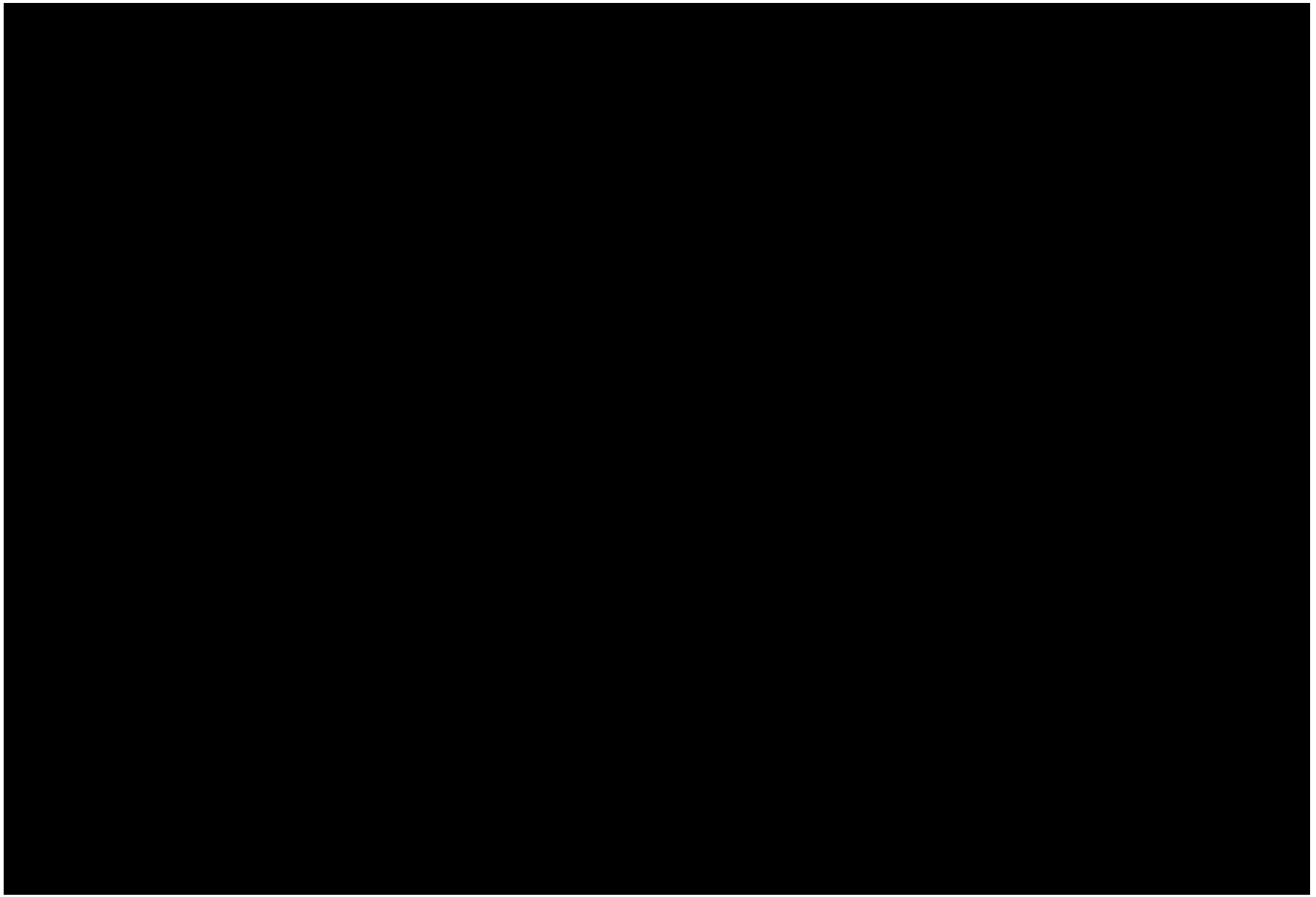

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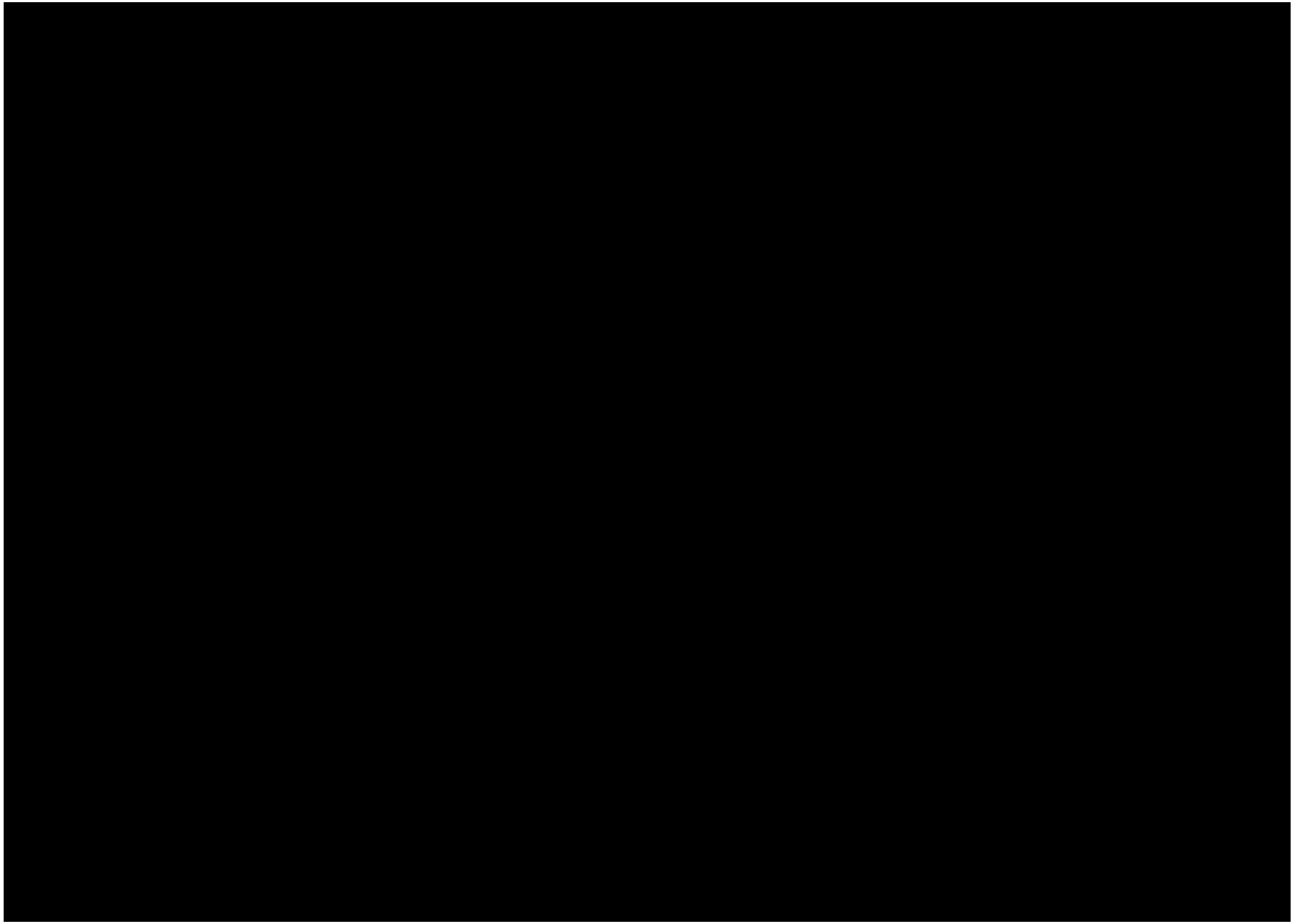

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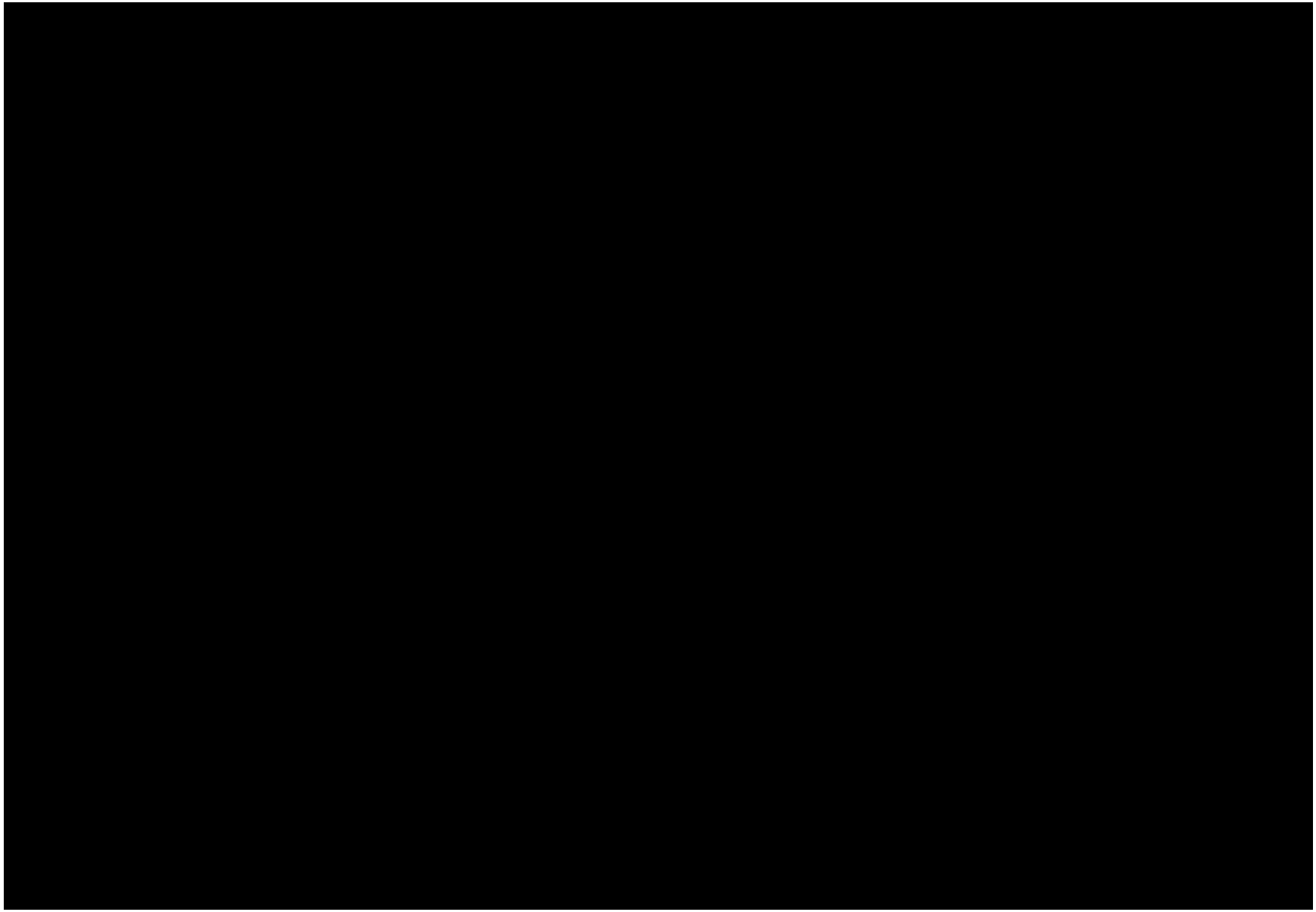

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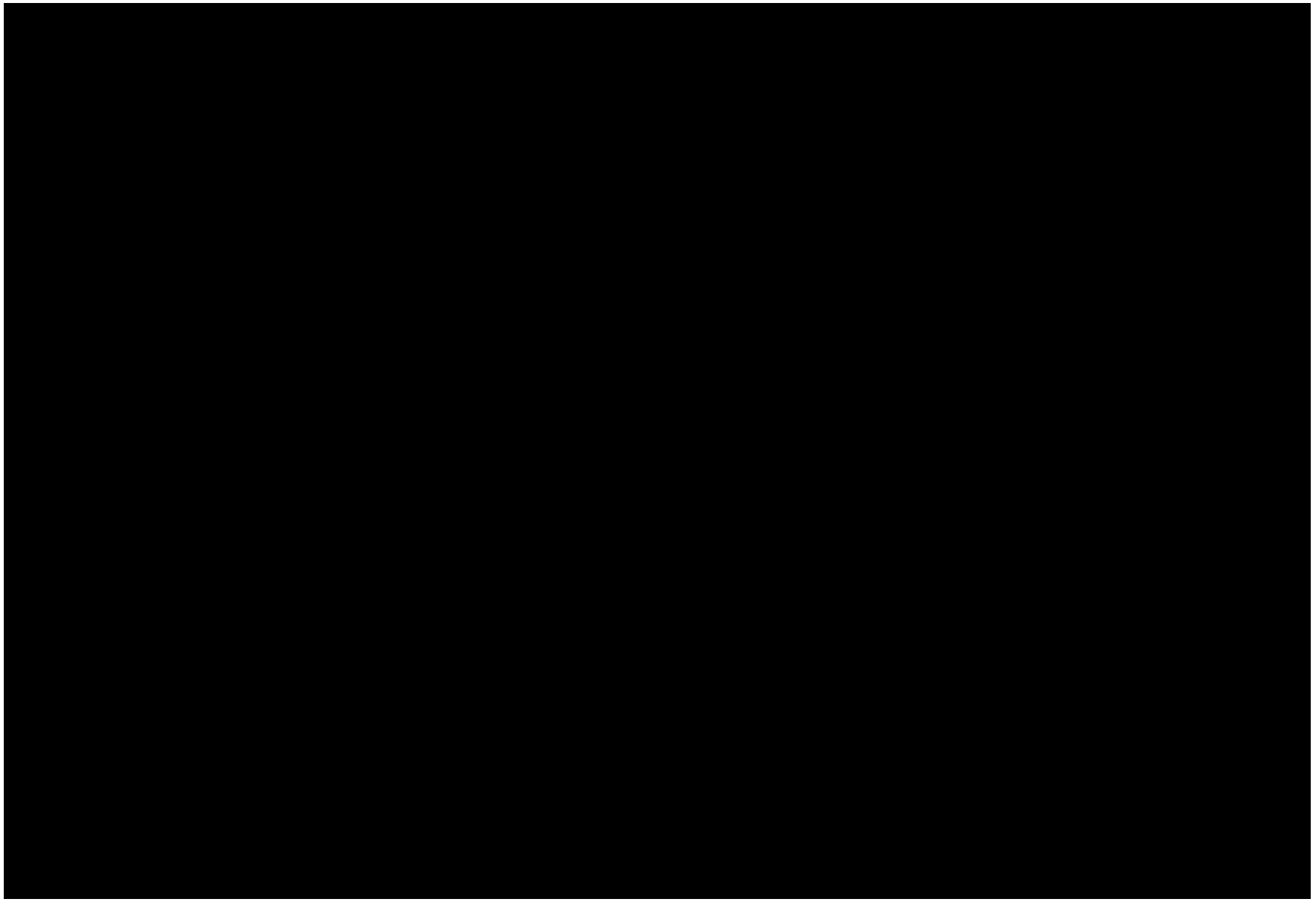

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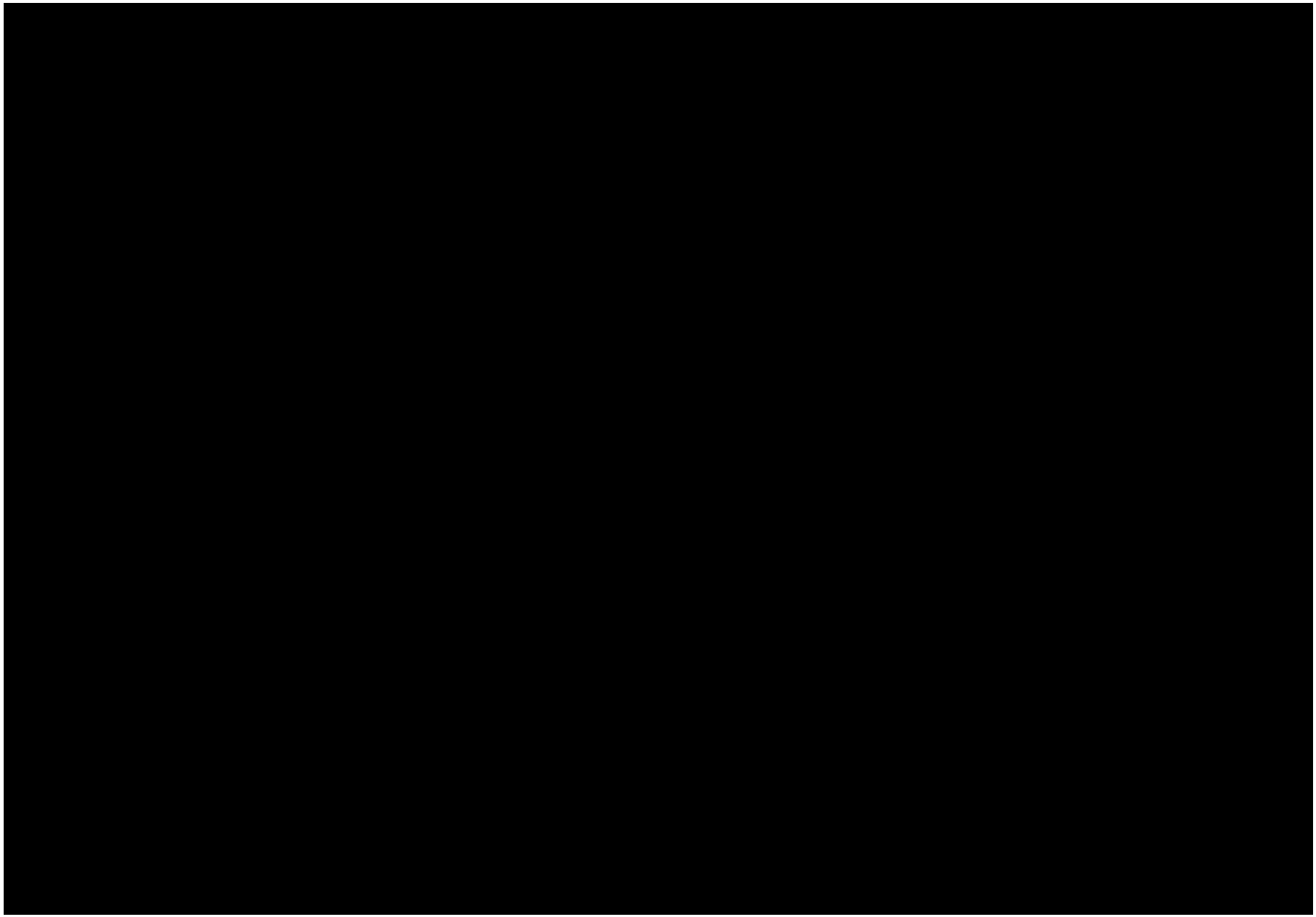

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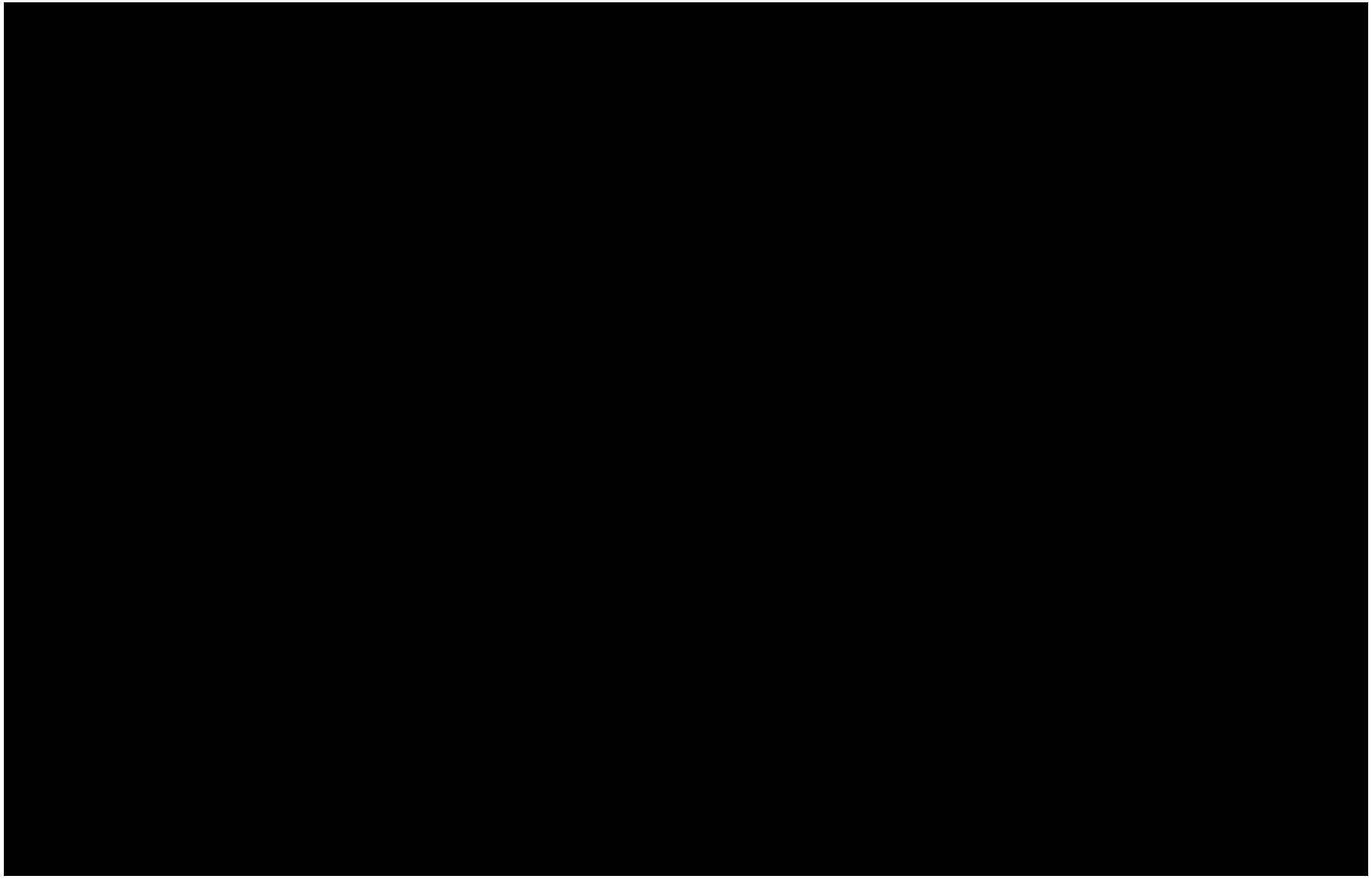

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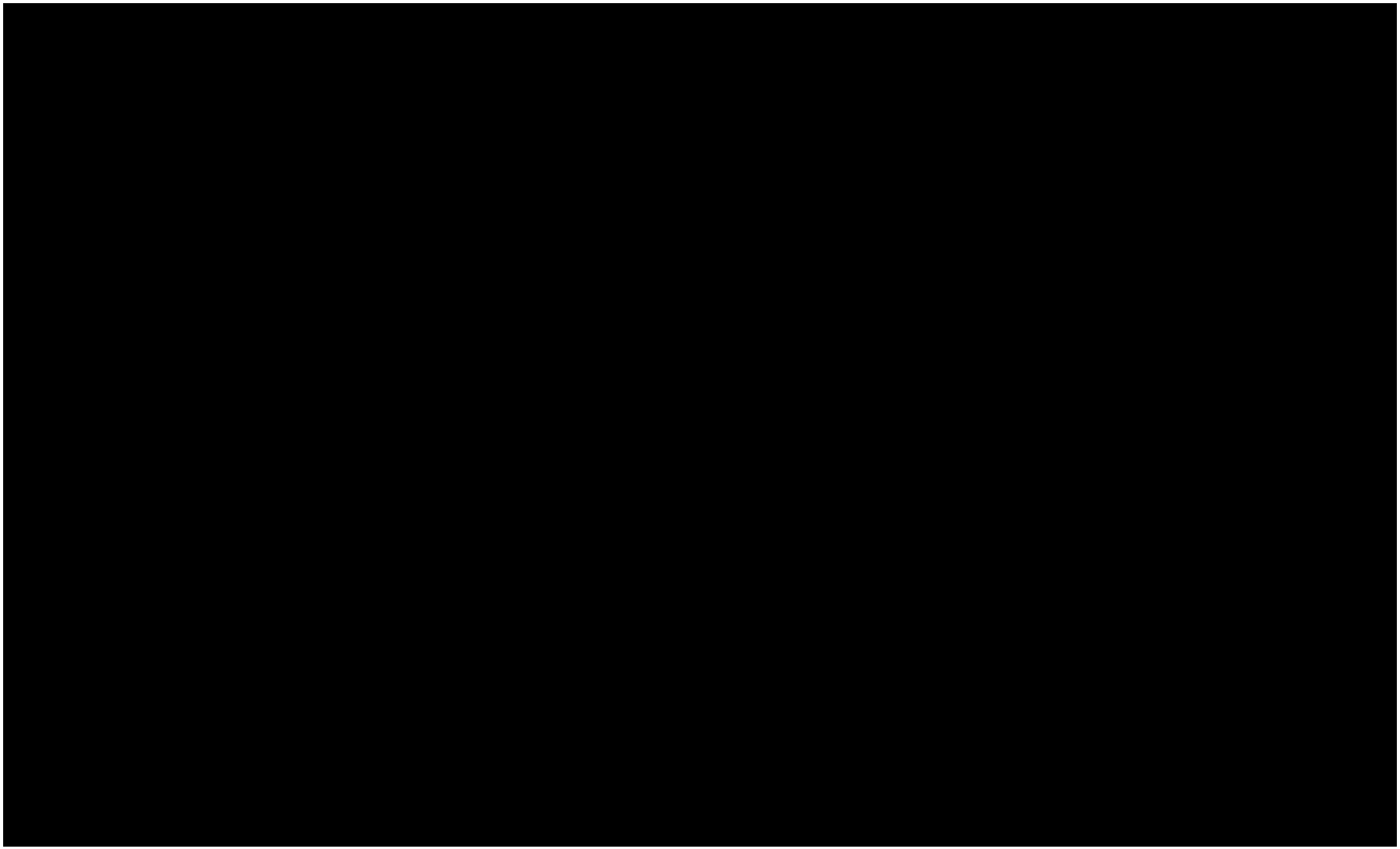

Table 5.1-7: On treatment Period Procedural Outline - Nivolumab plus Ipilimumab Combination Cohort			
Procedure	**During Treatment Arms A and B**	**During Treatment Arm C**	**Notes**
Safety Assessments			
Targeted Physical examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Skin
Physical Measurements	X	X	Weight and ECOG performance status within [redacted] prior to dosing.
Child-Pugh Score	X	X	
Vital Signs	X	X	Including BP, HR, temperature, and respiratory rate. Obtain vital signs within [redacted] prior to dosing.
Adverse Events Assessment	X	X	
Review of Concomitant Medication	X	X	
Laboratory Tests	X		Performed locally [redacted] prior to re-dosing to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase. In addition, the following tests at Week [redacted], then every [redacted] weeks (3 cycles of nivolumab monotherapy) thereafter: glucose, TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available).

