

Pembrolizumab and all-trans retinoic acid combination treatment of advanced melanoma: long-term survival update

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Abstract

Background: Primary analysis of the phase I/II clinical trial combining pembrolizumab with all-trans retinoic acid (ATRA) for patients with metastatic melanoma showed a median progression-free survival (PFS) of 20.3 months and median overall survival (OS) not reached.

Objective: Report 5-year OS and PFS rates.

Design: In this single-center, single-arm trial (NCT03200847), 24 anti-PD-1 naïve patients with metastatic melanoma were enrolled between 10/2017 and 07/2020.

Methods: The Kaplan–Meier method was used to estimate OS and PFS.

Results: At data cutoff (May 14, 2024), all patients had completed treatment, and 58% ($n = 14$) remained alive with a median follow-up of 48 months. The updated 5-year OS rate is 54.7% [95% confidence interval (CI): 36.4–82.1], and the 5-year PFS is 36.1% [95% CI: 21.0–62.2], with 33% ($n = 8$) having an ongoing complete response.

Conclusion: These results underscore the long-term clinical benefit of combining anti-PD-1 with ATRA, with survival rates comparable to anti-PD-1/combinations but with lower toxicity.

Keywords: anti-PD-1, ATRA, clinical trial, immune-checkpoint blockade, melanoma

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Introduction

Immune checkpoint inhibitors have dramatically improved outcomes for a subgroup of patients with melanoma; however, the majority do not respond or develop resistance.¹ One potential resistance mechanism involves the presence of tumor-associated myeloid-derived suppressor cells (MDSCs), a heterogeneous population of myeloid lineage cells.^{2,3} Through directed cell:cell interactions, and the secretion of soluble factors including interleukin (IL)-10, transforming growth factor (TGF)- β , reactive oxygen species, arginase-1, and indoleamine 2,3-dioxygenase 1 (IDO1), MDSCs prevent effective anti-tumor immunity.^{2–5} Differentiating agents such as the vitamin A-derivative all-trans retinoic acid (ATRA) reduce the frequency and function of MDSCs through the activation of ERK1/2, upregulating glutathione synthase, and

subsequent accumulation of glutathione, thereby promoting their differentiation into mature myeloid cells.⁶ This maturation is associated with decreased mRNA expression of IDO1, NADPH oxidase 1 (NOX1), IL10 (IL-10), CD274 (PD-L1), and TGFB1 (TGF- β 1), and increased expression of class II major histocompatibility complex transactivator (CIITA), a positive regulator of Human Leukocyte Antigen (HLA)-DR cell surface expression.⁵ Furthermore, previous studies have shown that ATRA-treated MDSCs lose their immunosuppressive functions, resulting in improved T cell-mediated anti-tumor responses.^{5,7–9}

This formed the rationale for our phase I/II clinical trial combining the anti-PD-1 agent pembrolizumab with ATRA for patients with metastatic melanoma.¹⁰ The primary analysis

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demonstrated that this is a well-tolerated treatment strategy to enhance the efficacy of pembrolizumab by reducing the frequency and attenuating the function of MDSCs.⁸ While patient numbers were small, the reduction in MDSCs improved the anti-tumor functions of T cells in responding patients, as described in the primary manuscript.¹⁰ At median follow-up of 15 months, an overall response rate (ORR) of 71% and disease control rate (DCR) of 88%, with median progression-free survival (PFS) of 20.3 months, were observed. The median overall survival (OS) rate was not reached.

Here, we report 5-year OS and PFS rates to assess the long-term benefit of this treatment combination.

