P-075

Benchmarking efficacy outcomes for patients with relapsed/refractory advanced melanoma previously treated with immunotherapy: Utility of a systematic pooled clinical analysis

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BACKGROUND

- Rapid advances in immunotherapy (IO), including the development of checkpoint inhibitors, have resulted in remarkable improvements in outcomes for patients with previously untreated (IO-naïve/first-line) advanced melanoma[1–4]
- However, clinical benefit in terms of objective responses and long-term survival is not achieved in the majority of patients with currently approved interventions,[1–4] resulting in a high unmet need for novel therapies to treat patients with relapsed/refractory (R/R) disease

RATIONALE

- Measuring efficacy endpoints in clinical trials of the R/R patient population is complicated by the pronounced intra-tumoral, inter-tumoral, and inter-patient heterogeneity that occurs as melanoma progresses,[5] resulting in a large variation in reported efficacy outcomes
- Other factors driving this variability in reported outcomes may include differences in trial designs, eligibility criteria, and agents used

OBJECTIVE

- We conducted a pooled analysis of efficacy outcomes with IO in patients with R/R advanced melanoma reported in published clinical trial and real-world practice settings to define a benchmark for response in this population
- We sought to answer the persisting question: *"What is a truer response rate to, and a more appropriate benchmark for, IO-based regimens in patients with R/R advanced melanoma?"*

METHODS

Literature search

- MEDLINE-, EMBASE- and Cochrane-indexed publications and conference abstracts were searched between January 2018 and July 2020 for clinical and real-world studies reporting efficacy outcomes with IO (single agent or in combination) in patients with R/R advanced melanoma after failure of an approved first-line therapy (including anti-programmed death (PD)-1, anti-PD-ligand 1, or BRAF/MEK inhibitor therapy)
- The search terms were: "melanoma" + "relapsed" + "refractory" + "objective response rate" + "complete response" + "disease control rate"

Outcomes included

- Key outcomes extracted were objective response rate (ORR), complete response (CR) rate, and disease control rate (DCR) by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

Statistical analysis

- Clinical efficacy outcomes were analyzed using the R package (Version 4.0.3), with the results presented here as forest plots
- The Hartung-Knapp random-effects method (meta package Version 4.14-0) was used to obtain weighted means along with the corresponding 95% confidence intervals (CI).[6] To assess the sensitivity of these results, means were also derived using a fixed-effects model
- A test using the Q-statistic was performed to assess inter-study heterogeneity ($p<0.05$)[7]
- I^2 describes the percentage of variation across clinical studies that is due to the expected heterogeneity rather than sampling error
- τ^2 describes the between-study variance

RESULTS

Literature search and reported results

- A total of 14 clinical studies with IO agents in the R/R advanced melanoma patient population (911 unique patients) reported ORRs[8–21]
  - Thirteen of these studies (740 unique patients) reported CR rates,[8–14,16–21] and 12 of these studies (789 unique patients) reported DCRs[8–10,12–16,18–21]
- Eighteen treatment arms, for 10 different agents, in 12 unique regimens were included in the analysis of the overall population[8–21]
  - ORRs reported ranged from 4–36%
  - CR rates reported ranged from 0–6%
  - DCRs reported ranged from 13–80%
- All clinical studies used RECIST v1.1 for tumor assessments[22]
- Patient characteristics are summarized in **Table 1**

Table 1. Key characteristics of patients from studies included in the systematic pooled clinical analysis

Patient characteristic	Range
Sample size, N	13–103
Age, median years	55–71
Female sex, %	31–50
Number of previous lines of therapy, mean	1–3

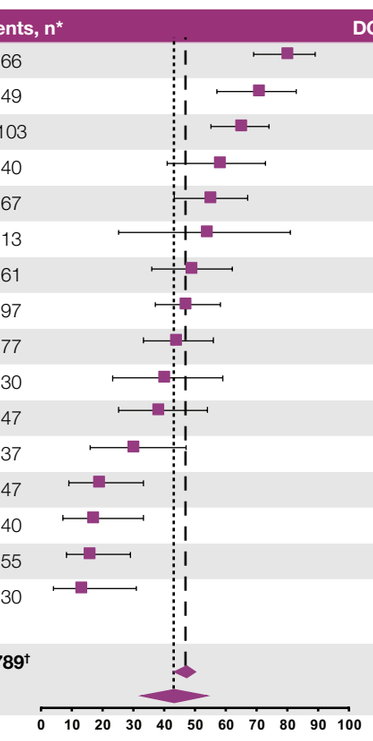
Pooled analysis of ORR

- Of 14 studies reporting ORRs (911 unique patients), the pooled ORR was 18% (95% CI: 16–21%) based on the fixed-effect model and 17% (95% CI: 13–21%) based on the random-effects model (**Figure 1**)