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Table 5.1-7: On treatment Period Procedural Outline - Nivolumab plus Ipilimumab Combination Cohort			
Procedure	**During Treatment Arms A and B**	**During Treatment Arm C**	**Notes**
Laboratory Tests		X	Performed locally [redacted] prior to re-dosing to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase. In addition, the following tests every third cycle of nivolumab (3, 6, 9, etc.): glucose, TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available)
Viral biomarkers (for HCV and HBV infected subjects)	X		For HCV infected--HCV RNA at Week [redacted], and then every [redacted] weeks on nivolumab monotherapy treatment For HBV infected--HBV DNA at Week [redacted], and then every [redacted] weeks on nivolumab monotherapy treatment Testing to be completed at the Central Laboratory.
Viral biomarkers (for HCV and HBV infected subjects)		X	For HCV infected--HCV RNA every [redacted] weeks on treatment For HBV infected--HBV DNA every [redacted] weeks on treatment Testing to be completed at the Central Laboratory.
Pregnancy test (WOCBP only)	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within [redacted] hours prior to first dose, and then at Week [redacted], and thereafter monthly regardless of dosing schedule
Pregnancy test (WOCBP only)		X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within [redacted] hours prior to first dose, and then monthly regardless of dosing schedule

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Table 5.1-7: On treatment Period Procedural Outline - Nivolumab plus Ipilimumab Combination Cohort			
Procedure	**During Treatment Arms A and B**	**During Treatment Arm C**	**Notes**
Coagulation profile	X	X	Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead.
Efficacy Assessments			
Tumor imaging assessment	See note	See note	Tumor imaging assessments will occur 6 weeks from the date of first dose, then every 6 weeks thereafter up to 48 weeks, then it will be every 12 weeks until radiographic progression or treatment is discontinued (whichever occurs later). • CT or MRI of the chest, abdomen and pelvis with IV contrast, including required tri-phasic evaluation of the liver. • MRI is acceptable if CT is contraindicated. • Modality (CT or MRI) used at baseline should be used across all imaging timepoints, if possible. • Bone scan is required if clinically indicated. • Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.
Other Assessments			
PK/IMG sampling	See note	See note	See Table 5.1-14 for Arms A and B, and Table 5.1-15 for Arm C.
Serum sample (soluble factors)	See note	See note	See Table 5.1-14 for Arms A and B, and Table 5.1-15 5or Arm C.

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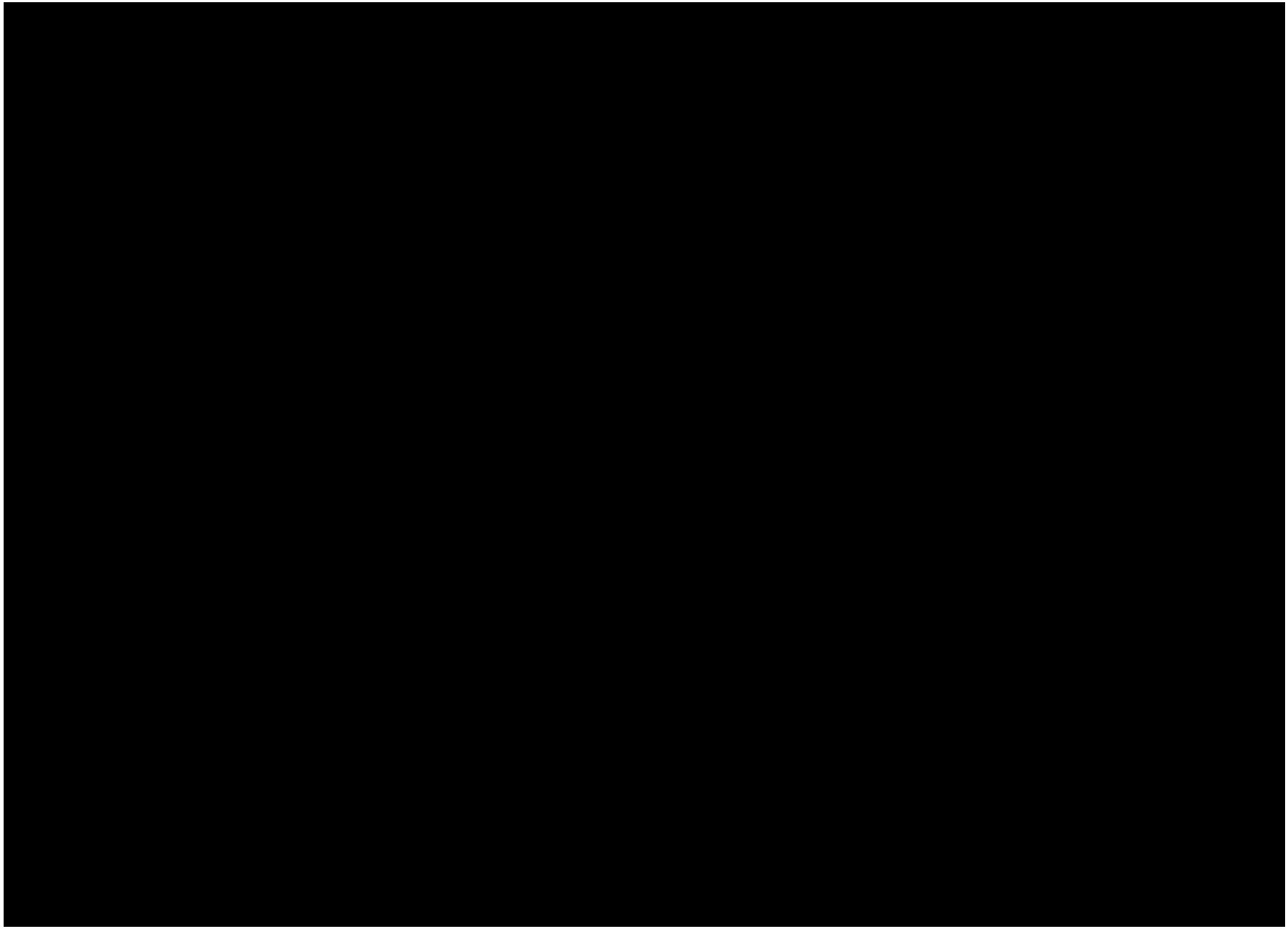
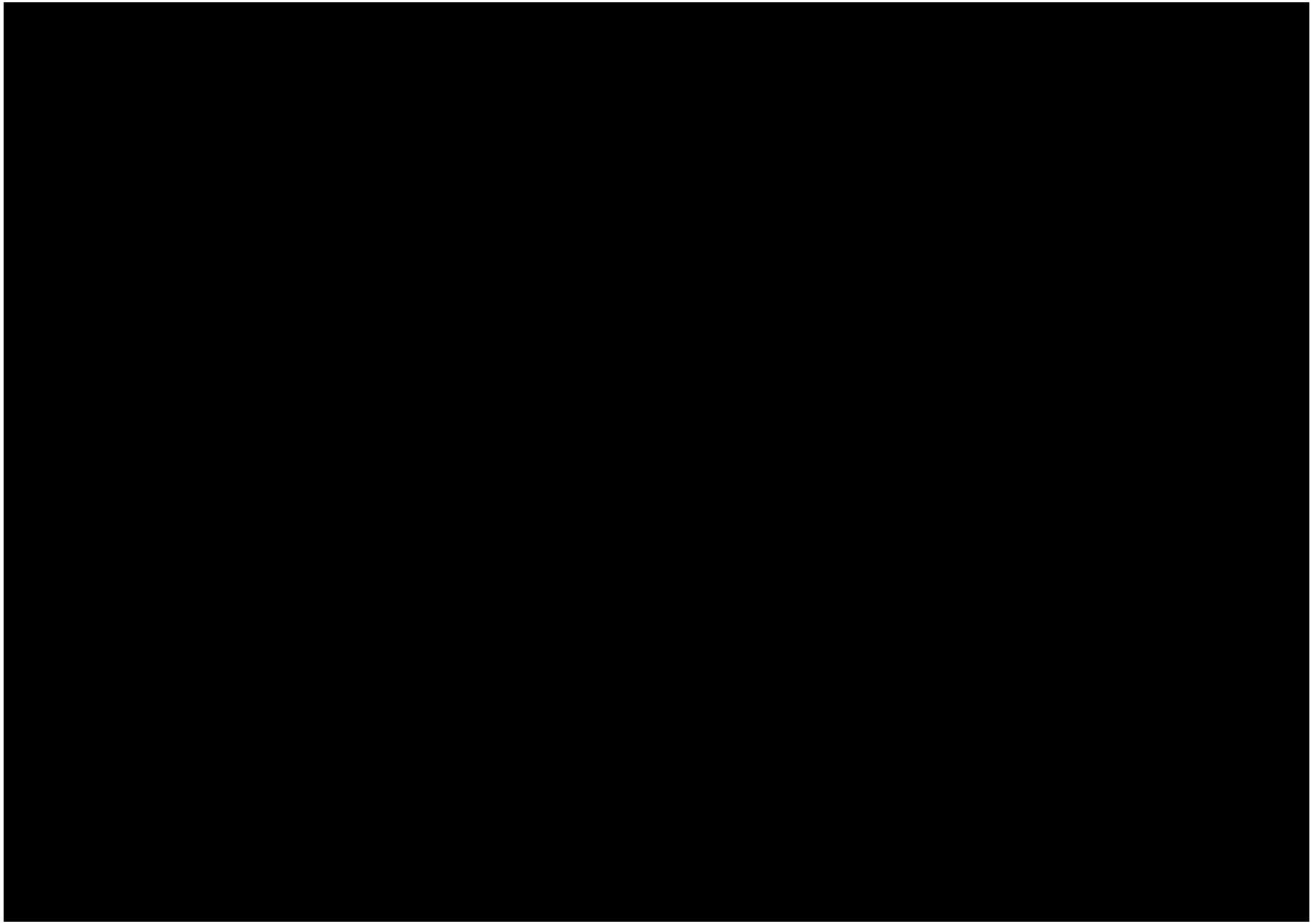
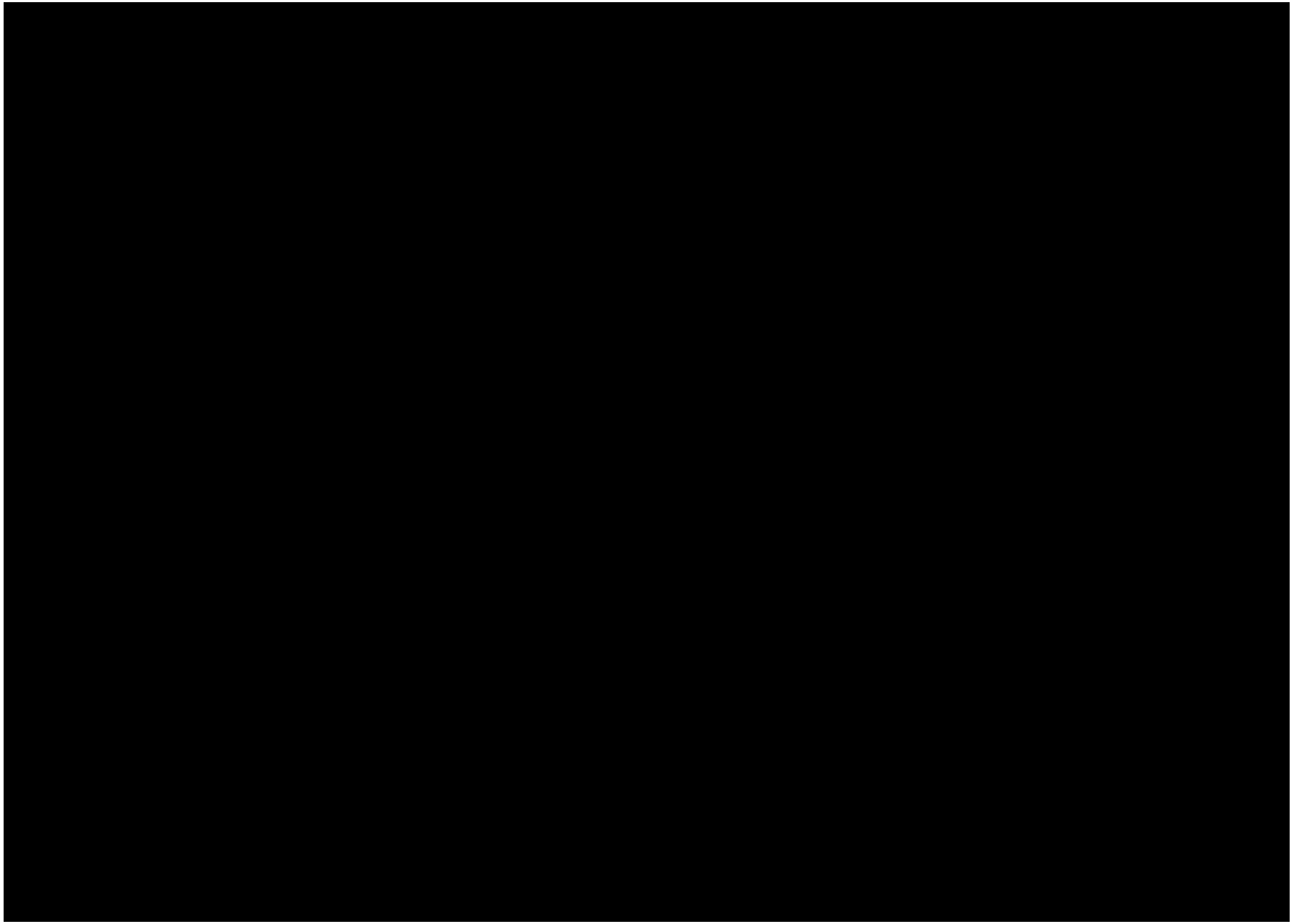
Table 5.1-7: On treatment Period Procedural Outline - Nivolumab plus Ipilimumab Combination Cohort			
Procedure	**During Treatment Arms A and B**	**During Treatment Arm C**	**Notes**
Outcomes Research Assessment			The EQ-5D should be administered at the start of the visit, before the subject sees the physician and before any study related procedures are done (with the exception of procedures completed 72 hours prior to visit).
EQ-5D-3L	See note	See note	For Arms A and B, to be completed at Week [redacted] and then every other visit thereafter. For Arm C, to be completed at Week [redacted] and then every other visit thereafter.
Clinical Drug Supplies			
Contact central randomization IVRS center	X	X	
Dispense Study Drug	X	X	Within [redacted] days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than [redacted] days between q3week doses in Arms A and B, and no less than [redacted] days for nivolumab monotherapy after completion of ipilimumab induction. In Arm C, subjects may be dosed no less than [redacted] days for nivolumab and [redacted] weeks for ipilimumab.







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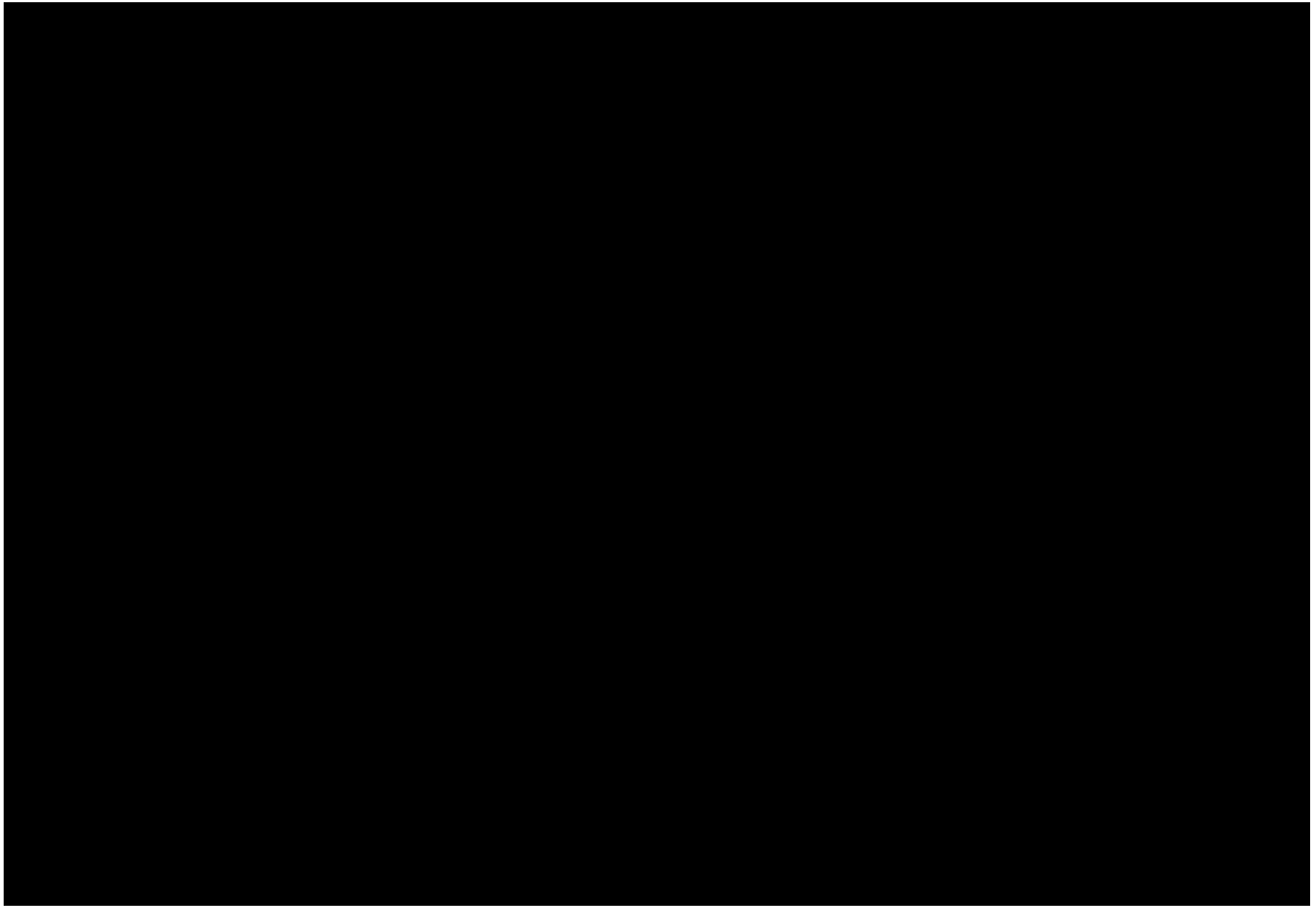

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Table 5.1-10: Follow-Up Procedural Outline - [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted]			
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical examination	X		Targeted examination must include at a minimum the following body systems: Cardiovascular, Gastrointestinal, Pulmonary, Skin
Adverse Events Assessment	X		
Review of Concomitant Medications	X		Subsequent cancer therapy
Vital Signs	X		Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes
Electrocardiogram (ECG)	See Note		ECG must be performed only for subjects in the Cabozantinib Combination Cohort. Fridericia corrected QT (QTcF) required. If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.
Laboratory Tests	X		CBC w/ differential and platelet count, LFTs - (ALT, AST, total bilirubin, alkaline phosphatase), Alpha fetoprotein (AFP), Alkaline Phosphatase (ALP), BUN or serum urea level, albumin, creatinine, Ca++, Mg++, Na+, K+, Cl-, LDH, Glucose, amylase, lipase, TSH - reflex testing (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available). To be done at FU1. To be repeated at FU2 if study related toxicity persists. For Cabozantinib Combination Cohort Only : Phosphorus will also be tested Urine protein and urine creatinine (for UPCR, preferred) or urine dipstick for protein
Viral biomarkers (for HCV and HBV infected subjects)	X		For HCV infected--HCV RNA For HBV infected--HBV DNA In addition, for HBV subjects in Child Pugh B Cohort, qHBsAg, qHBeAg, HBsAb, and HBeAb. Testing to be completed at the Central Laboratory

Table 5.1-10: Follow-Up Procedural Outline - [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted]			
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow Up Visits[b]**	**Notes**
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
Coagulation profile	X		Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead.
Efficacy Assessments			
Tumor imaging assessment	See note	See note	**Only for subjects without radiographic progression:** [redacted] For the other cohorts, tumor imaging assessments will occur 6 weeks from the randomization/treatment allocation, then every 6 weeks (± 2 days) thereafter up to 48 weeks, then it will be every 12 weeks (± 1 week) until radiographic progression. • CT or MRI of the chest, abdomen and pelvis with IV contrast, including required tri-phasic evaluation of the liver. • MRI is acceptable if CT is contraindicated. • Modality (CT or MRI) used at baseline should be used across all imaging timepoints, if possible. • Bone scan is required if clinically indicated. • Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.
Other Assessments			
PK/IMG sampling	X		[redacted] Table 5.1-14 and Table 5.1-15 for Nivolumab plus Ipilimumab Combination Cohort. See

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Table 5.1-10:	**Follow-Up Procedural Outline - [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted]**		
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow Up Visits[b]**	**Notes**
			[redacted]
Outcomes Research Assessment			
EQ-5D-3L	X	X	EQ-5D to be assessed during clinical visit (before the subject sees the physician and before any study related procedures are done) or via a phone for survival follow-up visits
[redacted]	X	X	[redacted]
[redacted]	X		[redacted]
Subject Status			
Survival Status		X	Additional survival and subsequent anti-cancer therapy collections, after completion of the On-site Follow-up visits 1 & 2 can occur by phone or visit approximately every 3 months.

[a] Subjects must be followed for at least 100 days after last dose of study therapy. Follow-up visit #1 (FU1) occurs 35 days (± 7 days) after last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose. Follow up visit #2 (FU2) occurs 80 days (± 7 days) after FU1.

[b] Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2.

