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Rescue addition of ipilimumab to pembrolizumab or nivolumab in metastatic melanoma after resistance to anti-PD-1 monotherapy: a monocentric case series

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Background

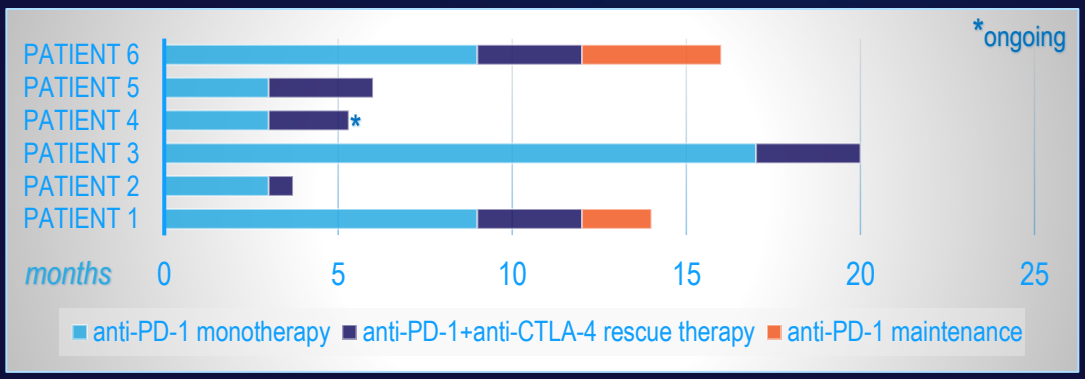
Most patients with advanced melanoma are resistant to anti-PD-1 monotherapy. In Italy, the approval of combination immunotherapy with the anti-CTLA-4 ipilimumab and the anti-PD-1 nivolumab is restricted to patients with asymptomatic brain metastases or patients with tumors not expressing PD-L1 (namely, immunohistochemical assay on tumor cells with <1% PD-L1 positivity). Thus, patients without such characteristics and not candidates for BRAF/MEK inhibition receive anti-PD-1 pembrolizumab or nivolumab as first-line treatment. In this setting, significant antitumor activity was demonstrated by adding ipilimumab immediately after progression to pembrolizumab monotherapy (1). Also, a retrospective study reported a response in 21% of patients with combination therapy after progression to nivolumab vs. 16% with ipilimumab monotherapy (2).

Methods

Hypothesizing that a subset of patients resistant to anti-PD-1 monotherapy would benefit from rescue combination with anti-CTLA-4, after authorization by the local regulatory entity, we administered salvage ipilimumab in addition to ongoing pembrolizumab or nivolumab in 6 pts with advanced melanoma.

Results

Of 6 patients treated with the rescue strategy, 2 had uveal, 1 mucosal, and 3 cutaneous melanoma; 3 were females; the age range was 51-72 years. All patients had PD-L1 positive (≥1%) metastatic melanoma without brain metastases. All received anti-CTLA-4 + anti-PD-1 after primary (3 patients) or acquired (3 patients) resistance to first-line anti-PD-1 monotherapy (**Table**). Two patients received pembrolizumab 200 mg q21 followed by ipilimumab 1 mg/kg + pembrolizumab 2 mg/kg q21 (3), 4 received nivolumab 480 mg q28 followed by ipilimumab 4 mg/kg + nivolumab 1 mg/kg q21 (4). Disease-control rate was 50%: 2 patients achieved stable disease with clinical benefit (CB) after combination salvage therapy, 1 achieved an objective response and is still ongoing with combination therapy; 3 had progressive disease. Monotherapy maintenance was resumed after combination therapy in 2 patients with CB and is planned for the patient with objective response to the rescue. At the median follow-up of 16 months, 5 patients permanently discontinued treatment for disease progression; time-to-treatment failure (TTF) ranged from 3 to 26 months, and overall survival (OS) from 7 to 21 months. No additional toxicity was reported after ipilimumab introduction.



Conclusions

Rescue combination therapy with anti-CTLA-4 in addition to ongoing anti-PD-1 is feasible and potentially beneficial for patients with advanced melanoma after primary or acquired resistance to I-line monotherapy.

Table

Patient and disease	Anti-PD-1 monotherapy & duration (months)	Rescue combination therapy & n° of cycles	Monotherapy maintenance & duration (months)	Best response to the rescue	TTF* (months)	OS* (months)
Patient 1 MM	Nivo 9	Ipi+Nivo 4	Nivo 2	SD	26	30
Patient 2 CM	Nivo 3	Ipi+Nivo 1	-	PD	3	7
Patient 3 CM	Nivo 17	Ipi+Nivo 4	-	PD	19	20
Patient 4 CM	Nivo 3	Ipi+Nivo ongoing (3)	N/A	RP	5 censored	5 censored
Patient 5 UM	Pembro 3	Ipi+Pembro 4	-	PD	5	12
Patient 6 UM	Pembro 9	Ipi+Pembro 4	Pembro 4	SD	17	21

Treatment sequence, duration, and outcome for each patient of the case series.

TTF = time-to-treatment failure; OS = overall survival; MM = mucosal melanoma; CM = cutaneous melanoma; UM = uveal melanoma; Nivo = nivolumab; Pembro = pembrolizumab; Ipi = ipilimumab; N/A = not applicable; SD = stable disease; PD = progressive disease; NE = not evaluable. *calculated from anti-PD-1 monotherapy start