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OX40 T-Cell Costimulatory Agonist BMS-986178 Alone or in Combination With Nivolumab in Patients With Advanced Solid Tumors: Initial Phase 1 Results

Anthony J. Olszanski,[1] Ignacio Melero,[2] Michael Ong,[3] Anna Spreafico,[4] Kimberley Heinhuis,[5] Richard D. Carvajal,[6] Maria Ochoa de Olza,[7] Quincy Chu,[8] Anke Klippel,[9] Yun Shen,[9] Yan Feng,[9] Bryan Barnhart,[9] Alan Korman,[9] Michael Quigley,[9] Paula M. Fracasso,[9] Praveen Aanur,[9] Martin Gutierrez[10]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Clínica Universidad de Navarra, Pamplona, Spain; [3]The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]The Netherlands Cancer Institute, Amsterdam, Netherlands; [6]Columbia University Medical Center, New York, NY, USA; [7]Vall d'Hebron University Hospital, Barcelona, Spain; [8]Cross Cancer Institute, University of Alberta/Alberta Health Services, Edmonton, AB, Canada; [9]Bristol-Myers Squibb, Princeton, NJ, USA; [10]Hackensack University Medical Center, Hackensack, NJ, USA

Presenter Disclosures

- Dr Olszanski has no relationships related to this presentation to disclose
  - He has had a consulting or advisory role for, Bristol-Myers Squibb, G1 Therapeutics, Kyowa Hakko Kirin, Merck, and Takeda
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There will be discussion about the use of products for non–FDA-approved indications in this presentation

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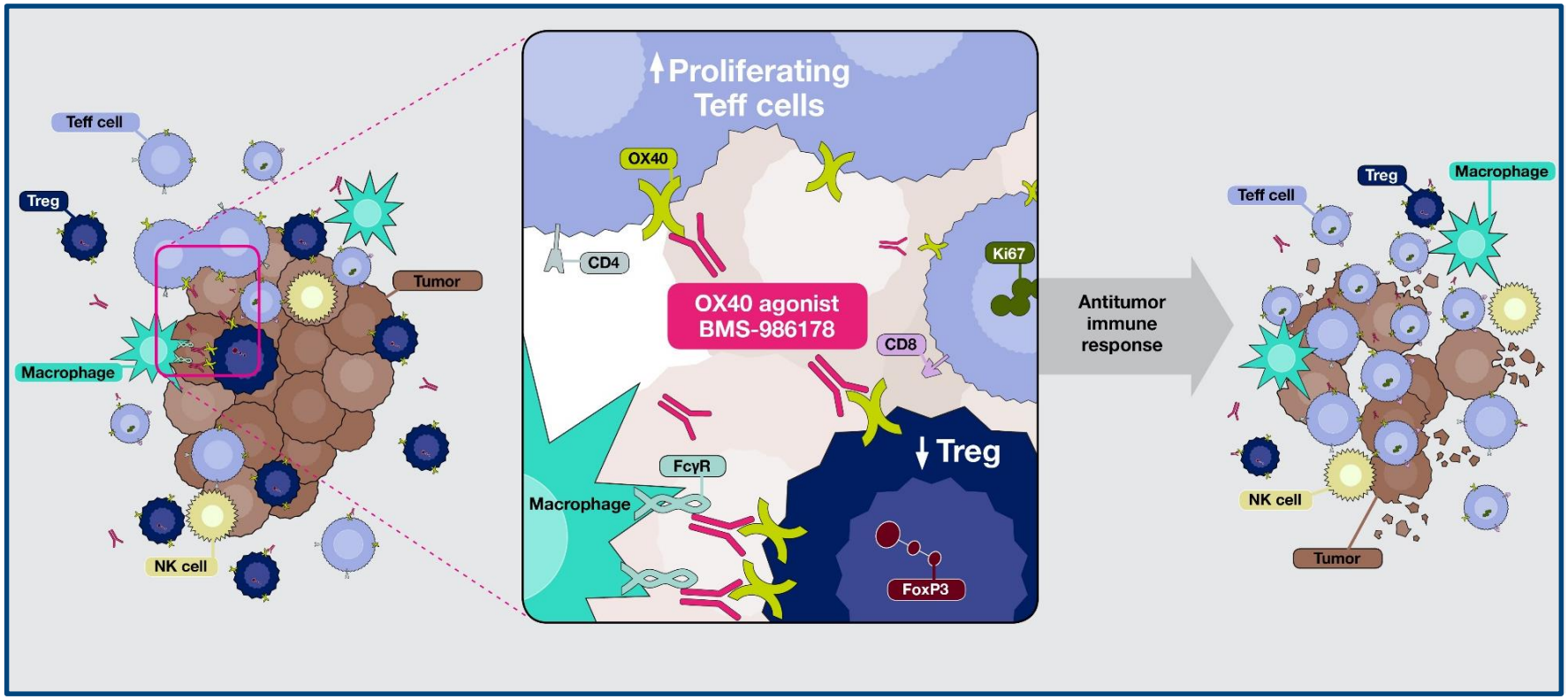
Rationale for Anti-OX40 Agonist Therapy