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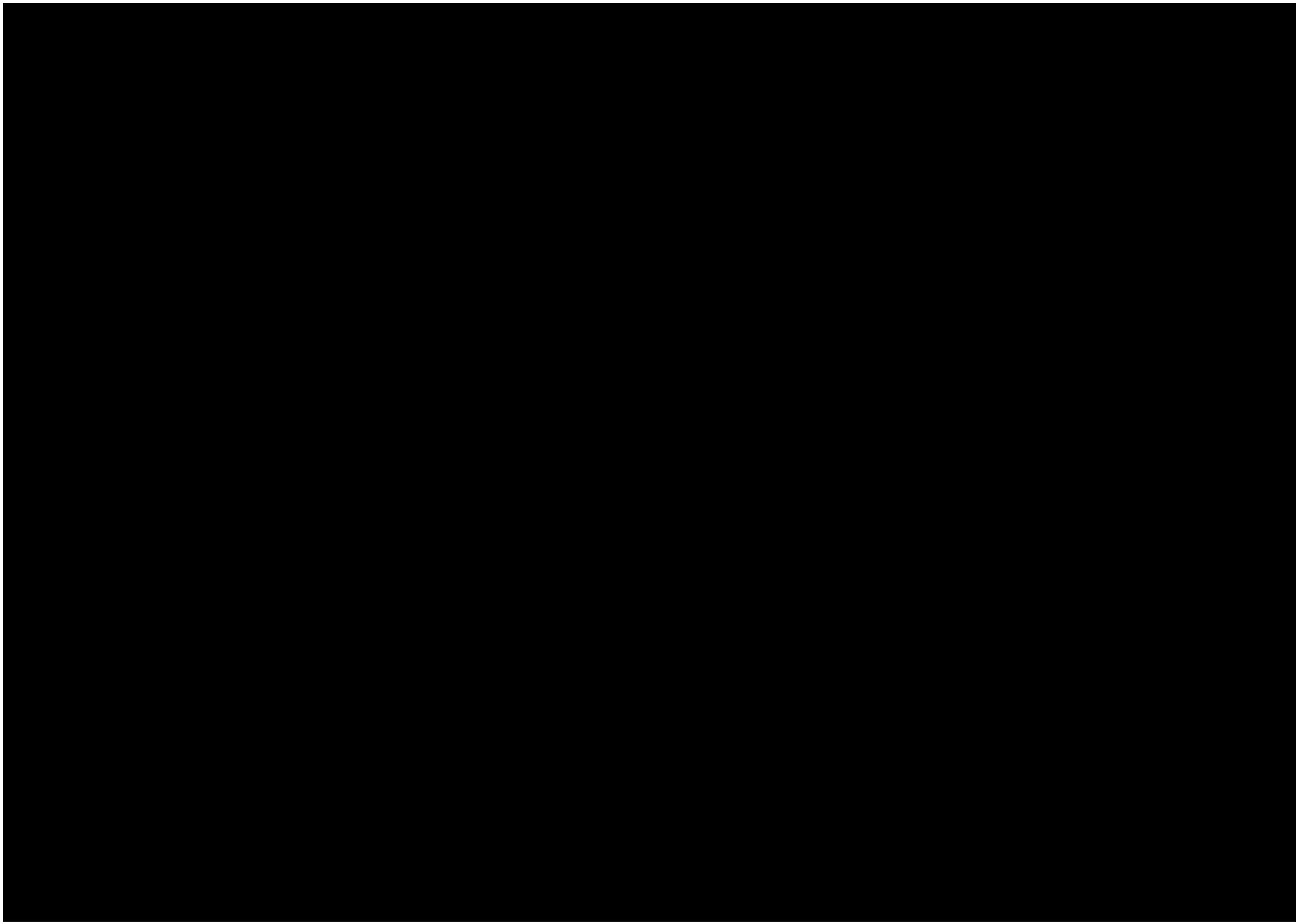

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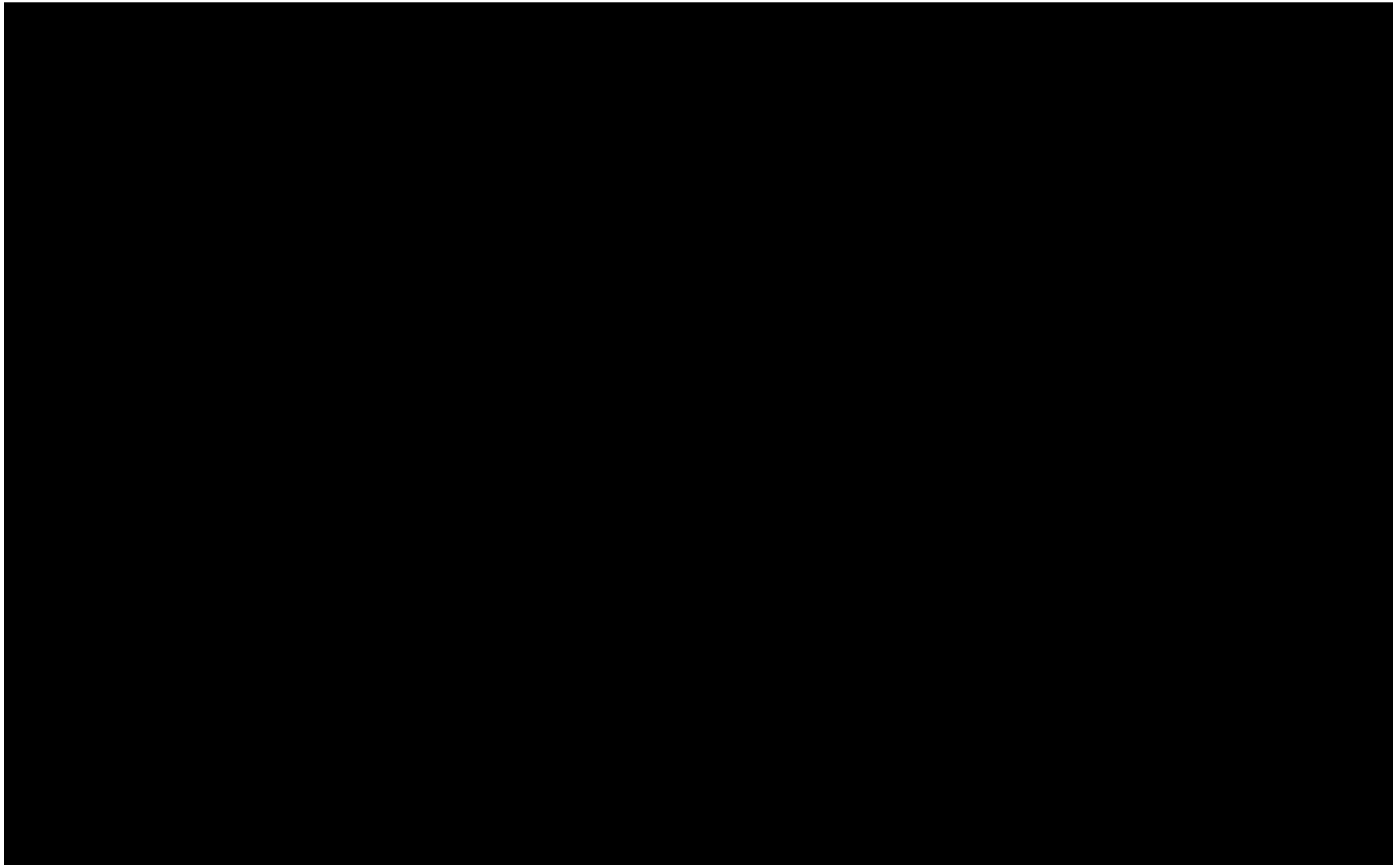

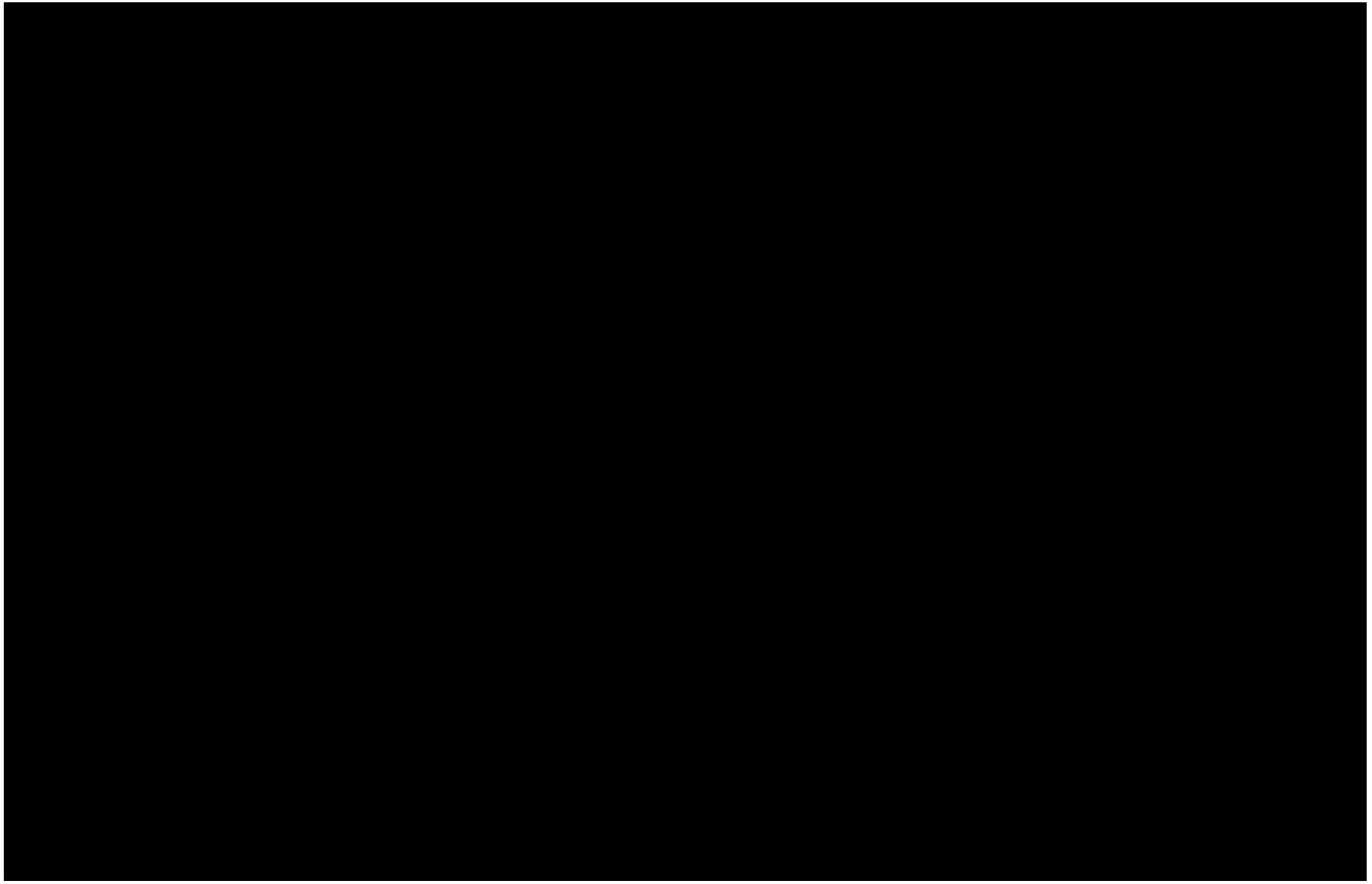

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Table 5.1-14: Pharmacokinetic and Pharmacodynamic Sampling Schedule for Subjects in the Nivolumab plus Ipilimumab Combination Cohort (Nivo 1/Ipi 3 or Nivo 3/Ipi 1) (Arms A and B)

Part[a]	Study Day 1[b] Cycle = 3 Weeks (Part A) 1 Cycle = 2 Weeks (Part B)	Time (Event Hours) Hour	Time (Relative To Dosing) Hour:Min[c]	PK Blood Sample for Nivo and Ipi	ADA Sample for Nivo and Ipi	SNP and HLA Type and DNA Sample	Tumor Biopsy	Serum (Soluble Factors)	Whole Blood RNA for Gene Exp. Analysis	PBMC for Antigen Specific Responses and Flow Cytometry	MDSC	HBV DNA or HCV RNA[d]
	Screening (Day -28 to Day [redacted] pre dose)					X	X (required archive or fresh)					X
A	Cycle 1 Day [redacted]	0 (predose)	00:00	X	X			X	X	X	X	X
A	Cycle 1 Day [redacted]	0 (predose)	00:00							X		
A	Cycle 2 Day [redacted]	0 (predose)	00:00	X	X			X	X	X		X
A	Cycle 3 Day [redacted]	0 (predose)	00:00	X	X			X	X	X		X
A	Cycle 4 Day [redacted]	0 (predose)	00:00					X	X	X		X
B	Cycle 5 Day [redacted] (Start of nivolumab monotherapy at Week 13)	0 (predose)	00:00	X	X					X	X	X

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Table 5.1-14: Pharmacokinetic and Pharmacodynamic Sampling Schedule for Subjects in the Nivolumab plus Ipilimumab Combination Cohort (Nivo 1/Ipi 3 or Nivo 3/Ipi 1) (Arms A and B)

Part[a]	Study Day 1[b] Cycle = 3 Weeks (Part A) 1 Cycle = 2 Weeks (Part B)	Time (Event Hours) Hour	Time (Relative To Dosing) Hour:Min[c]	PK Blood Sample for Nivo and Ipi	ADA Sample for Nivo and Ipi	SNP and HLA Type and DNA Sample	Tumor Biopsy	Serum (Soluble Factors)	Whole Blood RNA for Gene Exp. Analysis	PBMC for Antigen Specific Responses and Flow Cytometry	MDSC	HBV DNA or HCV RNA[d]
B	After Cycle 5 Day [redacted], Day [redacted] of every 3rd cycle thereafter	0 (predose)	00:00							X		
B	After Cycle 5 Day [redacted], Day [redacted] of every 8th cycle thereafter[b]	0 (predose)	00:00	X	X							
B	Cycle 7 Day [redacted] and every other cycle thereafter	0 (predose)	00:00									X
	Follow-up Visit 1 and 2			X	X							X

[a] Part A indicates first 12 weeks of treatment (nivolumab + ipilimumab dosing). Part B indicates nivolumab monotherapy period starting from Week 12.

[b] If a subject permanently discontinues both study drug treatments during the sampling period, they will move to sampling at the follow up visits. If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table. If nivolumab is discontinued and ipilimumab continues, nivolumab PK and ADA should be collected only for the next 2 time points (corresponding to ipilimumab sample collection) according to the PK table.

[c] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[d] Viral biomarkers to be collected for all subjects at screening. On treatment and during follow-up visits, only for HBV-infected subjects or HCV-infected subjects.

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Table 5.1-15: Pharmacokinetic and Pharmacodynamic Sampling Schedule for Subjects in the Nivolumab plus Ipilimumab Combination Cohort (Nivolumab 3 mg/kg q2week + Ipilimumab 1 mg/kg q6week) (Arm C)

Study Day[a] 1 Cycle = 2 weeks (nivolumab)	Time (Event Hours) Hour	Time (Relative To Dosing) Hour:Min[b]	PK Blood Sample for Nivolumab and Ipilimumab	ADA Sample for Nivolumab and Ipilimumab	SNP and HLA Type and DNA Sample	Tumor Biopsy	Serum (Soluble Factors)	Whole Blood RNA for Gene Exp. Analysis	PBMC for Antigen Specific Responses and Flow Cytometry	MDSC	HBV DNA or HCV RNA
Screening (Day -28 to Day [redacted] pre dose)	0 (predose)	00:00			X	X (required archive or fresh)					X
Cycle 1 Day [redacted]	0 (predose)	00:00	X	X			X	X	X	X	X
Cycle 1 Day [redacted]	0 (predose)	00:00							X		
Cycle 2 Day [redacted]	0 (predose)	00:00					X				
Cycle 3 Day [redacted]	0 (predose)	00:00					X	X	X		X
Cycle 4 Day [redacted]	0 (predose)	00:00	X	X			X				
Cycle 5 Day [redacted] and every other cycle thereafter	0 (predose)	00:00									X
Cycle 6 Day [redacted]	0 (predose)	00:00						X			

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Table 5.1-15: Pharmacokinetic and Pharmacodynamic Sampling Schedule for Subjects in the Nivolumab plus Ipilimumab Combination Cohort (Nivolumab 3 mg/kg q2week + Ipilimumab 1 mg/kg q6week) (Arm C)

Study Day[a] 1 Cycle = 2 weeks (nivolumab)	Time (Event Hours) Hour	Time (Relative To Dosing) Hour:Min[b]	PK Blood Sample for Nivolumab and Ipilimumab	ADA Sample for Nivolumab and Ipilimumab	SNP and HLA Type and DNA Sample	Tumor Biopsy	Serum (Soluble Factors)	Whole Blood RNA for Gene Exp. Analysis	PBMC for Antigen Specific Responses and Flow Cytometry	MDSC	HBV DNA or HCV RNA
Cycle 6 Day [redacted] and every 3rd cycle thereafter	0 (predose)	00:00							X		
Cycle 7 Day [redacted]	0 (predose)	00:00								X	
Cycle 10 Day [redacted]	0 (predose)	00:00	X	X							
After Cycle 10 Day [redacted], Day [redacted] of every 9th cycle thereafter	0 (predose)	00:00	X	X							
Follow-up Visit 1 and 2			X	X							X

[a] If a subject permanently discontinues both study drug treatments during the sampling period, they will move to sampling at the follow up visits. If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table. If nivolumab is discontinued and ipilimumab continues, nivolumab PK and ADA should be collected only for the next 2 time points (corresponding to ipilimumab sample collection) according to the PK table.

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

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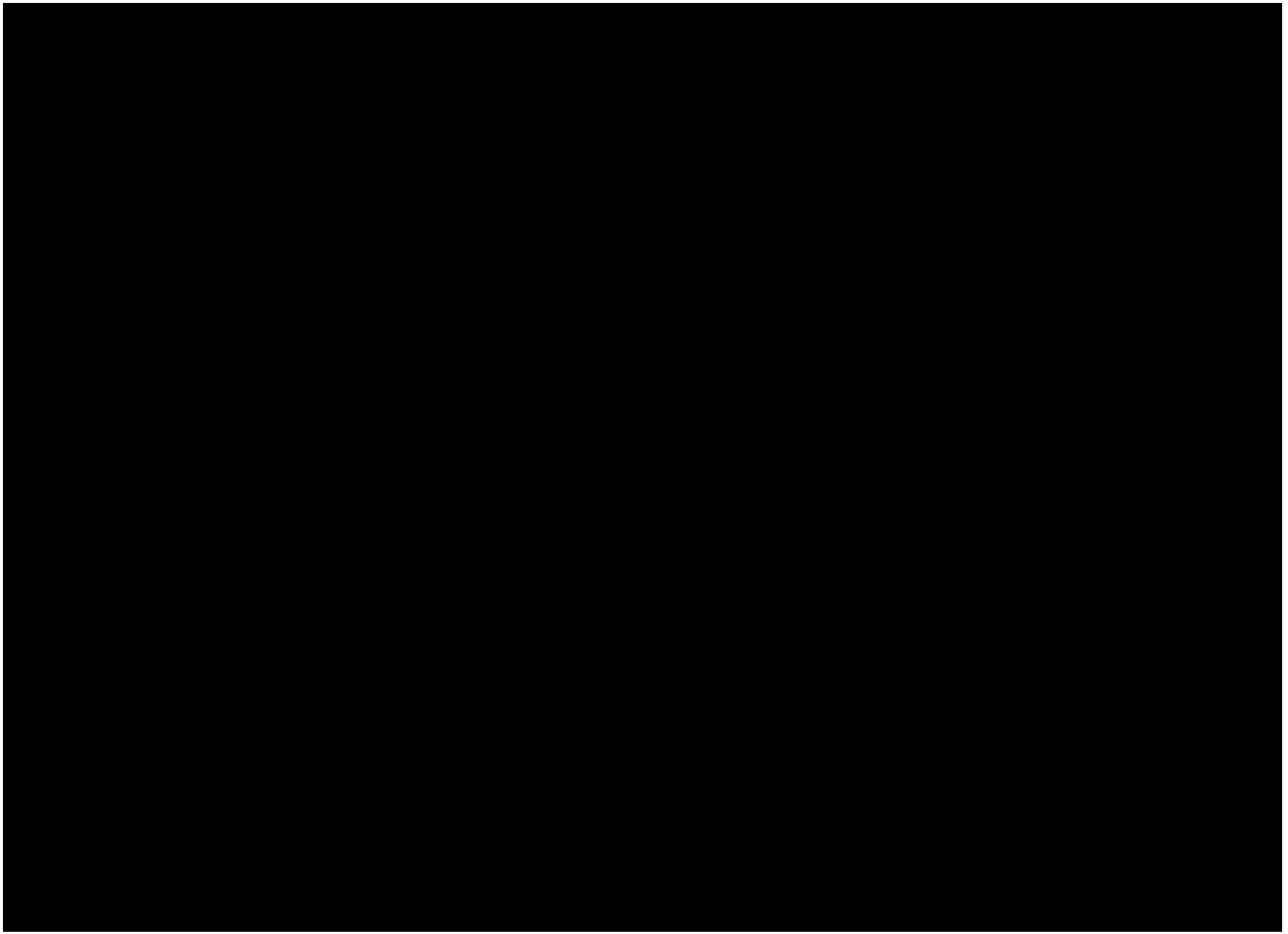

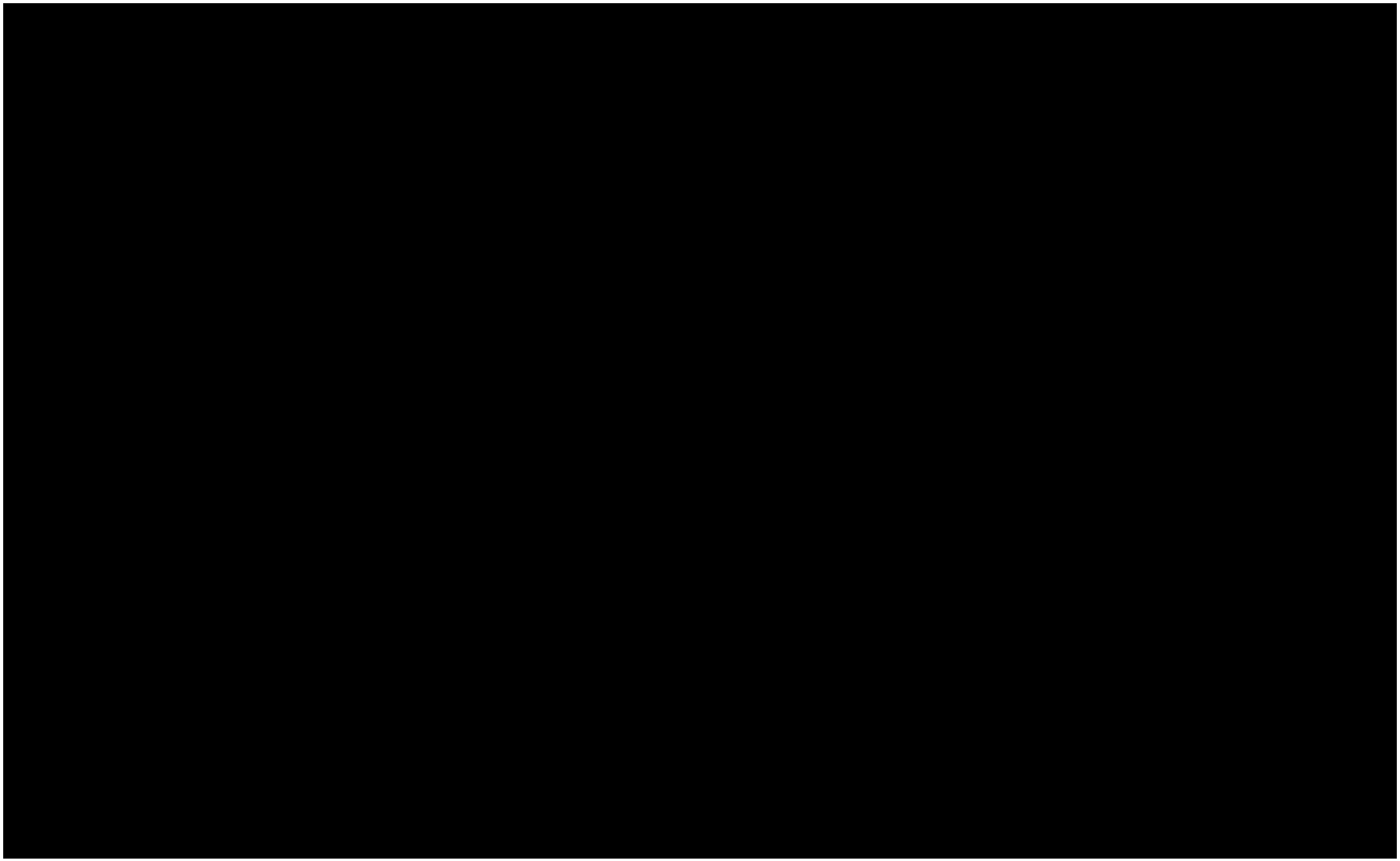

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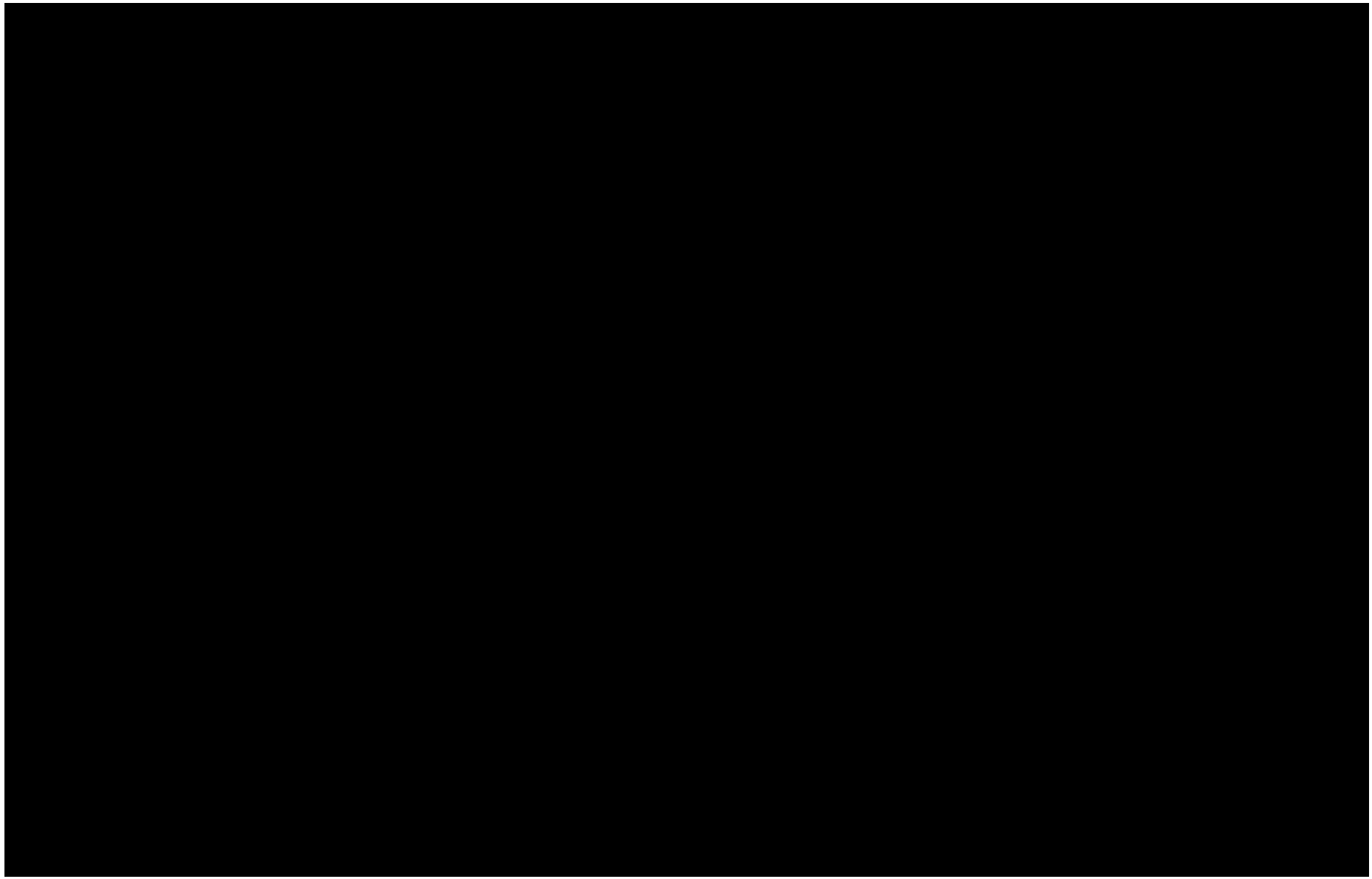

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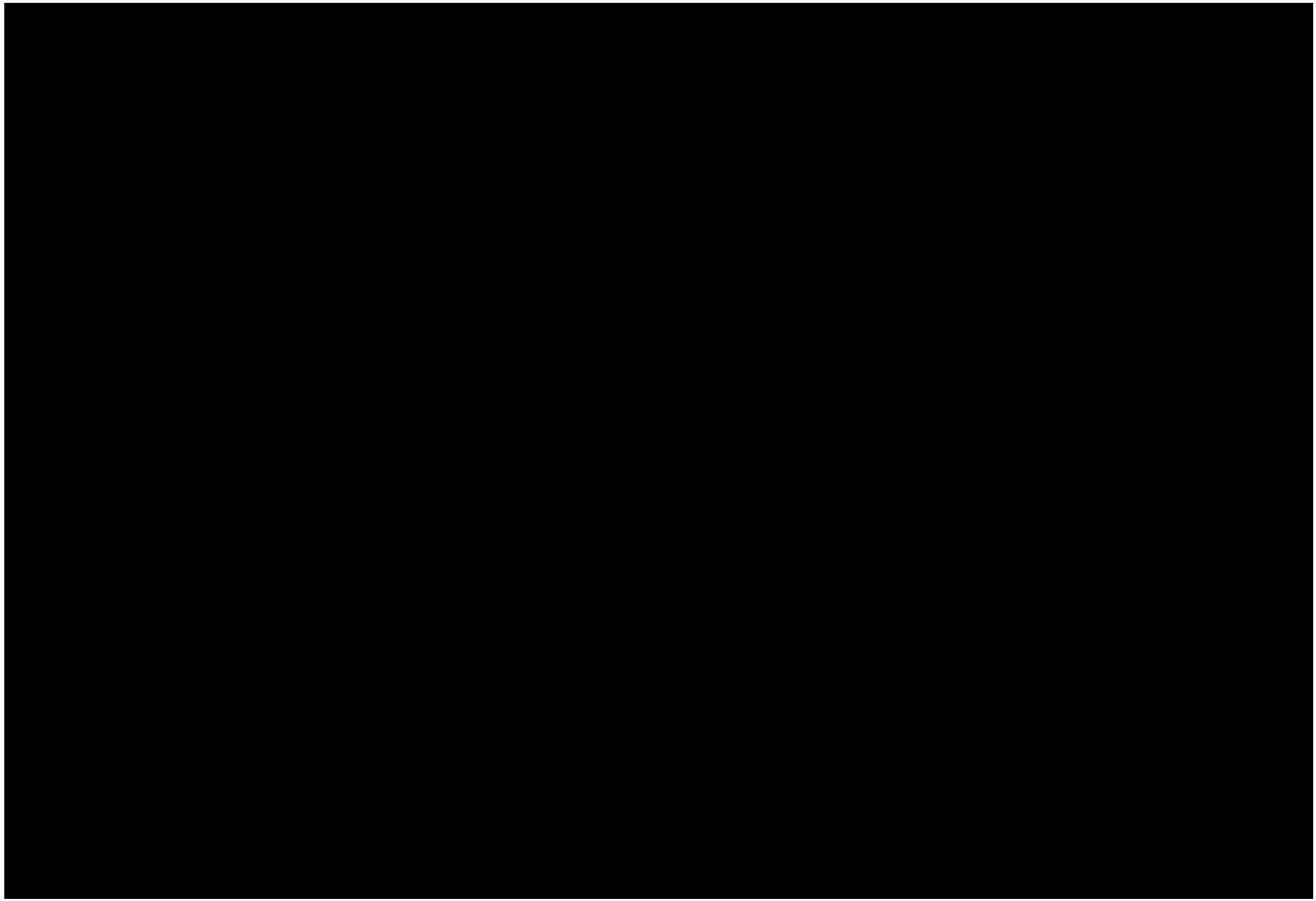

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5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests, pulse oximetry, etc.). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support (ACLS) cart will be immediately available on the premises. The site will have, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The EQ-5D-3L and The FACT-Hep paper questionnaire will be provided by BMS.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), investigator brochures for nivolumab, ipilimumab [redacted], pharmacy manual with drug preparation instructions, NCI CTCAE version 4.0, CA209040 imaging manual, central lab manual with kits for the collection of blood and tissue samples, IVRS registration instructions, pregnancy surveillance forms and manual for entry of local laboratory data. Case report forms (electronic) will be provided by BMS.

