Immune Checkpoint Inhibitor (ICI) Treatment After Progression on Anti–PD-1 Therapy in Advanced Melanoma: A Systematic Review of the Literature

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Background

- ICI and targeted therapies have revolutionized the treatment of advanced (unresectable or metastatic) melanoma in the last 2 decades; however, a majority of patients experience disease progression after initial treatment with anti–PD-1 ± BRAF/MEK inhibitor, if indicated
  - About 20% to 75% of the patients receiving first-line ICI therapy (single or combination) progress by 12–18 months,[1-3] thus requiring a subsequent line of treatment
  - Although BRAF/MEK inhibitors have high response rates,[4-6] responses are often not durable, and disease can progress rapidly[4-6]
- Patients with advanced melanoma progressing after ICI and targeted agents have limited options
- ICI retreatment is common despite lack of comparative evidence to support use in this setting
  - The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) V1.2023) recommend selection of systemic therapy regimen informed by response to prior systemic therapies and to consider agents of a different class for patients who progress during or shortly after the prior therapy[7,a]
  - No USPI for an FDA-approved ICI therapy includes data supportive of its efficacy when used as retreatment following progression on the same ICI
- We report findings from our systematic literature review of published data on the efficacy of ICI mono- or combination therapy in patients with advanced melanoma that progressed on or after anti–PD-1 therapy

[a]Per the NCCN guidelines, in patients with progression of melanoma during or shortly after adjuvant or first-line therapy, second-line agents should be considered if not used first line and if from a different class. Anti–PD-1/ipilimumab or BRAF/MEK inhibitor combination therapy or ipilimumab monotherapy should be considered in patients who progressed on single-agent anti–PD-1 checkpoint immunotherapy. Re-induction with the same agent or same class of agents may be considered in patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation.[7]

Methods

- A systematic search of PubMed and Embase was conducted to identify full-text articles published between January 2017 and June 2022 reporting efficacy outcomes among patients with advanced melanoma who were treated with an ICI (ipilimumab, nivolumab, pembrolizumab) with an approved indication in advanced melanoma as mono- or combination therapy after progression on an anti–PD-1 ± BRAF/MEK inhibitor (if *BRAF* mutated)
- Two reviewers selected articles per prespecified criteria, and a third reviewer resolved discrepancies
- PICOS-T criteria (**Table 1**) were used to select articles for full text review
- Eligibility for inclusion in the SLR was determined after 3 levels of screening:
  - Level 1: Abstracts screened against the PICOS-T criteria based on the title and abstract of the document. Articles that had inadequate data in the title and abstract to decide were included at Level 2
  - Level 2: All articles that passed Level 1 screening and had full-text articles available. Studies not fulfilling the PICOS-T criteria were excluded
  - Level 3: Articles that passed Level 2 screening were selected based on sample size and appropriate comparator
- Data on study design, patient characteristics, ORR, DOR, and mOS were abstracted into an evidence table
- Articles from prospective and retrospective studies with sample sizes >50 patients retreated with ICI were considered informative and are included in **Table 2**

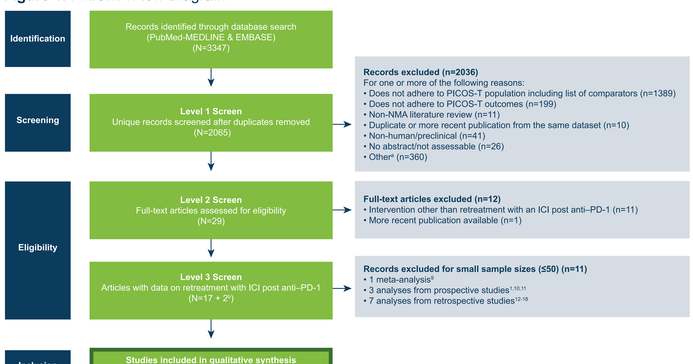
Methods (continued)