- OX40 is a costimulatory receptor upregulated upon T-cell activation[1-3]
- BMS-986178 is a fully human IgG1 agonist mAb that binds with high affinity to OX40[4] and:
  - Increases the activation, proliferation, and survival of CD4+ and CD8+ Teffs[1-3,5]
  - Inhibits Treg suppression and depletes Tregs via ADCC/ADCP[1-3,5,6]

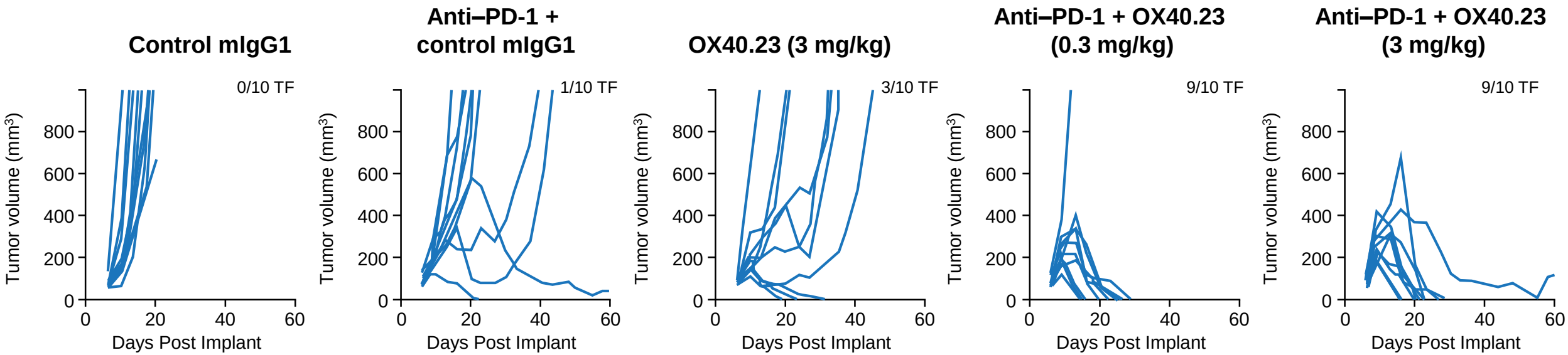


- FcγR-mediated cross-linking of BMS-986178 is required to enhance proliferation of Teffs and inhibit Treg suppression[4]

ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; Ig = immunoglobulin; mAb = monoclonal antibody; Teff = effector T cell; Treg = regulatory T cell

1. Aspeslagh S, et al. *Eur J Cancer* 2016;52:50–66. 2. Piconese S, et al. *J Exp Med* 2008;205:825–839. 3. Jensen S, et al. *Semin Oncol* 2010;37:524–532. 4. Bristol-Myers Squibb. Data on file. 5. Valzasina B, et al. *Blood* 2005;105:2845–2851. 6. Voo K, et al. *J Immunol* 2013;191:3641–3650.

Anti–PD-1 Enhances Preclinical Antitumor Activity of Anti-OX40



- In a CT26 mouse tumor model, the mIgG1 isotype of the ligand-blocking agonist OX40.23,[a] achieved maximal antitumor activity as monotherapy (at doses between 1 and 3 mg/kg)
- In combination with anti–PD-1, maximal antitumor activity was achieved at a 10-fold lower dose of OX40.23 (0.3 mg/kg) in the mouse model

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Gao C et al, No. P373
Date: Nov 10–11
Time: 12:30-2pm & 6:30–8PM

[a]OX40.23 is a murine ligand-blocking agonist that was used as a preclinical surrogate for the clinical anti-OX40 mAb
mIgG1 = murine immunoglobulin G1; TF = tumor-free mice

