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Safety and efficacy outcomes of early cessation of anti-PD1 therapy in patients 80 years or older: A retrospective cohort study

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ABSTRACT

Older patients have similar immune checkpoint inhibitor efficacy and rates of adverse events as younger patients, but appear to have decreased tolerability, particularly in the oldest patient cohort (>80 years), often leading to early cessation of therapy. We aimed to determine whether early discontinuation impacts efficacy of anti-PD-1 therapy in patients ≥80 years old. In this retrospective, multicenter, international cohort study, we examined 773 patients with 4 tumor types who were at least 80 years old and treated with anti-PD-1 therapy. We determined response rate, overall survival (OS), and progression-free survival (PFS) in patients who discontinued

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therapy early (<12 months) for reasons other than progression or death. We used descriptive statistics for demographics, response, and toxicity rates. Survival statistics were described using Kaplan Meier curves. Median (range) age at anti-PD-1 initiation was 83.0 (75.8–97.0) years. The cancer types included were melanoma (n = 286), non-small cell lung cancer (NSCLC) (n = 345), urothelial cell carcinoma (UCC) (n = 108), and renal cell carcinoma (RCC) (n = 34). Of these, 102 met the primary endpoint of <12 months to discontinuation for reasons other than death or progression. Median PFS and OS, respectively, for these patients were 34.4 months and 46.6 months for melanoma, 15.8 months and 23.4 months for NSCLC, and 10.4 months and 15.8 months for UCC. This study suggests geriatric patients who have demonstrated therapeutic benefit and discontinued anti-PD-1 therapy at less than 12 months of duration for reasons other than progression may have durable clinical benefit without additional therapy.

1. Introduction

Immune checkpoint inhibitors (ICI) are used across cancer types and patient ages. Older patients (>65 years) derive similar ICI efficacy and immune related adverse event rates (irAEs) as younger patients in clinical trials [1,2]. One study further suggested that older patients preferentially benefit from ICIs due to favorable CD8 T cell/regulatory T cell balance [3]. However, older patients may have more difficulty tolerating irAEs due to decreased physiologic reserve [4,5]. In our previous study, we demonstrated comparable efficacy without obvious increase in irAEs in patients ≥80 years old, but irAE-related ICI discontinuation increased with age [6]. This included discontinuing therapy for low grade toxicities in many cases.

Given the challenges of tolerating ongoing therapy, determining the consequences of early ICI discontinuation in older patients who have demonstrated therapeutic benefit is an important unmet need. Although several studies have suggested patients discontinuing therapy due to irAEs have similar outcomes, these were largely in younger patients experiencing high-grade irAEs; thus these findings may not translate to older patients [7–10]. Further, the impact of discontinuing therapy for low-grade irAEs is unclear.

Herein, we used a large, previously published multicenter cohort [6] of patients ≥80 years old who received ICI monotherapy to characterize the outcomes of patients who discontinued therapy early (less than 12 months) for irAEs or other reasons other than disease progression.

2. Methods

After IRB review, deidentified data for patients treated with ICI monotherapy between 2010 and 2019 was collected retrospectively from 18 institutions in the US and Europe. Patients who turned 80 years during ICI treatment (n = 19) or were ≥80 years at ICI initiation (n = 754) were included. Single-agent ICIs included anti–programmed death protein-1/programmed death-ligand 1 (PD-1/PD-L1); anti-cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) therapies were excluded. Combination regimens were not included [6].

The primary endpoint population included patients who discontinued therapy early (before 12 months) either electively, for irAEs or other toxicities, or other reasons prior to progression. Exclusion criteria included ≥12 months of therapy, ongoing therapy at data collection, notation of "completed therapy" at 11–12 months duration (to avoid patients who completed approximately 12 months), and stopping therapy for progression or death (Supplementary Fig. 1). Patients who discontinued therapy prior to first response evaluation but progressed at their first scan were excluded. Demographics, treatment (agent, time on treatment), outcomes (response, progression, death), and irAEs (grade, type) were collected and de-identified. Response and progression-free survival was defined by RECIST 1.1 criteria and extracted from chart review.

Within the endpoint population, we used descriptive statistics to describe demographics, response, and toxicity rates. Survival statistics were described using Kaplan Meier curves and compared with the log rank test.

