A Systematic Literature Review of Clinical Outcomes and Treatments in Post-Anti-PD-(L)1 Advanced Mucosal Melanoma from Interventional and Real-World Studies

Chen Z,[1] Kwon C,[2] Chen L[3]

[1]Cytel, Toronto, ON, Canada; [2]Cytel, Cambridge, MA, US*; [3]Mural Oncology, Waltham, MA, US

Poster 139

Take Away

- There is a lack of standard of care (SoC) for patients with mucosal melanoma (MM) whose tumor progressed on programmed cell death protein 1/programmed death-ligand 1 (PD-[L]1) inhibitors. Heterogeneity in subsequent treatments and poor outcomes were reported in these patients. Future research is warranted to explore treatment options to address this high unmet need.

Conclusions

- There is a scarcity of data in patients with MM whose tumor progressed on anti-PD-(L)1 and most studies had sample sizes of 16 or less.
- Among various subsequent treatments, the most common approach was immunotherapy re-challenge (anti-PD[L]1 and anti-CTLA-4, alone or in combination).
- Poor outcomes were reported across studies. However, heterogeneity in subsequent treatments and small sample sizes makes it hard to interpret.
- This systematic literature review (SLR) highlighted a lack of SoC and a high unmet need in patients with MM whose tumor progressed on prior anti-PD-(L)1. More research in larger samples is needed.

Background

- MM is a rare sub-type of melanoma with distinct etiology, differentiated mutational profile and a relatively poor prognosis compared to cutaneous melanoma (CM). Because of the lack of clinical trials, MM treatment generally follows the guidance for CM.
- PD-(L)1 inhibitors are routinely used in the first line but have shown lower efficacy in MM than in CM. Little is known about treatments and outcomes in patients with MM whose tumor progressed on prior anti-PD-(L)1 therapy.
- The objective of this study was to conduct a SLR to identify interventional and real-world (RW) studies assessing treatments and clinical outcomes in patients with advanced MM whose tumor progressed on prior anti-PD-(L)1 therapy.

Methods

- The SLR was conducted in accordance with the methodological and reporting requirements outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[1] and the Cochrane Handbook for Systematic Reviews of Interventions.[2]
- Databases such as Embase, MEDLINE, and Cochrane were searched. Other sources included ClinicalTrials.gov, key conference proceedings, and the bibliographies of relevant SLRs/meta-analyses identified by the database searches.
- Interventional or RW studies were included if they met the following criteria:
  - Reported outcomes specifically for patients with MM who received any systemic therapy following treatment with PD-(L)1 inhibitor(s)
  - Had a sample size of ≥3
  - Investigated subsequent treatments that were either commercially approved or used off label (the latter only applied to RW studies)
  - Were published in English between January 1, 2010, and November 22, 2023 (the last search date of databases)
- The subsequent treatments and clinical outcomes (including overall response rate [ORR], progression-free survival [PFS], and overall survival [OS]) were extracted.

Results

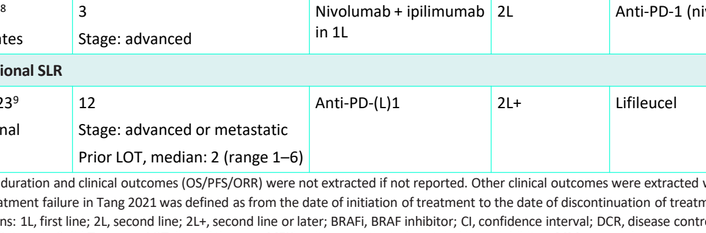
- Eleven RW studies and one interventional study were included in the SLR (**Figure 1**).

Subsequent treatments in patients with MM post anti-PD-(L)1

- In the RW studies, post anti-PD-(L)1 treatments included checkpoint inhibitors (e.g., ipilimumab, and/or anti-PD-[L]1 rechallenge), cytotoxic agents, targeted therapies, radiation therapy, best supportive care, and treatments used off label such as tyrosine kinase inhibitors.
- No cell therapy was reported in the RW studies.
- In the interventional study, the reported post anti-PD-(L)1 treatment was lifileucel monotherapy, a tumor-infiltrating lymphocytes cell therapy.

