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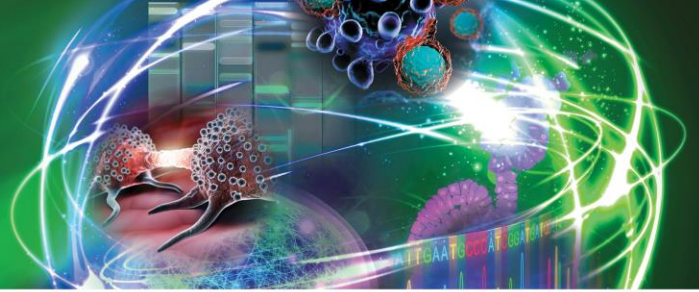

Safety/tolerability and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with PD-(L)1 refractory/resistant unresectable or metastatic melanoma from a Phase 1b study

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Disclosure information

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I have no financial relationships to disclose

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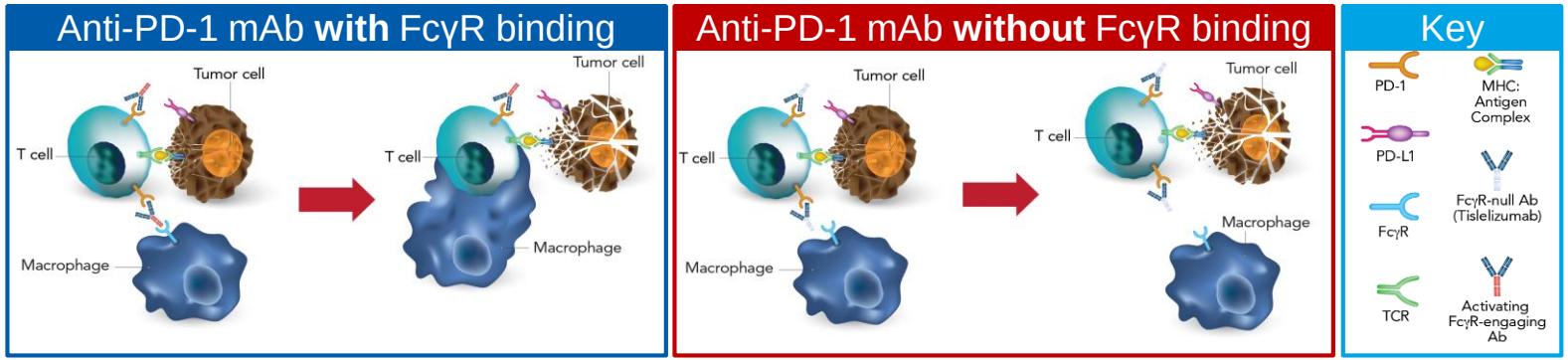
Background

- Immune CPIs are established as the standard of care in the first-line setting for patients with unresectable or metastatic melanoma[1–3]
- However, not all patients respond and a subset of patients who initially respond to CPI, later relapse and develop drug resistance[4]
- Tislelizumab is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T cell clearance and potential anti-PD-1 resistance[5–7]

Tislelizumab MoA



Ab, anitbody; CPI, checkpoint inhibitor; MHC, major histocompatibility complex; MoA, mechanism of action; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

1. Hodi FS, et al. N Engl J Med 2010;363:711–23; 2. Robert C, et al. N Engl J Med 2015;372:2521–32; 3. Larkin J, et al. N Engl J Med 2015;373:23–34; 4. Gide TN, et al. Clin Can Res 2018;24:1260–70 5. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 6. Dahan R, et al. Cancer Cell 2015 Sep 14;28:285–95; 7. Qin S, et al. Future Oncol 2019 15:1811–1822