5.3 Safety Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the sponsor.

Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be evaluated according to the NCI CTCAE Version 4.0 dated 14-Jun-2010. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Safety will be monitored on an ongoing basis.

At baseline (all subjects), a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include Physical Examination, height, weight, ECOG performance status, BP, HR, temperature, respiratory rate, ECG, safety labs, and should be performed as described in Table 5.1-1, Table 5.1-2, and Table 5.1-3 notes.

- If screening labs are drawn within 4 days of first treatment then these labs will also qualify as Day 1 (pre-dose) labs.
- If the screening PE is performed within 96 hrs of dosing on Day 1 then a single exam may count as both the screening and pre-first dose evaluation.
- Pregnancy testing (serum or urine) for WOCBP must be done within 24 hrs prior to first dose of cycle 1, and then every 4 weeks (± 1 week) regardless of dosing schedule.
- [redacted]

- ECGs must be done prior to dosing.
- Chest X-Ray may be performed on-treatment as clinically indicated.
- In addition there will be 2 follow-up visits within 100 days after last dose of study therapy (Follow-Up visits 1 and 2). Those follow-up visits will include targeted physical examination, weight, ECOG performance status, vital signs, safety labs and Child-Pugh score.

5.4 Efficacy Assessments

All subjects [redacted] will undergo tumor assessments at every q6 week (± 2 days) for the first 48 weeks, and then q12 week (± 1 week) thereafter until disease progression. [redacted]

Imaging assessments should be scheduled regardless of dose delay or missed doses in all cohorts.

Images will be submitted to a central reading lab for review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209040 Imaging Manual to be provided by the central vendor.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Disease evaluation with computed tomography (CT) scans of the chest, abdomen, and pelvis, including (contrast-enhanced) **triphasic CT** of the abdomen will be performed at baseline, then prior to each cycle [redacted] for 1 year, and then prior to every other cycle thereafter until disease progression. Triphasic CT is acquired with 2.5-mm (preferred) - 5-mm contiguous axial slices.

Should a subject have a contraindication for IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of < 5 mm with no gap (contiguous). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

The original protocol provided for the assessment of tumor response to be based on RECIST modified for HCC (mRECIST) (Appendix 5). This instrument was developed in 2008 by the American Association for the Study of Liver Diseases (AASLD) to provide a common framework for the design of clinical trials in HCC and adapted the concept of viable tumor - tumoral tissue showing uptake in arterial phase of contrast enhanced radiologic imaging techniques.[130] In recent years, the validity of mRECIST for tumor response assessment in HCC has been challenged. Guidelines are not unanimous in their support of mRECIST for HCC.[131,132,133] To date, mRECIST for HCC has not been prospectively validated. Furthermore, the instrument was developed for the assessment of locoregional therapy and subsequently extrapolated for use in anti-angiogenic therapy. Its utility for assessing tumor response to

immunooncology therapies has not been tested. In addition, mRECIST for HCC is relevant only for the assessment of liver tumors. In advanced HCC, the target lesions may be metastatic lesions outside the liver. Such lesions are not amenable for assessment by mRECIST for HCC.

The protocol is therefore being revised in Amendment 4 to provide for tumor response assessment by RECIST 1.1 (Appendix 2).[134] The latter is well established for tumor response assessment and provides for a more conservative estimation of response than mRECIST for HCC. This will also permit comparison of the CA209040 data with pivotal HCC trials, eg, sorafenib SHARP trial.

If a non-target lesion is managed with local treatment such as radiotherapy or surgery, that lesion will not be counted in the radiologic response assessment.

For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later. Responders are the subjects with BOR of confirmed CR or confirmed PR. In the case of stable disease (SD), measurements must have met the SD criteria [redacted] at least once after first dose of study medication at a minimum of approximately 6 weeks for other cohorts.

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetics: Collection and Processing

[redacted] Table 5.1-14 (Nivolumab plus Ipilimumab Combination Cohort - Arms A), Table 5.1-15 (Nivolumab plus Ipilimumab Combination Cohort - Arm C) [redacted] list the sampling schedule to be followed for the assessment of both nivolumab and ipilimumab pharmacokinetics. [redacted] Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration, and end-of-infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). If the infusion was interrupted, the reason for interruption should also be documented on the CRF. Blood samples will be processed to collect serum [redacted]. The serum samples will be analyzed for nivolumab by validated methods. Further details of blood collection, labeling, processing, storage and shipping will be provided to the site in the procedure manual.

5.5.2 Pharmacokinetic Sample Analyses

Blood samples will be analyzed for nivolumab, ipilimumab [redacted] by validated assays.

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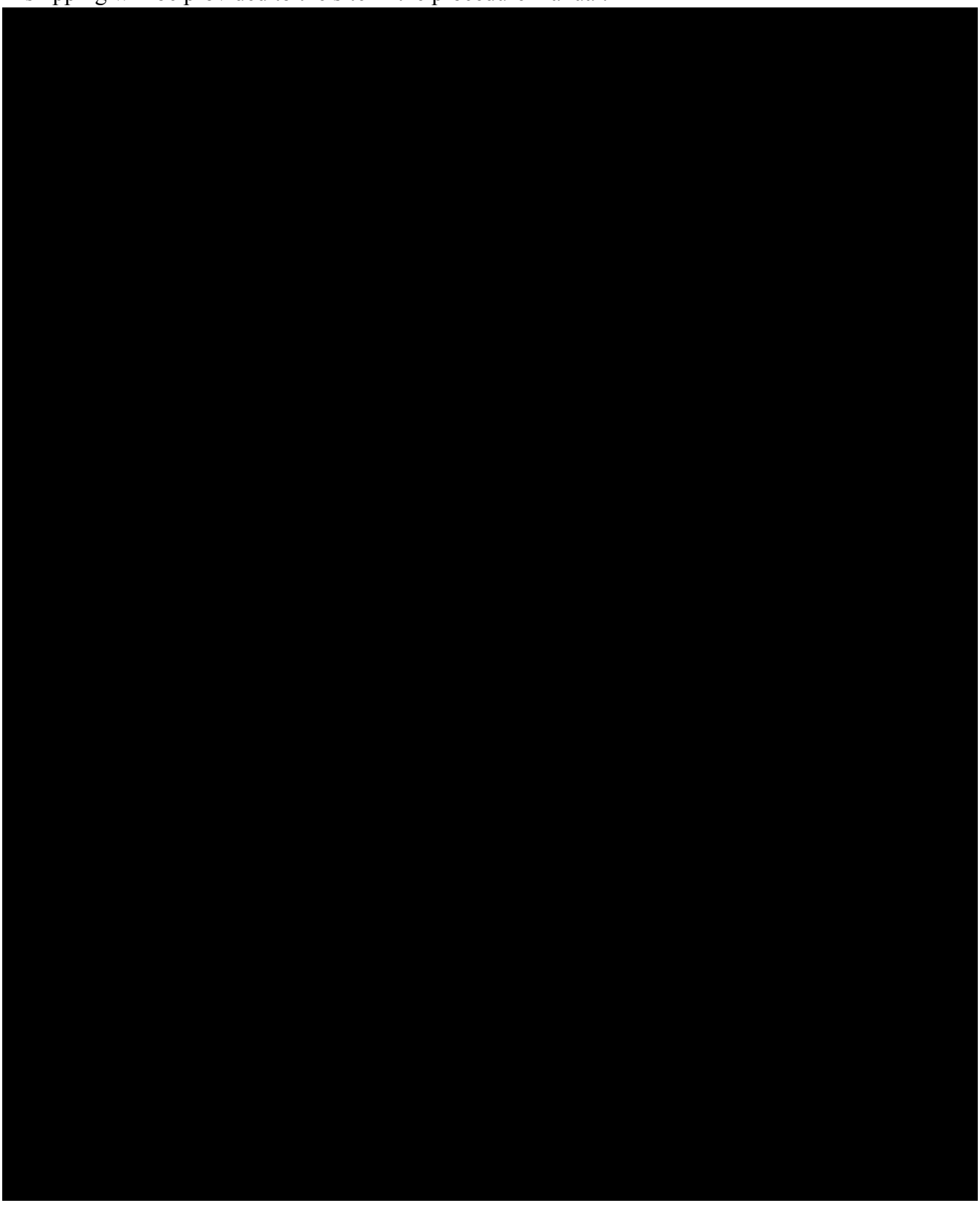
5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.



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5.7 Outcomes Research Assessments

Subjects will be asked to complete the EQ-5D-3L (Appendix 9) in the [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted] These will be completed before any clinical activities are performed during on-study clinic visits and at designated visits during the follow-up phase. The questionnaires will be provided in the subject's preferred language and may be administered by telephone during the follow-up phase. A standardized script will be used to facilitate telephone administration of the EQ-5D. A similar script does not exist for the FACT-Hep, though subjects will be provided with a hard copy of the FACT-Hep to take home and use as a visual aid during telephone interviews. Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-7, Table 5.1-9, Table 5.1-8, Table 5.1-10 and provide information regarding the timing of outcomes research assessments using the EQ-5D and FACT-Hep.

Subjects' reports of general health status will be measured using the EQ-5D-3L (Appendix 9) in [redacted] the Nivolumab plus Ipilimumab Combination Cohort, [redacted]
These data will be collected to assess the impact of nivolumab on generic health-related quality of life and may be used to inform future economic evaluations of nivolumab for the treatment of HCC.

The EQ-5D is a standardized instrument used to measure self-reports of general health status. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at Level 1, while a dimension for which there are extreme problems is said to be at Level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes the EQ-VAS, which allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

[redacted]

5.8 Other Assessments

5.8.1 Immunogenicity Assessment

Blood samples for nivolumab immunogenicity analysis will be collected from all subjects at time points specified in Table 5.1-11, Table 5.1-12, Table 5.1-13, Table 5.1-16 and Table 5.1-17. Blood samples for ipilimumab immunogenicity analysis will be collected from all subjects in the combination cohort at time points specified in Table 5.1-14, Table 5.1-15 and Table 5.1-17. Serum will be analyzed by validated immunogenicity assays. All on-treatment immunogenicity sampling time-points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the sampling should be adjusted accordingly. Selected serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AEs).

5.9 Results of Central Assessments

Site will be informed of quality issues or needs for repeat scanning via queries from the corelab. Results of Central Imaging analysis through the BICR will not be returned to the site.

6. ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs.

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the nivolumab and ipilimumab Investigator Brochure (IB), [redacted] represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. Subjects who are randomized and never treated, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the events and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

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6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details). An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

6.6 Potential Drug Induced Liver Injury (DILI)

Potential drug induced liver injury for this study was initially defined as:

Hepatotoxicity as evidenced by any of the following:

- AST or ALT > 10 x ULN for > 2 weeks,
- AST or ALT > 15 x ULN irrespective of duration,
- T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated total bilirubin at study entry or > 5 x ULN for those with normal total bilirubin at entry,
- Clinical deterioration manifested by drug-related hepatic decompensation not identified above.

Upon activation of amendment 8, the DILI definition listed above will no longer be used in CA209040, and a new definition will be utilized. The rationale for updating DILI language as follows:

- Standardization of the DILI definition so that a unified approach is taken across the BMS HCC program.
- Concern that the previous language may not be sensitive to capture all potential cases given the lack of a requirement for a concomitant elevation in transaminases and bilirubin, and the significant increase in total bilirubin regardless of baseline value.
- Alignment with the Daclatasvir DAA program which has criteria that have been developed after consultation with health authorities for subjects with chronic HCV infection with underlying liver disease and therefore consistent with the patient population in this study.

Therefore, the revised potential drug induced liver injury for this study is defined as:

- Concurrent ALT ≥ 10 x ULN AND total bilirubin ≥ 2 times ULN or baseline value (if elevated bilirubin at study entry), AND
- no other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

This change in pDILI definition is not anticipated to pose any risk for subjects since management of hepatic events will follow pre-established algorithms that are not impacted by the DILI definition, and include dose delay and/or discontinuation as well as intervention with immunosuppressants.

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6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

For the [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted] a Data Monitoring Committee (DMC) will not be utilized in this study. As of 06-Mar-2015, > 7,600 subjects have received nivolumab in BMS-sponsored trials. The AE profile appears to be independent of tumor type, and AEs observed are manageable and generally reversible with the use of existing treatment algorithms (Appendix 1). Clinical benefit has been shown with nivolumab with improvement in survival in melanoma and lung cancer, and anti-tumor activity supports the benefit-risk assessment in multiple tumor types.

Subject safety will be monitored on an ongoing basis. The BMS medical monitor is a physician responsible for reviewing on a systematic and continuous basis, the safety of subjects in this study. This includes a review of serious and non-serious adverse events. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program. The MST is independent from the BMS medical monitor. The MST has the primary responsibility within BMS for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans.

[redacted]

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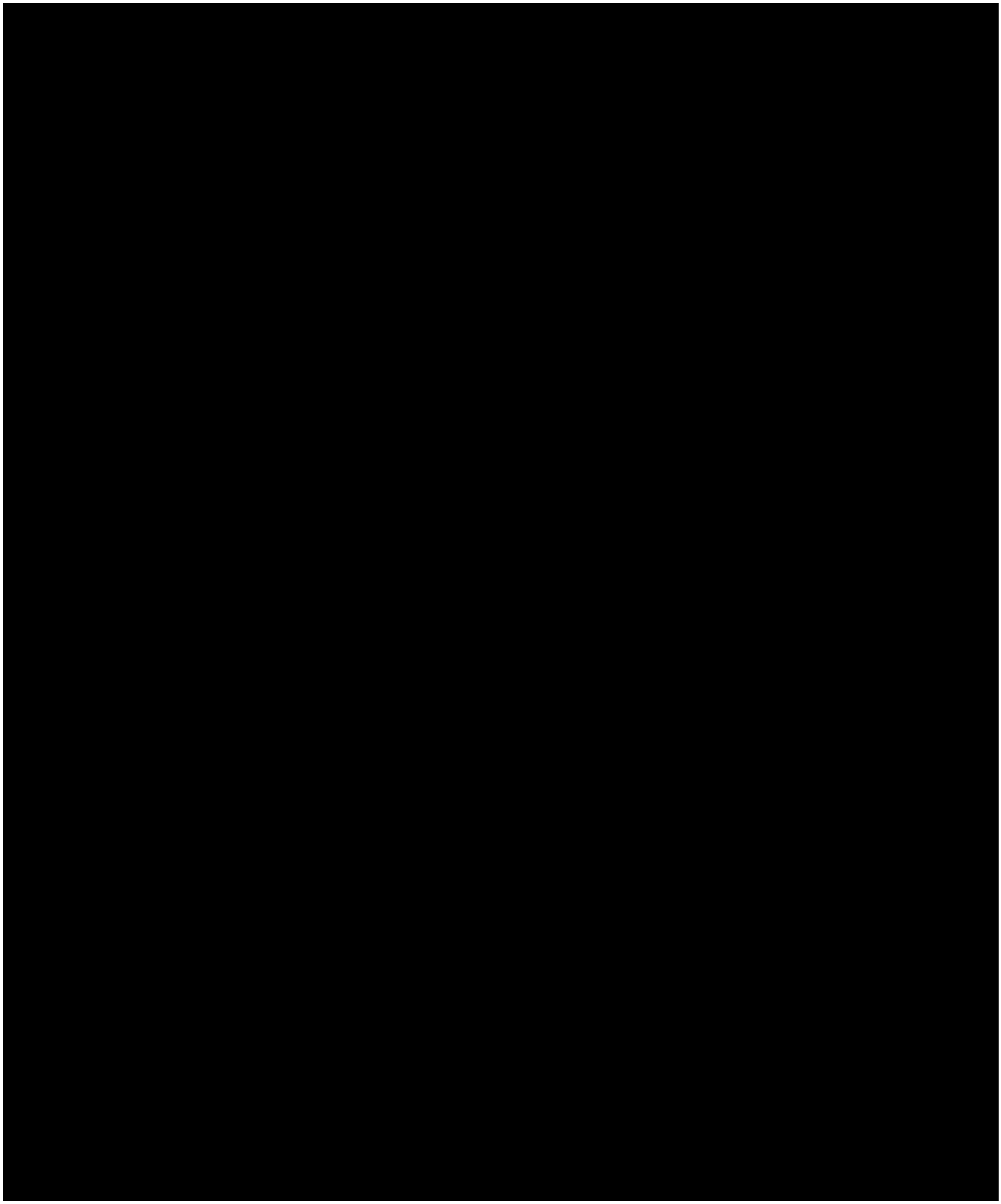
A blinded independent central review (BICR) will be used in this study to review all available tumor assessment scans in the [redacted] Nivolumab plus Ipilimumab Combination Cohort, [redacted] The BICR-determined response will be used in the analyses of ORR, TTP, duration of objective response, and time to response using RECIST 1.1. The BICR may also perform a similar analysis using mRECIST for HCC criteria.

[redacted]



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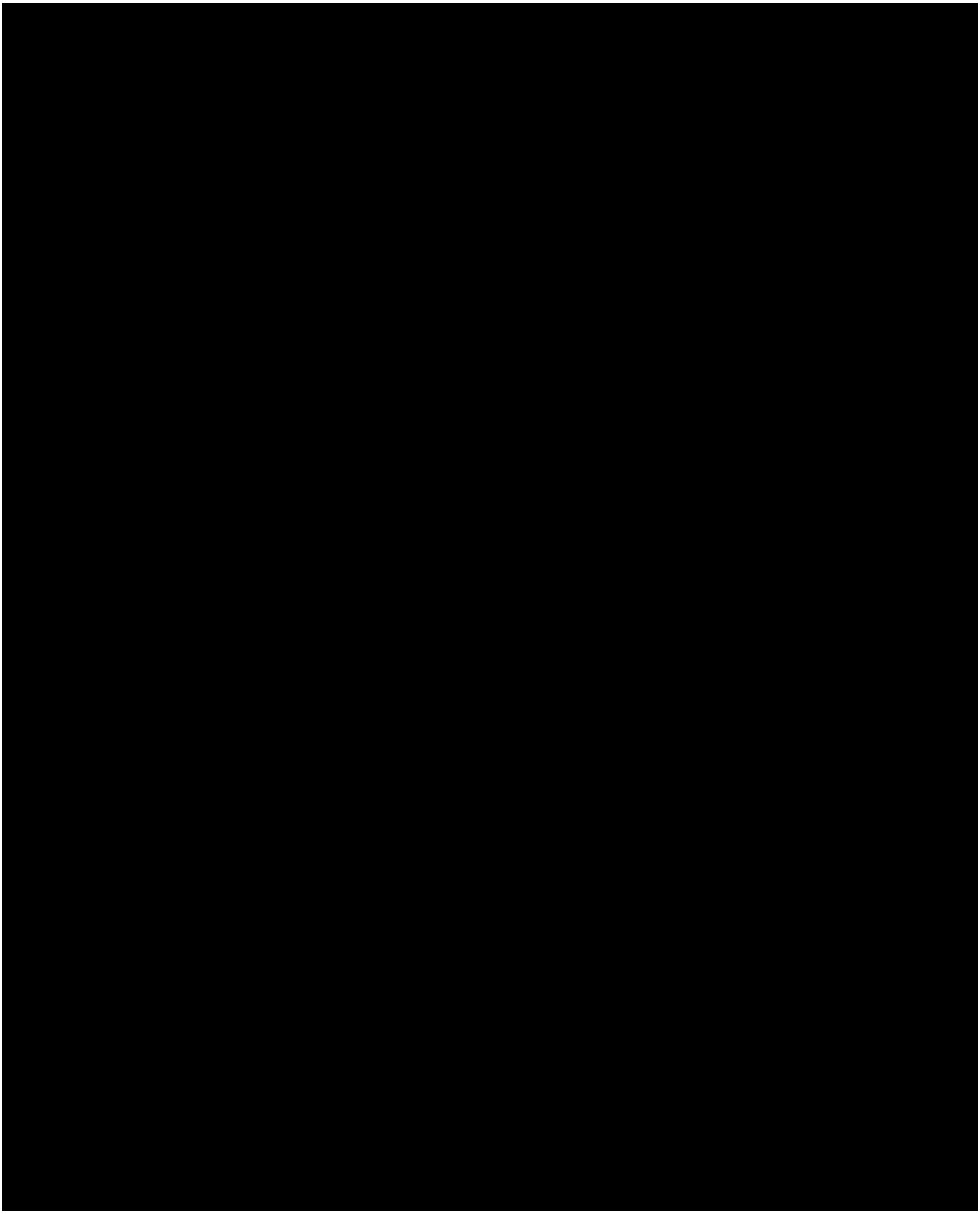

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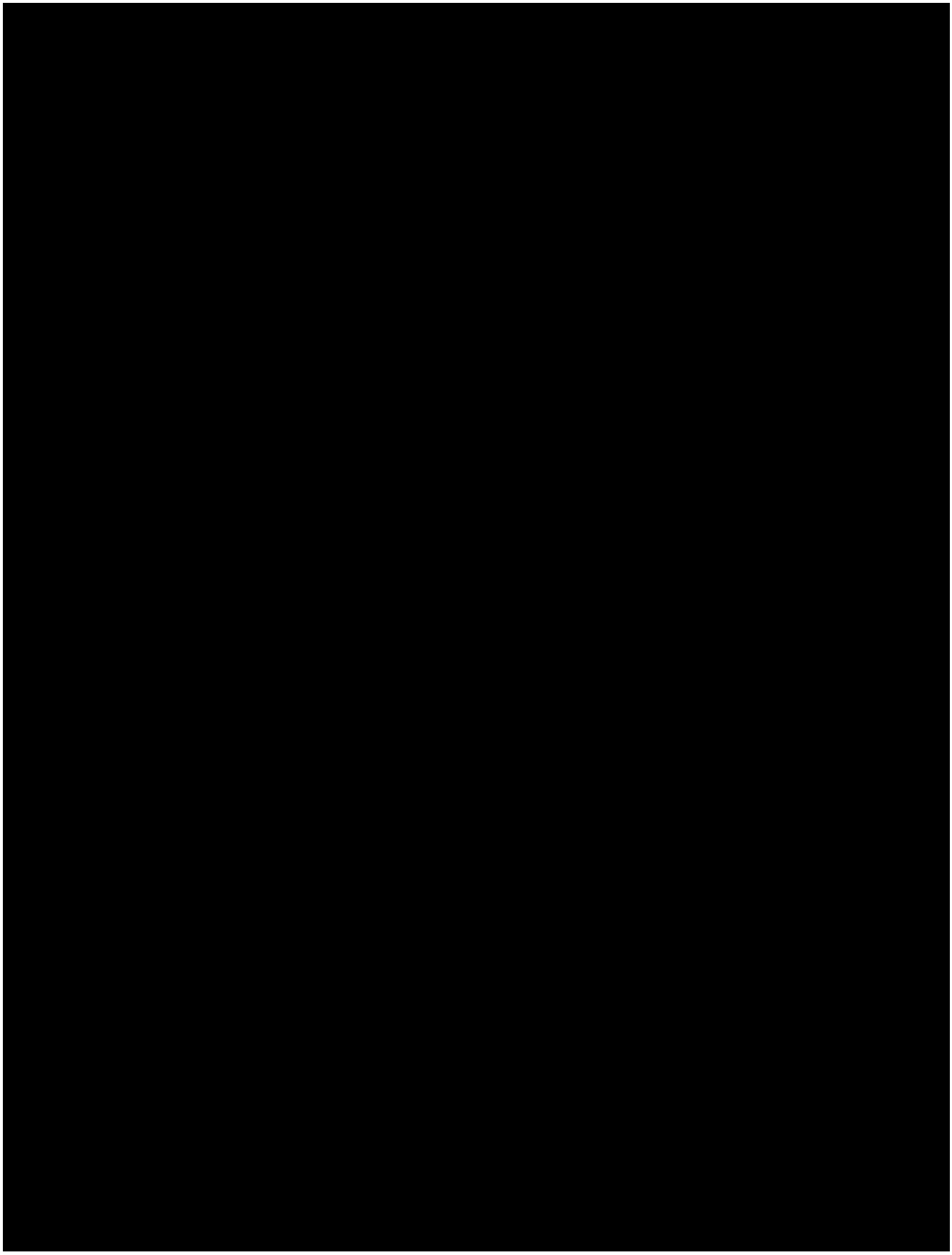