Methods

Patients and study design

Details of the study design, eligibility criteria, and sample size calculation of this single-center, single-arm, phase I/II clinical trial (NCT03200847) have been described previously.¹⁰ Briefly, eligible patients were ≥ 18 years of age, ECOG ≤ 1 , without prior exposure to anti-PD-1. Study treatment is shown in Figure 1. Endpoints included the recommended phase II dose (primary); safety and MDSC frequency (secondary); and anti-tumor activity (exploratory). The trial was approved by the Colorado Multiple Institutional Review Board (COMIRB #16-1080), conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the

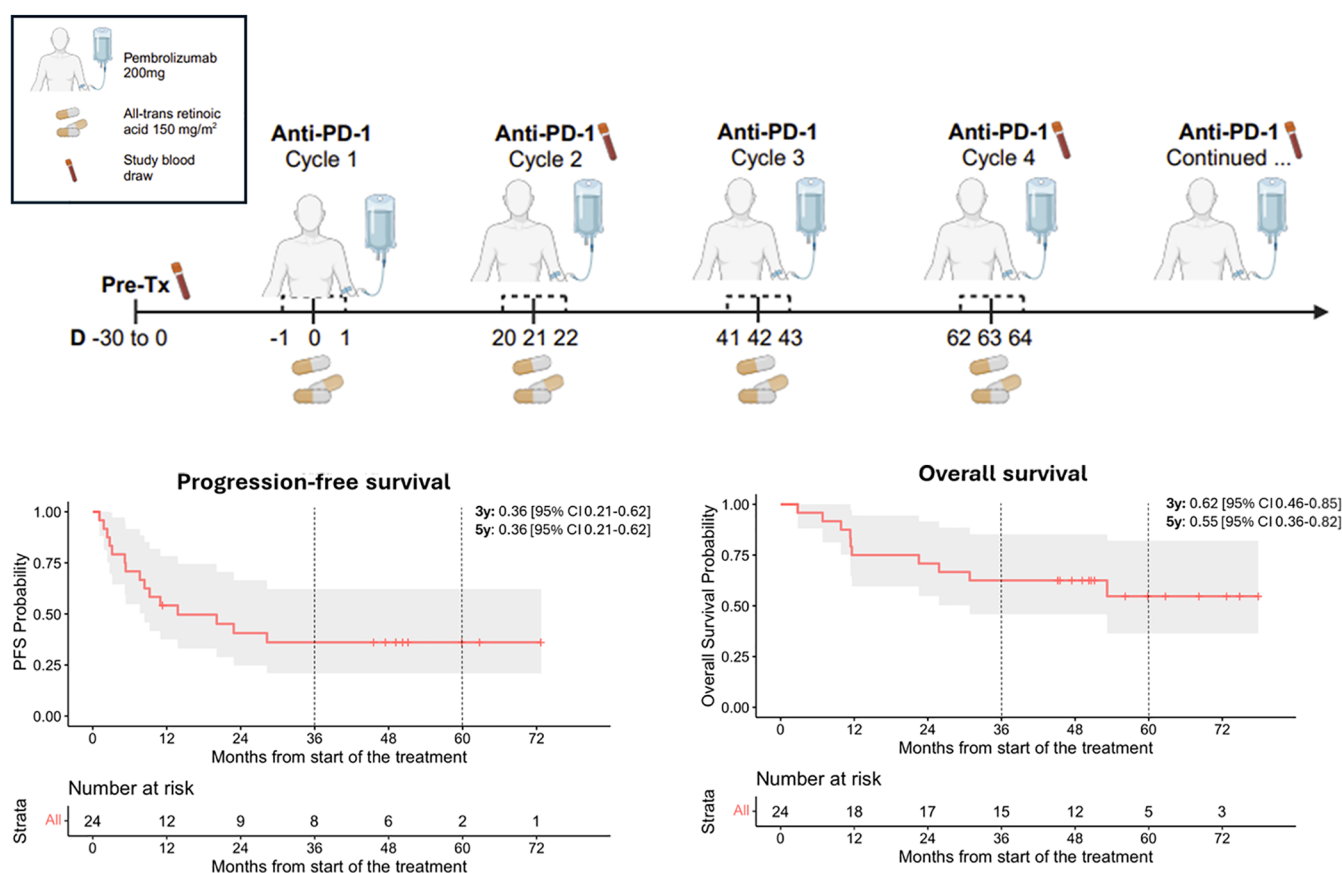


Figure 1. Clinical trial overview and survival curves. Study treatment consisted of the RP2D of pembrolizumab 200 mg IV Q3W, combined with ATRA (VESANOID) 150 mg/m² orally for 3 days surrounding the first four pembrolizumab cycles (day -1, day 0, and day +1), followed by single-agent pembrolizumab for up to 2 years until confirmed disease progression or unacceptable toxicity (top panel). Kaplan-Meier curves showing the long-term progression-free survival (bottom left) and overall survival (bottom right), including the number of patients at risk. ATRA, all-trans retinoic acid; RP2D, recommended phase II dose.