3. Results

3.1. Demographics

A total of 773 patients treated with anti–PD-1 (702 [90.8 %]) or anti–PD-L1 (71 [9.2 %]) were included. Patients had melanoma (n = 286), non-small cell lung cancer (NSCLC) (n = 345), urothelial cell carcinoma (UCC) (n = 108), and renal cell carcinoma (RCC) (n = 34). Median (range) age at ICI initiation was 83.0 (75.8–97.0) years, with 522 (67.5 %) patients <85, 203 (26.3 %) aged 85–89 years, and 48 (6.2 %) aged ≥90 years. Comprehensive demographics may be viewed in Supplementary Table 1.

3.2. Clinical outcomes

3.2.1. Clinical outcomes (all tumor types)

Across tumor types, 102 patients met the endpoint criteria (13.2 %). Of these, 60 patients stopped early for irAE, including 53.3 % (n = 32) with grade 1–2 and 46.7 % with grade 3–4 toxicities (n = 28). ORR for patients who stopped for irAEs was 66 %. Among the other 42 patients in the endpoint population, 15 stopped early for declining performance status and 27 stopped electively/for treatment holiday. This group had ORR of 61.5 %. For these 42 patients that stopped for reasons other than irAE, 12 (28.6 %) patients nevertheless experienced grade 1–2 irAEs, and 1 had grade 3 toxicity.

3.2.2. Melanoma

Of 286 patients with melanoma, 59 (20.6 %) were in the endpoint population (completed <12 months of therapy and stopped for reasons other than progression or death). Five received adjuvant therapy, with median time on therapy of 4.2 months. At 17.5-month median follow up, 1 progressed and 4 had not progressed. 54 patients were treated for metastatic disease; 38 discontinued therapy for irAEs, 5 for declining performance status, and 11 electively. Median time on treatment was 5.0 months. ORR was 72 % (22 CR, 14 PR, 12 SD, 6 with PD/unknown); median PFS was 34.4 months, and median OS was 46.6 months (Fig. 1A–B). Thirty-one patients (57.4 %) received <6 months of treatment, and had ORR of 70.4 %, median PFS of 38.8 months, and median OS was not reached. PFS by treatment duration (<3 months, 3–6 months, and >6 months) was similar ($p = 0.44$). OS was statistically different ($p < 0.01$) though the number of patients with treatment duration between 3 and 6 months was small, and appeared to drive this difference, with similar outcomes in the patients who received ≤3 months and >6 months of therapy (Fig. 1C–D).

3.2.3. NSCLC

Of 345 patients with NSCLC, 30 (8.7 %) met the endpoint. All were treated for metastatic disease. Thirteen patients discontinued therapy for irAE, 8 for declining performance status, and 9 electively. Median time on treatment was 4.1 months, and median follow up was 13.2 months. ORR was 58.6 %. (5 CR, 12 PR, 12 SD, 1 unknown); median PFS was 15.8 months, and median OS was 23.4 months (Fig. 2A–B). Ten patients spent ≤3 months on treatment; 7 responded (ORR 70 %). Nineteen patients had <6 months on treatment; ORR was 57.9 %. PFS

did not differ by treatment duration (median not reached vs 16.8 months vs. not reached, p = 0.71 for treatment ≤3 months, 3–6 months, and >6 months) (Fig. 2C). Similarly, OS was not different between groups (median 23.4 vs. 18.7 vs. not reached, p = 0.41) (Fig. 2D).

3.2.4. UCC and RCC

Of 108 patients with UCC and 34 with RCC, 9 (8.3 %) and 4 patients (11.8 %) met the primary endpoint. Among the 9 patients with UCC, 4 responded (5 had SD), with median PFS and OS of 10.4 months and 15.8 months (all 4 non-progressing patients remained alive at last follow up). Of the 4 patients with RCC, all had SD, and 3 were progression free (the only progressing patient did so at 29.3 months); 3 were alive.

4. Discussion

We found that older patients (≥80 years) who discontinued ICI therapy before 12 months for reasons other than progression or death had overall excellent outcomes. Although most of the total cohort discontinued for progression or received >1 year of treatment, approximately 20 % (with melanoma) and 10 % (with NSCLC, RCC, and UCC) discontinued for irAEs or electively. These patients had high ORR, PFS, and OS, particularly in melanoma. Our findings suggest that early discontinuation potentially may not compromise anti-PD-1 monotherapy outcomes in geriatric patients with tolerability concerns.

IrAEs were the most common reason for older patients to stop ICI early, with a mix of severe irAEs that mandated discontinuation, and lower-grade irAEs which may have induced "semi-elective" discontinuation. In some older adult patients who are not tolerating therapy, discontinuation may provide improved quality of life and perhaps reduce chronic irAEs or complications from steroids.