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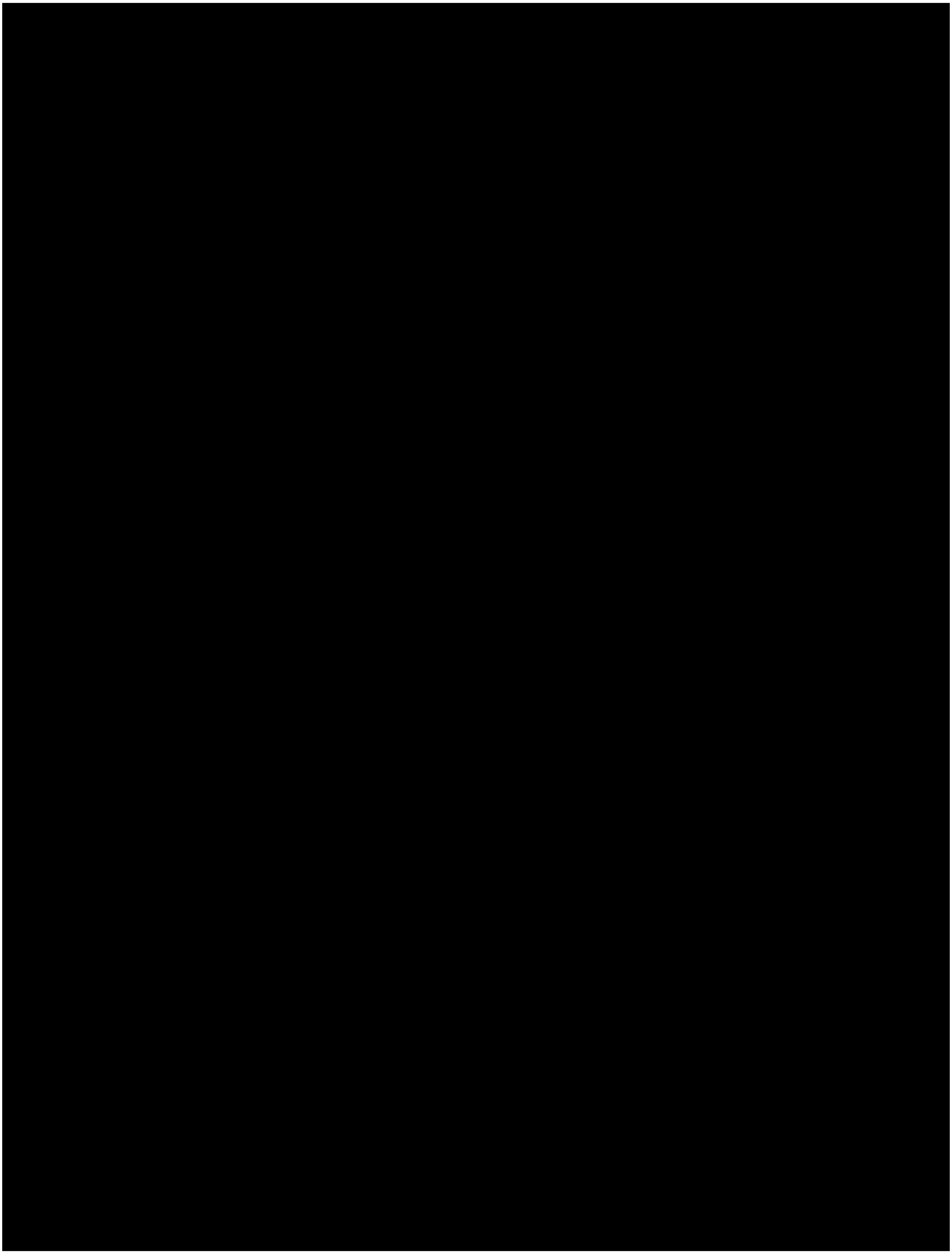

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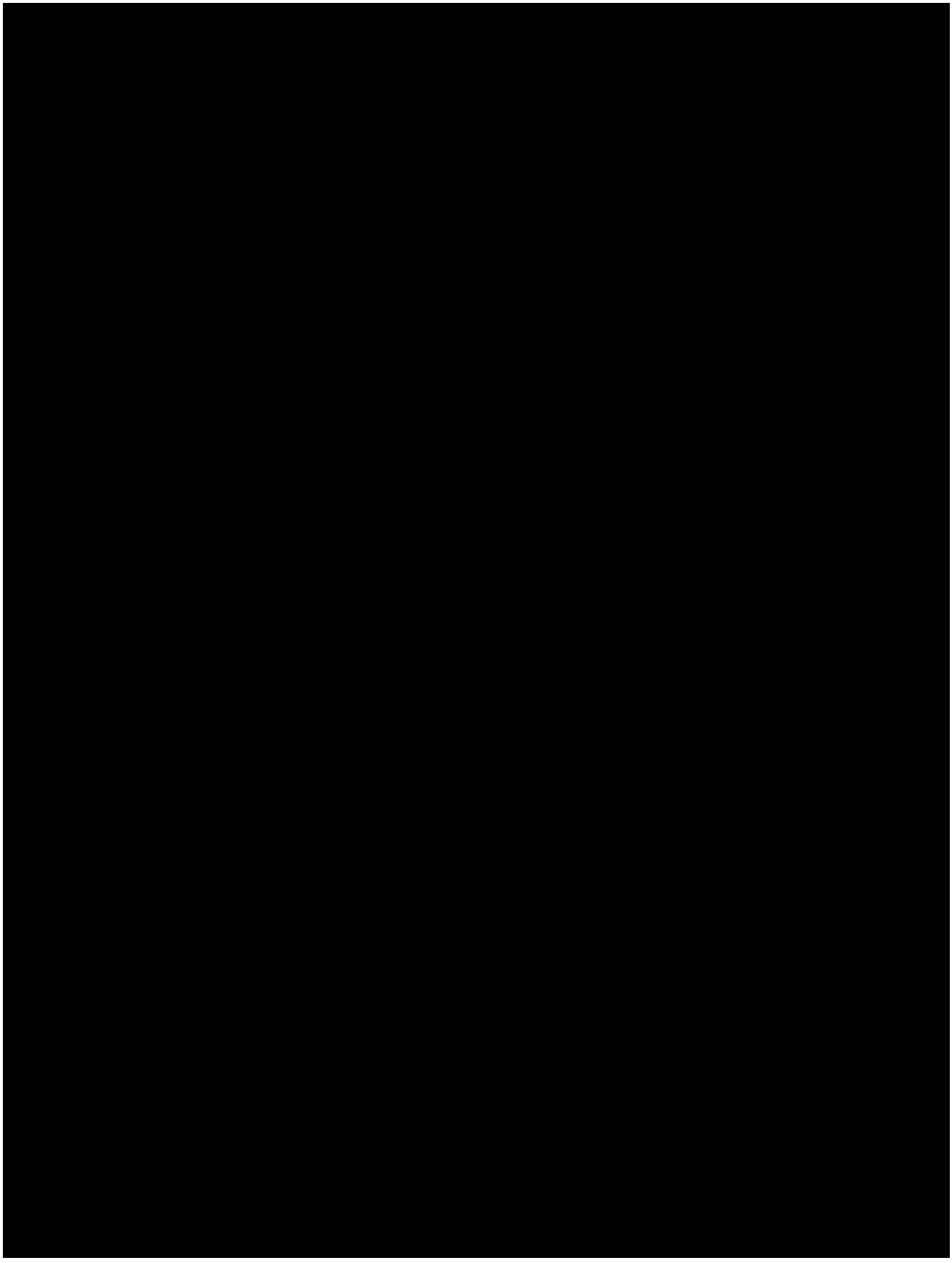

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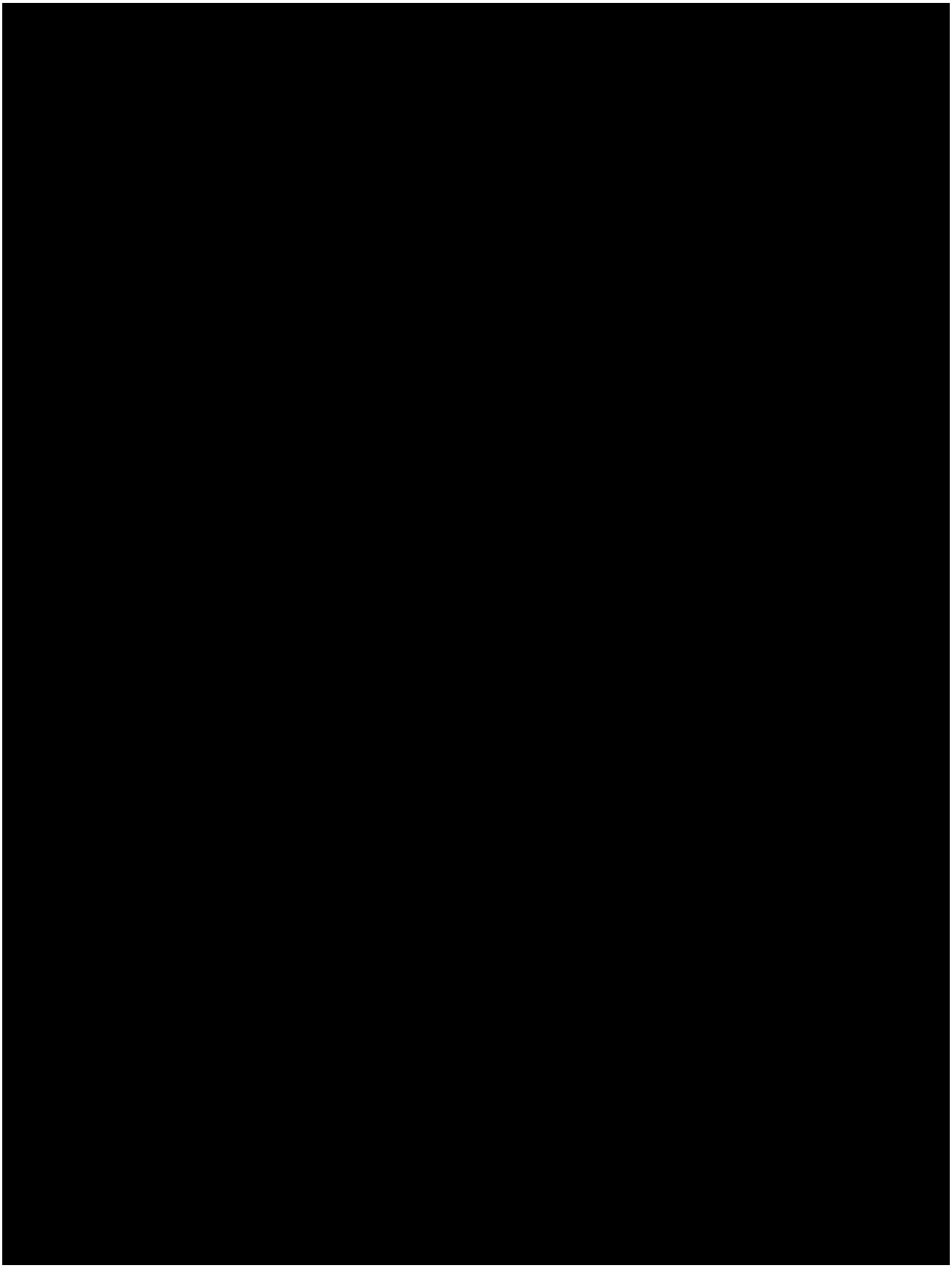

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9. STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects

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currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS)is maintained at each study site where study drug and the following noninvestigational product(s) are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage

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- nonstudy disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

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9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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10. GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved investigational product)

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11. LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AFP	Alpha-feto protein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BICR	Blinded Independent Central Review
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	Calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	Chloride
CLcr	creatinine clearance
CLT	total body clearance

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Term	Definition
CLT/F	apparent total body clearance
Cm	Centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CR	Complete Response
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CRPC	castration-resistant prostate cancer
CV	coefficient of variation
D/C	Discontinue
DCR	disease control rate
dL	Deciliter
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
Eg	exempli gratia (for example)
EGFR	Epidermal Growth Factor Receptor
EQ-5D	Euro Quality of Life 5 Dimensions
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
%FE	percent fecal excretion
G	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	Hour
HBsAg	hepatitis B surface antigen

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Term	Definition
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCC RECIST	RECIST modified for hepatocellular carcinoma
HCV	hepatitis C virus
HCO_3^-	Bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
Ie	id est (that is)
IEC	Independent Ethics Committee
IO	Immuno-Oncology
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	Potassium
Kg	Kilogram
KM	Kaplan-Meier
L	Liter
LDH	lactate dehydrogenase
Ln	natural logarithm
LOQ	limit of quantification
M	Meter
MDSC	Myeloid Derived Suppressor Cell
Mg	Milligram
Mg^{++}	Magnesium
Min	Minute
mL	Milliliter
mmHg	millimeters of mercury

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Term	Definition
MTD	maximum tolerated dose
NSCLC	Non-Small-Cell Lung Cancer
μg	Microgram
N	number of subjects or observations
Na^+	Sodium
N/A	not applicable
Ng	Nanogram
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	Overall Survival
PBMC	peripheral blood mononuclear cell
PD	Progressive Disease
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PPES	Palmar-Plantar Erythrodysesthesia Syndrome
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
R^2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SD	standard deviation
SNP	single nucleotide polymorphism
SOP	Standard Operating Procedures
sp.	Species
Subj	Subject

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Term	Definition
T	temperature
T	Time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	half-life
TTP	time to progression
Tmax, TMAX	time of maximum observed concentration
VAS	Visual Analog Scale
Vss	volume of distribution at steady-state
W	Washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 ALGORITHMS FOR MANAGEMENT OF SIDE EFFECTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

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GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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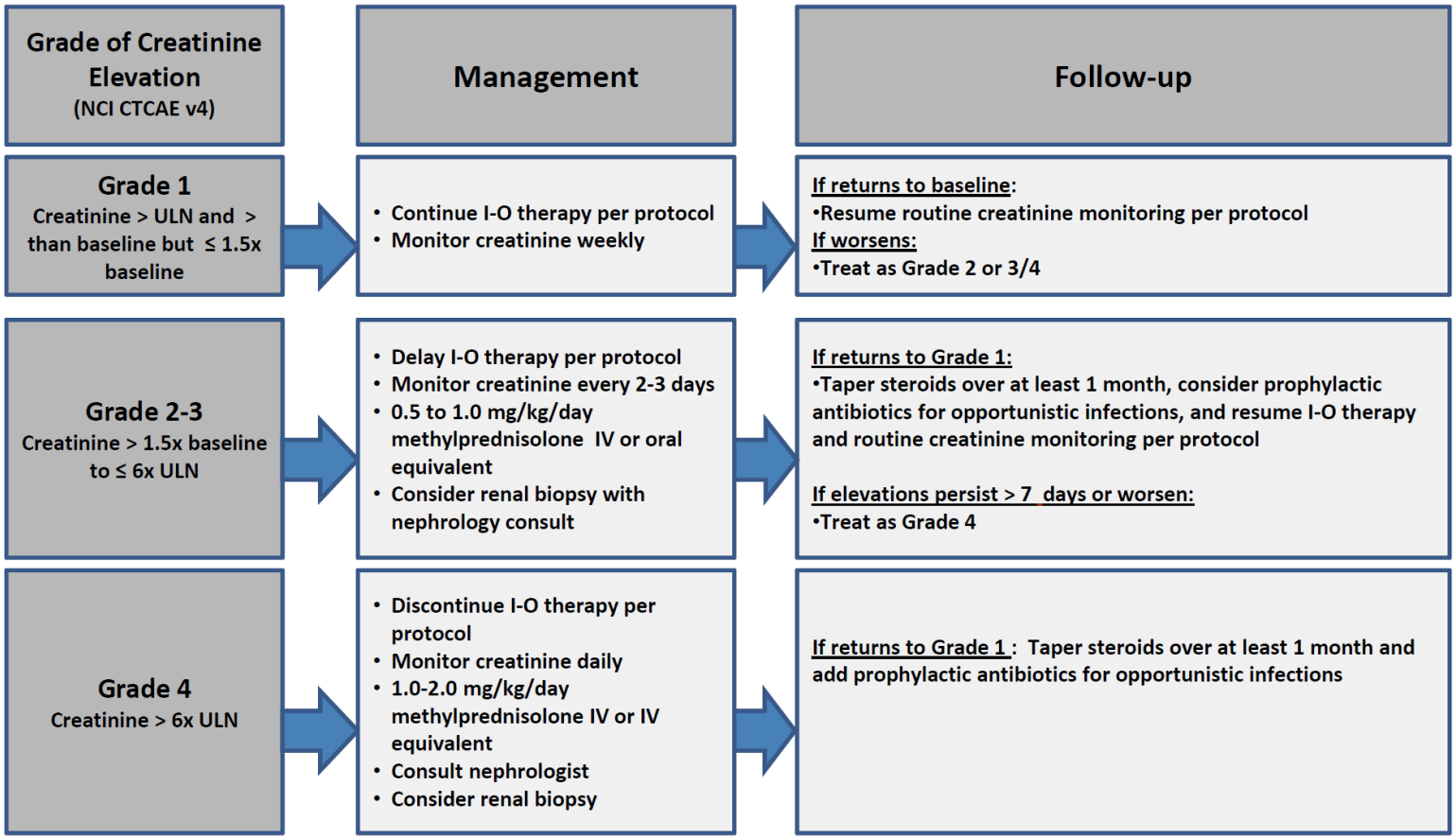
Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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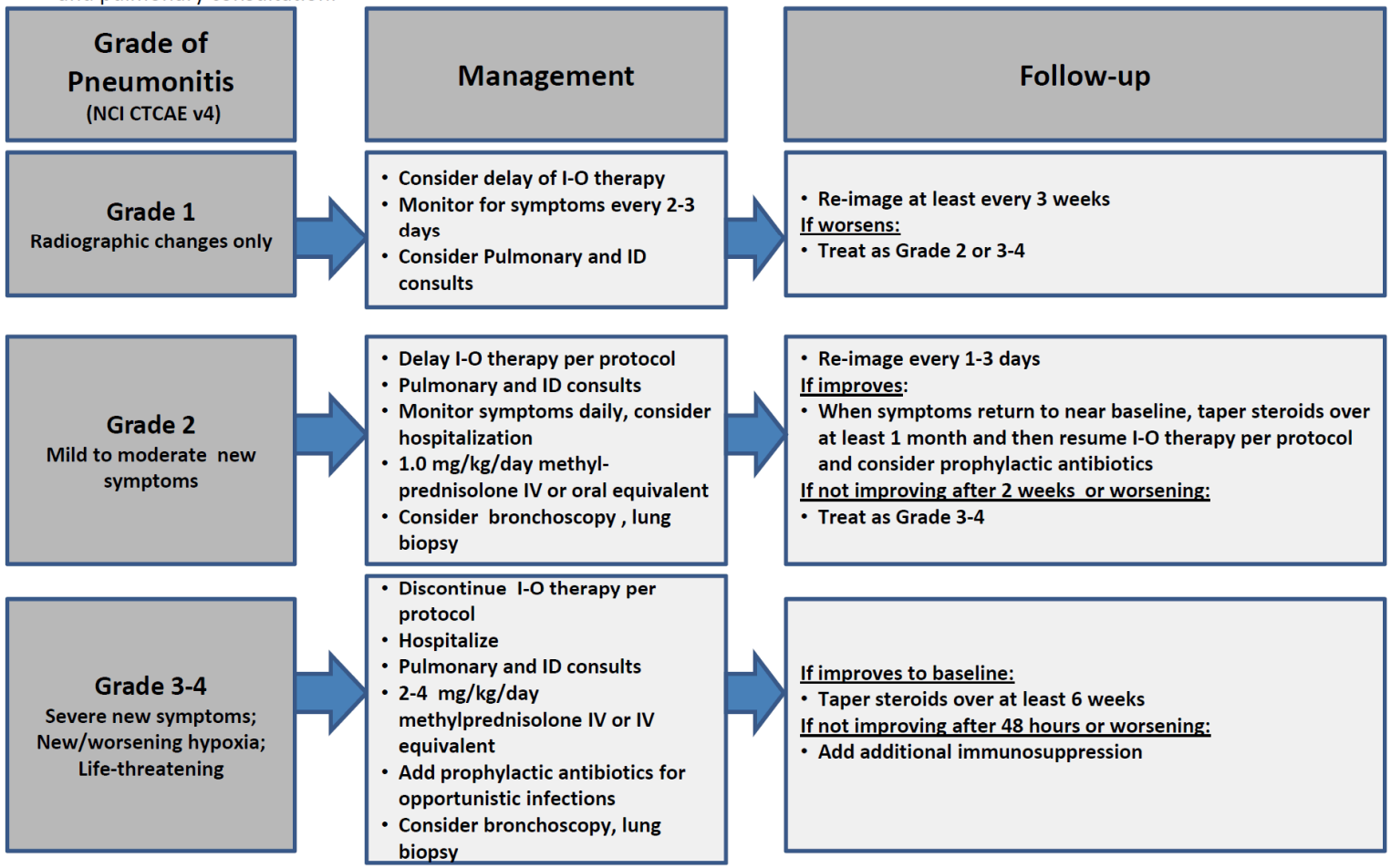
Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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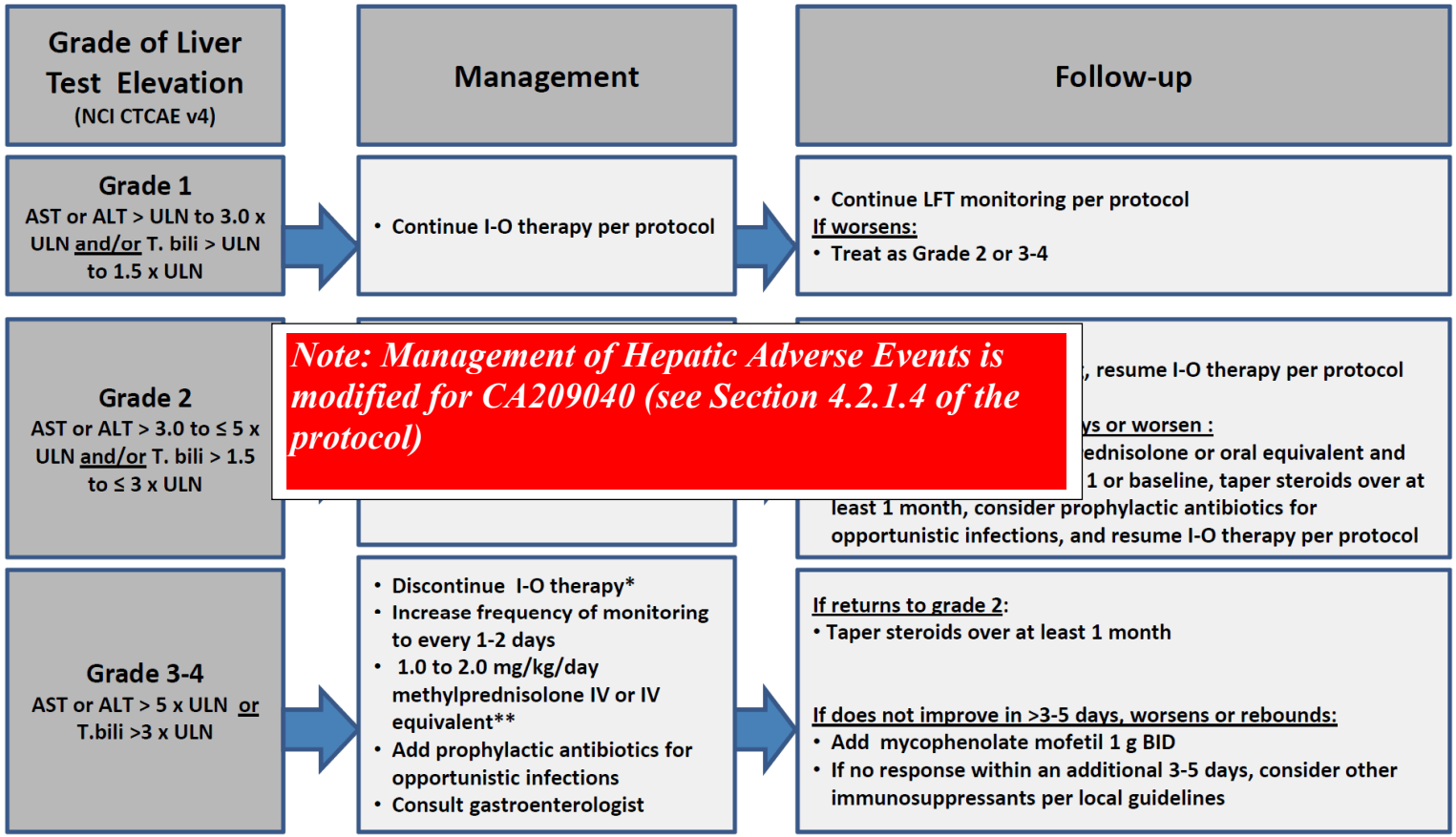
Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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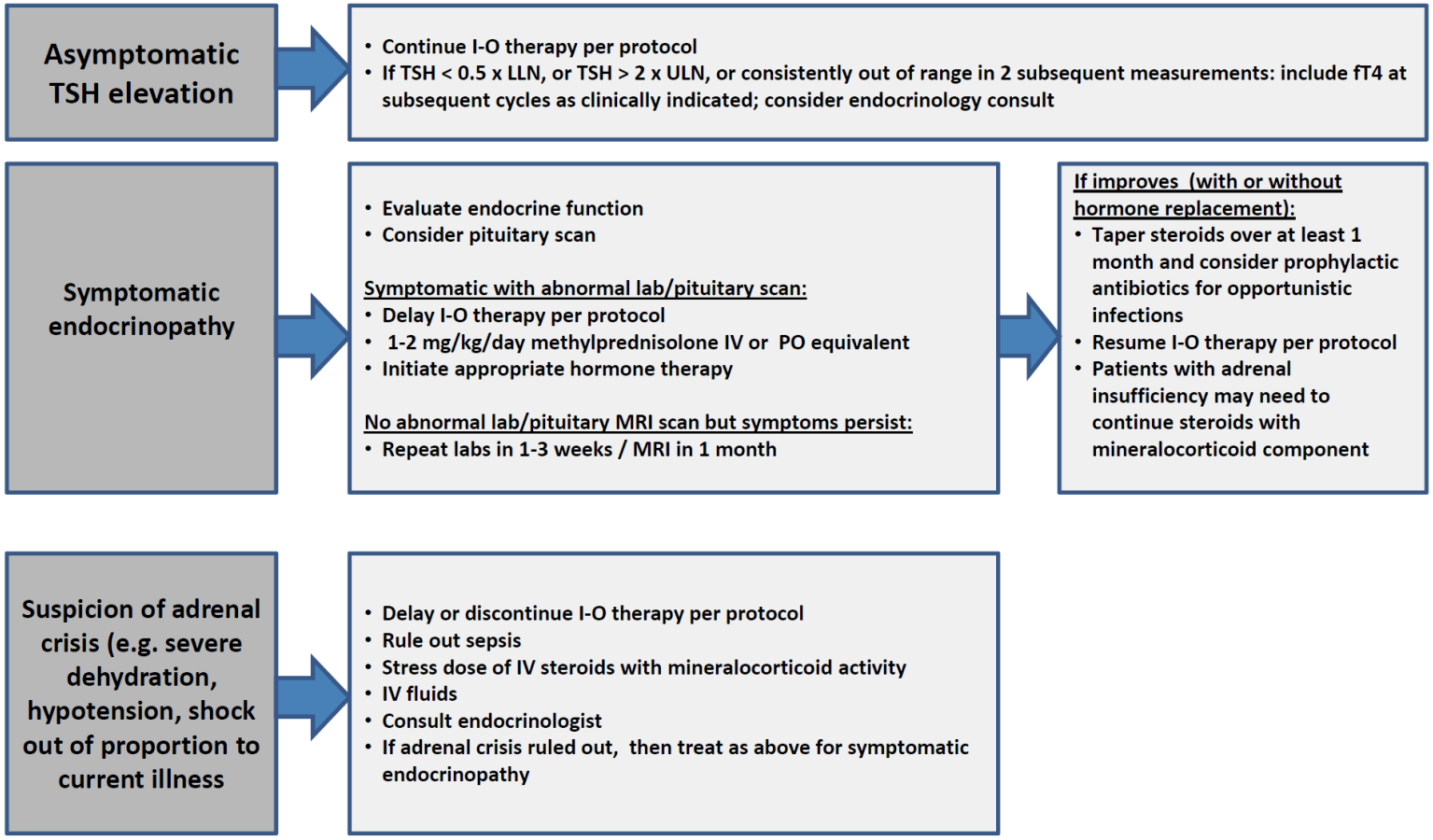
Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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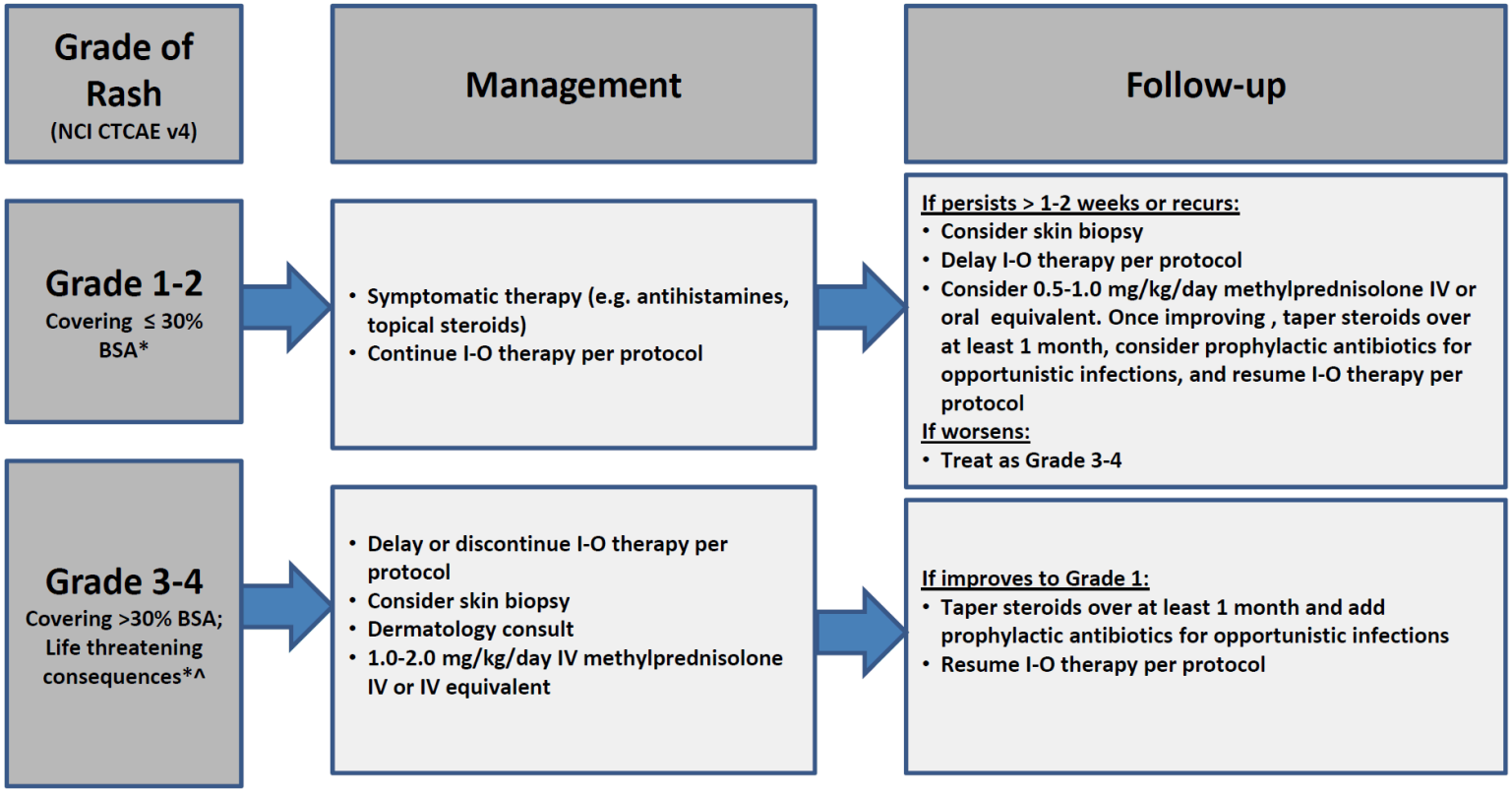
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