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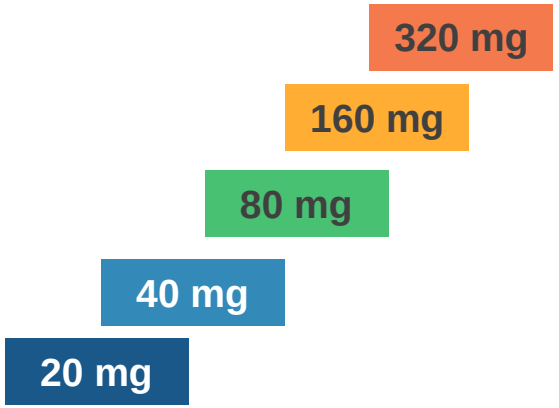
Phase 1/2a Study of BMS-986178 ± Nivolumab or Ipilimumab in Advanced Solid Tumors

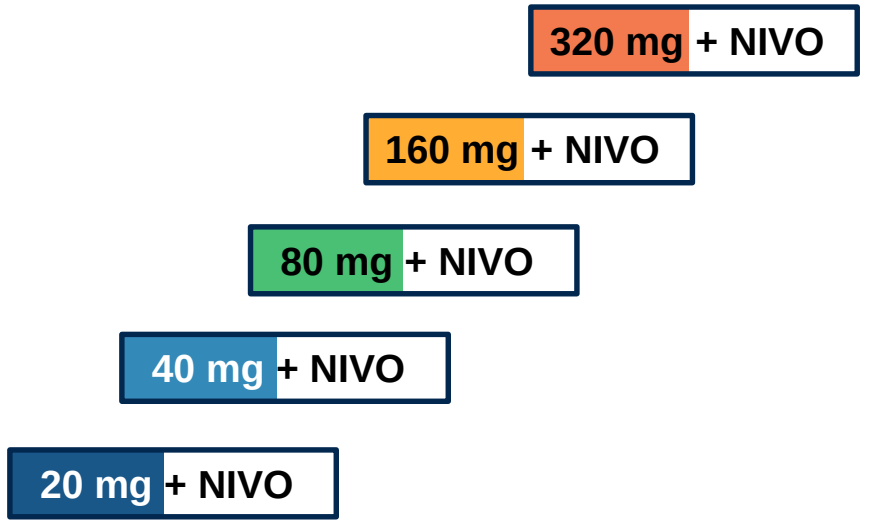
Monotherapy dose escalation: BMS-986178 IV Q2W



First-in-human starting dose of 20 mg selected based on PK/PD preclinical model (Huang C, et al. SITC 2017, P420)

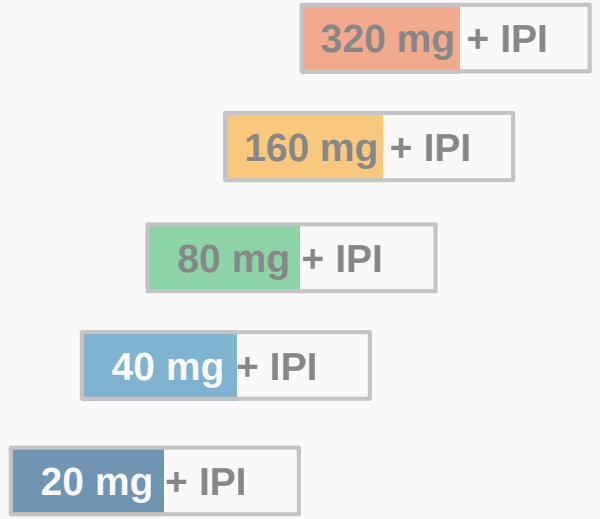
Combination dose escalation: BMS-986178 + nivolumab IV Q2W

Nivolumab 240 mg



Combination dose escalation: BMS-986178 + ipilimumab IV Q3W

Ipilimumab 1 mg/kg



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Primary Objectives: safety/tolerability, DLT, MTD, RP2D
Secondary Objectives: immunogenicity, PK/PD, preliminary antitumor activity

- Here we present data from the nivolumab combination arm

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DLT = dose-limiting toxicity; IV = intravenous; MTD = maximum tolerated dose; PD = pharmacodynamics; PK = pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; RP2D = recommended phase 2 dose

Baseline Demographics, Prior Therapy, and Tumor Types

		BMS-986178 monotherapy (n = 20)	BMS-986178 + nivolumab (n = 39)
Median age (range), years		61 (24-80)	61 (32-82)
Gender, n	Male/female	13/7	20/19
ECOG PS, n	0–1	19	38
	Not reported	1	1
Race, n	White	16	38
	Black	2	0
	All others	2	1
No. of prior therapies, n	0	0	4
	1	9	9
	2	3	8
	≥ 3	8	18
Prior immunotherapy, n	Prior anti–PD-1/PD-L1	6	12
	Prior anti–CTLA-4	4	4
	Both	4	4
Tumor type, n	CRC	7	8
	Melanoma	4	6
	Pancreatic cancer	4	3
	Other[a]	5	22

