# 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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# Disclosures

- Chuanliang Cui has no financial relationships to disclose

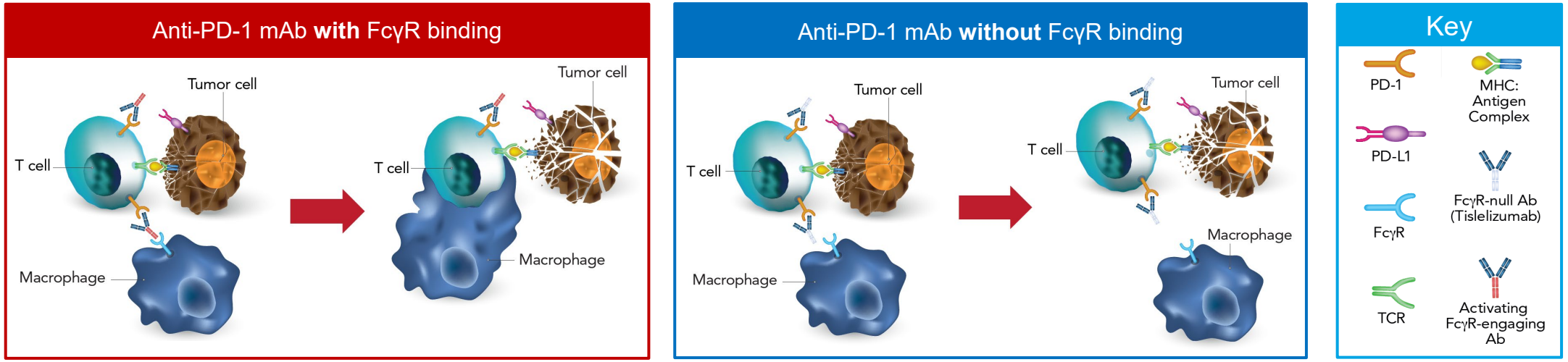
# Background

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




MoA, mechanism of action; mAb, monoclonal antibody; PD-1, programmed death protein-1

1. Hodi F.S, 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, et al. Cancer Cell 2015 Sep 14;28:285-95; 7. Qin, 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]

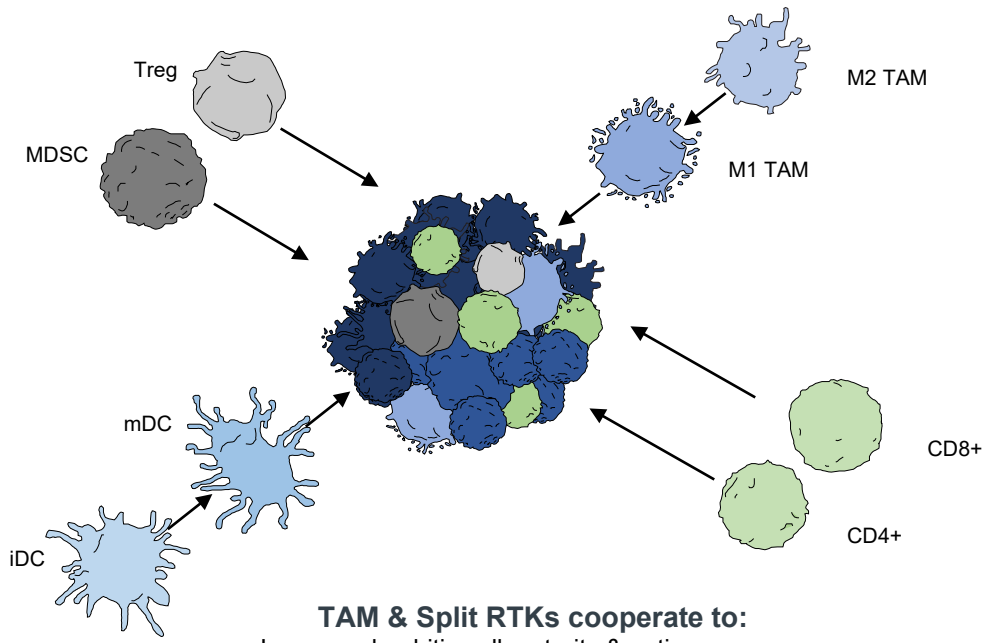
Tislelizumab plus sitravatinib is currently being investigated in several solid tumor types, including metastatic melanoma (NCT03666143)