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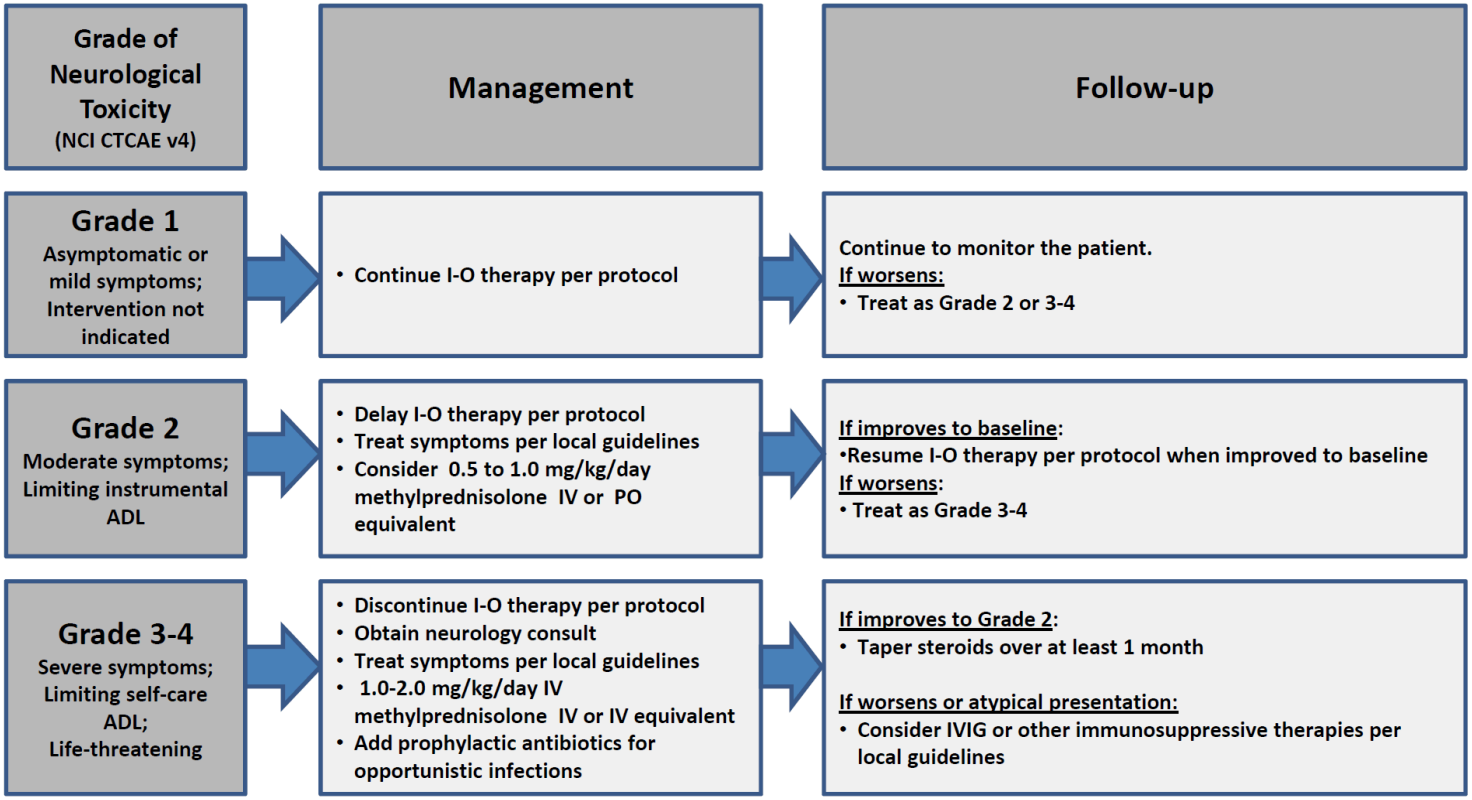
Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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APPENDIX 2 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of Tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

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Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted

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above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

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3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have

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coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For

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example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constituted PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor Markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Appendix Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Summary of the Overall Response Status Calculation [Time point response: patients with target (+/-) non-target disease]

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best Overall Response - All Timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix Table 2. Minimum duration for SD is 6 weeks.

Table 2: Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall response
CR	CR	CR
CR	PR	SD, PD, PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1 and Table 2.

For equivocal findings of progression (eg. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that Disappear and Reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the

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sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009); 45:228-247.

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APPENDIX 3 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

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APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	dead

[1] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.

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APPENDIX 5 MODIFIED RECIST CRITERIA FOR HCC

In this protocol, the RECIST criteria modified for the assessment of HCC tumor lesions, published in the Journal of the National Cancer Institute (JNCI) [1] will be applied. This modified RECIST for HCC criteria is based on RECIST (version 1.0) but introduce the concept of the longest diameter of the viable tumor tissue for "typical" intrahepatic HCC lesions. Intrahepatic lesions are considered "typical" if they display hypervascularity in the arterial phase and a wash-out in the portal or late venous phase in dynamic contrast-enhanced spiral CT or MRI. Differentiating between viable versus necrotic liver tumor tissue may allow a more accurate representation of ant-cancer treatment effects. In the context of this protocol, these criteria will be termed '***Modified RECIST for HCC***'.

Method of Tumor Assessment

Imaging Studies – Imaging studies, including contrast enhanced CT or MRI, and tumor assessments will be performed no more than 4 weeks prior to the initial dose of study therapy. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and subsequent assessments.

Contrast-enhanced spiral CT or MRI

Spiral CT and magnetic resonance imaging (MRI) are requested as the best currently available and reproducible methods to measure target lesions selected for response assessment. **For this trial CT scans of chest/abdomen/pelvis including (contrast enhanced) triphasic CT imaging of the liver (abdomen) is mandatory.** Triphasic CT is acquired with 2.5-mm (preferred) - 5-mm contiguous axial slices. MRI is acceptable if CT is contraindicated. Modality (CT or MRI) used at baseline should be used across all imaging timepoints. Optimization of image acquisition protocols and consistency in the application of the protocol throughout follow-up examinations are essential for high quality imaging and the proper application of the *modified RECIST for HCC criteria*.

In general, spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

A full tumor staging at baseline and during all scheduled follow-up assessments will consist of imaging of the chest, abdomen and pelvis. For the assessment of chest lesions, MRI is not recommended and should only be used under specific clinical circumstances. Accordingly, for patients that are followed with MRI for the assessment of abdominal and pelvic lesions, should receive a spiral CT scan of the chest.

Chest X-ray and Abdominal Ultrasound

Lesions on chest X-ray are not acceptable as measurable lesions. Ultrasound is not an acceptable method to measure disease.

Brain Scans

Baseline brain scans are not required unless clinically indicated. Also, scans during treatment will be done when clinically indicated.

Bone Scans

Baseline bone scans is not required unless clinically indicated. Abnormal findings on bone scans at baseline that are suggestive or compatible with metastatic disease require radiographic confirmation (with plain films, CT, or MRI) that each suspected site represents metastatic disease. It is understood that abnormal findings on bone scans may not demonstrate pathology on plain films given the higher sensitivity of bone scans in detecting metastatic disease. Bone scans that are positive at baseline should be repeated at each imaging time point, as should confirmatory plain film, CT, or MRI studies. Bone scans should be performed if there is clinical suspicion of progression in bone. Subjects with positive bone scans showing metastatic disease at baseline should have bone scans performed at confirmation of objective response.

Complete response (CR) assessment requires normalization of any bone scan abnormalities suspicious for tumor at baseline, and normalization of confirmatory imaging studies as well. If progressive disease is assessed based only on a new lesion(s) found on bone scans, additional imaging studies of the lesion(s) should be performed to confirm the malignant nature of the new findings on the bone scan. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless the lesions seen on the correlative imaging studies

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performed of this area meet the criteria for progression. New areas of abnormal uptake on a bone scan that are suggestive or compatible with progressive disease require radiographic confirmation (with plain films, CT, or MRI).

Definition of Measurable Disease

Measurable tumor lesions must have a size of ≥ 10 mm in one dimension when evaluated with spiral CT (with 5 mm contiguous reconstruction algorithm) or ≥ 20 mm when evaluated with MRI scanning using contiguous cuts of 5 mm in slice thickness.

Definition of Non-measurable Disease

Malignant disease evident on clinical (physical or radiographic) examination, but not measurable by ruler or calipers (i.e., pelvic and abdominal masses, lymphangitic or confluent multi-nodular lung metastases, skin metastases) or lesions smaller than 10 mm on spiral CT or than 20 mm on MRI are considered non-measurable. In addition, non-measurable lesions include bone lesions, lepto-meningeal disease, ascites, pleural/pericardial effusions, lymphangitis, inflammatory breast disease, abdominal masses (not followed by spiral CT or MRI), cystic lesions and lesions within a previously irradiated region. Malignant portal vein thromboses should be considered as non-measurable lesions. Porta hepatis lymph nodes with a short axis smaller than 20 mm are considered reactive and not malignant.

Tumor Measurements

The site will perform radiographic tumor assessments at pre-treatment (Baseline) visit (within 28 days prior to the start of treatment). Subjects meeting the criteria for a complete or partial response should have confirmatory tumor measurements obtained within 4 to 8 weeks of initially demonstrating a response. All documented measurable lesions are to be followed. All tumor measurements must be made in millimeters (or decimal fractions of millimeters).

Target Lesions Definition and Selection

A new concept of 'Typical' Intrahepatic Lesions in modified RECIST for HCC

The selection of target lesions will be initially guided by the presence of 'typical'intrahepatic lesions.

'Typical' intrahepatic lesions MUST meet the following criteria:

- Lesions can be classified as measurable lesion
- Lesions are suitable for repeated measurements
- Lesion shows typical vascular pattern of HCC in contrast-enhanced spiral CT or MRI studies, defined as:
  - Well delineated intrahepatic lesions
  - Hypervascularity in the arterial phase
  - Contrast agent wash-out in the portal and late venous phase

Measurable lesions in the liver meeting the criteria for 'typical' target lesions present at baseline, should be chosen as the sole intrahepatic target lesions. Up to five 'typical' intrahepatic lesions will be selected as target lesions. Measurement of the longest viable diameter, which is the longest diameter of the viable tumor lesion, will be applied to these lesions.

HCC lesions that show local recurrence and/or residual disease after loco-regional therapy and have typical hypervascular patterns of HCC can be selected as target lesions. All other 'atypical' intrahepatic lesions will NOT be considered as target lesions. If measurable extrahepatic lesions are present in addition to the 'typical' intrahepatic lesions at baseline, up to five lesions per organ except the liver, representative of all involved organs will be identified as target lesions. Measurement of the longest diameter will be applied to these lesions.

Other Target Lesions ('atypical' intrahepatic and all extrahepatic lesions)

If NO 'typical' intrahepatic lesions exist, 'atypical' intrahepatic lesions may be considered as Target Lesions.

'Atypical' intrahepatic lesions and all extrahepatic lesions must meet the following criteria to be considered as Target lesions:

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- Lesions can be classified as measurable lesions
- Lesions are suitable for repeated measurements

All measurable lesions up to a maximum of five lesions per organ and ten lesions in total should be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs and should be selected based on their size (lesions with largest area). Measurement of the longest diameter will be applied to these lesions.

Non-Target Lesions

Measurable lesions other than the target lesions and all sites of non-measurable disease will be identified as 'non-target' lesions.

Non-target lesions may include:

Intrahepatic lesions:

- Poorly delineated HCC lesions including infiltrative-type and diffuse HCC
- HCC lesions with atypical contrast-agent enhancement patterns
- HCC lesions showing local recurrence after previous loco-regional treatment without meeting the criteria for 'viable' lesions i.e. lack of clear-cut hypervascular recurrence and /or well-delineation from the surrounding liver tissue
- Portal vein tumor invasion and/or thrombosis
- Porta hepatis lymph node(s) considered as malignant i.e. > 20mm in the short axis
- Intrahepatic viable lesions in excess to the 5 lesions in the liver selected as target lesions

Extrahepatic lesions:

- Extrahepatic lesions in excess to the 5 lesions per organ selected as target lesions
- Non-measurable but evaluable disease, i.e., cutaneous or bone lesions, etc.

General Recommendation:

Target and non-target lesions will be recorded in the CRF and evaluated at the same time points. Once target and non-target lesions have been defined at baseline, these designations should not change at subsequent evaluations. For example, if a target lesion became smaller following treatment such that it was less than 10 mm on a spiral CT scan, its designation as a target lesion should not change.

Calculation of Target Lesions (Disease)

If'Typical' Intrahepatic Lesions exist:

The sum of the longest viable diameters of all typical intrahepatic target lesions (up to five lesions total) and of the longest diameters of extrahepatic target lesions up to a maximum of 10 target lesions in total will be calculated and reported as sum of the longest diameters **(SLD)**. The baseline SLD of target lesions or the smallest SLD of target lesions recorded since the treatment started will be used as the reference for determining tumor response of the target lesions. Note the longest viable diameter may not be on the same section of the liver as the longest diameter.

If NO 'Typical' Intrahepatic Lesions exist:

The sum of the longest diameters for all target lesions will be calculated and reported as the sum of the longest diameters **(SLD).** The baseline SLD of target lesions or the smallest SLD of target lesions recorded since the treatment started will be used as the reference for determining tumor response of the target lesions.

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Definitions of Response

Complete Response (CR):

- For typical intrahepatic target and non-target lesions, complete disappearance of any intratumoral contrast-agent enhancement in the arterial phase of spiral CT or MRI
- For **atypical intra- and extrahepatic target, and non-target lesions**, complete disappearance of all evidence of target and non-target tumor lesions. CR must be confirmed by a second evaluation no less than 4 weeks after the date the CR was first obtained.

Partial Response (PR):

- Decrease of > 30% in the SLD of target lesions taking as reference the baseline SLD.
- PR must be confirmed by a second evaluation no less than 4 weeks after the date the PR was first obtained.

Stable Disease (SD):

- Failure to meet criteria for complete or partial response, in the absence of progressive disease.

Pro**gressive disease (PD)**

- Increase of > 20% in the SLD of target lesions taking as reference the smallest SLD of target lesions recorded since the treatment started.
- In the case of an equivocal or small increase in the sum of all target lesions and in the absence of clinical progression, a repeat evaluation at 3 - 6 weeks should be performed. If the 20% or more increase is observed in two consecutive determinations, the date of PD is the date of the first evaluation.

OR

- New hepatic lesion with the longest diameter of at least 10 mm with the vascular pattern characteristic for HCC i.e. hypervascularization in the arterial phase with wash-out in the portal venous (or late venous) phase of contrast-enhanced spiral CT or MRI imaging

OR

- New hepatic lesion larger than 10 mm without the vascular pattern characteristic for HCC but evidence of growth of a least 10 mm in subsequent scans. Note: individual radiological events will be adjudicated retrospectively as PD at the time when it was first detected by imaging techniques, if the criteria are fulfilled (≥ 20 mm) on subsequent radiological testing.

OR

- Unequivocal progression of existing truly non measurable lesions. However, any new or worsening of preexisting effusion (ascites, pleural effusion, etc.) will not be considered progression unless there is cyto-pathological confirmation of malignancy.

OR

- Appearance of one or more new extrahepatic lesions of any size

OR

- Unequivocal progression of existing intra- or extrahepatic non-target lesion(s).
- In the absence of clinical progression or concurrent progression in target lesions, progression of non-target lesions that is equivocal should be confirmed by a repeat evaluation at 3 - 6 weeks. If the progression is confirmed, the date of the first (equivocal) assessment will be taken as the date of progression.

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Overall best objective response will be tabulated, based on evaluation of target- and nontarget lesions as well as new lesions:

Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Objective Response
CR	**CR**	**No**	**CR**
CR	**SD**	**No**	**PR**
PR	**Non-PD**	**No**	**PR**
SD	**Non-PD**	**No**	**SD**
PD	**Any result**	**Yes or No**	**PD**
Any result	**PD**	**Yes or No**	**PD**
Any result	**Any result**	**Yes**	**PD**

For PD to be considered the best overall response, there must be no prior SD, PR, or CR.

General Recommendations:

Every effort should be made to document tumor measurements and extent of disease, even after discontinuation of therapy, in order to classify subjects for best response as described above. Subjects who do not have tumor response assessment due to rapid progression or toxicity will be considered as non-responders and will be included in the denominator for the response rate.

1. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-710.

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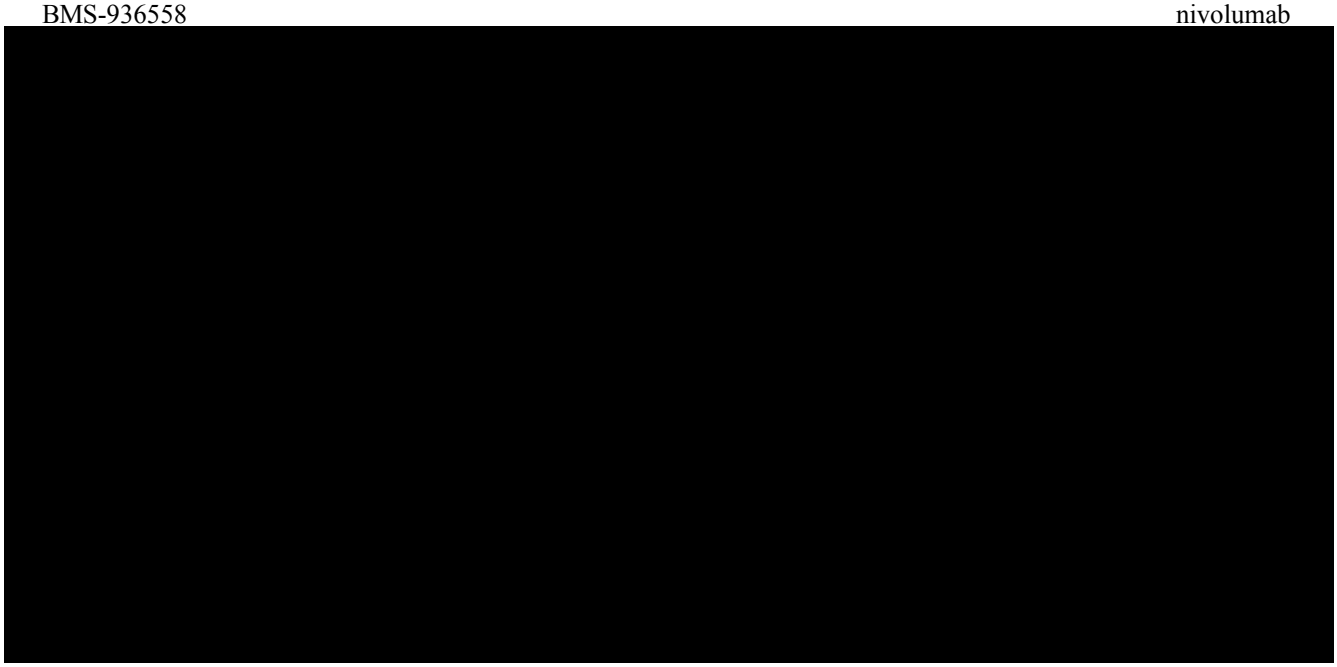

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APPENDIX 9 EUROQOL GROUP (EQ-5D) HEALTH QUESTIONNAIRE

In this revised protocol, the EQ-5D questionnaire will be used to obtain subject health outcomes information. The questions specified below will be incorporated into the electronic case report form for the study. These questions should be reported by the subject during site visits.