Our study does not endorse early discontinuation in the absence of toxicity, and does not prove that early discontinuation has equivalent survival outcomes as longer durations of therapy. This would be very difficult to analyze in a retrospective fashion; simple comparisons with longer or shorter duration would be necessarily confounded (e.g. patients who received treatment for >12 months by definition lived >12 months). Ultimately though, we did not observe a clear trend towards improved PFS or OS benefit with increased therapy duration for melanoma or NSCLC (within the 3–12 month range). This suggests that even very short courses (less than 3 months) could be beneficial in some patients. Further, treatment rechallenge could salvage some patients that ultimately progress, and may be a good "safety" option for patients who discontinue early. However, formal clinical trials would be optimal to support this finding (e.g. the ongoing Stop Safe Trial).

5. Limitations

This study specifically analyzes geriatric patients who have demonstrated therapeutic benefit to ICI; thus, survival outcomes in this population are likely better than that of the total population. Small sample size limits the findings for geriatric patients with UCC, RCC or other cancers. Though larger, the sample sizes for melanoma and NSCLC are still modest; a larger or prospective study is necessary to confirm the findings of this study. This study lacks a younger comparator group; thus it may not generalize to a wider population. Follow up time for many patients was relatively short, thus potentially obscuring possible late progression. We were not able to collect data on subsequent therapy due to limitations of the database, however the excellent PFS in the absence of additional treatments suggests that at least much of the OS data was driven by ICI therapy. Finally, many patients are now treated with combination immunotherapy, which this cohort did not include.

6. Conclusions

Geriatric patients (≥80 years old) receive similar benefit as younger patients from ICI, however, disproportionately discontinue therapy before course completion. This study suggests that patients who discontinue ICI therapy early for reasons other than progression or death had excellent outcomes overall. The range of appropriate ICI therapy durations remains unclear in this population, but may include short courses.

Ethics approval and consent to participate

This study was conducted in accordance with IRB guidelines and approved by the Vanderbilt University IRB committee #150488. Waiver of informed consent was obtained.

CRediT authorship contribution statement

Kylie Fletcher: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Alessio Cortellini:** Writing – review & editing, Resources, Investigation. **Teja Ganta:** Writing – review & editing, Resources, Investigation. **Roma Kankaria:** Writing – review & editing, Writing – original draft, Visualization, Investigation.