**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

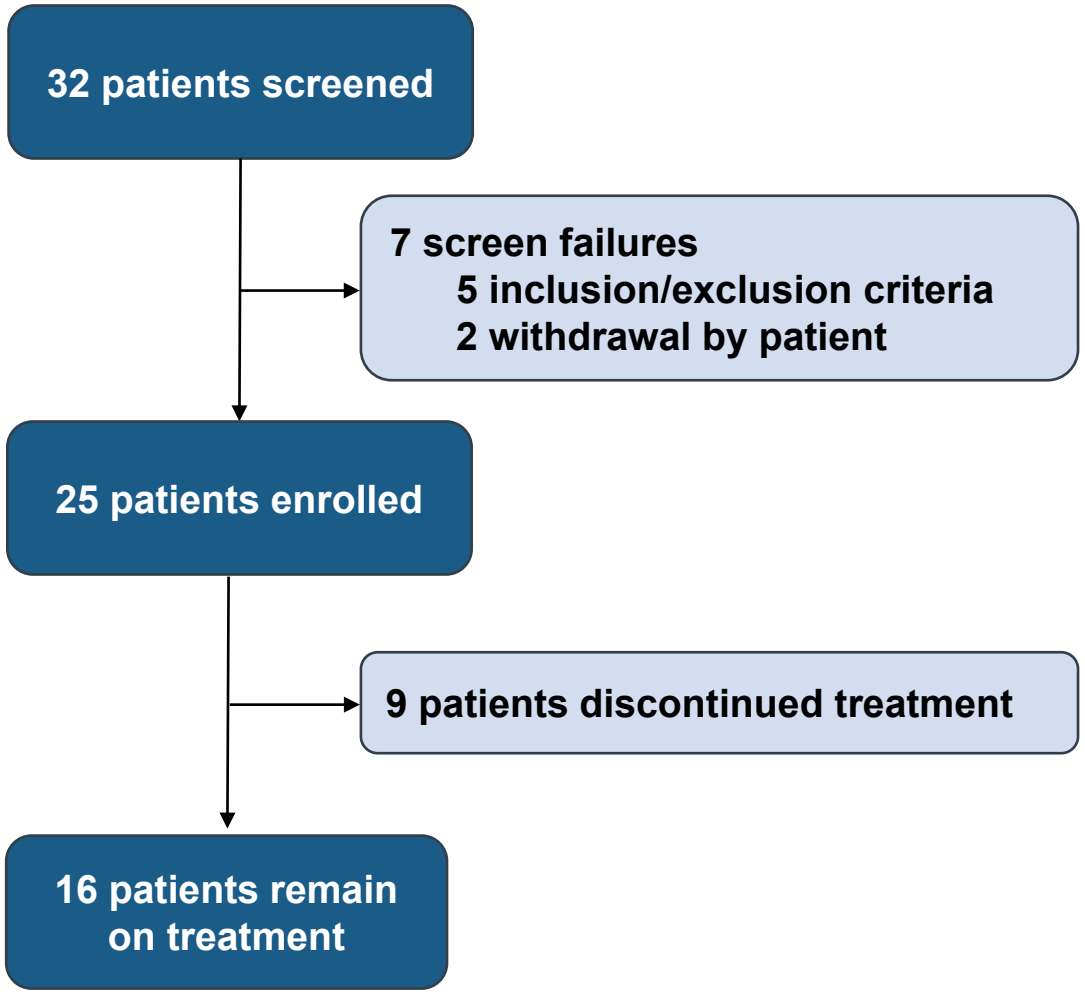
**Key endpoints:**

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

**Data cut-off:**
**October 13, 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, October 13, 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

| | Melanoma (N=25) |
|---|---|
| **Median age, years (range)** | 51 (23–79) |
| **Sex, n (%)** | |
| Male | 13 (52) |
| Female | 12 (48) |
| **Race, n (%)** | |
| Asian | 23 (92) |
| White | 2 (8) |
| **ECOG performance status, 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) |

| | 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) |
| Median duration of last therapy, months (range) | 7 (2–28) |