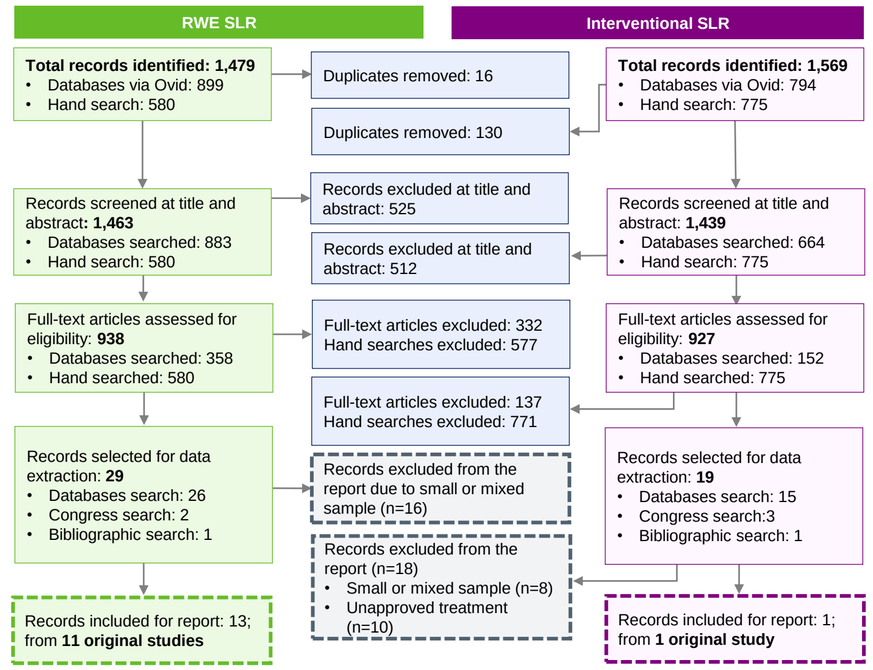
Clinical outcomes in patients with MM post anti-PD-(L)1

- The sample sizes of studies with clinical outcomes reported were 16 or less except in one retrospective chart review study conducted in Japan (n=197 [n=148 with evaluable outcomes]).[3]
- Six of the 11 RW studies reported clinical outcomes (**Table 1**); all were retrospective in design except for one single-center prospective cohort analysis.[4] The range of outcomes is depicted below.



- In the interventional, non-randomized, phase 2 study, the efficacy of lifileucel was reported in a subgroup of 12 patients with MM; ORR was 50%, median OS was 19.4 months, and median PFS was not reached.

