Anti-PD-1 (PD1) monotherapy or in combination with anti-CTLA-4 for metastatic melanoma patients with liver metastases.

Ines Pires da Silva[1,2], Isabel Li[1], Selma Ugurel[3], Patricio Serra-Bellver[4], Avanti Andhale[4], Hannah Burnette[5], Francisco Aya[6], Jordan W. Conway[1], Matteo S. Carlino[1,2], Alexander A. Menzies[1,2,7], Michael Weichenthal[8], Peter Mohr[9], Ralf Gutzmer[10], Ana M. Arance[6], Douglas B. Johnson[5], Paul Lorigan[4], Dirk Schadendorf[3], Serigne N. Lo[1], Georgina V. Long[1,2,7]

[1]Melanoma Institute Australia, University of Sydney, Sydney, NSW, Australia; [2]Crown Princess Mary Cancer Centre Westmead, Blacktown Hospital, Sydney, Australia; [3]University Hospital Essen, Essen, Germany; [4]The Christie NHS Foundation Trust, Manchester, UK; [5]Vanderbilt University Medical Center, Nashville, TN, United States of America; [6]Hospital Clinic, Barcelona & IDIBAPS, Barcelona, Spain; [7]Royal North Shore and Mater Hospitals, Sydney, Australia; [8]University Skin Cancer Center Kiel, University Hospital of Schleswig-Holstein, Kiel, Germany; [9]Elbe-Klinikum Buxtehude, Buxtehude, Germany; [10]Ruhr University Bochum Campus Minden, Minden, Germany

Background

- Immune checkpoint inhibitors, including PD1 and anti-CTLA-4 (ipilimumab; IPI), have greatly improved survival rates in patients with advanced melanoma patients, with better overall survival (OS) with IPI+PD1 compared to PD1 (5-year OS rate of 52% vs 44%)[1].
- Liver metastases have been associated with poor response and survival in patients with metastatic melanoma treated with PD1 alone[2,3] or with IPI+PD1[3,4]. Whether these patients benefit from IPI+PD1 over PD1 is unknown.

Objectives

In patients with melanoma liver metastases, we sought to:

- Determine objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) to PD1 vs IPI+PD1.
- Identify clinical factors associated with response and survival to PD1+/- IPI.

Methods

- Cohort: 533 patients with metastatic melanoma with liver metastases treated with 1st line PD1 or IPI+PD1 at 9 centers from Australia, Europe and USA.
- Variables: Demographics, patient and disease characteristics, baseline blood parameters and clinical outcomes
- Endpoints: ORR, PFS and OS
- Statistical Analysis:
  - Univariate and multivariate (MVA) analyses were performed to identify clinical factors associated with response and survival.
  - Multiple imputation was used address missing values.

Results

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

Characteristics	PD1 (n=284)	IPI+PD1 (n=249)	*P-value*
Male (n, %)	173 (61)	173 (70)	**0.045**
Age (median, range)	73 (26 – 93)	62 (22 –97)	0.366
BRAF V600E (n, %)	40 (15)	75 (33)	**<0.001**
ECOG PS >= 1 (n.%)	133 (53)	79 (34)	**<0.001**
AJCC staging M1d (n, %)	43 (15)	76 (31)	**<0.001**
Elevated LDH (n, %)	130 (50)	132 (56)	0.151

Results

Objective response, Progression-free & Overall Survival to PD1 monotherapy (n=284) or in combination with IPI (n=249)