Background

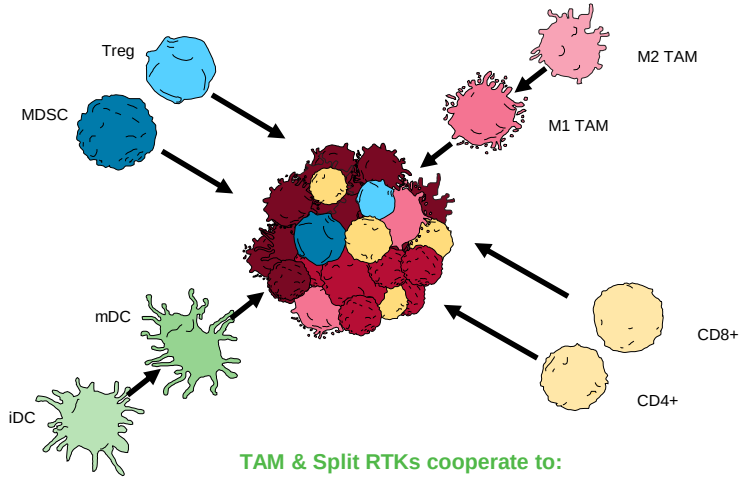
- Sitravatinib is an oral spectrum-selective TKI targeting TAM (TYRO3, AXL, MER) and split (VEGFR2/KIT) receptors[1]
- Inhibition of these receptors reduces the number of MDSCs and regulatory T cells, while increasing the ratio of M1/M2-polarized macrophages, which may overcome an immunosuppressive tumor microenvironment and augment antitumor immune responses[1]
- Combining an anti-PD-1 CPI with an agent that has both pleiotropic and antitumor properties could enhance the antitumor efficacy observed with either agent alone[2,3]
- Tislelizumab plus sitravatinib is currently being investigated in several solid tumor types, including metastatic melanoma (NCT03666143)

Targeting Split RTKs (VEGFR2, KIT)

- Targeting VEGFR2 reduces Tregs & MDSCs
- Targeting KIT also depletes MDSCs
- Releases brakes for expansion of CD8+ T cells via PD-1 inhibition

Targeting TAM (TYRO3, AXL, MER)

- Targeting MERTK & AXL shifts TAM type to M1
- M1 macrophages secrete cytokines that enhance immune response (IL-12, TNF)



TAM & Split RTKs cooperate to:

- Increase dendritic cell maturity & antigen presentation capacity
- Increase NK cell response
- Increase T cell expansion & trafficking into tumors

iDC, induced dendritic cell; mDC, myeloid dendritic cell; MDSCs, myeloid-derived suppressor cells; NK, natural killer; PROC, platinum-resistant ovarian cancer; TKI, tyrosine kinase inhibitor; Treg, regulatory T-cell.

1. Du W, et al. JCI Insight 2018;3:e124184; 2. Demircan NC, et al. Ann Transl Med 2020;8:1714; 3. Arance Fernandez AM, et al. Ann Oncol 2020;31:S1142–215

Study design

Eligibility criteria:

- Age ≥18 years old
- Histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors
- ECOG PS 0,1
- Adequate organ function

Cohort G: Anti-PD-1/PD-L1 antibody refractory/resistant unresectable or metastatic melanoma
Tislelizumab 200 mg IV Q3W + sitravatinib 120 mg PO QD

N = 20 for all cohorts
Cohort A: Nsq NSCLC; Anti-PD-1/PD-L1 Ab R/R
Cohort B: Nsq NSCLC; Anti-PD-1/PD-L1 Ab naïve
Cohort C: RCC; Anti-PD-1/PD-L1 Ab R/R
Cohort D: (China): RCC; Metastatic/advanced without prior systemic therapy
Cohort E: Anti-PD-1/PD-L1 Ab naïve recurrent platinum-resistant OC
Cohort F: Sq NSCLC; Anti-PD-1/PD-L1 Ab treated metastatic
Cohort H: Nsq NSCLC; Treatment-naïve, metastatic, positive (≥1%) PD-L1
Cohort I: Sq NSCLC; Treatment-naïve, metastatic, positive (≥1%) PD-L1

- Progressive disease
- Unacceptable toxicity
- Death
- Withdrawal of consent
- Study termination by sponsor