Declaration of Helsinki, and the reporting of this study conforms to the SPIRIT 2013 statement¹¹ (Supplemental File 1).

Assessments

Adverse events (AEs) were monitored according to Common Terminology Criteria for Adverse Events v4. Efficacy endpoints, including ORR, DCR (complete response (CR), partial response, or stable disease as best overall response), and PFS were measured every 3 months by standard-of-care imaging, interpreted by certified radiologists according to RECIST v1.1 criteria, and verified by treating medical oncologists. Survival status was captured by the treating physician.¹⁰

Statistical analysis

All analyses were performed in patients who received ≥ 1 dose of ATRA + pembrolizumab. The Kaplan–Meier method was used to estimate OS and PFS. Surviving patients and those without progression events were censored at the date of last follow-up/cutoff date of May 14, 2024. Analyses were performed using IBM SPSS Statistics (version 29.0, Armonk, New York, USA) and R packages “survival” version 3.5-7 and “survminer” version 0.4.9. Figures were made using R and BioRender.

Results

Patients

Baseline characteristics were described previously.¹⁰ To summarize, 24 anti-PD-1-naïve patients (87% male) were enrolled between October 31, 2017 and July 30, 2020. The median age at enrollment was 66 years (42–92), 83% had normal lactate dehydrogenase levels, the average number of metastatic sites was 2, and three patients received ipilimumab prior to enrollment. Patients with cutaneous (67%), unknown primary (21%), uveal (8%), and mucosal (4%) primaries were included, with 50% having a *BRAF* V600E mutation (Table 1). At data cutoff, with a median follow-up time of 48 months (range 3–77), all patients had completed the protocol-defined treatment (ATRA + pembrolizumab for up to 2 years). The mean exposure to study treatment was 14 months (range 2–24), with seven patients completing the full 2 years; three of

whom continued treatment with pembrolizumab afterward.

Efficacy

At data cutoff, with a median follow-up time of 48 months (range 3–77), 33 months longer than in the initial report, 14 patients (58%) were still alive, resulting in an estimated 5-year OS rate of 54.7% (95% confidence interval (CI): 36.4–82.1), median not reached (Table 1).

The 5-year estimated PFS is 36.1% (95% CI: 21.0–62.2), with a median of 13.8 months (95% CI: 8.39–Not Available (NA); Figure 1). This is lower than the previously reported median PFS of 20.3 months due to an additional PFS event at 13.8 months in a patient with a previously reported short follow-up time (Supplemental Table 1). Eight of the 12 patients with CR were still alive with ongoing CR at data cutoff (33%). Two patients in CR relapsed with nodal disease 7 and 11 months after achieving CR, and one patient relapsed with a new brain lesion 3 months after reaching a CR. One patient passed away at age 90 without evidence of disease progression (Supplemental Table 1). Twelve patients (50%) received subsequent treatments at a median of 62.5 days (range 0–580) after their off-treatment date. These patients received a median of three subsequent lines (range 1–7), with most receiving a BRAF/MEK inhibitor (MEKi) regimen ($n=5$), followed by anti-PD-1 + anti-CLTA-4, anti-PD-1 monotherapy or an experimental agent ($n=2$, each), and anti-PD-1 + anti-Lymphocyte-activation gene 3 (LAG)-3 ($n=1$) as first subsequent treatment after the trial.

Safety

Consistent with the initial analysis, this combination had a well-tolerated safety profile without new safety signals or treatment-related deaths. All patients had completed ATRA at the time of the initial report; no additional ATRA-related safety concerns were observed in the long-term follow-up. However, one of the nine patients still receiving pembrolizumab developed grade 4 hyperglycemia and was subsequently diagnosed with type 1 diabetes. With this AE, five patients (21%) experienced a grade 3–4 pembrolizumab-induced immune-related AE: colitis ($n=2$), hepatitis ($n=1$), polymyalgia rheumatica-like myalgias ($n=1$), and diabetes ($n=1$). And, as reported

Table 1. Baseline characteristics clinical trial, and survival update.

