

Atezolizumab in a CoHort of pretreated, advanced, non-small cell lung cancer patients with rare Histological Subtypes (CHANCE trial)

Francesco Gelsomino^{ID}, Giuseppe Lamberti^{ID}, Marcello Tiseo, Danilo Rocco, Giulia Pasello, Fabiana Letizia Cecere, Antonio Chella, Giada Grilli, Marcella Mandruzzato, Michele Tognetto, Marina Chiara Garassino, Marianna Macerelli, Silvia Novello, Fausto Roila, Ida Colantonio, Francesco Grossi, Michelangelo Fiorentino and Andrea Ardizzoni

Abstract

Background: Although immunotherapy with immune-checkpoint inhibitors (ICIs) has profoundly changed the therapeutic scenario in the treatment of advanced non-small cell lung cancer (NSCLC), trials of ICIs only enrolled NSCLC patients with common histology. Atezolizumab was approved by the United States Food and Drug Administration (US FDA) in October 2016 and by the European Medicines Agency (EMA) in September 2017 for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy, regardless of PD-L1 expression.

Methods: We designed a single-arm, multicenter, two-stage phase II study and plan to enroll 43 patients. The primary objective of the study is to evaluate the antitumor activity of atezolizumab in advanced NSCLC patients with rare histology subtypes. Patients with prior atezolizumab or ICI treatment and with untreated, symptomatic, or progressing brain metastases will be excluded. The primary endpoint is disease control rate. Secondary objectives are toxicity and safety, overall response rate, progression-free survival, overall survival, and time to progression. Diagnosis of NSCLC with rare histology will be confirmed by central pathology revision, and will include: colloid carcinoma, fetal adenocarcinoma, non-endocrine large cell carcinoma, sarcomatoid carcinoma, salivary gland-type tumor, lymphoepithelioma-like carcinoma, and NUT-nuclear protein in testis carcinoma. Archival tumor tissue is required for correlative studies of PD-L1 expression on tumor cells and tumor infiltrating lymphocytes.

Conclusions: Therapeutic options in NSCLC with rare histology subtypes, to be assessed in specifically designed trials, are an unmet need. This trial will help elucidate the role of atezolizumab as a viable option in this setting.

Keywords: atezolizumab, immune checkpoint, immunotherapy, PD-L1, rare histologic NSCLC subtypes

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Introduction

Immune-checkpoint inhibitors (ICIs) enhance immune system response against tumor cells and have dramatically changed the therapeutic

algorithm of non-small cell lung cancer (NSCLC). Along with improvement in outcomes, ICIs have a toxicity profile different from standard chemotherapy and are usually better tolerated.

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Correspondence to:

Francesco Gelsomino
Medical Oncology Unit,
Policlinico S.Orsola-
Malpighi, Via Albertoni 15,
Bologna, 40138, Italy
francesco_gelsomino@
aosp.bo.it

Giuseppe Lamberti
Giada Grilli
Marcella Mandruzzato
Michele Tognetto
Andrea Ardizzoni
Medical Oncology Unit,
Policlinico S.Orsola-
Malpighi, Bologna, Italy

Marcello Tiseo
Medical Oncology Unit,
Azienda Ospedaliero-
Universitaria di Parma,
Parma, Italy

Daniilo Rocco
Onco-Pneumology Unit,
AORN Monaldi-Cotugno
Hospital, Napoli, Italy

Giulia Pasello
Medical Oncology Unit 2,
Istituto Oncologico Veneto,
Padova, Italy

Fabiana Letizia Cecere
Medical Oncology Unit,
IFO – Istituto Regina Elena,
Roma, Italy

Antonio Chella
Pneumology Unit, Azienda
Ospedaliero-Universitaria
Pisana, Pisa, Italy

Marina Chiara Garassino
Medical Oncology
Department, Fondazione
IRCCS Istituto Nazionale
dei Tumori, Milano, Italy

Marianna Macerelli
Medical Oncology
Unit, Azienda Sanitaria
Universitaria Integrata di
Udine, Udine, Italy