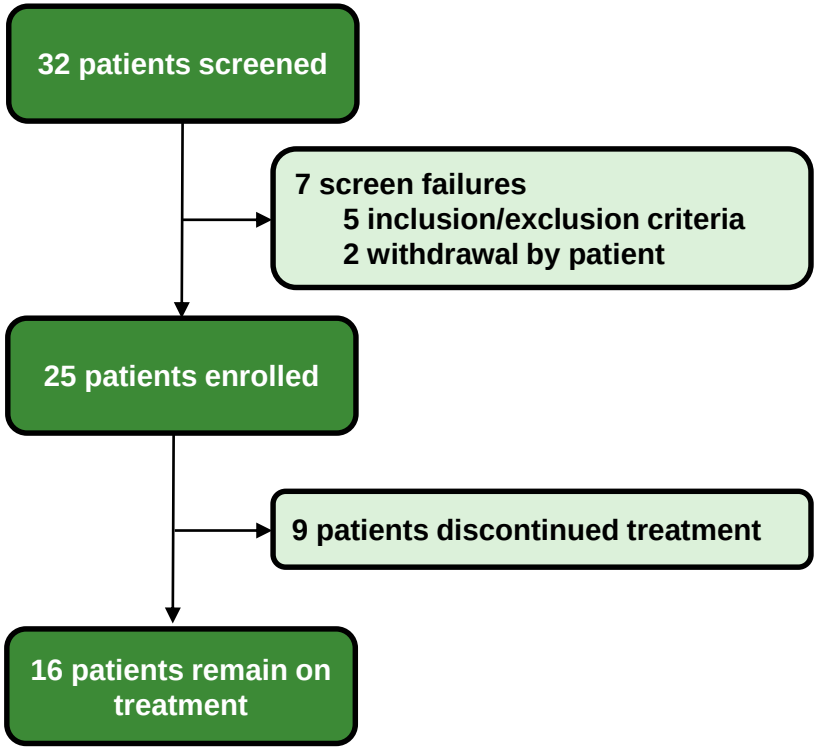
Key eligibility for Cohort G melanoma:
- PD on or after 1L anti-PD-1/PD-L1
- No other prior immunotherapy (including but not limited to anti-CTLA-4)
- No prior exposure to anti-VEGF or VEGFR TKIs
- Documented *BRAF* mutation status

Key endpoints:
- **Primary**: Safety and tolerability
- **Secondary**: Antitumor activity
- **Exploratory**: PK and immunogenicity

Data cut-off 13 Oct 2020

ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSq, non-squamous; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PK, pharmacokinetic; PO, orally; QD, once-daily; Q3W, once every three weeks; RCC, renal cell carcinoma; R/R, resistant/refractory; Sq, squamous; VEGF, vascular endothelial growth factor; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor

Patient disposition – Cohort G



At the data cut-off, 13 October, 2020, a total of 25 patients had been enrolled into the cohort and 16 patients remained on treatment

	Melanoma (N = 25)
Median duration of follow-up, months (range)	5.5 (1.5–13.3)

Baseline characteristics

Baseline characteristics		Melanoma (N = 25)
Age, years	Median (range)	51 (23–79)
Sex, n (%)	Male	13 (52)
	Female	12 (48)
Race, n (%)	Asian	23 (92)
	White	2 (8)
ECOG PS, n (%)	0	3 (12)
	1	22 (88)
Histology at initial diagnosis, n (%)	Cutaneous, chronic sun-induced damage	4 (16)
	Cutaneous, without chronic sun-induced damage	8 (32)
	Acral	7 (28)
	Mucosal	4 (16)
	Unknown	2 (8)

Baseline characteristics		Melanoma (N = 25)
BRAF mutation, n (%)	Positive	7 (28)
	Negative	18 (72)
Prior systemic therapy, n (%)	Anti-PD-1/PD-L1	25 (100)
Prior lines of anticancer therapy, n (%)	1	25 (100)
Duration of last therapy, months	Median (range)	7 (2–28)

Safety summary

Event, n (%)		Melanoma (N = 25)
Patients with at least one TEAE		25 (100)
Treatment-related		25 (100)
Grade ≥3 TEAE		12 (48)
Treatment-related		9 (36)
Serious TEAE		1 (4)
Treatment-related		1 (4)
TEAE leading to treatment discontinuation	Tislelizumab	1 (4)
	Sitravatinib	1 (4)
TRAE leading to treatment discontinuation	Tislelizumab	0 (0)
	Sitravatinib	1 (4)