Figure 1. Pooled analysis of ORR in the overall population

Study	Treatment	Events	Patients, n*	ORR (%)	95% CI
Sarnaik A, et al. 2020[8]	TIL therapy (lifileucel)	24	66	36	25–49
Olson DJ, et al. 2020[9]	Pembro + IPI	21	67	31	21–44
Muto Y, et al. 2019[10]	NIVO or pembro	8	30	27	12–46
Milhem M, et al. 2018[11]	TLR9 agonist (CMP-001) + pembro	15	69	22	13–33
Haymaker C, et al. 2020[12]	TLR9 agonist (tilsotolimod) + IPI	11	49	22	12–37
Fernandez A, et al. 2020[13]	MKi (lenvatinib) + pembro	22	103	21	14–31
Bowyer S, et al. 2016[14]	NIVO or pembro	8	40	20	9–36
Weichenthal M, et al. 2019[15]	NIVO + IPI	15	77	19	11–30
Zimmer L, et al. 2017[16]	NIVO + IPI	7	37	19	8–35
Sullivan RJ, et al. 2019[17]	HDACi (entinostat) + pembro	10	53	19	9–32
Ribas A, et al. 2018[19]	TLR9 agonist (SD-101) + pembro	2	13	15	2–45
Zimmer L, et al. 2017[16]	IPI	7	47	15	6–28
Long G, et al. 2016[20]	IPI	13	97	13	7–22
Ascierto PA, et al. 2017[18]	Anti-LAG-3 (BMS-986016) + NIVO	7	61	11	5–22
Bowyer S, et al. 2016[14]	IPI	4	40	10	3–24
Muto Y, et al. 2019[10]	IPI	2	30	7	1–22
Weichenthal M, et al. 2019[15]	IPI	2	47	4	1–15
Fujisawa Y, et al. 2018[21]	IPI	2	55	4	0–13
Fixed-effect model			**911†**	**18**	**16–21**
Random-effects model				**17**	**13–21**

Heterogeneity: $I^2 = 65\%$; $\tau^2 = 0.2467$; $p<0.01$



*Efficacy evaluable population; †Represents the total number of unique patients included in the analysis.
CI, confidence interval; HDACi, histone deacetylase inhibitor; IPI, ipilimumab; LAG-3, lymphocyte activation gene-3; MKi, multikinase inhibitor; NIVO, nivolumab; ORR, objective response rate; pembro, pembrolizumab; TIL, tumor-infiltrating lymphocyte; TLR, toll-like receptor.

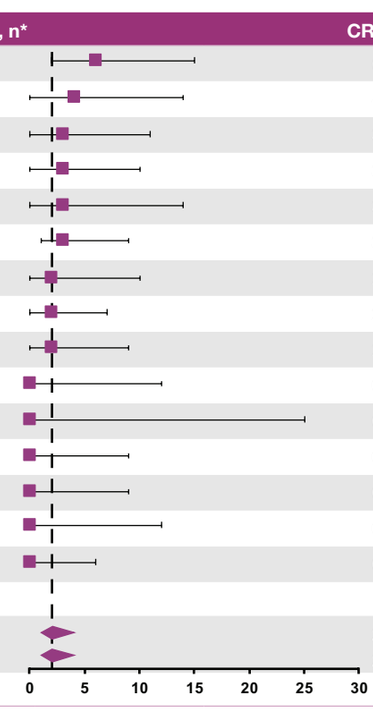
Pooled analysis of CR rates

- Of 13 studies reporting CR rates (740 unique patients), the pooled CR rate was 2% (95% CI: 1–4%) based on the fixed-effect model and 2% (95% CI: 1–4%) based on the random-effects model (**Figure 2**)

Figure 2. Pooled analysis of CR rates in the overall population

Study	Treatment	Events	Patients, n*	CR (%)	95% CI
Olson DJ, et al. 2020[9]	Pembro + IPI	4	67	6	2–15
Haymaker C, et al. 2020[12]	TLR9 agonist (tilsotolimod) + IPI	2	49	4	0–14
Sarnaik A, et al. 2020[8]	TIL therapy (lifileucel)	2	66	3	0–11
Milhem M, et al. 2018[11]	TLR9 agonist (CMP-001) + pembro	2	69	3	0–10
Zimmer L, et al. 2017[16]	NIVO + IPI	1	37	3	0–14
Long G, et al. 2016[20]	IPI	3	97	3	1–9
Sullivan RJ, et al. 2019[17]	HDACi (entinostat) + pembro	1	53	2	0–10
Fernandez A, et al. 2020[13]	MKi (lenvatinib) + pembro	2	103	2	0–7
Ascierto PA, et al. 2017[18]	Anti-LAG-3 (BMS-986016) + NIVO	1	61	2	0–9
Muto Y, et al. 2019[10]	NIVO or pembro	0	30	0	0–12
Ribas A, et al. 2018[19]	TLR9 agonist (SD-101) + pembro	0	13	0	0–25
Bowyer S, et al. 2016[14]	NIVO or pembro	0	40	0	0–9
Bowyer S, et al. 2016[14]	IPI	0	40	0	0–9
Muto Y, et al. 2019[10]	IPI	0	30	0	0–12
Fujisawa Y, et al. 2018[21]	IPI	0	55	0	0–6
Fixed-effect model			**740†**	**2**	**1–4**
Random-effects model				**2**	**1–4**