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about □
I have some problems in walking about □
I am confined to bed □

Self-Care
I have no problems with self-care □
I have some problems washing or dressing myself □
I am unable to wash or dress myself □

Usual Activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities □
I have some problems with performing my usual activities □
I am unable to perform my usual activities □

Pain/Discomfort
I have no pain or discomfort □
I have moderate pain or discomfort □
I have extreme pain or discomfort □

Anxiety/Depression
I am not anxious or depressed □
I am moderately anxious or depressed □
I am extremely anxious or depressed □

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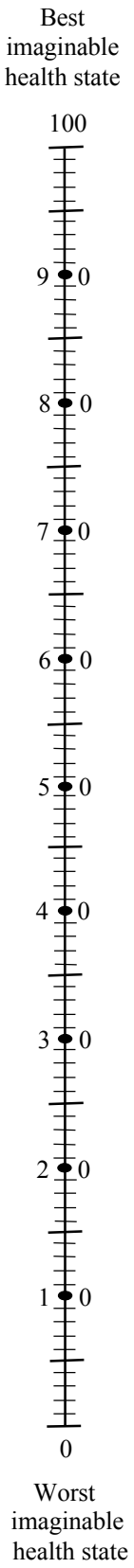
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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APPENDIX 10 FACT-HEP

Sorafenib subjects: FHSI-8 score (8 questions outlined in boxes) is to be derived from responses to FACT-Hep for determination of sorafenib criteria for symptomatic progression (see Protocol Section 4.5.3.4)

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

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STATISTICAL ANALYSIS PLAN

A PHASE 1/2 STUDY OF NIVOLUMAB OR NIVOLUMAB IN COMBINATION WITH IPILIMUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA SUBJECTS WITH OR WITHOUT CHRONIC VIRAL HEPATITIS; AND A RANDOMIZED, OPEN-LABEL STUDY OF NIVOLUM VS SORAFENIB IN ADVANCED HEPATOCELLULAR CARCIN

PROTOCOL(S) CA209040

1L, NIVO+IPI COMBO, AND CABO COMBO COHORTS

VERSION # 1.0

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1 BACKGROUND AND RATIONALE

This document describes statistical analysis plan for the final analysis of the randomized cohorts in study CA209040 per protocol amendment 14: - 1L cohort, Nivo+Ipi Combo cohort, and Cabo Combo cohort. Outputs from the final analysis will be presented in the study's interim CSR. The analysis plan for Escalation Cohort and Expansion Cohort was prepared separately (CA209040 SAP for Escalation and Expansion Cohorts, Version 2.0). For all other cohorts, separate statistical analysis plan will be prepared.

A Phase 1/2, Dose-escalation, Open-label Study of Nivolumab or Nivolumab in Combination with Other Agents in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis.

The study was initially designed as a Phase 1 dose escalation study to investigate safety, immunoregulatory activity, pharmacokinetics, and preliminary anti-tumor activity of nivolumab in advanced HCC subjects with or without chronic viral hepatitis. Based on preliminary findings from the escalation cohort, BMS amended the protocol by adding an expansion cohort. In addition, three randomized cohorts were added to investigate Nivolumab monotherapy efficacy as compared to Sorafenib in the HCC 1L population (1L cohort), Nivolumab plus Ipilimumab safety and efficacy in HCC 2L population (Nivo+Ipi Combo cohort), and safety and efficacy of Nivolumab Cabozantinib combination with/without Ipilimumab in HCC 1L or 2L population (Cabo Combo cohort). The phase 2 1L cohort was later amended to close its enrollment early due to planned Phase 3 study of Nivolumab vs Sorafenib in the same population.

Please refer to Section 1 of CA209040 protocol for details of background and rationale.

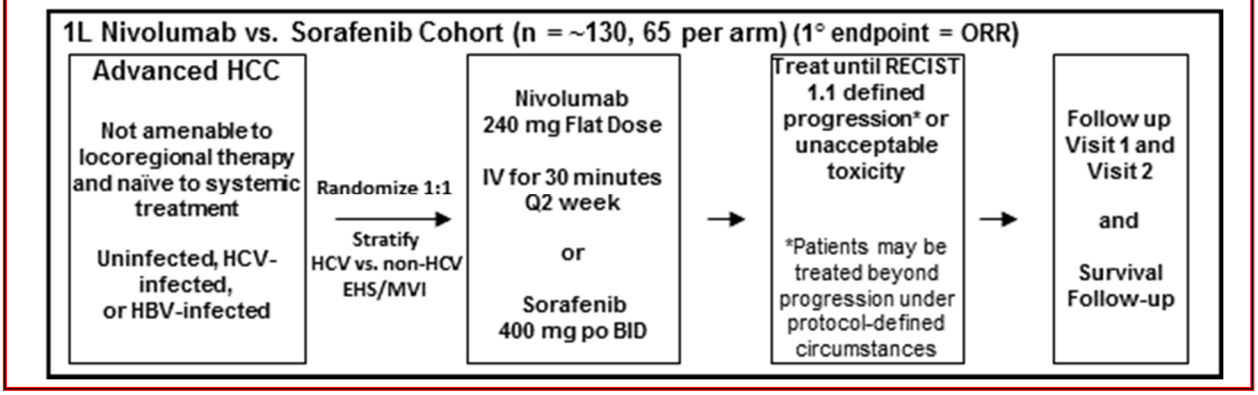
2 STUDY DESCRIPTION

2.1 Study Design

1L Cohort:

The 1L Nivolumab vs Sorafenib Cohort will consist of approximately 130 advanced HCC subjects who are naive to systemic therapy. Uninfected, HCV-infected, or HBV-infected subjects will be enrolled. Subjects will be randomized 1:1 to receive open label flat dose nivolumab 240 mg Q2 week IV or sorafenib 400 mg po BID until unacceptable toxicity or RECIST 1.1 disease progression or study discontinuation for any other reason. Subjects will be stratified by viral status (HCV vs non-HCV [HBV infected or uninfected]) and presence of macrovascular invasion (MVI) or extrahepatic spread (EHS). Subjects with resolved HCV infection will be stratified into the HCV group. Study design of the 1L cohort is illustrated in Figure 2.1-1: 1L Cohort Study Design.

Figure 2.1-1: 1L Cohort Study Design



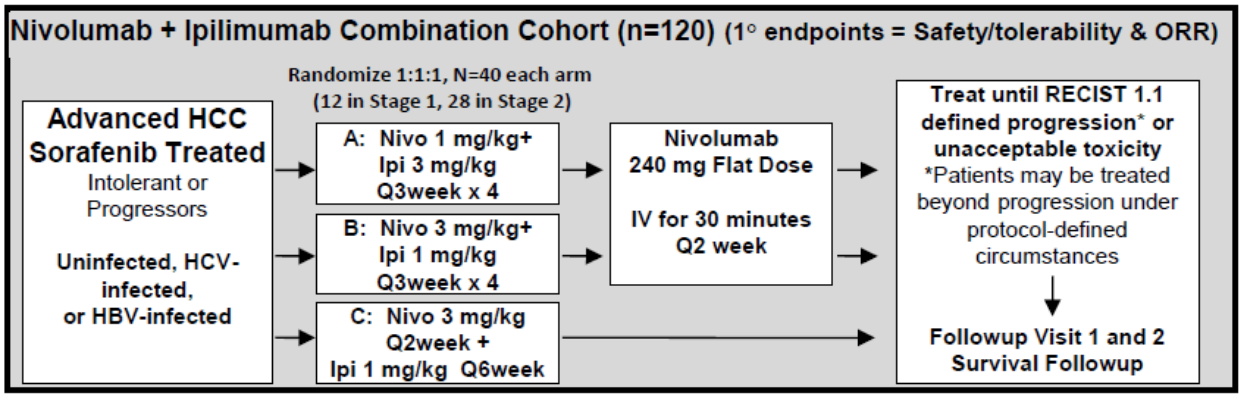
Nivo+Ipi Combo Cohort

The Nivolumab and Ipilimumab Combination Cohort will consist of approximately 120 subjects. Uninfected, HCV-infected, or HBV-infected subjects with advanced HCC and previous treatment with sorafenib will be randomized 1:1:1 into 3 different dose arms:

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week until toxicity or disease progression (n = 40).

A 2-stage design will be employed for each of the 3 dose arms. Twelve subjects in each dose arm will undergo a safety and tolerability assessment at Week 13 (or prior to Week 13 if discontinued). The safety evaluation will be conducted independently for each dose cohort. No additional subjects will be enrolled until the safety evaluation at Week 13 occurs. After completion of Stage 1, enrollment in Stage 2 of the subsequent 28 subjects can occur in each dose arm and is contingent upon the results of the safety evaluation. Study design of Nivo+Ipi Combo cohort is illustrated in Figure 2.1-2: Nivo+Ipi Combo Cohort Study Design.

Figure 2.1-2: Nivo+Ipi Combo Cohort Study Design



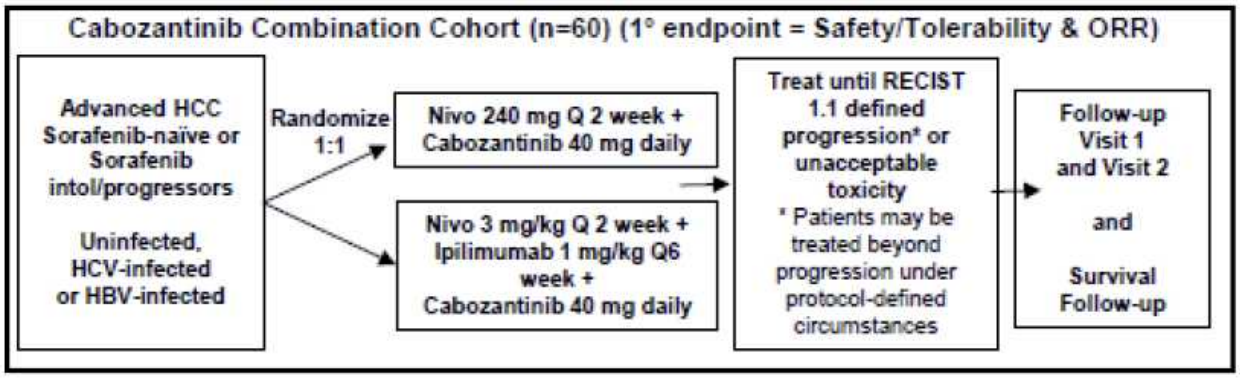
Cabo Combo Cohort

The Cabozantinib Combination Cohort will consist of approximately 60 advanced HCC subjects who are naive to sorafenib or previously treated with sorafenib, uninfected, HCV-infected, or HBV-infected. Subjects will be randomized 1:1 into 2 different dose arms:

- doublet arm--nivolumab 240 mg q2week + Cabozantinib 40 mg daily (n = 30)
- triplet arm --nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week + Cabozantinib 40 mg daily (n = 30).

Study design of Cabo Combo Cohort is illustrated in Figure 2.1-3: Cabo Combo Cohort Study Design.

Figure 2.1-3: Cabo Combo Cohort Study Design



2.2 Treatment Assignment

Each enrolled subject will be randomized through interactive voice response system (IVRS) to be assigned a treatment group (as randomized). Please see Table 2.2-1 for the descriptions of each arm under all the randomized cohorts.

Table 2.2-1: Cohort and Arm Descriptions

Study Cohort	Arm ID	Arm Code	Description
1L Cohort	H	Nivolumab 240 mg	nivolumab 240 mg flat dose Q2 week IV
	I	Sorafenib 400 mg	sorafenib 400 mg po BID
Nivo+Ipi Cohort	J	Nivo 1 + Ipi 3 Q3	nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week
	K	Nivo 3 + Ipi 1 Q3	nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week
	L	Nivo 3 Q2 + Ipi 1 Q6	nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week
Cabo Combo Cohort	Q	Nivo240 + Cabo	nivolumab 240 mg q2week + Cabozantinib 40 mg daily, also referred to by doublet arm
	R	Nivo3+Ipi1 Q6 + Cabo	nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week + Cabozantinib 40 mg daily, also referred to by triplet arm

2.3 Blinding and Unblinding

This is an open-label study for all cohorts. However, subjects' treatment group information were blinded in the database after enrolling into randomized cohorts. The 1L and Nivo+Ipi cohorts were unblinded at the database lock in Nov. 2016. The Cabo combo cohort has not had FPFV yet as of this SAP finalization.

2.4 Protocol Amendments

This statistical analysis plan (SAP) incorporates the amendments in Table 2.4-1.

Table 2.4-1: Protocol Amendments Related to the Randomized Cohorts

Amendment	Date of Issue	Summary of Major Changes
Original Protocol	25-May-2012	Not applicable
Amendment 08	31-Jul-2015	Addition of two new cohorts to the study: 1L cohort; Nivo+Ipi combo cohort
Amendment 14	26-Oct-2016	Changed the primary efficacy analysis from a comparison of ORR between two treatment arms to an estimation of ORR in each nivolumab and sorafenib arms in the 1L Nivolumab vs Sorafenib Cohort

2.5 Data Monitoring Committee

Only the 1L Cohort, together with the phase III study of CA209459, is included in a Data Monitoring Committee (DMC) for safety and efficacy considerations.

The DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Adjudicated events will be submitted to the DMC and Health Authorities when required for review on a specified timeframe in accordance with the adjudication documentation. Details of the DMC responsibilities and procedures will be specified in the DMC charter. The DMC review of the safety of 1L cohort stopped after the unblinding at the Nov 2016 database lock.

2.6 Blinded Radiology Review Committee

In addition to local tumor assessments, images from this study will undergo a blinded, independent central review (BICR) to assess response based on the RECIST 1.1 and mRECIST assessment criteria. The centrally reviewed response data will be used in the analyses of ORR, PFS, duration

of response (DOR), and time to response (TTR). All final determinations on centrally reviewed image-based endpoints will be made based on the independent assessments for a uniform and unbiased assessment of outcome. Details of the procedures and the criteria for the central review are defined in a separate imaging charter[1].

3 OBJECTIVES

3.1 Primary

1L Cohort

To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

Nivo+Ipi Combo Cohort

- To establish the safety and tolerability of nivolumab plus ipilimumab in subjects with advanced HCC.
- To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

Cabo Combo Cohort

- To establish the safety and tolerability of nivolumab combined with cabozantinib and nivolumab and ipilimumab combined with cabozantinib in subjects with advanced HCC who are naive to sorafenib or have been previously treated with sorafenib.
- To estimate the ORR and duration of response for nivolumab combined with cabozantinib and nivolumab and ipilimumab combined with cabozantinib in subjects with advanced HCC who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

3.2 Secondary

1L Cohort

- To estimate TTP and PFS of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
- To evaluate the overall survival (OS) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
- To evaluate the relationship between PD-L1 expression and efficacy

Nivo+Ipi Combo Cohort

- To assess antitumor activities (TTP and PFS) based on results of BICR and/or Investigators using RECIST 1.1.
- To evaluate overall survival (OS) in subjects treated with nivolumab plus ipilimumab.
- To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

Cabo Combo Cohort

- To assess antitumor activities (TTP and PFS) based on results of BICR and/or Investigators using RECIST in doublet and triplet regimens.
- To evaluate overall survival (OS) in subjects treated in doublet and triplet regimens.
- To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival, in doublet and triplet regimens.

3.3 Exploratory

1L Cohort

- To evaluate the safety of nivolumab and sorafenib.
- To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
- To assess antitumor activities of nivolumab vs sorafenib based on results of BICR using mRECIST for HCC.
- To evaluate disease control rate (DCR), duration of disease control, and time to response of nivolumab and sorafenib.
- To evaluate overall survival in subjects who have intrahepatic vs extrahepatic progression for nivolumab and sorafenib.
- To evaluate overall survival in subjects with baseline AFP < 400 ng/mL vs > 400 ng/mL for nivolumab and sorafenib.
- To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
- To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood in subjects with HCC.
- To investigate the potential association between selected biomarker measures in tumor tissue specimens and blood samples and clinical efficacy measures including overall survival.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
- To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab in subjects with advanced HCC.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.

- To assess the subject's cancer-related QoL using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.

Nivo+Ipi Combo Cohort

- To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
- To assess antitumor activities based on results of BICR using mRECIST for HCC.
- To describe the effects of nivolumab plus ipilimumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
- To investigate the pharmacodynamic activity of nivolumab plus ipilimumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
- To assess the relationship between nivolumab plus ipilimumab exposure and measures of hepatic dysfunction.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
- To characterize the pharmacokinetics of nivolumab and ipilimumab in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.

Cabo Combo Cohort

- To estimate the ORR and duration of response in doublet and triplet regimens in subjects with advanced HCC who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
- To assess antitumor activities based on results of BICR using mRECIST for HCC.
- To investigate the potential association between selected biomarker measures, such as MET, VEGFR2 and AXL expression, immune cell composition, tumor mutational burden, etc and clinical efficacy measures including overall survival.
- To describe the effects of doublet and triplet regimens in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
- To investigate the pharmacodynamic activity of doublet and triplet regimens on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.

- To assess the relationship between nivolumab combined with cabozantinib and nivolumab and ipilimumab combined with cabozantinib exposure and measures of hepatic dysfunction.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
- To assess the subject's cancer-related QoL using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.
- To characterize the pharmacokinetics of nivolumab, ipilimumab and cabozantinib in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.

4 ENDPOINTS

4.1 Safety and Tolerability

Safety will be analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, immune mediated adverse events, select adverse events and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP.

4.1.1 Immunogenicity

Refer to Core Safety SAP.

4.1.2 Select AE

Refer to Core Safety SAP.

4.2 Efficacy Endpoints based on Tumor Assessment

Tumor assessment based efficacy endpoints such as ORR, DOR, TTR, and PFS will be determined per RECIST 1.1 or mRECIST for HCC by BICR or investigators. In general, investigator-assessed RECIST 1.1 results will be reported as primary analysis, BICR-assessed RECIST 1.1 results will be reported, and mRECIST results will be reported as secondary or exploratory analyses.

4.2.1 ORR

ORR is defined as the proportion of subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) among all randomized subjects in a population of interest. BOR is defined as the best response designation recorded between the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later. In the case of stable disease (SD), measurements must have met the SD criteria at least once after randomization at a minimum of 7 weeks (49 days) for 1L Cohort and 40 days for Nivo+Ipi Combo Cohort and Cabo Combo Cohort.
Responder is defined as a subject whose BOR is either a CR or PR.

In the 1L Cohort, Tumor imaging assessments will occur 8 weeks from the date of randomization (+/-1 week), then every 8 weeks (+/- 1 week) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression or treatment is discontinued (whichever occurs later).

In the Nivo+Ipi Combo Cohort and Cabo Combo Cohort, tumor imaging assessments will occur 6 weeks from the date of randomization, then every 6 weeks thereafter up to 48 weeks, then it will be every 12 weeks until disease progression or treatment is discontinued (whichever occurs later).

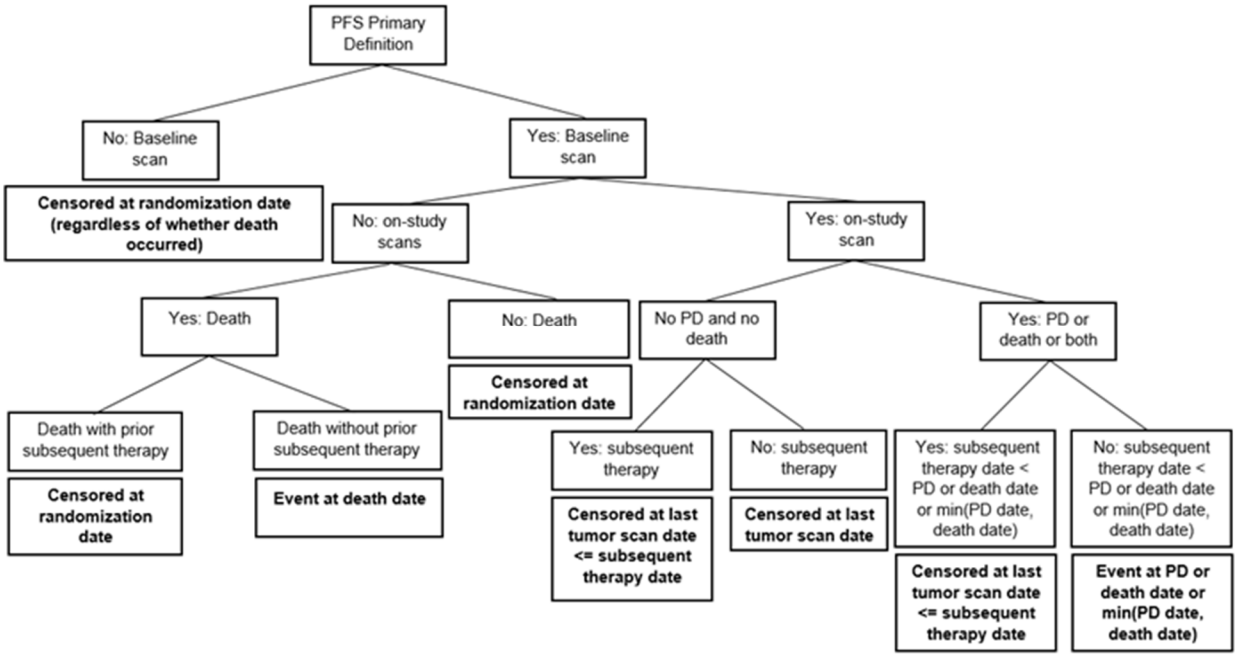
4.2.2 PFS

PFS is defined as the time from the date of randomization to the date of the first objectively documented tumor progression or death due to any cause in all randomized subjects. Subjects who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have baseline tumor assessment will be censored on the date they were randomized. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to subsequent anti-cancer therapy. Censoring rules for the primary analysis of PFS are summarized in Table 4.2.2-1. Further explanation for various censoring scenarios for the primary definition of PFS are presented in Figure 4.2.2-1: Graphical Display of PFS Derivation

Table 4.2.2-1: Censoring Scheme used in PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of the first documented tumor progression	Progressed
No progression and no death	Date of last tumor assessment	Censored
Subsequent anti-cancer therapies started without a prior reported progression	Date of last tumor assessment prior to or on the initiation of the subsequent therapy	Censored
Death without progression and without initiation of subsequent anti-cancer therapy	Date of death	Progressed

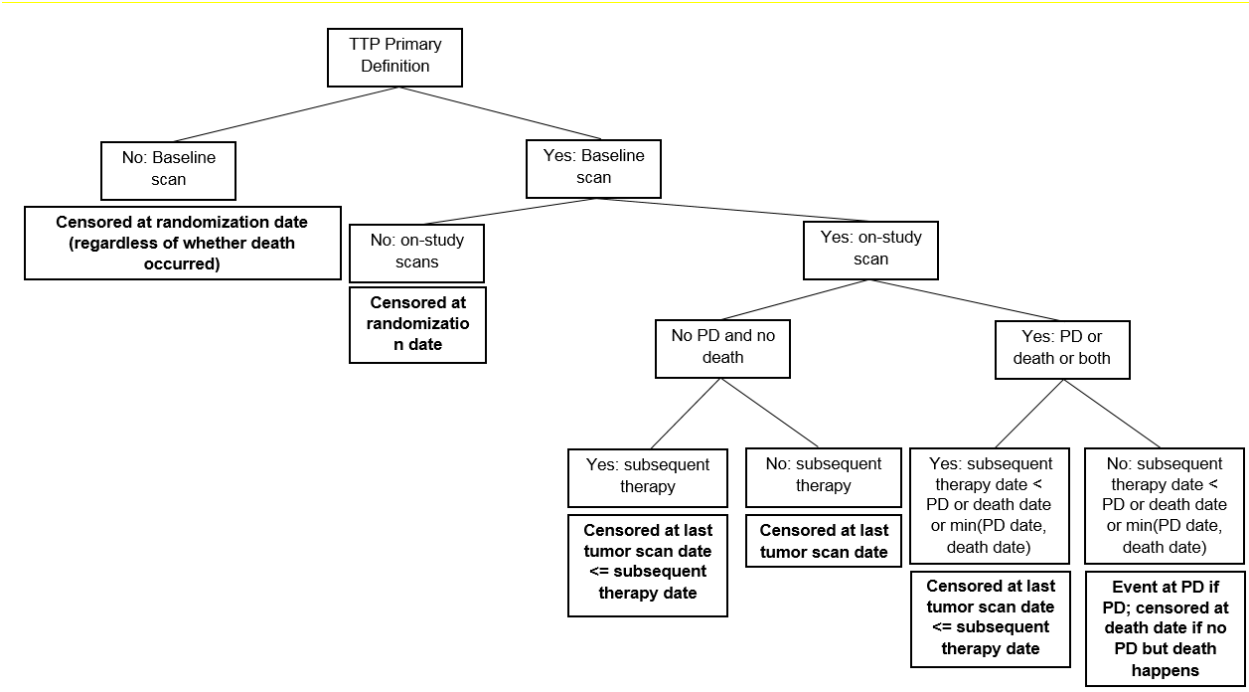
Figure 4.2.2-1: Graphical Display of PFS Derivation



4.2.3 TTP

Time to Progression (TTP) is defined as the time from the date of randomization to the date of the first objectively documented tumor progression in all randomized subjects. The censoring scheme for the primary definition of TTP follows the graphical display in Figure 4.2.3-1: Graphical display of TTP Derivation.

Figure 4.2.3-1: Graphical display of TTP Derivation



4.2.4 DOR

DOR is defined as the time between the date of first documented response (CR or PR as defined in Section 4.2.1) to the date of first documented tumor progression or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored at the same time they will be censored according to the same censor scheme as for the primary definition of PFS (Section 4.2.2). DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) only.

4.2.5 TTR

Time to response (TTR) is defined as the time from randomization to the date of the first confirmed CR or PR. TTR is derived for responders only.

4.2.6 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of subjects whose BOR is CR or PR or SD or NON-CR/NON-PD among all randomized subjects of a population of interest **based on BICR-assessed** BOR. DCR is defined as the proportion of subjects whose BOR is CR or PR or SD among all randomized subjects of a population of interest **based on investigator-assessed BOR**,

4.2.7 Duration of Disease Control

Duration of disease control (DDC) is defined as the time from the date of randomization to the date of the first documented tumor progression or death due to any cause in subjects whose BOR

is CR or PR or SD or NON-CR/NON-PD **based on BICR-assessed BOR or Investigator-assessed BOR**. Disease of these subjects is considered to be controlled till progression or death. DDC follows the same censoring scheme as in for the primary definition of PFS (Section 4.2.2). Therefore, DDC is essentially PFS of subjects whose BOR is CR or PR or SD or NON-CR/NON-PD.

