#1042P: Anti-PD1 (PD1) monotherapy or in combination with ipilimumab (IPI) after BRAF/MEK inhibitors (BRAF/MEKi) in BRAF mutant metastatic melanoma (MM) patients (pts).

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BACKGROUND & AIMS

- Immunotherapy loses efficacy when given as 2nd line of treatment or later (for example, after BRAF/MEK inhibitors)[1,2,3,4], likely due to a larger volume of disease, poorer condition of patient as well as possible changes in biology as a result of previous treatments[5].
- Patients with V600BRAF mutant metastatic melanoma have numerically higher rates of progression-free survival (PFS) and overall survival (OS) with 1st line IPI+PD1 versus PD1[6,7]. Whether this is also true after BRAF/MEKi therapy is yet to be determined.

The **AIMS** of this study are:

1. To determine the efficacy (objective response rare [ORR], PFS and OS) and safety of PD1 vs IPI+PD1 after BRAF/MEKi.
2. To identify the subgroup of patients with >3 years OS with PD1+/-IPI after BRAF/MEKi.

METHODS

- Cohort: 200 patients with metastatic melanoma treated with IPI+PD1 or PD1 after BRAF/MEKi at 8 centers from Australia, Europe and USA.
- Variables: demographics, disease characteristics and baseline blood parameters.
- Endpoints:
  - Efficacy: ORR, PFS and OS.
  - Safety: proportion of patients with >=G3 immune-related adverse events.
- Statistical Analysis:
  - Predictive model to identify those patients with >3 years OS was selected using multivariate Cox proportional hazard model, logistic regression and LASSO.

RESULTS

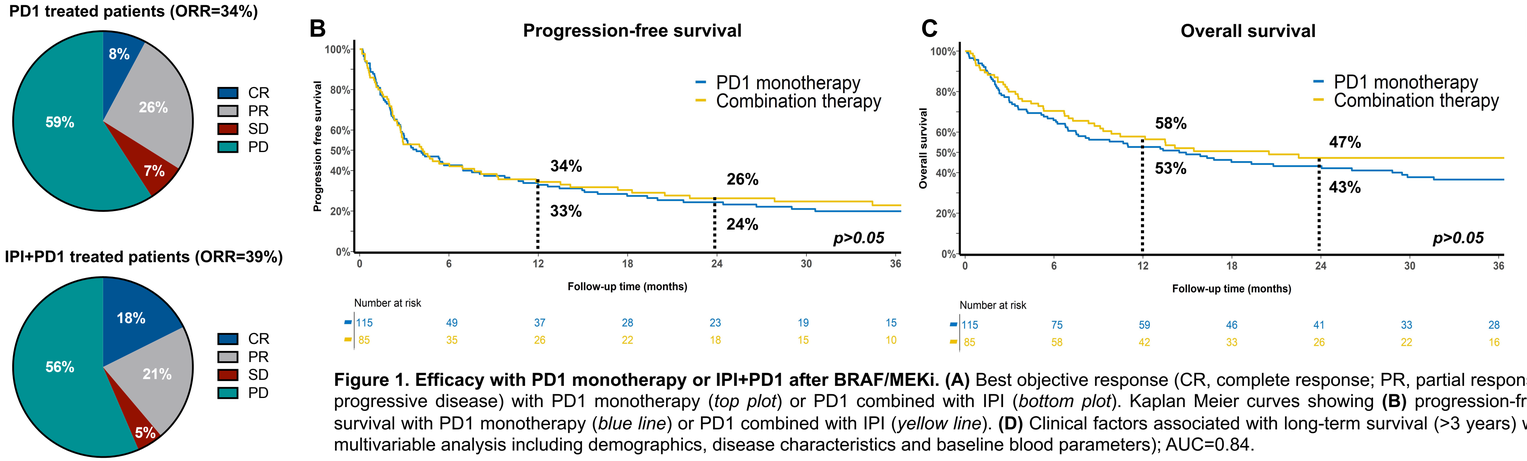
Table 1. Summary of patients characteristics stratified by treatment type.

Characteristics	PD1 (n=115)	IPI+PD1 (n=85)	*P-value*
Male (n, %)	78 (68)	59 (69)	0.9325
Age (median, range)	63 (22 – 91)	54 (19 – 81)	**0.0002**
BRAF V600E (n, %)	80 (70)	70 (82)	0.0575
ECOG PS >= 1 (n.%)	70 (62)	34 (40)	**0.0232**
Reason for BRAF/MEKi cessation (n, %) Recurrence/PD	90 (78)	64 (75)	0.7468
AJCC staging M1c/M1d (n, %)	83 (72)	80 (94)	**0.0002**
Presence of brain mets (n, %)	44 (38)	55 (65)	**0.0004**
Presence of liver mets (n, %)	36 (31)	28 (33)	0.9267
Elevated LDH (n, %)	42 (37)	40 (47)	0.3701

ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; AJCC staging, American joint cancer committee, staging; mets, metastases, LDH, lactate dehydrogenase.

