Patterns and management of progression on 1st line ipilimumab combined with anti-PD-1 (IPI+PD1) in metastatic melanoma (MM) patients

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Background

- 1st line PD1 combined with ipilimumab (IPI+PD1) induces the highest long-term outcomes, compared to other systemic treatments, including ipilimumab (IPI)[1], anti-PD1 (PD1)[1,2,3] or BRAF/MEK inhibitors (BRAF/MEKi)[4], with 5-year PFS and OS of 36% and 52%[2], respectively, in patients with metastatic melanoma.
- The majority of patients with metastatic melanoma will progress after 1st line IPI+PD1 and may require further treatment.
- The management and outcomes after progression on 1st line IPI+PD1 have not been systematically investigated.

Objectives

1. Describe patterns of progression to 1st line IPI+PD1.
2. Identify clinical factors associated with specific patterns of progression.
3. Determine management strategies for progressors to 1st line IPI+PD1 and respective outcomes.

Methods

- Cohort: 310 patients with metastatic melanoma treated with 1st line IPI+PD1 at 14 melanoma centers from Australia, Europe and USA were included.
- Variables: demographics, disease characteristics, baseline blood parameters, nature of progressive disease and subsequent treatments.
- Endpoints:
  - Patterns of progressive disease
    - Innate resistance = progressive disease (PD) or stable disease (SD) < 6 months as best response.
    - Acquired resistance = PD after initial response or SD ≥ 6 months.
    - Pseudoprogression = PD followed by response without changing treatment.
  - Efficacy
    - Objective response rate (ORR) = proportion of complete and partial responses to IPI+PD1.
    - Progression-free survival (PFS) = time from start IPI+PD1 until progression or last follow-up.
    - Overall survival (OS) = time from start of IPI+PD1 until death or last follow-up.
- Statistical Analysis:
  - Univariate and Multivariable analysis were performed to identify factors associated with each pattern of progressive disease.
  - Predictive model to identify superprogressors (= progressive disease <1.5 months) was selected using multivariate Cox proportional hazard model, logistic regression and LASSO.

Conclusions

- Patients with acquired resistance have longer OS compared to patients with innate resistance, independent of the type of subsequent systemic treatment.
- Patients with primary head & neck melanoma and with lung metastases are more likely to be superprogressors (progressive disease < 1.5 months).
- BRAF/MEKi, rechallenge with PD1+/-IPI and investigational drugs showed activity after progressive disease to 1st line IPI+PD1, and can be considered a treatment option in this context; chemotherapy has no role in patients who progressed with 1st line IPI+PD1.

References

1. Robert C, *et al.* Lancet Oncol 2019
2. Larkin J, *et al.* NEJM 2019
3. Robert C, *et al.* NEJM 2015
4. Long GV, et al. NEJM 2014

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RESULTS

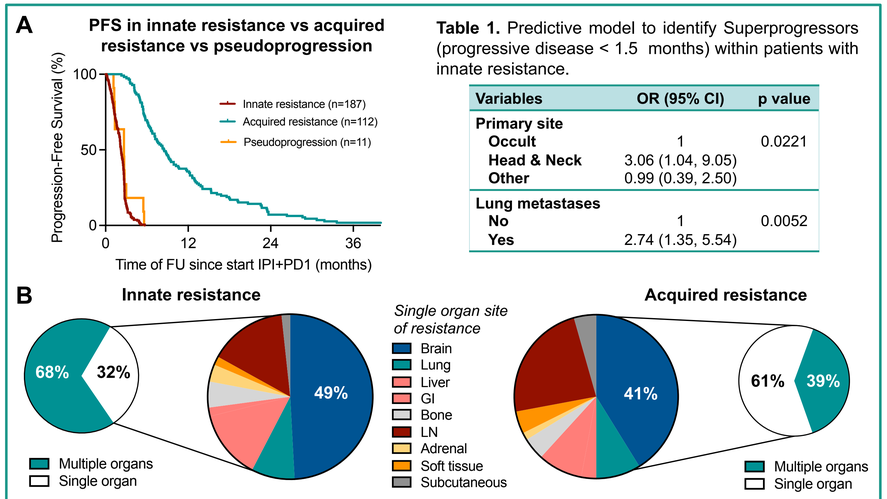

Table 1. Predictive model to identify Superprogressors (progressive disease < 1.5 months) within patients with innate resistance.

Variables	OR (95% CI)	p value
Primary site		
Occult	1	0.0221
Head & Neck	3.06 (1.04, 9.05)	
Other	0.99 (0.39, 2.50)	
Lung metastases		
No	1	0.0052
Yes	2.74 (1.35, 5.54)	

Figure 1. (A) Progression-free survival in patients with innate resistance, acquired resistance and pseudoprogression to 1st line IPI+PD1. **(B)** Sites of innate (*left*) and acquired (*right*) resistance.