Serious TEAE was an anal abscess, was associated with sitravatinib

Tislelizumab discontinuation was due to vaginal hemorrhage

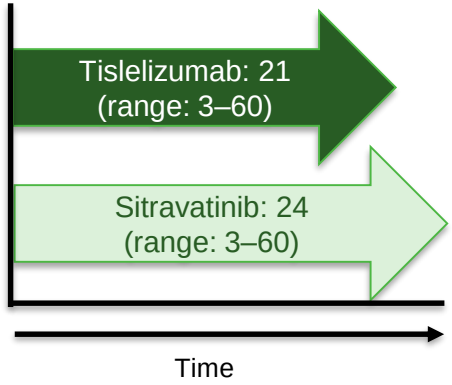
Sitravatinib discontinuation due to increased BCK

No TEAE or TRAE lead to death

BCK, blood creatine phosphate; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

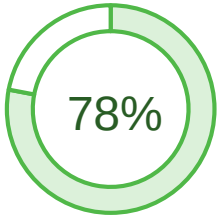
Safety summary

Median duration of treatment in weeks



Mean dose intensity

Tislelizumab



Sitravatinib

Tislelizumab

40% had their dose delayed*

Sitravatinib

72% had their dose interrupted

52% had their dose reduced

*Dose delay was defined as drug is withheld beyond the visit window. Dose interruption of sitravatinib was defined as interruption up to ~28 days consecutively.

All grade and Grade ≥3 TEAEs

All grade with a frequency of ≥20%

Event, n (%)	All Grades (N = 25)	Event, n (%)	All Grades (N = 25)
Increased ALT	19 (76)	Increased BB	9 (36)
Increased AST	17 (68)	Abnormal electrocardiogram T wave	9 (36)
Increased blood cholesterol	14 (56)	Hypertension	9 (36)
Hypertriglyceridemia	13 (52)	Palmar-Plantar erythrodysaesthesia syndrome	8 (32)
Hypothyroidism	12 (48)	CK-MB increased	7 (28)
Weight decreased	12 (48)	Hyperuricemia	7 (28)
Increased BCK	10 (40)	Upper abdominal pain	6 (24)
Diarrhea	10 (40)	Vomiting	6 (24)
Increased GGT	10 (40)	Hypokalemia	5 (20)
Proteinuria	10 (40)		

Grade ≥3 with a frequency of ≥5%

Event, n (%)	≥Grade 3 (N = 25)
Hypertension	3 (12)
Increased ALT	2 (8)
Increased GGT	2 (8)

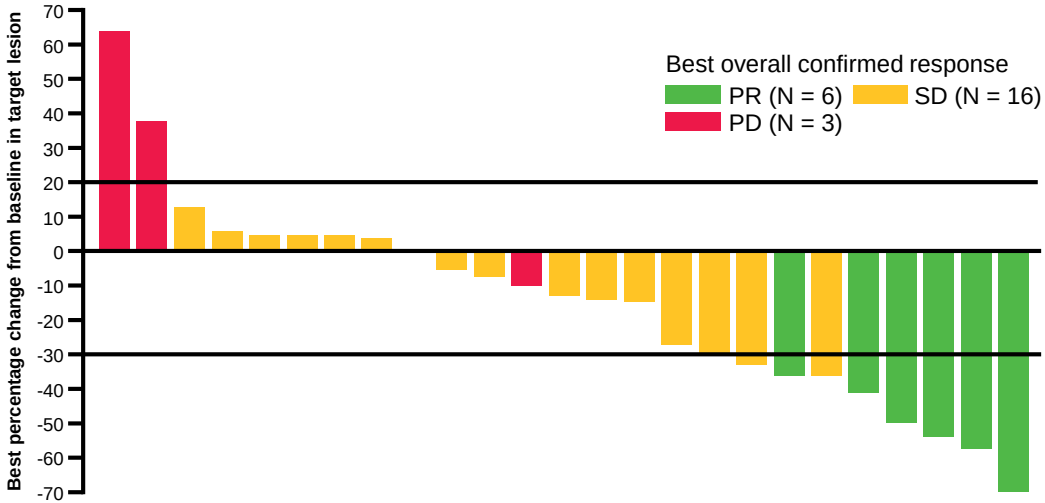
Hypertension (12%) was the most common ≥Grade 3 TEAE