Silvia Novello
Thoracic Oncology Unit,
Azienda Ospedaliero-
Universitaria S. Luigi
Gonzaga di Orbassano,
Torino, Italy

Fausto Roila
Medical Oncology Unit,
Azienda Ospedaliera di
Perugia, Perugia, Italy

Ida Colantonio
Medical Oncology
Department, Azienda
Ospedaliera S. Croce e
Carle, Cuneo, Italy

Francesco Grossi
Medical Oncology Unit,
Fondazione IRCCS
Ca'Granda Ospedale
Maggiore Policlinico,
Milano, Italy

Michelangelo Fiorentino
Anatomical Pathology
Unit, Ospedale Maggiore,
AUSL Bologna, Bologna,
Italy

In chemo-naïve metastatic NSCLC patients, pembrolizumab, a monoclonal antibody against programmed death 1 (PD-1), is the standard of therapy if programmed death ligand 1 (PD-L1) is expressed in $\geq 50\%$ of tumor cells.¹ More recently, pembrolizumab or atezolizumab, an anti-PD-L1 monoclonal antibody, added to standard first-line platinum-based chemotherapy showed an increase in survival regardless of PD-L1 expression in both squamous and non-squamous NSCLC.²⁻⁴

In the second-line setting, an improved survival over standard second-line chemotherapy with docetaxel was observed in patients treated with nivolumab, an anti-PD-1 monoclonal antibody, atezolizumab, irrespective of PD-L1 expression, and with pembrolizumab in tumors with PD-L1 $\geq 1\%$.⁵⁻⁸ In particular, in a phase III trial of atezolizumab in advanced NSCLC patients (OAK study), survival was longer in patients treated with atezolizumab than in those treated with docetaxel (13.8 *versus* 9.6 months, respectively; HR: 0.73, $p=0.0003$).⁷ The survival benefit was consistent regardless of histology and PD-L1 expression and was associated with a lower incidence of treatment-related and severe adverse events (AEs). In the atezolizumab group, 58 patients (14%) had an objective response, while in 150 (35%) disease was stable. Although the group deriving durable survival benefit from atezolizumab was enriched in patients with responsive disease and those with a higher PD-L1 score, long-term survivors (i.e. patients with an OS ≥ 24 months) included also patients with stable or progressive disease (PD) as best response on atezolizumab and those with no PD-L1 expression.⁹

Finally, there is no study specifically designed for NSCLC with rare histology to date, since all of the mentioned studies included NSCLC patients with common histology. Data on safety and activity of ICIs in NSCLC with rare histology are lacking.

We present the design of a study that aims to assess atezolizumab activity and its safety and tolerability profile in NSCLC with rare histology.

Material and methods

Objectives

The primary objective of this study is to evaluate activity of atezolizumab in patients with pre-treated advanced NSCLC with rare histology subtypes.

Secondary objectives are evaluation of safety and efficacy of atezolizumab in patients with pre-treated advanced NSCLC with rare histology subtypes.

Study design

The trial is a multicenter, prospective, single-arm phase II study which is summarized in Figure 1. The estimated sample size will be approximately 43 subjects, to be enrolled in 12 high-volume lung cancer Italian centers.

Endpoints

The primary endpoint is an investigator-assessed disease control rate (DCR) according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1).¹⁰ DCR is defined as the sum of patients with complete response (CR), partial response (PR) or stable disease (SD) out of the patients in the modified intention-to-treat (mITT) population.

Secondary endpoints include toxicity, objective response rate (ORR), overall survival (OS), time to progression (TTP), and progression-free survival (PFS).

Frequency and severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be assessed for safety evaluation. ORR is defined as the sum of patients with CR or PR out of the patients in the mITT.

OS is defined as the time from enrollment in the trial to death by any cause. TTP is defined as the time from enrollment to objective tumor progression and PFS is the time from enrollment to objective tumor progression or death from any cause.