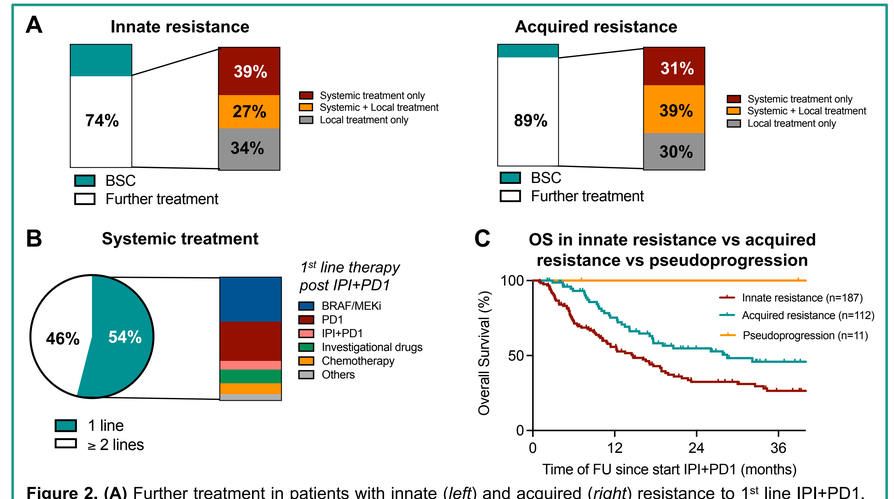

Figure 2. (A) Further treatment in patients with innate (*left*) and acquired (*right*) resistance to 1st line IPI+PD1. **(B)** Subsequent systemic treatment after 1st line IPI+PD1. **(C)** Overall survival in patients with innate resistance, acquired resistance and pseudoprogression to 1st line IPI+PD1.

Table 2. Clinical outcomes (ORR, PFS and OS) with BRAF/MEKi, PD1, IPI+PD1, investigational drugs or chemotherapy as 1st line or any line setting, **after progression on (n=124; 66%) or off (n=63; 34%) IPI+PD1**.

Systemic treatment after progression to IPI+PD1	BRAF/MEKi	PD1	IPI+PD1	Investigational drugs	Chemotherapy
ORR for 1st line therapy post IPI+PD1, n/N (%)					
Innate Resistance to IPI+PD1	30/51 (59)	7/27 (26)	1/5 (20)	1/15 (7)	0/15 (0)
Acquired Resistance to IPI+PD1	13/20 (65)	11/36 (31)	3/9 (33)	1/6 (17)	0/3 (0)
Total	43/71 (61)	18/63 (29)	4/14 (29)	2/21 (10)	0/18 (0)
ORR for any line therapy post IPI+PD1, n/N (%)	61/102 (60)	26/79 (33)	9/36 (25)	7/47 (15)	1/42 (2)
Disease control rate for 1st line therapy post IPI+PD1, n/N (%)	53/71 (75)	35/63 (56)	6/14 (43)	7/21 (33)	0/18 (0)
mPFS for 1st line therapy post IPI+PD1, mo (95% CI)	8.9 (6.0-15.4)	5.0 (3.6-12.6)	7.5 (2.7-NA)	2.9 (2.0-4.9)	1.7 (1.3-2.2)
12-mo PFS rate (%)	42	37	35	6	6
mOS for 1st line therapy post IPI+PD1, mo (95% CI)	18.9 (12.4-30.0)	32.6 (18.7-NA)	15.6 (10.5-NA)	17.7 (16.1-NA)	4.4 (3.2-13.5)

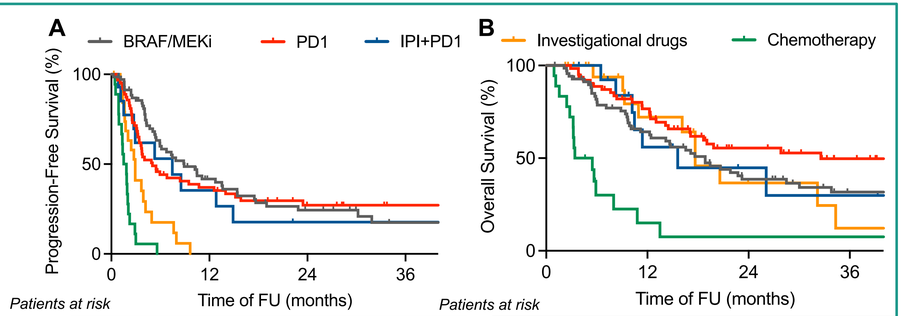

Figure 3. Progression-free survival **(A)** and Overall Survival **(B)** in patients treated with BRAF/MEKi, PD1, IPI+PD1, investigational drugs and chemotherapy as 1st line therapy after failing IPI+PD1.