No patients discontinued treatment due to hypertension

ALT, Alanine transaminase; AST, Aspartate aminotransferase; BB, Blood bilirubin; CK, creatine kinase; GGT, Gamma-glutamyltransferase; MB, myocardial band isozyme

Efficacy analysis

Maximum change in target lesion from baseline (%)

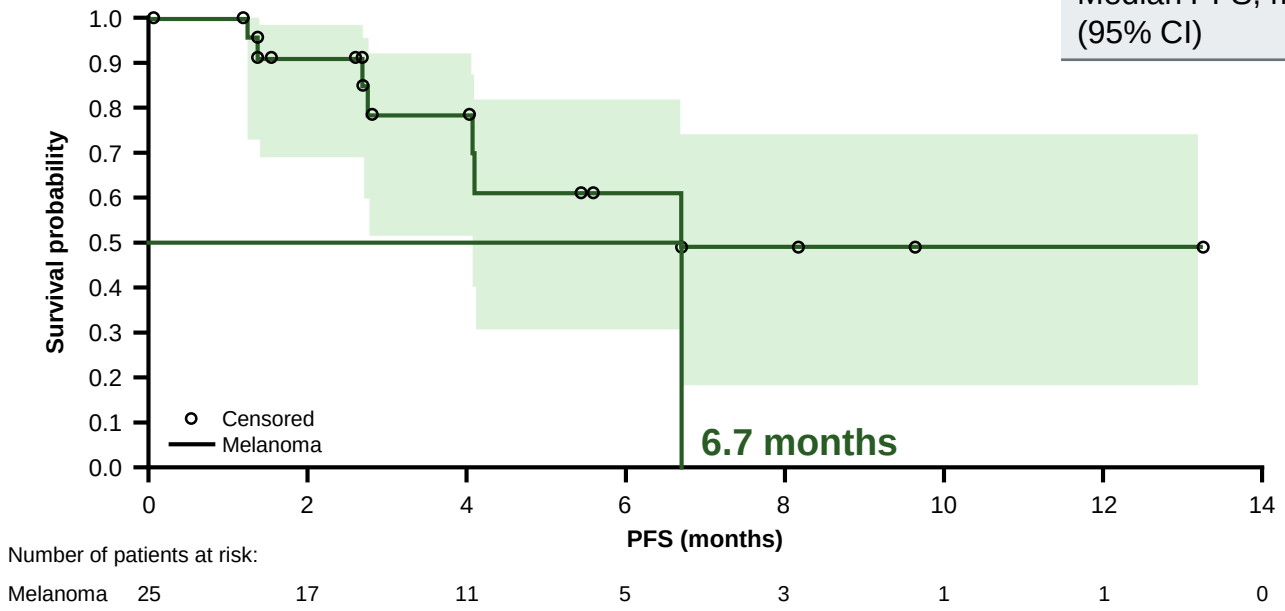


Clinical activity	Melanoma (N = 25)
Confirmed ORR, % (95% CI)	24 (9.4–45.1)
Best overall response, n (%)	
Complete response	0 (0)
Partial response	6 (24)
Stable disease	16 (64)
Progressive disease	3 (12)
DCR, % (95% CI)	88 (68.8–97.5)
Median DoR, months (95% CI)	NR (4.1–NR)

DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

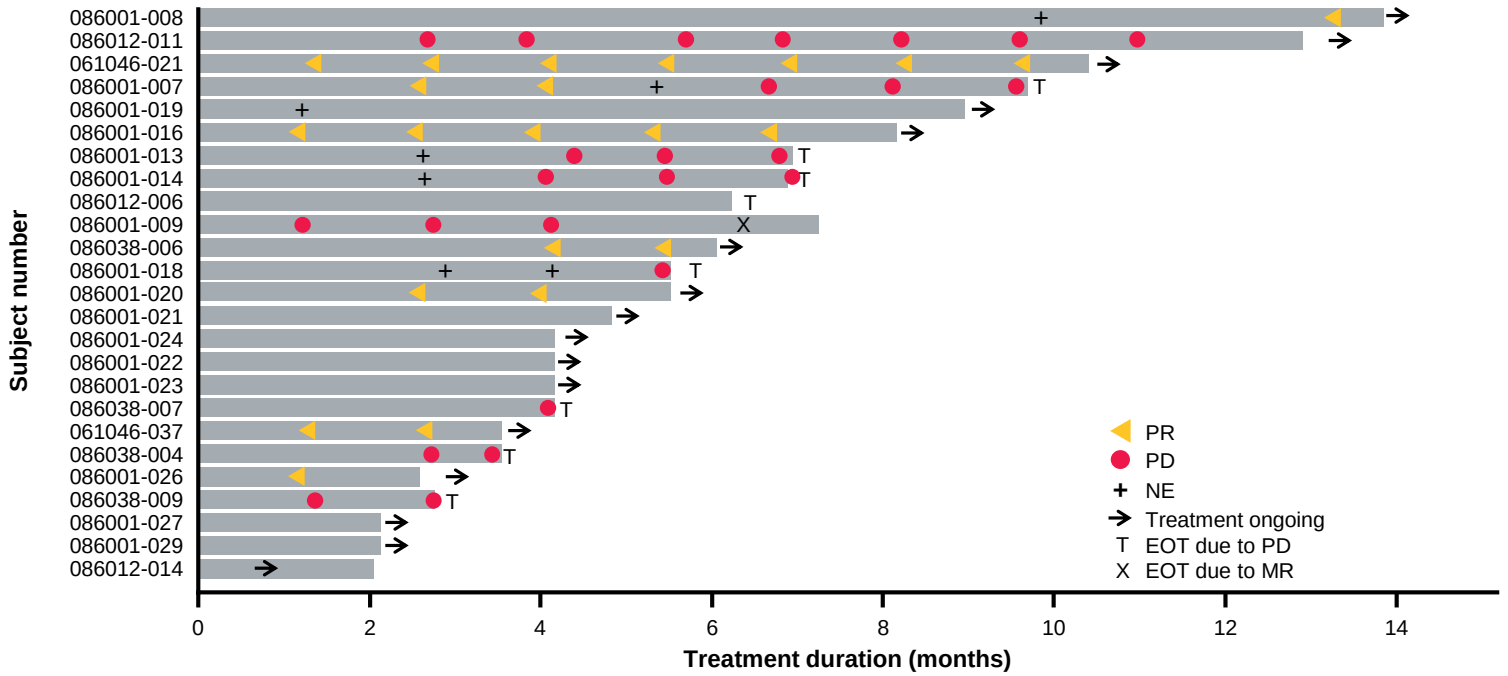
Investigator-assessed PFS

	Melanoma (N = 25)
Median PFS, months (95% CI)	6.7 (4.1–NE)



NE, non-evaluable ; PFS, progression-free survival

Duration of treatment with disease response in the melanoma cohort



EOT, end of treatment; MR, multiple reason; NE, non evaluable; PD, disease progression; PR, partial response

Conclusions

- Tislelizumab in combination with sitravatinib was generally well tolerated and had a manageable safety/tolerability profile in patients with anti-PD-1/PD-L1 refractory/resistant unresectable or metastatic melanoma
  - Most TEAEs were mild or moderate in severity and manageable
  - No TEAEs lead to death
- The combination treatment also demonstrated preliminary antitumor activity, with patients achieving an ORR of 24%, DCR of 88% and median PFS of 6.7 months (95% CI: 4.1–NE)
- The results from this Phase 1b study support tislelizumab in combination with sitravatinib as a potential treatment option for patients with refractory/resistant unresectable or metastatic melanoma and further investigation is warranted