[a]Includes breast cancer, bladder cancer, cervical cancer, endometrial cancer, gastric cancer, HCC, NSCLC, ovarian cancer, prostate cancer, RCC, and SCCHN

CRC = colorectal cancer; CTLA-4 = cytotoxic T lymphocyte antigen-4; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; RCC = renal cell carcinoma; SCCHN = squamous cell cancer of the head and neck

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Treatment-Related Adverse Events

	BMS-986178	BMS-986178 + nivolumab 240 mg					
	All Mono n = 20	20 mg n = 7	40 mg n = 8	80 mg n = 8	160 mg n = 8	320 mg n = 8	Total n = 39
Any TRAE, n	5[a]	4	3	3	6	4	20
Grade 1 or 2 TRAEs in ≥ 2 patients in total combination cohort, n							
Fatigue	0	0	1	1	3	0	5
Pyrexia	1	0	1	2	0	2	5
Arthralgia	0	0	1	1	2	0	4
Chills	0	1	0	0	1	0	2
Diarrhea	1	1	0	0	1	0	2
Hypothyroidism	0	0	1	0	0	1	2
Nausea	1	0	0	0	1	1	2
Any grade 3–4 TRAE	1[b]	0	0	0	1[c]	0	1[c]

- Maximum tolerated dose was not reached
- No treatment-related deaths
- Safety profile of BMS-986178 + nivolumab was similar to that of nivolumab monotherapy