PD-1, programmed death protein-1; PD-L1 programmed death ligand-1

# Safety summary

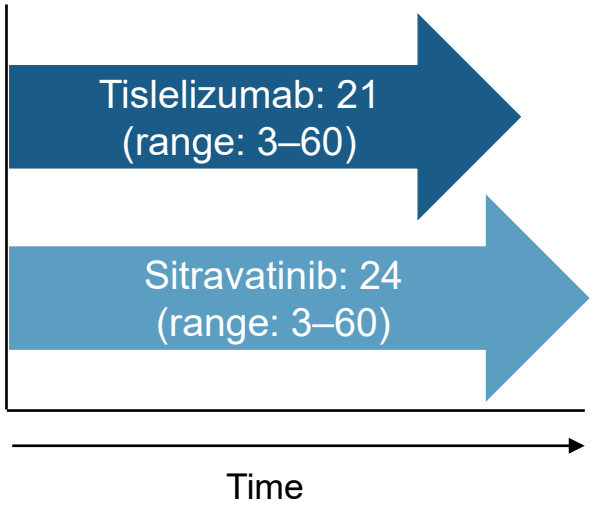
- Serious AE was an anal abscess, was associated with sitravatinib
- Tislelizumab discontinuation was due to vaginal hemorrhage
- Sitravatinib discontinuation due to increased BCK
- No AE or TRAE led to death

| n (%) | Melanoma (N=25) |
|---|---|
| Patients with at least one AE | 25 (100) |
| Treatment-related | 13 (52) |
| ≥ Grade 3 AE | 12 (48) |
| Treatment-related | 9 (36) |
| Serious AE | 1 (4) |
| Treatment-related | 1 (4) |
| AE leading to treatment discontinuation | |
| Tislelizumab | 1 (4) |
| Sitravatinib | 1 (4) |
| TRAE leading to treatment discontinuation | |
| Tislelizumab | 0 (0) |
| Sitravatinib | 1 (4) |

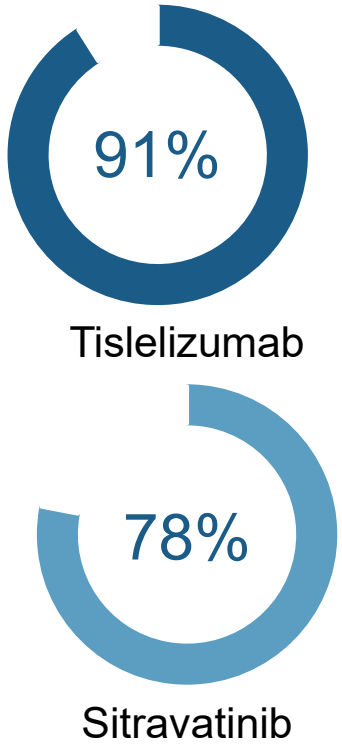
BCK, blood creatine phosphate; AE, treatment-emergent adverse event; TRAE, treatment-related adverse event

# Safety summary

## Median duration of treatment in weeks




## Mean dose intensity




## 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) |

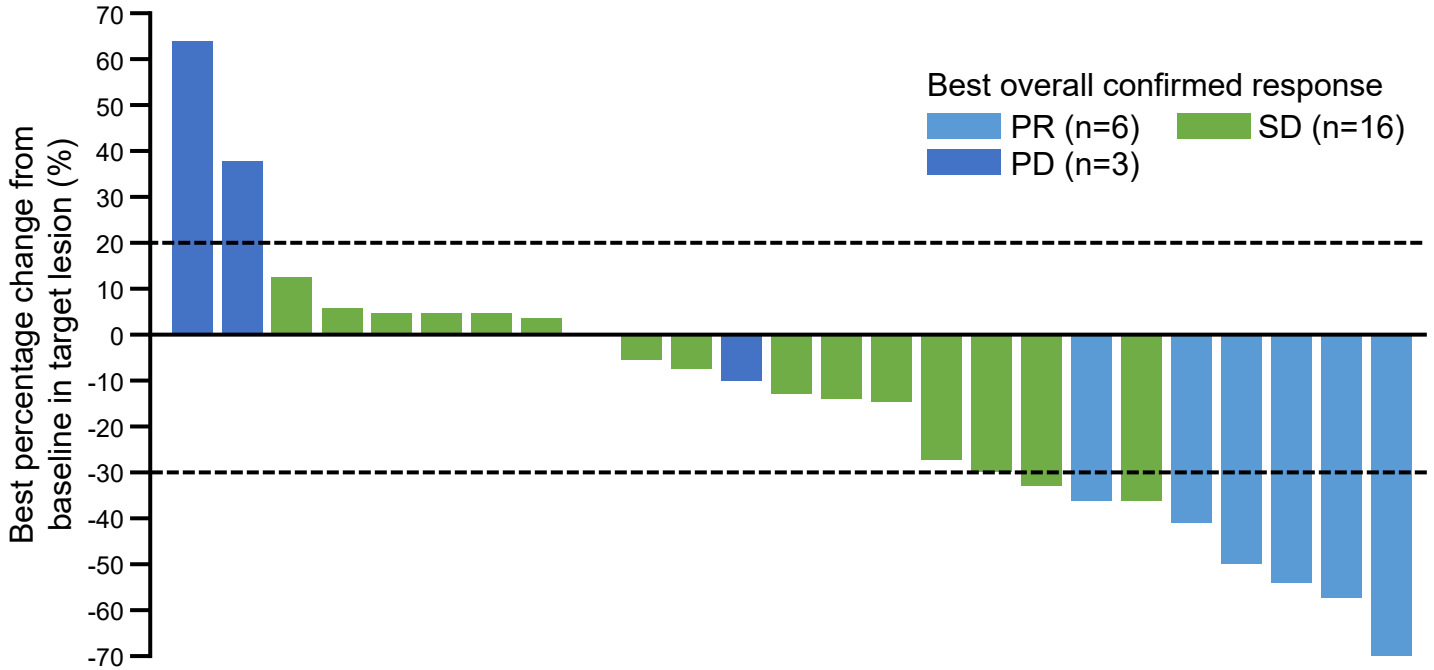
Hypertension (12%) was the most common ≥ Grade 3 TEAE