Baseline characteristics	Patients (n = 24)	
Enrollment dates	October 31, 2017–July 30, 2020	
Median age, years (range)	66 (42–94)	
Sex male, number (%)	21 (87%)	
ECOG performance status, number (%)		
0	14 (58%)	
1	10 (42%)	
Elevated LDH level, number (%)	4 (17%)	
Prior therapies, number (%)		
Ipilimumab	3 (13%)	
Local treatment only	3 (12%)	
No prior therapies	18 (75%)	
Primary melanoma subtype, number (%)		
Cutaneous	16 (67%)	
Uveal	2 (8%)	
Mucosal	1 (4%)	
Unknown	5 (21%)	
BRAF V600E status, number (%)		
Wild type	9 (38%)	
Mutant	12 (50%)	
Unknown	5 (21%)	
M stage, number (%)		
M1a	11 (46%)	
M1b	4 (17%)	
M1c	7 (29%)	
M1d	2 (8%)	
Survival update	Primary analysis ¹⁰ (03-2021)	Survival update (05-2024)
Median follow-up, months (range)	15 (3–35)	48 (3–77)
Mean exposure to treatment, months (range)	8 (2–24)	14 (2–73)
ORR, % (n)	71% (17)	–
CRR, % (n)	50% (12)	33% (8)

(Continued)

Table 1. (Continued)

Survival update	Primary analysis ¹⁰ (03-2021)	Survival update (05-2024)
Median PFS, months	20.3 [95% CI: 5.2–12.9]	13.8 [95% CI: 0.0–29.3]
6-Month PFS	63%	–
3-Year PFS	–	36.1% [95% CI: 21–62]
5-Year PFS	–	36.1% [95% CI: 21–62]
Median OS	Not reached	Not reached
1-Year OS	80%	–
3-Year OS	–	62.5% [95% CI: 45.8–85.2]
5-Year OS	–	54.7% [95% CI: 36.4–82.1]
3-Year melanoma-specific OS	–	65.6% [95% CI: 48.9–88.1]
5-Year melanoma-specific OS	–	57.4% [95% CI: 38.7–85.2]
Overview of the baseline characteristics prior to trial enrollment, and the response and survival rates, both from the original report and the long-term update. CI, confidence interval; LDH, lactate dehydrogenase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.		

previously, one patient (4%) experienced an ATRA-related grade 4 AE (meningitis/stroke).

Of the six patients who required systemic immunosuppression (corticosteroids ($n=4$); corticosteroids + infliximab ($n=2$)), three patients progressed (50%), while the other three patients either have an ongoing CR ($n=2$) or passed away without disease progression ($n=1$).

Discussion

While outcomes for patients with advanced-stage melanoma have greatly improved,^{1,12} there is still an unmet need for patients presenting with primary or acquired resistance, for which many (pre) clinical efforts are ongoing. One of these includes our phase I/II clinical trial combining pembrolizumab with ATRA, which reduces the frequency of MDSCs, thereby targeting a known resistance mechanism to immunotherapy.^{2,5,10} Here, we present the 5-year OS and PFS data from this trial, underscoring the long-term clinical benefit of combining anti-PD-1 and ATRA, with survival rates similar to those seen from combination treatment anti-PD-1 + anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), with lower toxicity.

While patient numbers are small, the population is similar to the landmark phase III CheckMate 067 trial, with the exception that two patients (8%) had uveal melanoma (excluded in CheckMate 067) and three (13%) received prior ipilimumab. In CheckMate 067, 5-year OS was 52% in the combination treatment and 44% and the anti-PD-1 monotherapy arm, and 5-year PFS was 36% (median 11.5 months) and 29% (median 6.9 months), respectively.⁹ Our long-term results demonstrate a 5-year OS of 54.7%, and a 5-year PFS of 36.1% (median 13.8 months), indicating that the outcomes appear similar to anti-PD-1 + anti-CTLA-4, despite having enrolled three patients with non-cutaneous melanoma (13% of our total study population) who, in line with the literature, experienced no benefit from this anti-PD-1-based treatment regimen.^{13,14} Furthermore, while already hinted at previously,^{15,16} the recently published 10-year outcomes from CheckMate 067 show that patients who remain progression-free at 3 years have a melanoma-specific survival of 96/97%.¹ A similar plateau can be observed in our patients (Figure 1, Supplemental Table 1).