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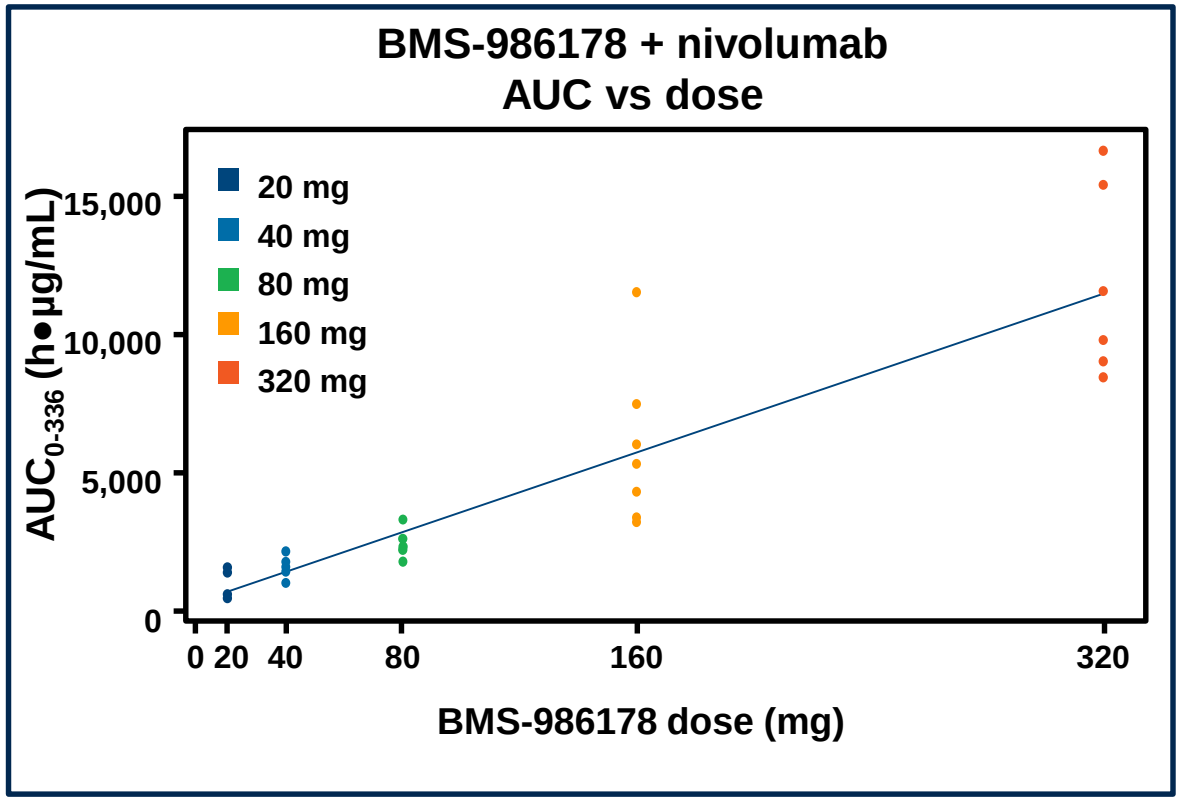
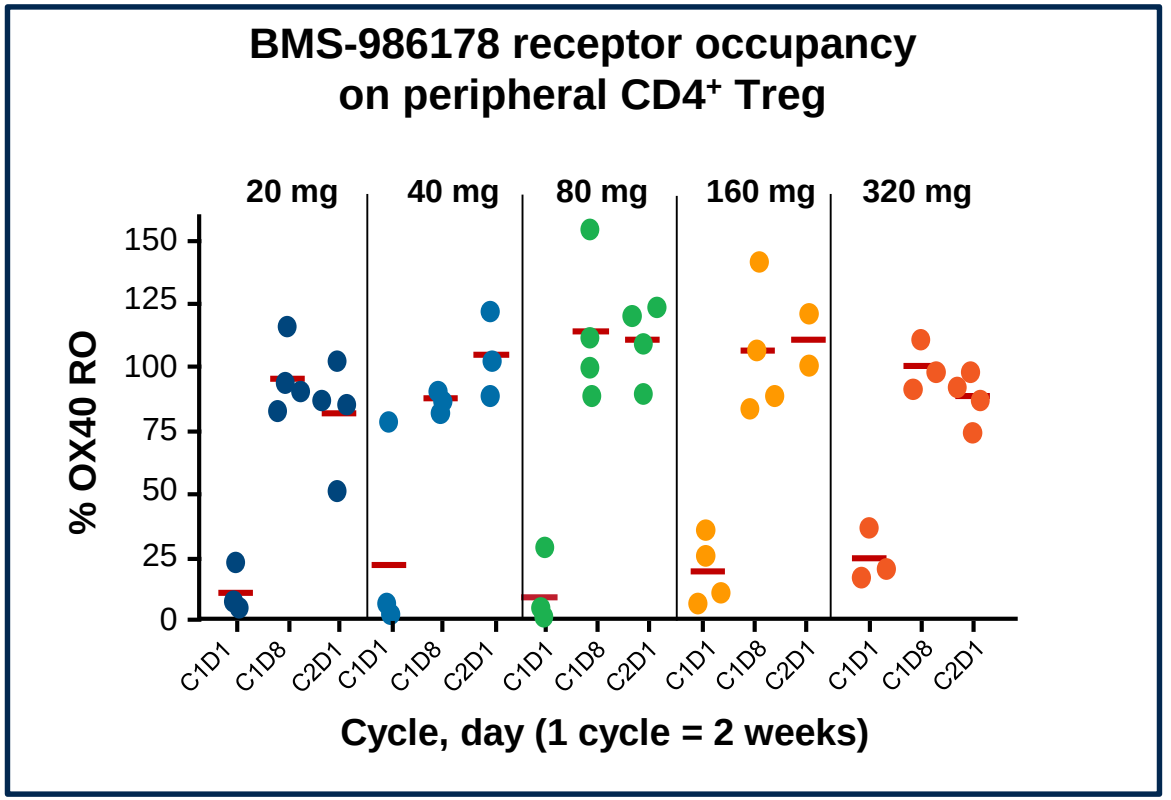
One patient each experienced a serious adverse event, [a]Grade 2 pneumonitis (BMS-986178 320 mg) and [c]Grade 3 pneumonitis, leading to discontinuation, which was considered a DLT; [b]One patient experienced Grade 3 fatigue
TRAE = treatment-related adverse event