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; TEAE, treatment-emergent adverse event

# Efficacy analysis

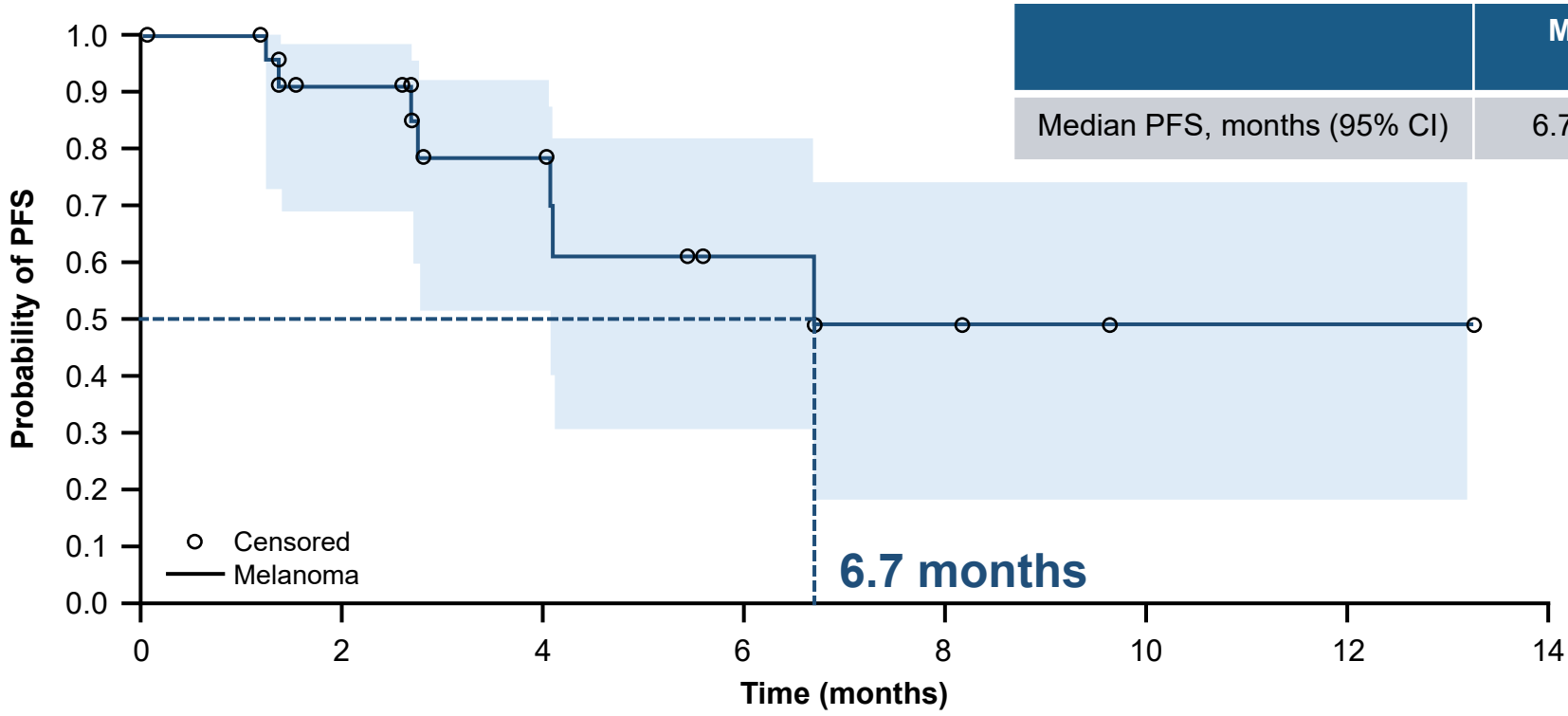
## Maximum change in target lesion from baseline (%)