Figure 1. PRISMA flow diagram



Abbreviations: RWE, real-world evidence; SLR, systematic literature review

Table 1. Clinical outcomes

Author, year Country	No. of MM post anti-PD-(L)1 Reported patient characteristics	Prior anti-PD-(L)1	LOT post anti-PD-(L)1	Treatment post anti-PD-(L)1	Outcomes† (response rate [95% CI], %; time to event, median [95% CI], months)
RWE SLR					
Nakamura 2021[3] Japan	197 (148 with outcomes) Stage: Unresectable or metastatic	177 patients received anti-PD-1 in 1L+, 20 patients received anti-PD-1+CTLA-4 in 1L+	2L+	**Post anti-PD-1 (n=177)** • Immunotherapy: **126 (71%)** Single-agent anti-CTLA-4: 23 (18%) Single-agent anti-PD-1: 64 (51%) Anti-PD-1+anti-CTLA-4: 39 (31%) • Small-molecular targeted therapy: **5 (3%)** • Cytotoxic agents: **38 (21%)** • Radiotherapy: **1 (1%)** • Surgery: **0 (0%)** • Clinical trial: **7 (4%)**	NR
				Post anti-PD-1 + CTLA-4 (n=20) • Immunotherapy: **7 (35%)** Single-agent anti-CTLA-4: 1 (14%) Single-agent anti-PD-1: 5 (71%) Immunomodulator (interferon): 1 (14%) • Small-molecular targeted therapy: **1 (5%)** • Cytotoxic agents: **6 (30%)** • Radiotherapy: **1 (5%)** • Surgery: **1 (5%)** • Clinical trial: **4 (20%)**	NR
			Subgroup with outcomes reported in 2L	Nivolumab + ipilimumab	N=35, response assessed by radiologists or INV, RECIST v1.1 **PFS: 2.7 (2.0, 3.5); OS: 9.4 (5.9, 21.6)**
				Ipilimumab	N=64, response assessed by radiologists or INV, RECIST v1.1 **PFS: 2.3 (1.7, 2.8); OS: 8.7 (5.5, 14.0)**
				Chemotherapy	N=15, response assessed by radiologists or INV, RECIST v1.1 **PFS: 2.1 (0.5, 3.9); OS: 6.1 (2.3, 11.6)**
Tang 2021[5] China	16 Stage: III–IV and metastatic	Anti-PD-1 in 1L+	2L+	Axitinib + (toripalimab or pembrolizumab)	N=16, response assessed by INV, RECIST v1.1, at follow-up of 20.1 months **ORR: 18.8% (2.7, 40.2); OS: 12.6 (2.9, 22.3)** **Time to treatment failure: 5.1 (0.4, 9.7)**
Owen 2020[6] International	11 Stage: III–IV	Anti-PD-1 in adjuvant setting	1L	Ipilimumab, BRAF/MEKi, anti-PD-(L)1, or radiation therapy	N=11, response assessed by INV, RECIST v1.1 **OS: 9.2 (6.9, not reached)**
			1L (subgroup)	Ipilimumab	N=5 (subgroup) **ORR: 0% (NR)**
Stoff 2023[7] Israel	4 Stage: metastatic	Anti-PD-1 (w/o ipilimumab) in lines 1–4	2L+	Anti-PD-1 (nivolumab or pembrolizumab) + lenvatinib	N=4, response assessed by physician, iRECIST v1.1 **ORR: 25.0% (NR)**
Moya-Plana 2019[4] France	4 Stage: advanced or metastatic ECOG PS 0–1: 100%	Pembrolizumab in 1L+	2L+	Ipilimumab	N=4, response based on RECIST v1.1, assessor NR, at follow-up of 24 months **ORR: 0% (NR)**
Trim 2023[8] United States	3 Stage: advanced	Nivolumab + ipilimumab in 1L	2L	Anti-PD-1 (nivolumab or pembrolizumab) w/o ipilimumab	N=3, assessor and criteria NR **ORR: NR; DCR: 33.3%**
Interventional SLR					
Kluger 2023[9] International	12 Stage: advanced or metastatic Prior LOT, median: 2 (range 1–6)	Anti-PD-(L)1	2L+	Lifileucel	N=12, response assessed by IRC, RECIST v1.1, at follow-up of 35.7 months **ORR: 50% (21, 79); PFS: Not reached; OS: 19.4**

† Follow-up duration and clinical outcomes (OS/PFS/ORR) were not extracted if not reported. Other clinical outcomes were extracted whenever the OS/PFS/ORR data were not available. OS or PFS were indexed from treatment initiation in Nakamura 2021, Owen 2020, and Tang 2021.
Time to treatment failure in Tang 2021 was defined as from the date of initiation of treatment to the date of discontinuation of treatment or death or censored at the last follow-up date or date of discontinuation for toxicity.
Abbreviations: 1L, first line; 2L, second line; 2L+, second line or later; BRAFi, BRAF inhibitor; CI, confidence interval; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; iRECIST, immune Response Evaluation Criteria in Solid Tumours; LOT, line of therapy; MEKi, mitogen-activated protein kinase inhibitor; MM, mucosal melanoma; no, number; NR, not reported; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed cell death protein 1 or programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; RWE, real-world evidence; SLR, systematic literature review; w/o: with or without

References

1. Page MJ, et al. *BMJ*. 2021; doi:10.1136/bmj.n71; 2. Higgins J. Cochrane Handbook for Systematic Reviews of Interventions. Second Edition ed. 2019; 3. Nakamura Y, et al. ESMO Open. 2021;6(6):100325; 4. Moya-Plana A, et al. *Cancer Immunology, Immunotherapy*. 2019;68:1171-1178; 5. Tang B, et al. *European Journal of Cancer*. 2021;156:83-92; 6. Owen C, et al. *Annals of Oncology*. 2020;31(8):1075-1082; 7. Stoff R, et al. *Frontiers in Oncology*. 2023;13:1180988; 8. Trim EP, et al. Abstract presented at: The 20th SMR; November 6-9, 2023; Philadelphia, PA, US; 9. Kluger H, et al. Abstract presented at: The 20th SMR; November 6-9, 2023; Philadelphia, PA, US.

Disclosures

- Funding was provided by Mural Oncology.
- C Lei is an employee of Mural Oncology. Z Chen is an employee of Cytel, a consulting company that has provided paid consulting services to Mural Oncology. C. Kwon, who was formerly employed by Cytel, contributed to the poster development.

*Employed by Cytel at the time of the poster development