BMS-986178 + Nivolumab Demonstrates Linear PK and High Receptor Occupancy





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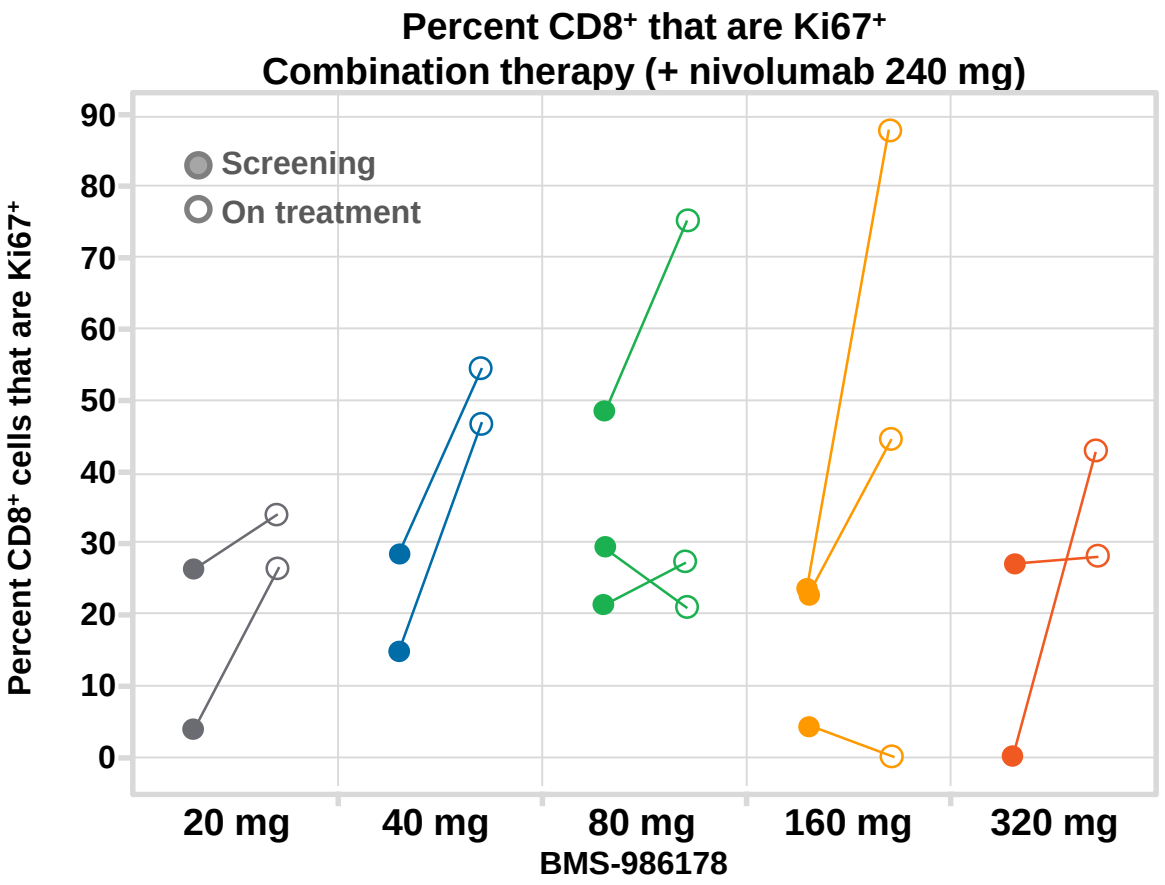
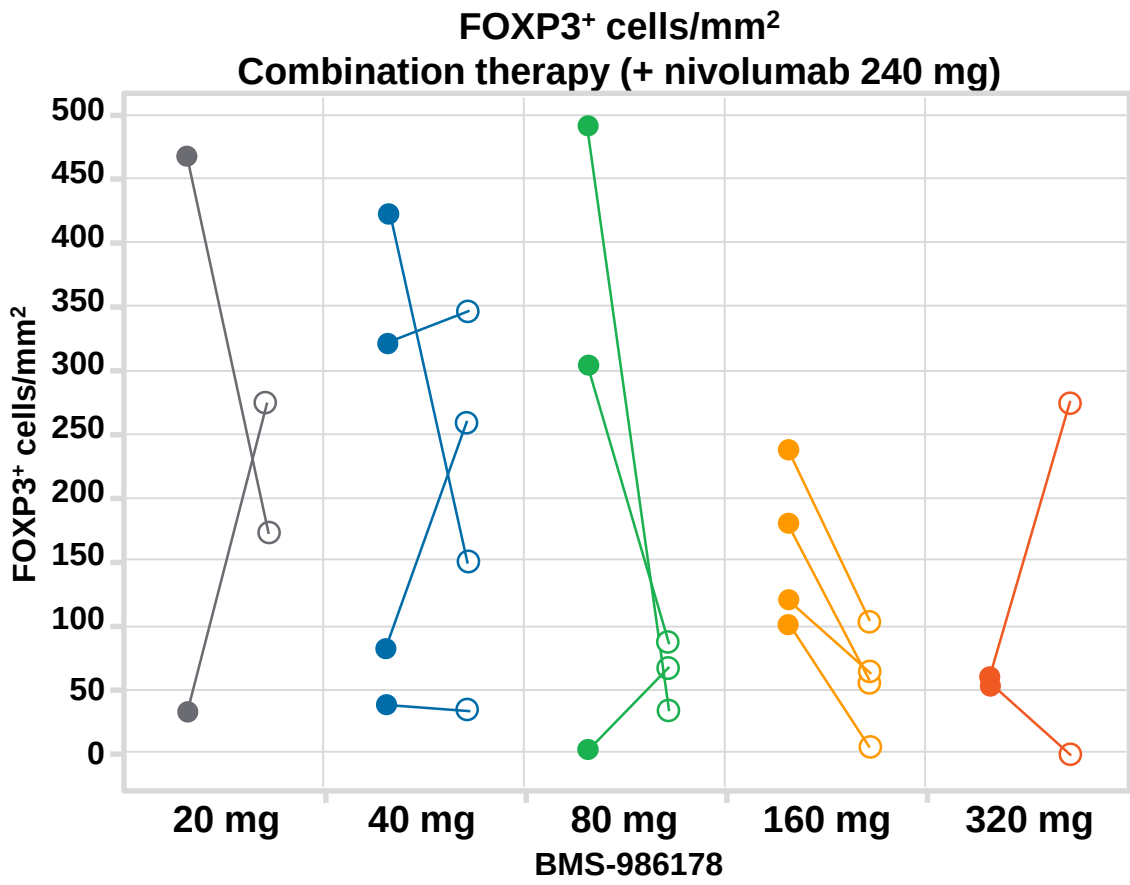
- PK is consistent with human IgG half-life ≈ 2 weeks
- Exposure of BMS-986178 alone or with nivolumab increased in dose-proportional manner in 20 mg–320 mg range
- BMS-986178 ± nivolumab demonstrated low immunogenicity by ADA
- Observed peripheral OX40 receptor occupancy was 80% at 20 mg and was saturated at doses ≥ 40 mg