| Clinical activity | Melanoma (N=25) |
|---|---|
| Confirmed ORR, % (95% CI) | 24 (9.4, 45.1) |
| Best overall response, n (%) | |
| CR | 0 (0) |
| PR | 6 (24) |
| SD | 16 (64) |
| PD | 3 (12) |
| DCR, % (95% CI) | 88 (68.8, 97.5) |
| Median DoR, months (95% CI) | NR (4.1, NR) |

CR, complete response; 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

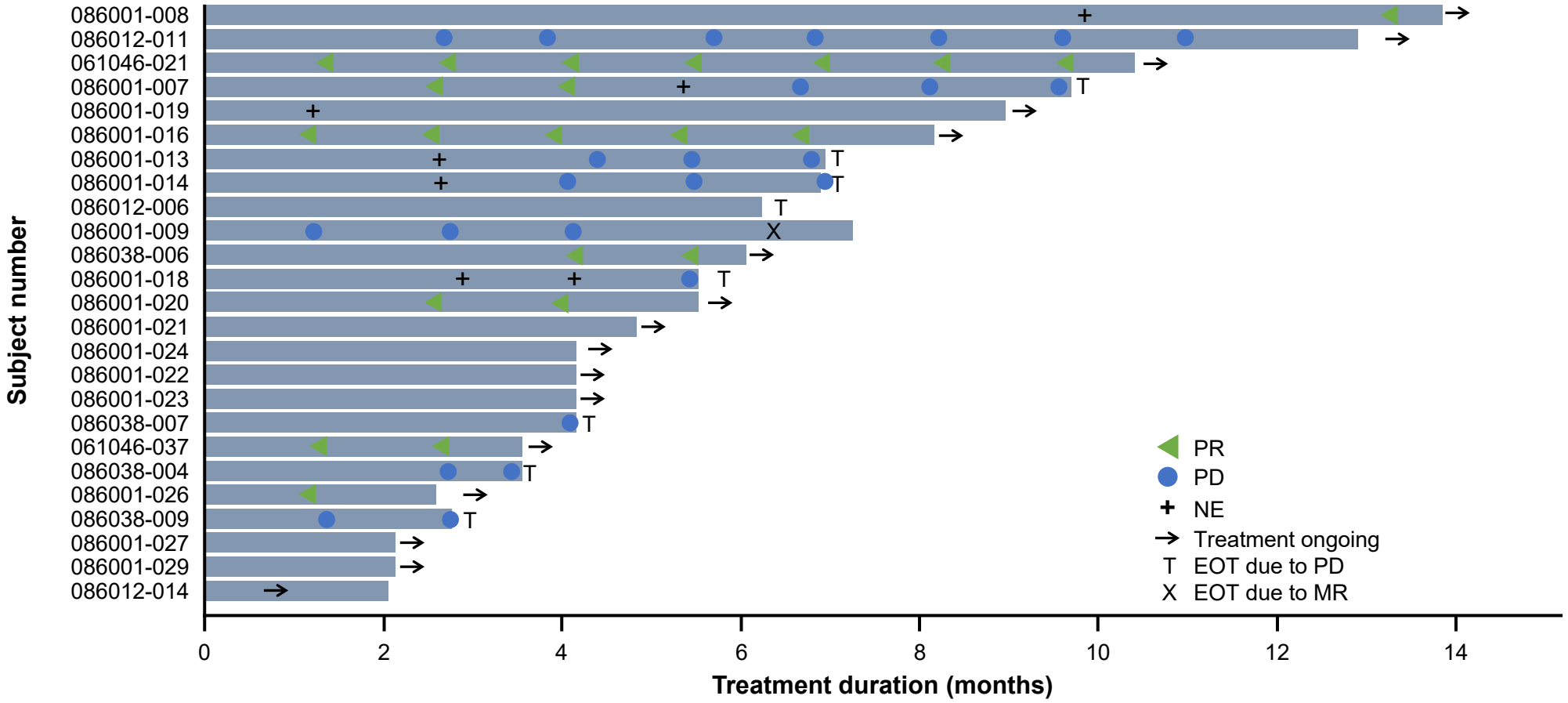



| | Melanoma (N=25) |
|---|---|
| Median PFS, months (95% CI) | 6.7 (4.1, NE) |

| Number of patients at risk: | 25 | 17 | 11 | 5 | 3 | 1 | 1 | 0 |
|---|---|---|---|---|---|---|---|---|