Table 1. PICOS-T Criteria

Criterion	Sub-Criteria
Population	Patients with advanced (unresectable or metastatic) melanoma progressing while on or following ≥1 prior systemic therapy, including • Anti–PD-1 treatment with approved indication in advanced melanoma • BRAF inhibitor alone or BRAF inhibitor in combination with a MEK inhibitor, if *BRAF* V600 mutation positive
Interventions	Not applicable
Comparators	Approved/commonly used in melanoma as single agent or in combination therapies - broken into treatment categories (to be utilized in the search) • Chemotherapy – Dacarbazine (DTIC-Dome®) – Taxane combination (eg, paclitaxel plus carboplatin)[8] – Temozolomide (TEMODAR®) • Targeted therapy (ie, BRAF and MEK inhibitors) – Encorafenib (BRAFTOVI®) – Vemurafenib (ZELBORAF®) – Binimetinib (MEKTOVI®) – Cobimetinib (COTELLIC®) – Dabrafenib (TAFINLAR®) – Trametinib (MEKINIST®) • Immunotherapy (limited to agents tested/approved for melanoma) – High-dose IL-2 (Aldesleukin, PROLEUKIN®) – Ipilimumab (anti–CTLA-4, BMS-734016, YERVOY®) – Nivolumab (anti–PD-1, BMS-936558, OPDIVO®) – Pembrolizumab (anti–PD-1, MK-3475, lambrolizumab, KEYTRUDA®)
Outcomes (as reported)	• Exposure – Line of therapy (LOT) • Outcome assessment – Response Evaluation Criteria in Solid Tumours (eg, RECIST v1.1, irRECIST) • Response – Response rate (RR) – Overall response rate (ORR)/objective response rate (ORR) – Complete response (CR) – Partial response (PR) – Progressive disease (PD) – Stable disease (SD) – Durable response rate (DRR) – Disease control rate (DCR) – Clinical benefit rate (CBR) – Duration of response (DOR) • Survival – Overall survival (OS) – Progression-free survival (PFS) – Disease-free survival (DFS) – Numbers alive (with or without progression) from total – Survival or mortality rate • Others – Time on treatment – Time to response – Time to next treatment – Treatment discontinuation
Study design	• Not restricted, but including – Randomized clinical trial (RCT) – Non-randomized clinical trial (NRCT) – Observational study – Retrospective study – Meta-analysis/indirect treatment comparisons
Time frame of the search	• Published from January 2017 to June 2022

Results

Figure 1. PRISMA Flow Diagram



*Other reasons for exclusion were articles that were opinions or editorials, protocols and lack of data in the subgroups of interest.
†Two records were missed by the search strategy: 1 was not identified because search terms did not include "Stage II/III"[1]; 1 was incorrectly indexed as a review article in the database.[18]

- Of 3347 records identified through the systematic search, 2065 unique records were screened (**Figure 1**)
  - Of the screened records, 29 met inclusion criteria for the full SLR
- Of these 29 unique full-text articles
  - 17 had data on retreatment with ICI post anti–PD-1 treatment
- Of the 17 articles identified in the SLR and 2 additional articles with data of interest
  - 11 studies were considered not informative (sample sizes <50 patients)[1,9-18]
  - 8 studies had sample sizes of >50 patients and were considered informative[19-26]

Figure 2. Summary of Included Studies

The selection criteria applied in the SLR identified the following study types (**Figure 2**):

Single-arm Phase 2 Trial
1 publication (N=70) from a study of pembrolizumab + low-dose ipilimumab after progression on anti–PD-1 (mean 1 line of prior therapy)[26]
• 29% ORR
• 16.6-mo DOR
• 24.7-mo mOS

Exploratory Subgroup Analysis
1 publication from a single clinical trial reported outcomes among 256 patients prospectively treated with ipilimumab or BRAFi ± MEKi as first subsequent therapy after progression on pembrolizumab[21]
• 15.5% ORR with ipilimumab
• DOR was not reported
• 9.8 mo mOS with ipilimumab

Retrospective Analysis
6 reports of ICI retreatment:
• 4 from small subgroups (N=57–84)[19,23,24,26]
• 2 from larger samples (N=116–355)[22,25]

Of these, 5 studies reported:
• ORR of 8%–33%

Among the 6 studies:
• Only 1 reported DOR (1.6 mo)
• mOS was 5.1–21 mo

- Most reports (6 of 8) were retrospective
- Treatment history was heterogeneous in type, number, and duration of prior regimens received
- Response criteria and index date for mPFS and mOS calculations were inconsistently reported