ADA = anti-drug antibody; AUC = area under the curve; RO = receptor occupancy

Treatment Increases Proliferating (Ki67$^+$) CD8$^+$ T Cells and Decreases FOXP3$^+$ Cells in Tumor Stroma

BMS-986178 + nivolumab = ↑ Ki67$^+$CD8$^+$ T cells ↓ FOXP3$^+$ cells

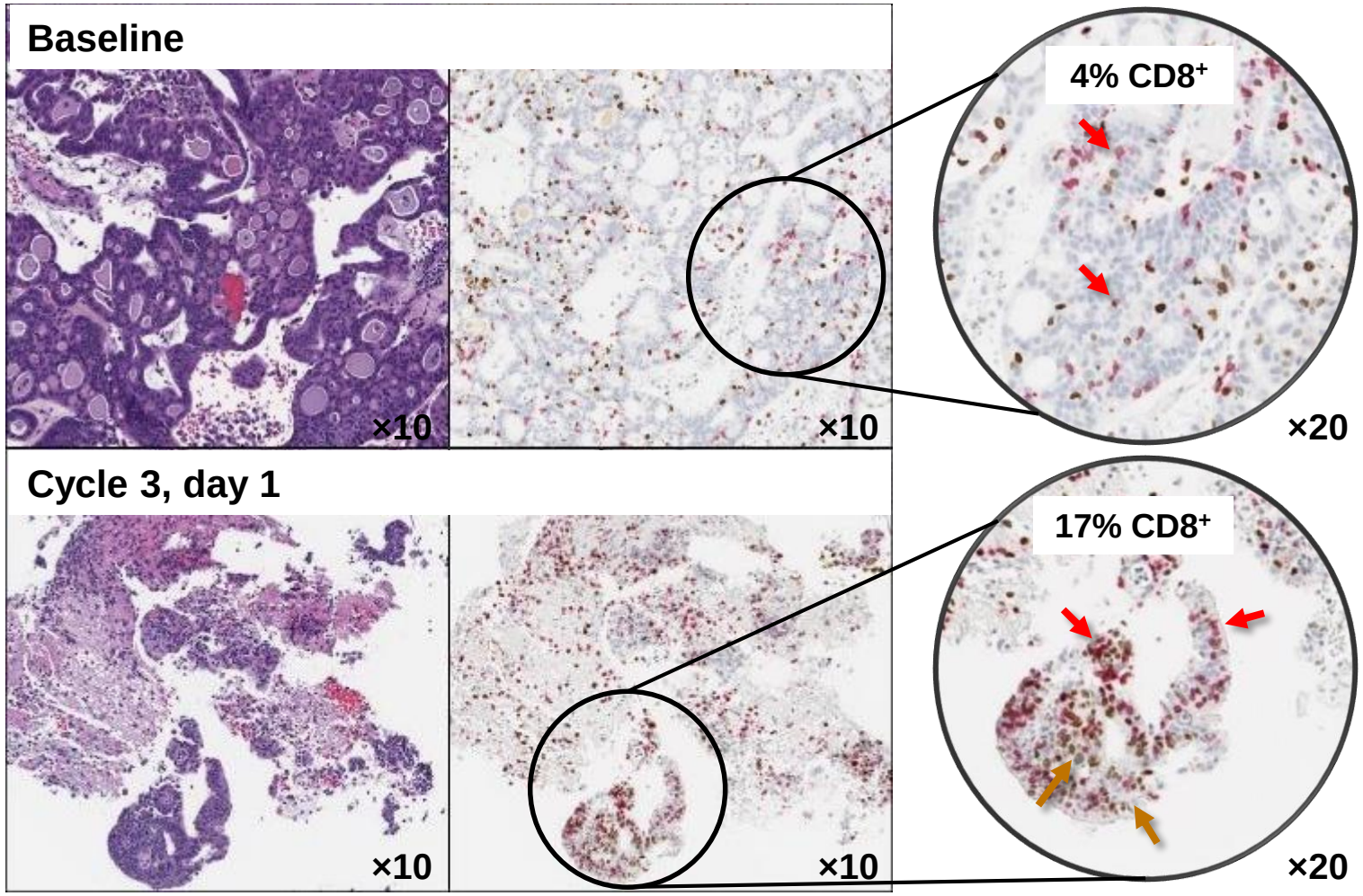




Antitumor Activity Correlates With Increased Proliferating Ki67+ CD8+ T Cells

Partial response in patient with endometrial cancer

- 68-year-old female patient with endometrial cancer
- Patient received 3 lines of prior therapy:
  - Medroxyprogesterone
  - Letrozole