Exploratory objectives and biomarker analysis

To enter the study, PD-L1 expression assessment by local laboratory immunohistochemistry staining is mandatory, but patients will be enrolled regardless of PD-L1 expression. Archival tumor tissue is required before enrollment to assess PD-L1 expression. Two PD-L1 immunohistochemistry assays will be used: VENTANA (Ventana Medical Systems, Inc, Tucson, AZ, USA) SP142 and SP263 antibodies. SP142 antibody PD-L1 expression assessment will be used because it is the atezolizumab companion

This study is an open-label , multicentre, phase II study

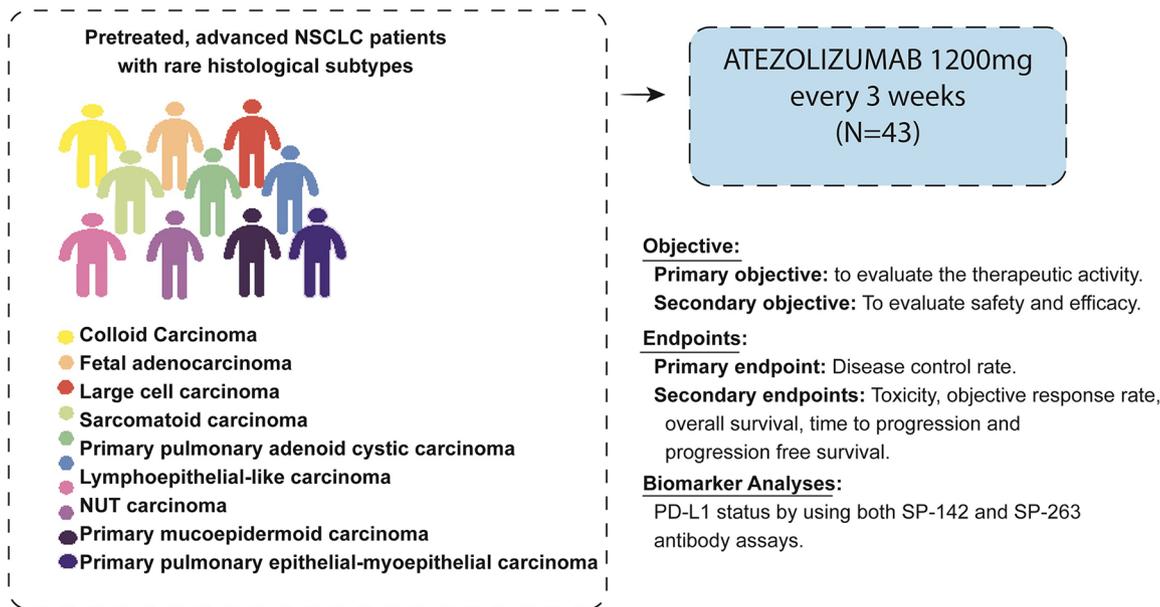


Figure 1. CHANCE study: patients' enrollment and objectives.

diagnostic assay. Accordingly, tumor cells expressing PD-L1 will be scored as a percentage of total tumor cells (TC3 \geq 50%; TC2 \geq 5% and $<$ 50%; TC1 \geq 1% and $<$ 5%; TC0 $<$ 1%) while tumor-infiltrating immune cells expressing PD-L1 will be scored as a percentage of tumor area (IC3 \geq 10%; IC2 \geq 5% and $<$ 10%; IC1 \geq 1% and $<$ 5%; IC0 $<$ 1%). By using SP263 antibody, PD-L1 status will be considered positive in the presence of membrane staining in at least 1% of total tumor cells (\geq 1%, \geq 5%, \geq 10%) and the percentage of positive tumor cells will be annotated for correlative analysis. PD-L1 expression on tumor cells, tumor infiltrating lymphocytes (TILs), and its correlation with PD-L1 tumor expression, and their value as predictive marker of tumor response will be explored. Only samples with a tumor-cell count of \geq 100 cells will be processed. Evaluation of the staining will be performed by trained pathologists using the net percentage of positive tumor cells over the entire tumor cell population and the presence and the number of positive TILs per high power field.