RESULTS

A — *Objective response, Progression-free & Overall Survival to PD1 monotherapy (n=115) or in combination (n=85) with IPI after BRAF/MEKi*



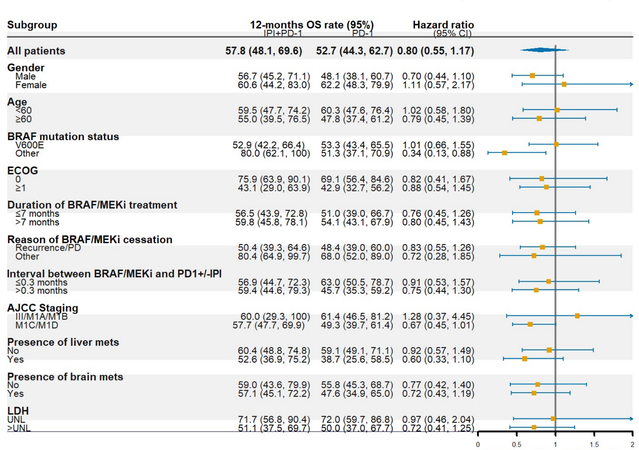
D Clinical factors associated with long-term survival (> 3 years)

Parameters	*P-value*
ECOG PS = 0	0.0009
Absence of liver metastases	0.0003
Normal LDH	0.0157

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase

Figure 1. Efficacy with PD1 monotherapy or IPI+PD1 after BRAF/MEKi. (A) Best objective response (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease) with PD1 monotherapy (*top plot*) or PD1 combined with IPI (*bottom plot*). Kaplan Meier curves showing **(B)** progression-free survival and **(C)** overall survival with PD1 monotherapy (*blue line*) or PD1 combined with IPI (*yellow line*). **(D)** Clinical factors associated with long-term survival (>3 years) with PD +/- IPI (results from multivariable analysis including demographics, disease characteristics and baseline blood parameters); AUC=0.84.

A — *Subgroup analysis (Overall Survival)*



B

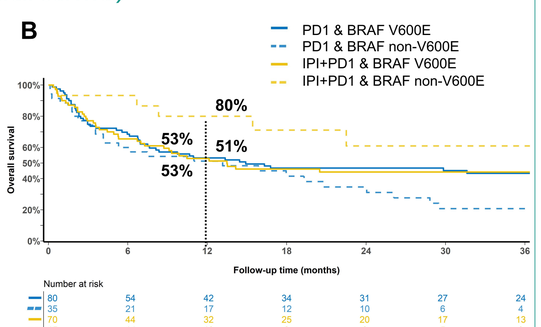


Figure 2. Overall survival subgroup analysis. (A) Forest plot showing the 12-months OS subgroup analysis. **(B)** Kaplan Meier curves showing overall survival stratified by treatment (PD1 vs IPI+PD1) and BRAF mutation type (V600E vs non-V600E).

Safety

Table 2. Proportion of stratified >=G3 immune-related adverse events (AE) by treatment type.

Adverse events	PD1 (n=115)	IPI+PD1 (n=85)
Any (n,%)	8 (7%)	26 (31%)**
Diarrhoea/colitis (n,%)	0	13 (15%)
Hepatitis (n,%)	3 (3%)	9 (11%)
Skin (n,%)	0	1 (1%)
Hypophysitis, thyroiditis (n,%)	0	1 (1%)
Pneumonitis (n,%)	1 (1%)	0
Nephritis (n,%)	0	1 (1%)
Fever (n,%)	0	0
Elevated Amylase/Lipase (n,%)	2 (2%)	0
Others (n,%)	2 (2%)*	5 (6%)***

* Inflammatory syndrome (cytokine release) and encephalitis.
** 4 patients had >1 G3 immune-related AD: 1 patient had G3 colitis & G3 hepatitis; 1 patient had G3 hepatitis & G3 thyroiditis; 1 patient had G3 hepatitis & T1MD and 1 patient had hepatitis & pericarditis.
*** T1MD, Myastenia Gravis, peripheral neuropathy, pericarditis and immune thrombocytopenic purpura.

REFERENCES

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CONCLUSIONS

- IPI+PD1 appears minimally superior to PD1 after BRAF/MEKi in ORR, PFS and OS (but smaller difference compared to 1st line treatment), although is more toxic.
- OS was significantly longer with IPI+PD1 vs PD1 in non-V600E mutations (1-year OS, 80% vs 51%), but no difference in V600E mutations (1-year OS, 53% vs 53%). PFS and OS were numerically longer with IPI+PD1 vs PD1 across all other subgroups except for OS in females & III/M1A/M1B stages.
- The combination of ECOG PS=0, absence of liver metastases and normal LDH can accurately identify patients with long-term survival (>3 years OS) with PD1 +/- IPI after BRAF/MEKi.

ACKNOWLEDGEMENTS

All patients and their families

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IPS had travel support by BMS and MSD, and speaker fee by Roche, BMS, MSD and Novartis.

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