Importantly, despite the similar response rates, only six patients (25%) experienced grade 3–4

AEs, compared to 59% with combination anti-PD-1 + anti-CTLA-4.¹⁶ In five cases this was anti-PD-1-related, and in one case due to ATRA. Both the anti-PD-1- and ATRA-related AEs were in line with previously described AEs and could be managed using established protocols.¹⁷

While these results are encouraging, it is important to consider that patients might benefit most from the addition of ATRA in frontline settings. The results of Substudy 02A of KEYMAKER-U02 (NCT04303169) described an ORR of 0% and a PFS of 2.1 months with the same combination in heavily pretreated patients.¹⁸ In KEYMAKER U02 Substudy 02A, all patients experienced progression on prior anti-PD-1, and, specifically in the ATRA + pembrolizumab arm, 85% of patients had received ≥ 2 lines of systemic therapy prior to enrollment. While responses are lacking, this trial does support our safety findings with only 15% of patients experiencing a grade 3–4 AEs. Common grade 1–2 AEs included headaches in approximately 50%, and nausea, vomiting, and fatigue, all occurring in about 20%, which is consistent with our findings.^{10,18} Important to note is that in this trial, ATRA was administered on the first day of pembrolizumab and the two consecutive days (day 0–day +2), as opposed to starting the day prior to the anti-PD-1 infusion, which may not have been enough time to alter MDSCs prior to PD-1 inhibition.

Given that the additional benefit of adding ATRA is likely to take place in early/frontline settings, our results should be discussed in the context of the recently approved first-line combination therapy of anti-PD-1 plus anti-LAG-3. A recent comparison of the patients in the combination treatment arms of RELATIVITY-047 (anti-PD-1 + anti-LAG-3) and CheckMate 067 (anti-PD-1 + anti-CTLA-4) suggests that 3-year OS and PFS are similar between the two arms, with a lower rate of grade 3–4 AEs in patients receiving anti-PD-1 + anti-LAG-3 (23%), compared to anti-PD-1 + anti-CTLA-4 (59%).^{16,19,20} Both the efficacy and toxicity data of RELATIVITY-047 are consistent with our trial (Table 1); therefore, it could be interesting to investigate whether the addition of ATRA to this approved first-line treatment regimen could further enhance responses, while avoiding the high rate of toxicities observed in anti-CTLA-4-based regimens. Finally, results from the ongoing Substudy 02C of KEYMAKER-U02 will determine whether

there might be a role for ATRA + anti-PD-1 in the neoadjuvant setting.

Conclusion

The 5-year results of this trial demonstrate that the combination of ATRA and pembrolizumab results in durable responses in anti-PD-1-naïve patients with metastatic melanoma. These data, along with those from the KEYMAKER U02 substudies, support the exploration of this well-tolerated combination either in the frontline setting or in anti-PD-1 naïve patients, including in the neoadjuvant space. Finally, the results indicate that targeting MDSCs prior to and during checkpoint inhibition may enhance the efficacy of current as well as potential next-generation immunotherapies for melanoma.

Declarations

Ethics approval and consent to participate

Colorado Multiple Institutional Review Board (COMIRB #16-1080). All patients provided written informed consent.

Consent for publication

Not applicable.

Author contributions

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William A. Robinson: Resources; Writing – review & editing.

Kasey L. Coutts: Writing – review & editing.

Elizabeth N. Katsnelson: Writing – review & editing.

Claire M. Muckle: Writing – review & editing.

Eduardo Davilla: Writing – review & editing.

Sapna P. Patel: Writing – review & editing.

Dexiang Gao: Formal analysis; Writing – review & editing.

Richard P. Tobin: Conceptualization; Writing – review & editing.

Martin D. McCarter: Conceptualization; Writing – review & editing.

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Competing interests

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Availability of data and materials

The datasets are available upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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