Eligibility criteria

Patients must have a locally advanced, relapsed, or metastatic NSCLC with histologically proven rare subtypes and have experienced disease

progression during or after at least one previous standard chemotherapy line.

Eligible NSCLC rare histology subtypes are defined according to World Health Organization (WHO) 2015 classification and include: colloid carcinoma (or adenocarcinoma with colloid features), fetal adenocarcinoma (or adenocarcinoma with fetal features), large cell carcinoma (non-neuroendocrine), sarcomatoid carcinoma (pleomorphic, spindle cell, and/or giant cell carcinoma, carcinosarcoma, pulmonary blastoma), salivary gland-type tumor (mucoepidermoid carcinoma, adenoid cystic carcinoma, epithelial-myoeplithelial carcinoma), other, and unclassified (lymphoepithelioma-like carcinoma, NUT-nuclear protein in testis carcinoma). Central pathology review and confirmation of histology subtype by a trained pathologist are mandatory.

Patients who already received atezolizumab or another ICI for their disease, those on treatment with immunosuppressive agents, with untreated symptomatic and/or progressive brain metastases or with carcinomatosis meningitis, with a history of past or active autoimmune disease, idiopathic pulmonary fibrosis or organizing pneumonia, or positive tests for viral hepatitis or HIV infection are excluded.

Eligibility criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> - Advanced, relapsed or metastatic NSCLC – stage IIIB/IV - Histological diagnosis of rare subtypes - Availability of tumor block or slides for histological confirmation and PD-L1 expression - Age \geq 18 years - Life expectancy \geq 12 weeks - At least one measurable target lesion according to RECIST v1.1 - Progressive disease during or after at least one previous standard chemotherapy line - ECOG \leq 2 - Adequate renal, hematologic and hepatic functions 	<ul style="list-style-type: none"> - Treatment with immunosuppressive agents - Untreated, symptomatic and/or progressive brain metastases, or with carcinomatous meningitis - History of autoimmune disease - Prior organ transplantation - Known human immunodeficiency virus (HIV) infection or positive test for hepatitis B virus or hepatitis C - History of idiopathic pulmonary fibrosis or organizing pneumonia

Figure 2. Eligibility criteria.

Key Inclusion and Exclusion Criteria are summarized in Figure 2.

Treatment

Eligible patients will be registered to receive an intravenous infusion of atezolizumab at 1200 mg flat dose once every 3 weeks (\pm 3 days). Treatment will be continued until PD according to RECIST v1.1 criteria, intolerable toxicity, patient refusal, or investigator's decision.

Follow-up and assessment

Radiological assessment will be performed by computed tomography scan every 6 weeks (\pm 1 week) until 1 year and every 8 weeks (\pm 1 week) thereafter. In presence of investigator-assessed PD, a radiographic confirmation of progression will be performed within 6 weeks. If PD is confirmed, atezolizumab treatment will be permanently discontinued. At the time of the evidence of PD, treatment beyond progression will be allowed in the presence of all of the following criteria: clinical benefit, good tolerance to study drug, stable performance status and absence of rapid disease progression, defined as \geq 2-fold increase of tumor growth rate.¹¹ In case of treatment beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD and/or the development of new measurable lesions. A blinded independent radiological committee review will be performed retrospectively to confirm the type of response, as per investigator assessment. The study recruitment period is expected to be approximately 24 months and the duration of the study of

48 months, with an additional survival follow-up until 6 months after the last subject receives the last dose of atezolizumab, so that results about primary endpoint are expected by the end of 2021.

Statistical analysis

According to the Simon's two stage design, the null hypothesis that the true DCR is \leq 50% will be tested against a one-sided alternative. In the first-stage, 15 patients will be accrued. If there are 8 or fewer patients with disease control (CR + PR + SD) in these 15 patients, the study will be stopped early for futility. Otherwise, 28 additional patients will be accrued for a total of 43 patients. The null hypothesis will be rejected if 27 or more patients with disease control (CR + PR + SD) are observed in 43 patients. This design yields a type I error rate of 0.050 and power of 0.804 when the true disease control rate is 0.70. Accrual will not be stopped during the first-stage analysis in order to avoid both losing patients who could benefit from treatment and slowing down the subsequent enrolment.