Table 2. Key Characteristics of Studies Included in the SLR

	Author/Year	Study Design/ Country	Number of Sites	Line of Therapy/ Study Population (N)	Prior ICI and BRAFi/MEKi Therapies: Therapies	Prior Lines	Reported Responses to Prior Anti–PD-1	Regimen Post Anti–PD-1	Sample Size (Receiving ICI Retreatment)	Disease Burden	Efficacy Estimates: ORR	Assessment	DOR	mOS (95% CI)
	PROSPECTIVE STUDY													
1	**Olson DJ[20] 2021**	**Open-label, single-arm phase 2 trial** *US*	7 centers	2L+ post anti–PD-1 as immediate prior therapy or progressed within 6 mo of adjuvant (N=70)	[a]	Mean=1 Range: Not reported Prior adjuvant therapy included	4.8 mo median time on prior anti–PD-1	Low-dose ipi + pembro	70	LDH >ULN: 24% LDH ≥2 × ULN: 7% Brain mets: 10% Liver mets: 24%	29%	irRECIST	16.6 mo (95% CI: 7.9, NR)	24.7 mo (15.2, NR)
	POST HOC EXPLORATORY SUBGROUP ANALYSIS OF A RANDOMIZED CLINICAL TRIAL													
2	**Long GV[21] (KEYNOTE 006) 2022**	**Randomized phase 3 study** *16 countries*	Multicenter	2L+ progressed post pembro in trial; received subsequent treatment (N=256)		1–2	17% ORR	Ipi	103	LDH elevated: 33% Brain mets: 8.7%	15.5% (95% CI: 9.2%, 24.0%)	RECIST v1.1 (independent radiology & oncology review)	Not reported	9.8 mo (7.7, 16.4)
	RETROSPECTIVE OBSERVATIONAL STUDIES													
3	**Da Silva P[22] 2021**	**Retrospective cohort** *AU, EU, US*	Multicenter	2L+ progressed post anti–PD-1 (N=355)	[a]	Range: Not reported Prior adjuvant therapy included	72% Innate resistance 28% Acquired resistance	Ipi Ipi + anti–PD-1	162 193	LDH >ULN: 38% Liver mets: 34% Brain mets: 27% <3 organs involved: 65% LDH >ULN: 42% Liver mets: 29% Brain mets: 37% <3 organs involved: 74%	13% 31%	RECIST v1.1 by investigator	Not reported	8.8 mo (6.1, 11.3) 20.4 mo (12.7, 34.8)
4	**Baron K[23] 2021**	**Retrospective EMR** *US EMR*	Multicenter	2L+ progressed post anti–PD-1 (N=57)		1–3+	Not reported	Ipi Ipi/nivo	22 35	LDH >ULN: 50% LDH >ULN: 43%	Not reported	Not reported	Not reported	6.0 mo (IQR: 3.1–11.8) 5.6 mo (IQR: 3.3–13.6)
5	**Mason R[24] 2020**	**Retrospective study of EAP patients** *AU*	Multicenter	2L Stage III/IV post failure on BRAFi therapy (N=57)	[a]	Range: Not reported Prior adjuvant therapy included	Not reported	Ipi/nivo	57	Elevated LDH: 56%	33%	RECIST v1.1	Not reported	9.6 mo (7.8, NR)
6	**Cybulska-Stopa B[25] 2020**	**Observational** *Poland*	Multicenter	2L progressed post anti–PD-1 (N=116)		1	Not reported	Ipi	116	LDH >normal: 47% Brain mets: 32% ≤2 metastatic sites: 33% >2 metastatic sites: 67%	8%	RECIST v1.1 by radiologist	Not reported	5.1 mo
7	**Betof Warner A[19] 2020**	**Observational** *US*	Single center	2L+ who discontinued single agent anti–PD-1 for any reason and progressed (N=78)		Not reported	4.8 mo median time on prior anti–PD-1	Anti–PD-1 Ipi/nivo	34 44	CNS mets: 14.9%	15% 25%	RECIST v1.1 by clinician and radiologist	1.6 mo (range: 1.0–28.3)	9.9 mo (6.8, 17.9)
8	**Zimmer L[26] 2017**	**Observational** *EU, US*	Multicenter	2L+ progressed post anti–PD-1 (N=84)		1 to ≥3	30%–40% DCR	Ipi Ipi/nivo	47 37	LDH ≥2 × ULN: 30% Brain mets: 45% LDH ≥2 × ULN: 5% Brain mets: 32%	16% 21%	RECIST v1.1	Not reported	Ipi (ECOG 0): 21 mo Ipi (ECOG 1-2): 8 mo Ipi + Nivo: Not reported

Prior ICI therapies Anti–PD-1 | Anti–PD-L1 | Anti–CTLA-4 | BRAFi/MEKi | Anti–PD-1/PD-L1 combination | Other investigational agents

[a]Prior adjuvant therapy was permitted.