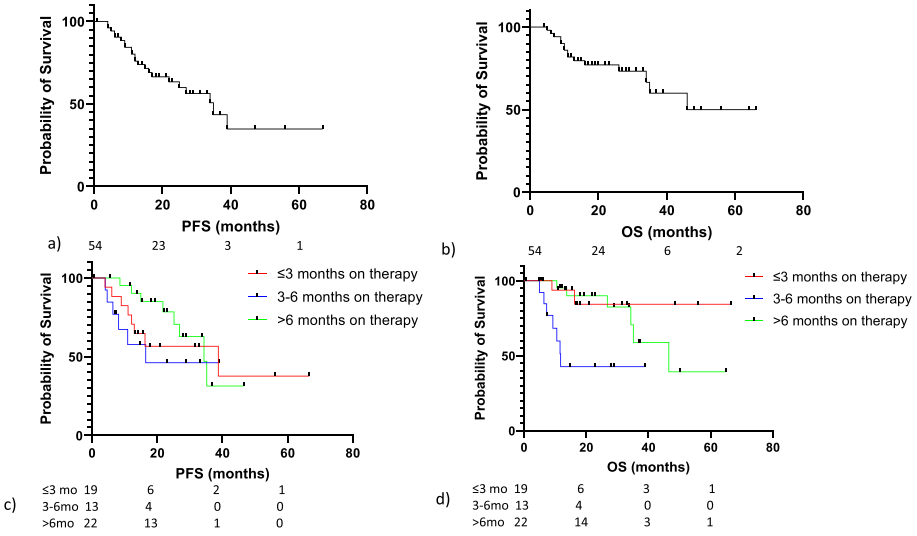

Fig. 1. Outcomes in melanoma patients; A) progression-free survival (PFS), B) overall survival (OS), C) PFS by treatment duration, and D) OS by treatment duration. Numbers below figure indicate the number of patients at risk at each time point.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alessio Cortellini declares grants for consultancies/advisory boards from MSD, OncoC4, IQVIA, AstraZeneca, Access Infinity, Ardelis-Health, Alpha Sight, Roche, REGENERON; speaker fees from AstraZeneca, Eisai, Pierre-Fabre, MSD, Sanofi/REGENERON; writing/editorial activity from BMS, MSD; travel support from Sanofi, MSD. Anwaar Saaed reports research grants (to institution) from AstraZeneca, Bristol-Myers Squibb, Merck, Clovis, Exelixis, Actuate therapeutics, Incyte Corporation, Daiichi Sankyo, Five prime therapeutics, Amgen, Innovent biologics, Dragonfly therapeutics, Oxford biotherapeutics, KAHR medical, Biontech, and advisory board/consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, Xilio therapeutics, Arcus therapeutics, Exelixis, Pfizer, and Daiichi Sankyo. Akiva Diamond served on an Advisory Board for Incyte. Christopher Hoimes has served on advisory boards or as a consultant for BMS, Merck, Seagen. Amin H. Nassar receives honoraria from OncLive, TEMPUS, and Korean Society for Medical Oncology and received consulting fees from Guidepoint Global. Dwight Owen discloses research funding (to institution) from BMS, Merck, Genentech, Palobiofarma, and Onc.AI. Toni Choueiri reports institutional and/or personal, paid and/or unpaid support for research, advisory boards, consultancy, and/or honoraria past 5 years, ongoing or not, from: Alkermes, AstraZeneca, Aravive, Aveo, Bayer, Bristol Myers-Squibb, Calithera, Circle Pharma, Deciphera Pharmaceuticals, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, Gilead, HiberCell, IQVA, Infinity, Ipsen, Jansen, Kanaph, Lilly, Merck, Nikang, Nuscan, Novartis, Oncohost, Pfizer, Roche, Sanofi/Aventis, Scholar Rock, Surface Oncology, Takeda, Tempest, Up-To-Date, CME events (Peerview, OncLive, MJH, CCO and others), outside the submitted work. TC also reports institutional patents filed on molecular alterations and immunotherapy response/toxicity, and ctDNA; equity: Tempest, Pionyr, Osel, Precede Bio, CureResponse, InnDura Therapeutics, Primium; committees: NCCN, GU Steering Committee, ASCO/ESMO, ACCRU, KidneyCan; medical writing and editorial assistance support may have been funded by Communications companies in part; no speaker's bureau. TC entored several non-US citizens on research projects with potential funding (in part) from non-US sources/Foreign Components. The institution of TC (Dana-Farber Cancer Institute) may have received additional independent funding of drug companies or/and royalties potentially involved in research around the subject matter. David J Pinato declares the following competing interests: Lecture fees: Bayer Healthcare, Astra Zeneca, EISAI, Bristol Myers-Squibb, Roche, Ipsen; Travel expenses: Bristol Myers-Squibb, Roche, Bayer Healthcare; Consulting fees: Mina Therapeutics, Boeringer Ingelheim, Ewopharma, EISAI, Ipsen, Roche,

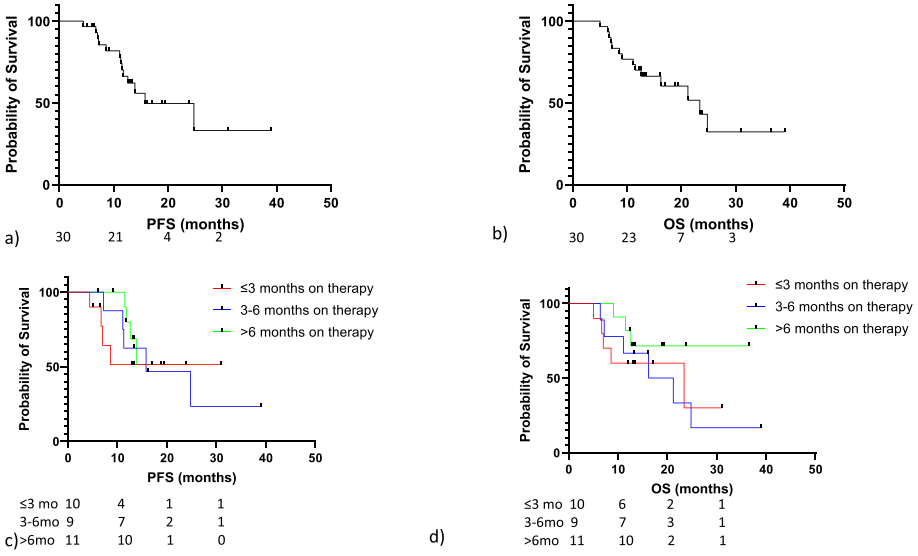

Fig. 2. Outcomes in NSCLC patients; A) progression-free survival (PFS), B) overall survival (OS), C) PFS by treatment duration, and D) OS by treatment duration. Numbers below figure indicate the number of patients at risk at each time point.

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Appendix A. Supplementary data

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