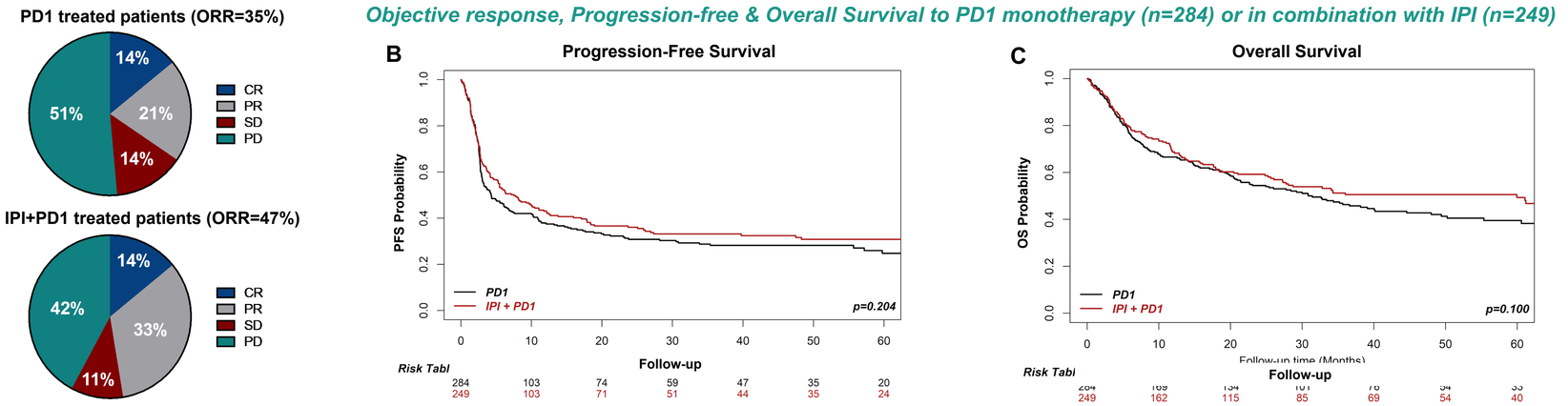

FIGURE 1. Efficacy of PD1 monotherapy or IPI+PD1 for patients with melanoma liver metastases. (A) Best objective response (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease) with PD1 monotherapy (*top plot*) or PD1 combined with IPI (*bottom plot*). Kaplan Meier curves showing **(B)** progression-free survival and **(C)** overall survival with PD1 monotherapy (*red line*) or PD1 combined with IPI (*black line*).

Table 2. Multivariate (MVA) analyses to identify clinical factors associated with response and survival

	Models for response		Models for PFS		Models for OS	
Characteristics	**OR (CI)**	***P-value***	**HR (CI)**	***P-value***	**HR (CI)**	***P-value***
Male vs Female	1.03 [0.69,1.52]	0.900	0.92 [0.74,1.15]	0.459	0.91 [0.71,1.19]	0.498
Age	1.40 [1.15,1.72]	**0.001**	0.83 [0.74,0.93]	**0.001**	0.93 [0.82,1.06]	0.284
Subtype						
Occult	1		1		1	
Cutaneous	1.27 [0.70,2.31]	0.433	0.83 [0.59,1.17]	0.285	0.81 [0.54,1.21]	0.304
Acral	0.12 [0.03,0.58]	**0.008**	2.56 [1.51,4.32]	**<0.001**	2.20 [1.22,3.99]	**0.009**
Mucosal	0.55 [0.22,1.36]	0.193	1.67 [1.03,2.70]	**0.037**	1.66 [0.95,2.89]	0.072
Mutation						
BRAF V600	1		1		1	
NRAS mut	1.02 [0.56,1.83]	0.955	1.00 [0.68,1.47]	0.997	1.14 [0.75,1.72]	0.543
BRAF/NRAS WT	1.48 [0.89,2.48]	0.130	0.70 [0.52,0.95]	**0.022**	0.81 [0.56,1.15]	0.234
ECOG PS >= 1 vs 0	0.68 [0.46,1.02]	0.060	1.40 [1.12,1.76]	**0.003**	1.62 [1.23,2.13]	**0.001**
AJCC staging M1d vs M1c	0.96 [0.61,1.52]	0.869	1.16 [0.89,1.51]	0.277	1.51 [1.12,2.04]	**0.008**
LDH elevated vs normal	0.77 [0.53,1.11]	0.160	1.31 [1.05,1.63]	**0.015**	1.48 [1.15,1.91]	**0.003**
IPI+PD1 vs PD1	2.21 [1.46,3.36]	**<0.001**	0.73 [0.57,0.92]	**0.009**	0.71 [0.54,0.94]	**0.018**

Reason for ceasing PD1 (n=260) or IPI+PD1 (n=237)

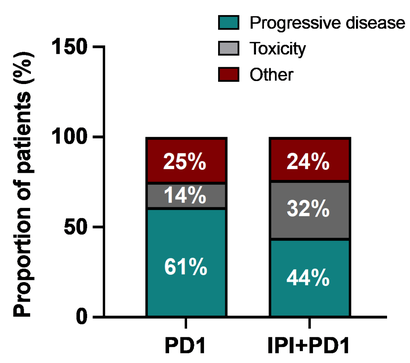

FIGURE 2. Reason for PD1 or IPI+PD1 cessation in patients with melanoma liver metastases. Percentage (%) of patients ceasing PD1 or IPI+PD1 due to progressive disease (61% vs 44%; p=0.0232), toxicity (14% vs 32%; p=0.004) or other reasons.

Conclusions

- In patients with liver metastases, 1st line IPI+PD1 showed higher ORR and improved survival compared with PD1 alone.
- In the absence of prospective randomized trials addressing this research question, findings from this large multicentre retrospective study will help guide treatment selection for patients with melanoma liver metastases.

References

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