Conclusions

- ICI retreatment is used in clinical practice; however, our SLR found no published prospective randomized trials that have studied use of ICI after anti–PD-1 therapy
- Limited evidence of efficacy was found in highly selected and heterogeneous patient populations in one prospective study or as subgroup analyses from retrospective studies that did not uniformly report response or define resistance to prior anti–PD-1 therapy
- Response rates were typically not independently assessed, using RECIST v1.1 or irRECIST criteria, and may differ meaningfully from blinded assessment
- Thus, comparison of outcomes across studies is difficult, and there is no robust, meaningful benchmark for novel therapies in this setting
- Standardizing data collection and reporting on responses to prior treatment, appropriately indexing search strings as nomenclatures become more standardized, and defining the index date to measure outcomes can allow better comparison/synthesis of data across studies and will be important to establish benchmarks to assess the impact of new therapies

References

1. Robert C, et al. *Lancet Oncol.* 2019;20(9):1239-51.
2. Tawbi HA, et al. *N Engl J Med.* 2022;386:24-34.
3. Wolchok JD, et al. *J Clin Oncol.* 2021;40:127-37.
4. Dummer R, et al. *Lancet Oncol.* 2018;19:603-15.
5. Robert C, et al. *N Engl J Med.* 2019;381:626-36.
6. Sosman, et al. *N Engl J Med.* 2012;366:707-14.
7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma, cutaneous V.1.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 4, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
8. Gupta A, et al. *Melanoma Manag.* 2017;4(2):125-36.
9. Alrabadi NN, et al. *Clin Transl Oncol.* 2021;23(9):1895-904.
10. Long GV, et al. *J Clin Oncol.* 2020;38(15_suppl):10013-13.
11. Friedman CF, et al. *J Immunother Cancer.* 2022;10(1):e003853.
12. Patrinely JR Jr, et al. *Cancer.* 2020;126(15):3448-55.
13. Vera Aguilera J, et al. *Melanoma Res.* 2020;30(4):364-75.
14. Blasig H, et al. *Melanoma Res.* 2017;27(4):321-5.
15. Spain L, et al. *Cancer Immunol Immunother.* 2017;66(1):113-7.
16. Hepner A, et al. *Eur J Cancer.* 2021;153:213-22.
17. Klee G, et al. *Melanoma Res.* 2021;31(5):464-71.
18. Chapman PB, et al. *J Immunother Cancer.* 2021;9:e003395.
19. Betof Warner A, et al. *J Clin Oncol.* 2020;38(15):1655-63.
20. Olson DJ, et al. *J Clin Oncol.* 2021;39(24):2647-55.
21. Long GV, et al. *Ann Oncol.* 2022;33(2):204-15.
22. Da Silva P, et al. *Lancet Oncol.* 2021;22(6):836-47.
23. Baron K, et al. *J Oncol Pharm Pract.* 2021;27(3):555-9.
24. Mason R, et al. *Pigment Cell Melanoma Res.* 2020;33(2):358-65.
25. Cybulska-Stopa B, et al. *Adv Med Sci.* 2020;65(2):316-23.
26. Zimmer L, et al. *Eur J Cancer.* 2017;75:47-55.

Abbreviations

2L, second line; AU, Australia; BRAFi/MEKi, BRAF/MEK inhibitors; CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DCR, disease control rate; DOR, duration of response; EAP, Early Access Program; ECOG, Eastern Cooperative Oncology Group; EMR, electronic medical record; EU, European Union; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitors; ipi, ipilimumab; IQR, interquartile range; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; LDH, lactate dehydrogenase; mets, metastases; mOS, median overall survival; mPFS, median progression-free survival; NCCN, National Comprehensive Cancer Network; nivo, nivolumab; NMA, network meta-analysis; NR, not reached; ORR, objective response rate; pembro, pembrolizumab; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PICOS-T, Population, Intervention, Comparator, Outcomes, Study Design, and Time; PR, partial response; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLR, systematic literature review; ULN, upper limit of normal; US, United States; USPI, United States Prescribing Information.

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Disclosures

DO: Site PI on sponsored studies testing therapies in PD-1 refractory melanoma including Immunocore IMC-F1063, Instil Bio Delta 1 and Delta 2, and Astellas DGK-inhibitor study for advanced melanoma; planned advisory board with Iovance Biotherapeutics; research funding from Iovance Biotherapeutics; and consulting fees from GLG Group and Alpha Insights
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AR: No conflicts to declare
WS and KLS: Employees of Iovance Biotherapeutics holding Iovance stock and/or stock options
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