4.3 Efficacy Endpoint of OS

OS is defined as the time from the date of randomization to the date of death due to any cause in all randomized population (see Section 6.3). Subjects who are alive will be censored at the last known alive dates.

4.4 Outcome Research

4.4.1 EuroQoL EQ-5D-3L

Subjects' overall health status will be assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L). EQ-5D essentially has 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations.

In addition, the EQ-5D includes a visual analog scale (EQ VAS) that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health (0 = worst imaginable health state; 100 = best imaginable health state).

4.4.2 FACT-Hep

The FACT-Hep questionnaire will be used to assess the effects of HCC and its treatment on health related quality of life (HRQL). As a generic cancer-related core, the questionnaire includes the FACT-General (FACT-G) to assess symptoms and treatment-related effects impacting physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well being (EWB; six items), and functional well-being (FWB; seven items). In addition, the FACT-Hep includes an 18-item disease-specific hepatobiliary cancer subscale (HCS) that assesses back and stomach pain, gastrointestinal symptoms, anorexia, weight loss, and jaundice.

Each item is rated on a five-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQL, while the FACT-G and HCS scores can be combined to produce a total score for the FACT-Hep, which provides a composite measure of general and targeted HRQL. Higher scores indicate better HRQL.

4.5 PD-L1 expression

Definition of PD-L1 expression is described as follows.

PD-L1 expression missing: Subjects without an available tumor biopsy specimen for PD-L1 evaluation will be considered as PD-L1 expression missing.

For subjects with an available tumor biopsy specimen(s), the following will be considered:

PD-L1 expression is defined as the percent of tumor cell membrane staining. This is referred as *quantifiable PD-L1 expression*. If the PD-L1 staining could not be quantified, it is further classifies as:

Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling

Not evaluable: Tumor biopsy specimen was not optimally collected or prepared (e.g. PD-L1 expression is neither quantifiable nor indeterminate)

Baseline PD-L1 expression: If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to randomization) with a quantifiable result. If more than one baseline PD-L1 expression measurement is available at the same day for a subject, the highest baseline PD-L1 expression measurement will be used. If all specimens for a given subject are either indeterminate or not evaluable, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered not evaluable.

PD-L1 status is a dichotomized variable using a 1% cut-off for quantifiable PD-L1 expression:

- PD-L1 $\geq$ 1 %: $\geq$ 1 % PD-L1 expression
- PD-L1 < 1 %: < 1 % PD-L1 expression

Additional cut off values may also be explored.

4.6 Pharmacokinetics

The Population PK model will be developed from serum concentration.

4.7 Biomarkers

AFP will be measured in blood. HBV and HCV viral load and quantitative HBsAg levels will be measured in the blood of infected patients throughout their duration on the study. Biomarkers within tumor tissue specimens and blood samples will be measured. SNPs may also be measured.

5 SAMPLE SIZE AND POWER

Please see the protocol.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Refer to Core Safety SAP for definitions of baseline period and post baseline period for AEs and evaluations of laboratory tests, pulse oximetry and vital signs.

6.2 Treatment Regimens

The treatment group **as randomized** will be retrieved from the IVRS system.

The treatment group **as treated** will be the same as the treatment group randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 Populations for Analyses

When appropriate, the following definitions of different types of subjects will be applied to different populations of interest defined later in this section:

- **Enrolled Subjects:** Subjects who signed an informed consent form and were registered into the IVRS.
- **Randomized Subjects:** Enrolled subjects who were randomized to any treatment group in the study. This is the type of subjects for analyses of study conduct, study population and efficacy.
- **Treated Subjects:** Randomized subjects who received at least one dose of study drug. This is the type of subjects for analyses of exposure and safety.
- **PK Subjects:** Randomized subjects who are dosed with nivolumab and have serum time-concentration data available.
- **Response Evaluable Subjects**: Randomized subjects who have target lesion(s) assessed at baseline and at least one post-randomization timepoint.
- **PD-L1 Quantifiable Subjects**: Randomized subjects with quantifiable baseline PD-L1 expression, which exclude randomized subjects with missing or indeterminate or not evaluable baseline PD-L1 expression (see Section 4.5).

The following populations are defined in this study per cohort.

- **All Enrolled Population**: All subjects enrolled to a cohort.
- **All Randomized Population:** All subjects randomized to a cohort.

7 STATISTICAL ANALYSES

All analysis will be performed per cohort and there is no integrated analysis across cohorts. The analyses methods described will be applied to each cohort unless otherwise specified. All analyses will be performed using the treatment group as randomized (intent-to-treat) with the exception of extent of exposure (dosing) and safety, for which the treatment group as treated will be used.

7.1 General Methods

Unless otherwise noted, the titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions (i.e. PFS, OS, DOR and DDC) will be estimated using the KM method. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed timepoints (e.g., OS at 12 months) will be derived from the KM estimate along with their corresponding log-log transformed 95% confidence intervals.

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[2].

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site and per month for all enrolled subjects. Randomization date, first dosing date, country, investigational site will be presented in a by-subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all randomized subjects, by treatment group and overall. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings. A by-subject listing will also be produced.

1L Cohort

At Entrance:

- Subjects with ECOG PS > 1.
- Subjects with Child-Pugh B or higher.
- Subjects without evaluable disease at baseline.
- Subjects who received prior systemic therapy.
- Subjects with serum albumin < 2.8 g/dL.
- Subjects with total bilirubin > 3 mg/dL.
- Subjects with AST > 5 times the institutional upper limits of normal.
- Subjects with ALT > 5 times the institutional upper limits of normal.

- Subjects with active co-infection of both hepatitis B and C (detectable HBV surface antigen or HBV DNA and HCV RNA).
- Subjects with active co-infection of Hepatitis D infection and hepatitis B.

On-study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, systemic therapy, radiation therapy, non-systemic therapy for HCC (local only), and surgery for HCC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

Nivo+Ipi Combo Cohort

At Entrance:

- Subjects with ECOG PS > 1.
- Subjects with Child-Pugh B or higher.
- Subjects without evaluable disease at baseline.
- Subjects with active co-infection of both hepatitis B and C (detectable HBV surface antigen or HBV DNA and HCV RNA).
- Subjects with active co-infection of Hepatitis D infection and hepatitis B.
- Subjects with radiotherapy within 2 weeks prior to study drug administration.
- Subjects who are sorafenib naive.
- Subjects with serum albumin < 2.8 g/dL.
- Subjects with total bilirubin > 3 mg/dL.
- Subjects with AST > 5 times the institutional upper limits of normal.
- Subjects with ALT > 5 times the institutional upper limits of normal.

On-study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, systemic therapy, radiation therapy, non-systemic therapy for HCC (local only), and surgery for HCC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

Cabo Combo Cohort

At Entrance:

- Subjects with ECOG PS > 1.
- Subjects with Child-Pugh B or higher.
- Subjects without evaluable disease at baseline.
- Subjects with Active co-infection of both hepatitis B and C (detectable HBV surface antigen or HBV DNA and HCV RNA).
- Subjects with active co-infection of Hepatitis D infection and hepatitis B.
- Subjects with radiotherapy within 2 weeks prior to study drug administration.

- Subjects with serum albumin < 2.8 g/dL.
- Subjects with total bilirubin >= 2 mg/dL.
- Subjects with AST > 5 times the institutional upper limits of normal.
- Subjects with ALT > 5 times the institutional upper limits of normal.

On-study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, systemic therapy, radiation therapy, non-systemic therapy for HCC (local only), and surgery for HCC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

7.2.3 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason of not being randomized.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized. This analysis will be performed only on randomized subjects only.

Number of subjects who discontinued treatment along with corresponding reason will be tabulated by treatment group as treated.

A subject listing for all randomized subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized.

7.2.4 Demographics and Other Baseline Characteristics

The following baseline characteristics will be summarized by treatment group as randomized. All baseline presentations identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age categories (<65, ⩾65 and <75, ⩾75)
- Gender (male, female)
- Race (White, Black/African American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Asian Indian, Chinese, Japanese, Asian Other, Other)
- Weight (descriptive statistics)
- Baseline ECOG Performance Status (0, 1, > 1)

7.2.4.1 HCC Etiology

HCC etiology is a description of disease subtype at baseline and includes HBV-infected, HCV-infected and uninfected. HCC etiology is derived based on risk factors as collected on CRF, and described below:

- Etiology is HBV-infected if HBV is a risk factor, and HCV is not included as a risk factor
- Etiology is HCV-infected if HCV is a risk factor, and HBV is not included as a risk factor

- Etiology is HBV-HCV if both HBV and HCV are included as risk factors
- Etiology is uninfected if neither HBV nor HCV is considered as a risk factor

7.2.4.2 HCC Disease Characteristics

The following disease characteristics will be summarized. All available data will be listed.

- HCC Risk Factors
- Vascular invasion (Yes/No)
- Extrahepatic spread (Yes/No)
- VI or EHS (Yes/No. Yes: if either VI or EHS is Yes; No: if both VI and EHS are No)
- Disease etiology (Uninfected/HCV-infected/HBV-infected/HBV-HCV)
- Child-Pugh Score (Class and Score)
- Liver Nodules (Yes/No)
- BCLC (Barcelona clinic liver cancer) stage (0, A, B, C, D)
- AFP (descriptive statistics)
- AFP Category (≥ 200, < 200, ≥ 400, < 400)
- Time from initial diagnosis of HCC to randomization
- Time from most recent anti-cancer therapy to randomization
- Time from Sorafenib to randomization (for Nivo+Ipi Combo cohort and Cabo Combo cohort)
- Time from most recent systemic therapy to randomization (for Nivo+Ipi Combo cohort and Cabo Combo cohort)

7.2.5 Medical History and Pre-treatment Events

General medical history will be listed by subject. HCC or prior treatment-related pre-treatment events will be summarized by worst CTC grade, system organ class and preferred term.

7.2.6 Prior Anti-Cancer Therapies

Prior anti-cancer therapies include the following therapies and will be summarized.

- Prior systemic cancer therapy (Yes/No)
- Prior surgery therapy (Yes/No)
- Prior radiotherapy (Yes/No)
- Prior non-systemic treatment related to HCC local only (Yes/No)

7.2.7 Baseline Examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria and by treatment group.

7.2.8 Discrepancies Between IVRS and CRF Stratification Factors

A summary table (cross-tabulation) by treatment group as randomized for stratification factor will be provided to show any discrepancies between what was reported through IVRS and what was derived with CRF data.

7.3 Extent of Exposure

Analyses in this section will be performed in all treated subjects by treatment group as treated. Table 7.3-1 and Table 7.3-2 summarize the key parameters used to calculate dosing data.

Nivo 1 + Ipi 3 Q3 Arm and Nivo 3 + Ipi 1 Q3 Arm Only:

In the above two arms of the combo cohort, Nivolumab is first dosed in weighted dose with Ipilimumab, referred to as combo period, and then dosed in the flat dose of 240mg without Ipilimumab, referred to as mono period. Summary of nivolumab exposure will be performed separately within the combo and mono periods.

Nivo+Ipi Combo and Cabo Combo Cohorts Only:

Duration of study therapy per arm, defined as the latest dosing date - the earliest dosing date + 1, will be derived and summarized. The dosing date is selected from any study medication administered in that arm.

Table 7.3-1: Statistics of Extent of Exposure - Weighted Dose

	Nivolumab or Ipilimumab Weighted Dose
Dose Level and Schedule	L mg/kg every K weeks[a]
Dose	Dose (mg/kg) is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the CRF
Number of dose received	Number of infusions received in the study. Interrupted infusions are counted as one infusion.
Duration of study medication	last dose date - first dose date +1
Cumulative dose	the sum of all actual dose levels received in the unit of mg/kg
Dose intensity	Cum dose (mg/kg) / [(Last dose date - Start dose date + 7K)L / (7K)] x 100
Relative dose intensity (%)	Dose intensity / intended dose * 100

[a] L could be 1 or 3 for both Nivolumab and Ipilimumab; K is 2 or 3 for Nivolumab and could be 3 or 6 for Ipilimumab

Table 7.3-2: Administration of study therapy - Flat Dose

	Nivolumab flat dose	Sorafenib	Cabozantinib
Dosing schedule per protocol	240mg every 2 weeks	400mg BID	40mg QD
Dose	*Dose (mg)* is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the CRF.	*Dose (mg)* is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the CRF.	*Dose (mg)* is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the CRF.
Cumulative Dose	*Cum dose (mg) is* sum of the doses (mg) administered to a subject during the treatment period.	*Cum dose (mg) is* sum of the doses (mg) administered to a subject during the treatment period.	*Cum dose (mg) is* sum of the doses (mg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg) / [(Last dose date - Start dose date + 14) x 240 / 14] x 100	Cum dose (mg) / [(Last dose date - Start dose date + 1) x 800] x 100	Cum dose (mg) / [(Last dose date - Start dose date + 1) x 40] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1	Last dose date - Start dose date +1

7.3.1 Administration of Study Therapy

The following parameters will be summarized by treatment group (descriptive statistics):

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ⩾ 110%.
- Number of doses received
- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a KM curve whereby the last dose date will be the event date for subjects who discontinued study therapy and last dose date will be the censoring date for subjects who are still on study therapy. Median duration of treatment and associated 95% CI will be provided using the method for time to event distributions (in Section 7.1).
- A by-subject listing of dosing of study medication (record of study medication and dose change) and a listing of batch number will be also provided. Infusion details will also be provided for nivolumab.
- Time from randomization to first dose of study medication (0 to 3 days, 4-5 days, 6-7 days, 8-14 days, 15-21 days, 22-28 days, > 28 days).

7.3.2 Modification of Study Therapy

7.3.2.1 Dose delay

Definition of dose delay is given in Table 7.3.2.1-1.

For nivolumab and ipilimumab, a dose given more than 3 days after the intended dose date will be considered a delay. Dose delays will be divided into following categories: 4 - 7 days, 8 - 14 days, 15 - 42 days, 43 - 84 days, and ⩾ 85 days. Dose delay events and reason for dose delay will be retrieved from CRF dosing pages. Number of subjects with at least one dose delayed, number of dose delayed per subject, length of delay, and reason for dose delay will be summarized.

For sorafenib and cabozantinib, dose delay will have two more categories: 0 day, 1 - 3 days. Number of subjects with dose delayed, length of delay, and reason for dose delay will be summarized.

Table 7.3.2.1-1: Definition of Dose Delay

Cohort	Arm		
1L	Nivolumab	Nivolumab	duration of interval from prior dose in days minus 14 days
	Sorafenib	Sorafenib	duration of interval from prior most recent dose in days
Nivo+Ipi Combo	Nivo 1 + Ipi 3 Q3 or Nivo 3 + Ipi 1 Q3	Nivolumab	Combo period: duration of interval from prior dose in days minus 21 days Mono period: duration of interval from prior dose in days minus 14 days
		Ipilimumab	Combo period: duration of interval from prior dose in days minus 21 days

Table 7.3.2.1-1: Definition of Dose Delay

Cohort	Arm		
	Nivo 3 Q2 + Ipi 1 Q6	Nivolumab	duration of interval from prior dose in days minus 21 days
		Ipilimumab	duration of interval from prior dose in days minus 42 days
Cabo Combo	Doublet or Triplet	Nivolumab	duration of interval from prior dose in days minus 14 days
		Ipilimumab	duration of interval from prior dose in days minus 42 days
		Cabo	duration of interval from prior most recent dose in days

7.3.2.2 Dose modifications

No dose modifications for nivolumab and ipilimumab are allowed.

For sorafenib, when dose reduction is necessary during the treatment of HCC, the sorafenib dose should initially be reduced to two tablets of 200 mg sorafenib once daily. For further dose reductions, refer to the sorafenib SmPC or locally approved product label for additional details. Number of subjects receiving sorafenib with at least one dose reduction and reasons for dose reduction will be summarized for sorafenib treatment group.

For cabozantinib, please refer to the protocol for dose mofication, and the same analysis as sorafenib will be provided to summarize its dose reduction.

7.3.2.3 Infusion interruptions and rate changes for nivolumab and ipilimumab

The following parameters will be summarized for nivolumab and ipilimumab:

- Number of subjects with at least one dose infusion interruption, number of infusion interruptions per subject, and the reason for interruption.
- Number of subjects with at least one IV infusion rate reduction, number of IV infusion rate reduction per subject, and the reason for reduction.

7.3.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.4 Efficacy

Unless otherwise specified, all analyses are based on treatment group as randomized. Efficacy results will be presented by cohort and potentially etiology.

7.4.1 ORR

Primary analysis of ORR is based on investigator assessments per RECIST 1.1 and sensitivity analysis of ORR is based on BICR assessments per RECIST 1.1. ORR will be presented along with its corresponding two sided 95% confidence interval using the Clopper-Pearson method for each treatment arm. BOR will be summarized by response category.

To assess concordance between BICR and investigator assessments, BOR will be cross-tabulated by assessment providers (BICR vs Investigator). Concordance Rate of Responders will be computed as the frequency with which Investigator and BICR agree on classification of a subject as responder/non responder as a proportion of the total number of subjects assessed.

7.4.1.1 Subgroup Analysis

ORR and its 95% confidence interval will be presented for the following categories to investigate potential different treatment effects. Results will be shown for different disease types and select efficacy population.

- Geography (Asia vs Non-Asia)
- Region (US/Canada, Europe, Asia, Rest of the World)
- Age categorization I (< 65, ≥ 65)
- Age categorization II (< 65, ≥ 65 - < 75, ≥ 75)
- Age categorization III (< 65, ≥ 65 - < 75, ≥ 75 - < 85, ≥ 85)
- Age categorization IV (< 30, ≥ 30 - < 45, ≥ 45 - < 60, ≥ 60)
- Gender (Male vs. Female)
- Race (White, Black/African American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Asian Indian, Chinese, Japanese, Asian Other, Other)
- Race (Asian/Non-Asian)
- ECOG (0, 1, > 1)
- Etiology (HCV-infected, HBV-infected, uninfected, HBV-HCV) from CRF
- Vascular invasion and/or extrahepatic spread (present or absent) from CRF
- AFP categorization I at baseline (AFP > 200 ng/ml, and AFP ⩽ 200 ng/ml)
- AFP categorization II at baseline (AFP < 400 ng/ml and AFP ≥ 400 ng/ml)
- BCLC category at baseline
- CP Score
- Initial Diagnosis (>=5 Years, <5 Years)

7.4.2 TTR

Summary statistics of TTR will be provided. Swimmer plot of time to and duration of response will be provided for responders only.

7.4.3 DCR

DCR will be presented along with their corresponding two-sided 95% confidence intervals using the Clopper-Pearson method for each treatment group and select efficacy population.

7.4.4 DOR, PFS, TTP and OS

DOR, PFS, TTP and OS distribution will be estimated using Kaplan Meier techniques. Median survival time along with 95% CI will be constructed based on Brookmeyer and Crowley method using log-log transformation.

DOR rates, PFS rates and OS rate at fixed timepoints will be derived from the Kaplan Meier estimate and corresponding two-sided 95% confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survival function. Timepoints of PFS rates include 3, 6, 9, 12, 18 and 24 months. OS rates timepoints include 6, 9, 12, 18, 24, 30, 36, 48 and 60 months. Minimum follow-up (defined below) must be longer than a time period to generate a rate. Timepoints of DOR rate include 6, 12, 18, and 24 months.

PFS Only:

The source of progression (death vs progression) will be summarized by treatment group.

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each treatment group using following categories:

- Never treated
- On-study (on treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, other).
- Received subsequent anti-cancer therapy

7.4.5 Target Lesion Change

Spider plot of tumor target lesion percent change from baseline will be provided. Waterfall plot of the best tumor percent change from baseline will also be provided. These analyses will be conducted respectively for BICR assessments and investigator assessments.

7.4.6 Subject Follow-up

The study minimum follow-up will be reported. The minimum follow-up is defined as the time interval between the last patient's randomization date and the clinical cutoff date.

The extent of follow-up is defined as the time between randomization date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all randomized subjects.

The currentness of follow-up for survival, defined as the time between last OS contact (ie, last known date alive or death date) and data cutoff date (defined by last patient last visit date), will be summarized by treatment group. Subjects who died before data cutoff date or subjects whose last known date alive is on or after data cut-off date will have currentness of follow-up set to zero. The

currentness of follow-up will be categorized into the following categories: 0 day, 1 - 30 days, 1 - 3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

7.4.7 Subsequent Therapy

Subsequent therapy will be summarized by treatment group. The following information pertaining to subsequent therapies will be summarized:

- Systemic anti-cancer therapy by drug name
- Surgery
- Radiotherapy
- Non-systemic treatment for HCC (local only)

A by-subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5 Safety

The analyses in this section will be conducted for the treated population.

7.5.1 Deaths

See Core Safety SAP.

7.5.2 Serious Adverse Events

See Core Safety SAP.

7.5.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.5.4 Adverse Events Leading to Dose Modification

See Core Safety SAP.

7.5.5 Adverse Events

See Core Safety SAP.

7.5.6 Select Adverse Events

See Core Safety SAP.

7.5.7 Immune modulating medication

See Core Safety SAP.

7.5.8 Multiple Events

See Core Safety SAP.

7.5.9 Other Events of Special Interest

See Core Safety SAP.

7.5.10 Immune-Mediated Adverse Events

See Core Safety SAP.

7.5.11 Laboratory Parameters

See Core Safety SAP.

7.5.12 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.5.13 Immunogenicity Analysis

See Core Safety SAP.

7.5.14 Pregnancy

See Core Safety SAP.

7.5.15 Adverse Events By Subgroup

See Core Safety SAP. Region subgroups are formed by US/Canada vs. Europe vs Asia vs. Rest of the World.

7.6 Pharmacokinetics

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab. In addition, exposure-response analyses with selected efficacy and safety endpoints may be conducted. Results of population PK and exposure response-analyses will be reported separately.

7.7 Biomarkers

Analyses for baseline PD-L1 expression are described below. Analyses of exploratory biomarkers other than the ones specified below may be performed and reported external to the clinical study report.

7.7.1 PD-L1 Expression

The definition of PD-L1 expression and PD-L1 status is described in Section 4.5. Analyses of PD-L1 expression are descriptive in nature and intended to examine the distribution of PD-L1 expression and assess potential association between PD-L1 expression and efficacy measures. All the analyses will be based on baseline PD-L1 expression.

7.7.1.1 Analyses of PD-L1

Analyses of PD-L1 will include:

1. Examine the distribution of PD-L1 expression
2. Assess potential association between PD-L1 expression and efficacy measures
3. Evaluate the potential predictive relationship of the PD-L1 status and efficacy measures

1. Descriptive statistics of PD-L1 expression and PD-L1 status

- Listing of all PD-L1 IHC data, all randomized subjects
- Summary of tumor specimen acquisition and characteristics, all randomized subjects
- Summary statistics of PD-L1 expression by treatment group as randomized and overall, all PD-L1 quantifiable subjects
- Frequency of PD-L1 categorization or status (≥ 1%, < 1%), including 'missing', 'indeterminate' and 'not evaluable', by treatment group as randomized and overall, all randomized subjects

2. Evaluation of associations between PD-L1 status and efficacy measures

Analyses will be based on all randomized subjects if not otherwise specified. Each analysis will be performed for the subgroups listed below if not otherwise specified.

- Each PD-L1 status subgroup
- PD-L1 expression missing or indeterminate or not evaluable subgroup

Analyses for ORR per Investigator RECIST 1.1:

For each of the subgroups:

- Frequency and percentage of BOR will be summarized for each treatment group as randomized.
- ORR will be computed by treatment group as randomized along with exact 95% CIs using the Clopper-Pearson method.

The above analyses will be repeated by etiology (HCV-infected, HBV-infected, uninfected).

For PD-L1 quantifiable subjects, box plots of PD-L1 expression versus response status will be provided by treatment group as randomized.

Analyses for OS, DOR, and PFS per RECIST 1.1:

For each of the subgroups:

- OS, DOR, and PFS per RECIST 1.1 curves will be estimated using the KM product limit method for each treatment group. Two-sided, 95% confidence intervals for median values will be computed by Brookmeyer and Crowley method.

7.8 Outcome Research Analyses

The analysis of EQ-5D and FACT-Hep data will be performed in all randomized subjects who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

7.8.1 EQ-5D

EQ-5D data will be described by treatment group as randomized in the following ways:

- EQ-VAS scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of subjects reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D dimensions at each assessment time point. Subjects with missing data will be excluded from the analysis.
- A by-subject listing of the level of problems in each dimension, corresponding EQ-5D health state (ie, 5-digit vector), and EQ-VAS score will be provided.

7.8.2 FACT-Hep

FACT-Hep data will be summarized by treatment group as randomized in the following way:

- Distributions of responses by category will be examined for each treatment group for the single item GP5 ("I am bothered by side effects of treatment."). The number and proportion of subjects will be summarized for each response category at each assessment time point.
- Descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum) will be presented for the derived score for the following five dimensions at each assessment time point: physical well-being (PWB), social/family well-being (SWB), emotional well being (EWB), functional well-being (FWB), disease-specific hepatobiliary cancer subscale (HCS).
- FACT-Hep total scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- The number and proportion of subjects achieving a change from baseline ≥ 8 points in FACT-Hep total score will be summarized at each post-baseline assessment time point.

8 CONVENTIONS

8.1 Date Imputation

The following conventions may be used for imputing partial dates for analyses requiring dates:

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[3].
- Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[4].
- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive day and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known date alive day
  - If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive day
- For date of progression, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For other partial/missing dates, the following conventions may be used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, “July 1” will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

8.2 Duration Calculation and Conversion

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

8.3 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

8.4 Analysis Software

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

The analyses in the ORR population described in this SAP will be included in a clinical study report based on the ORR population except where otherwise noted. The analyses in the all randomized population described in this statistical analysis plan will be included a clinical study report based on all randomized population except where otherwise noted. Additional exploratory analyses may be performed.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	Lixin Lang	Initial version dated 01-MAR-2017

11 REFERENCES

[1] Independent Radiology Review Charter - BMS CA209040.

[2] Clopper CJ and Pearson E S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934

[3] Adverse Event Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

[4] Non-Study Medication Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.2 April 24, 2012.