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 led 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

CI, confidence interval; DCR, disease control rate; NE, non-evaluable; ORR, objective response rate; PD-1, programmed death protein-1; PD-L1 programmed death ligand-1; PFS, progression-free survival; TEAE, treatment-emergent adverse event

# Acknowledgements

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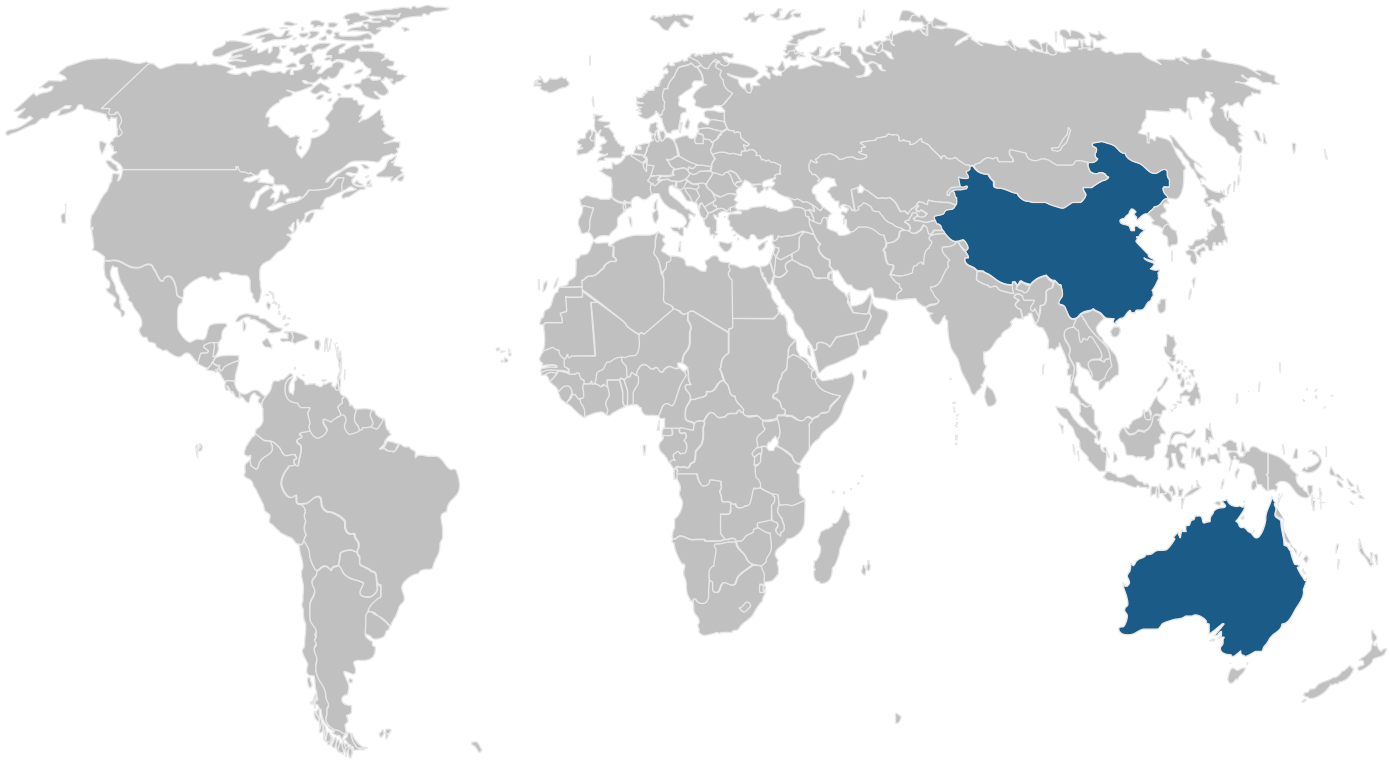

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