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $p = 1.00$



*Efficacy evaluable population; †Represents the total number of unique patients included in the analysis.
CI, confidence interval; CR, complete response; HDACi, histone deacetylase inhibitor; IPI, ipilimumab; LAG-3, lymphocyte activation gene-3; MKi, multikinase inhibitor; NIVO, nivolumab; pembro, pembrolizumab; TIL, tumor-infiltrating lymphocyte; TLR, toll-like receptor.

Pooled analysis of DCR

- Of 12 studies reporting DCRs (789 unique patients), the pooled DCR rate was 47% (95% CI: 43–50%) based on the fixed-effect model and 43% (95% CI: 32–54%) based on the random-effects model (**Figure 3**)

Figure 3. Pooled analysis of DCR in the overall population

Study	Treatment	Events	Patients, n*	DCR (%)	95% CI
Sarnaik A, et al. 2020[8]	TIL therapy (lifileucel)	53	66	80	69–89
Haymaker C, et al. 2020[12]	TLR9 agonist (tilsotolimod) + IPI	35	49	71	57–83
Fernandez A, et al. 2020[13]	MKi (lenvatinib) + pembro	67	103	65	55–74
Bowyer S, et al. 2016[14]	NIVO or pembro	23	40	58	41–73
Olson DJ, et al. 2020[9]	Pembro + IPI	37	67	55	43–67
Ribas A, et al. 20181[9]	TLR9 agonist (SD-101) + pembro	7	13	54	25–81
Ascierto PA, et al. 2017[18]	Anti-LAG-3 (BMS-986016) + NIVO	30	61	49	36–62
Long G, et al. 201620	IPI	46	97	47	37–58
Weichenthal M, et al. 2019[15]	NIVO + IPI	34	77	44	33–56
Muto Y, et al. 2019[10]	NIVO or pembro	12	30	40	23–59
Zimmer L, et al. 2017[16]	IPI	18	47	38	25–54
Zimmer L, et al. 2017[16]	NIVO + IPI	11	37	30	16–47
Weichenthal M, et al. 2019[15]	IPI	9	47	19	9–33
Bowyer S, et al. 2016[14]	IPI	7	40	17	7–33
Fujisawa Y, et al. 2018[21]	IPI	9	55	16	8–29
Muto Y, et al. 2019[10]	IPI	4	30	13	4–31
Fixed-effect model			**789†**	**47**	**43–50**
Random-effects model				**43**	**32–54**

Heterogeneity: $I^2 = 89\%$; $\tau^2 = 0.7371$; $p<0.01$

*Efficacy evaluable population; †Represents the total number of unique patients included in the analysis.
CI, confidence interval; DCR, disease control rate; HDACi, histone deacetylase inhibitor; IPI, ipilimumab; LAG-3, lymphocyte activation gene-3; MKi, multikinase inhibitor; NIVO, nivolumab; pembro, pembrolizumab; TIL, tumor-infiltrating lymphocyte; TLR, toll-like receptor.

CONCLUSIONS

- Analysis of data from >900 patients with R/R advanced melanoma treated with 10 different IO agents, in 12 unique regimens, across 18 treatment arms in 14 clinical studies using a fixed-effect model for pooled analyses of clinical efficacy endpoints was able to address the question ***regarding a truer response rate to, and more appropriate benchmark for, IO-based regimens in patients with R/R advanced melanoma***
  - ORR of 18% (95% CI: 16–21%)
  - CR rate of 2% (95% CI: 1–4%)
  - DCR of 47% (95% CI: 43–50%)
- Heterogeneity was observed across all efficacy endpoints reported from the clinical studies
  - The wide range of reported results from the clinical studies (4–36%, 0–6%, and 13–80% for ORR, CR rate, and DCR, respectively) could be attributed to multiple contributing factors, such as differences in patient populations, eligibility criteria, trial designs, lines of therapy, agents and regimens used (singlet or doublet), and their mechanisms of action
- The pooled analysis results were consistent across the fixed-effect and random-effects models for each endpoint and provide a novel benchmark for clinical efficacy outcomes that could help inform the design of non-registrational, proof-of-concept, signal finding, and other investigational studies in patients with R/R advanced melanoma
- Additional and more detailed analyses for other clinical efficacy endpoints will be presented in a future publication using the same methodology as for these outcomes

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