For the primary endpoint and all secondary endpoints, the mITT population will be analyzed, which includes all patients enrolled in the trial who received at least one dose of the study drug.

Ethical considerations

The protocol has been written, and the study will be conducted in compliance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice

(GCP). The protocol will be approved by the local review board of each participating center. Written informed consent is obtained from all patients before any screening or inclusion procedures.

The trial is an independent study sponsored by Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), which received an unrestricted grant from ROCHE. This protocol was registered in the European Clinical Trials Database (EudraCT) with number 2018-002607-34 and with ClinicalTrials.gov identification number: NCT03976518.

Discussion and conclusion

Immunotherapy with ICIs has been consolidating its role in the treatment of squamous and non-squamous NSCLC over the last few years across different settings and treatment lines. Atezolizumab as monotherapy is currently indicated for the treatment of locally advanced or metastatic NSCLC progressing on or after a prior chemotherapy (and an EGFR- or ALK-directed targeted therapy in presence of sensitizing Epidermal growth factor receptor (*EGFR*) or Anaplastic Lymphoma Kinase (*ALK*) genetic alterations). However, data about atezolizumab treatment, as well as other ICIs, in NSCLC of rare histology are lacking and whether these treatments can be an option for these patients is unknown. Few case reports, particularly in patients with pulmonary sarcomatoid and lymphoepithelioma-like carcinomas, have reported an encouraging clinical activity of ICIs in these rare populations.^{12–14} The significant expression of PD-L1 associated with either high mutational load^{15,16} or Epstein–Barr positive infection^{17–19} could explain the potential activity of ICIs in these rare histologies. The DART study is an ongoing phase II basket trial of dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) blockade in rare tumors, including also those of pulmonary origin.²⁰ As of September 4th, 2019, cohorts including salivary gland-type, adenoid cystic and neuroendocrine carcinomas have been closed to accrual. In the cohort of neuroendocrine carcinoma (33 patients), including also six patients with a lung tumor as the primary site, overall response rate was 24%. Interestingly, objective responses were reported only in patients with high-grade neuroendocrine carcinomas (8/19, 42%).²¹ Based on lung primary origin, the study is currently recruiting among cohorts of sarcomatoid, adenocarcinoma *in situ*/minimally

invasive adenocarcinoma/lepidic, or invasive mucinous adenocarcinoma (ClinicalTrials.gov Identifier: NCT02834013).

CHANCE trial is a prospective study enrolling patients with different rare histology cancers of only lung origin. DCR has been defined as the primary end-point of the study, based on the evidence reported from OAK trial in which the patients who obtained stable disease as the best response on atezolizumab had a chance to have a long survival time.^{7,9} Notably, the rare histology NSCLCs included in the study represent a heterogeneous group of lung cancers characterized by different behaviors and prognosis. This aspect might be a relevant issue in the future interpretation of trial results, but objective response rate alone could underestimate atezolizumab benefit. Based on statistical study design and heterogeneous population, the primary endpoint (DCR) has been set at a higher value than that reported from registration trials of atezolizumab (approximately 50%).^{7,22}

Finally, the results of our prospective rare lung cancers-oriented study could provide this missing piece of information for the treatment of this otherwise neglected population and possibly lead to the expansion of atezolizumab indication in NSCLC. Exploratory analysis on the role of PD-L1 expression on both tumor cells and TILs could help gaining further insight into the interaction between these disease and immune system and the potential role of PD-L1 as a predictive biomarker.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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ORCID iDs

Francesco Gelsomino  <https://orcid.org/0000-0002-9204-1728>

Giuseppe Lamberti  <https://orcid.org/0000-0003-3069-7630>

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