  - Carboplatin and paclitaxel
- Patient achieved a **partial response** with BMS-986178 320 mg + nivolumab 240 mg
  - Best change in tumor burden was –55%
  - Response is ongoing (8+ months)



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➡ CD8 ➡ Ki67

Treatment Decreases FOXP3^{+} Cells in Tumors

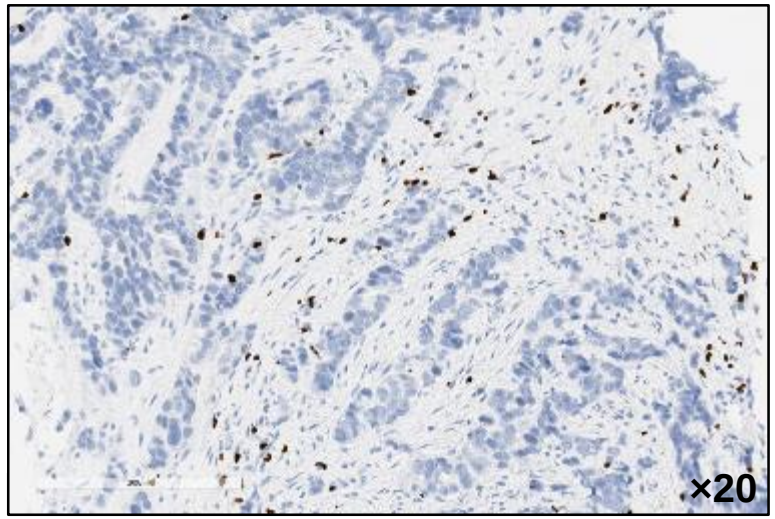
Stable disease in patients with ovarian cancer

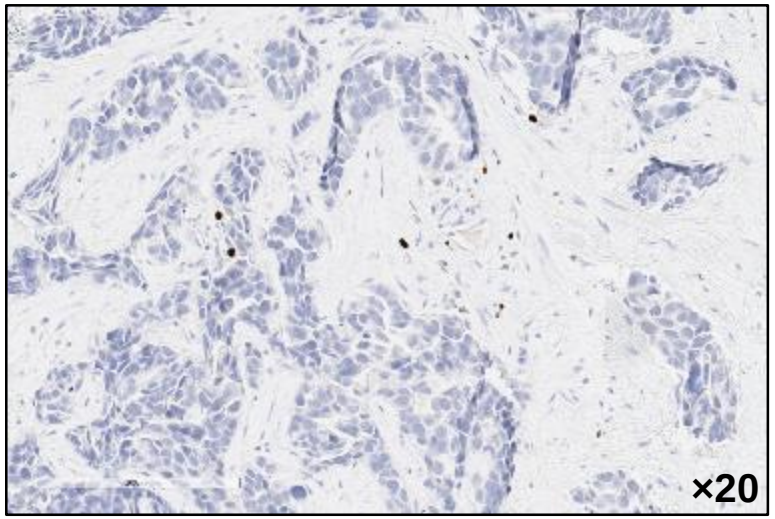
59-year-old female patient with ovarian serous carcinoma

- Patient received prior surgery and chemotherapy (carboplatin and paclitaxel)

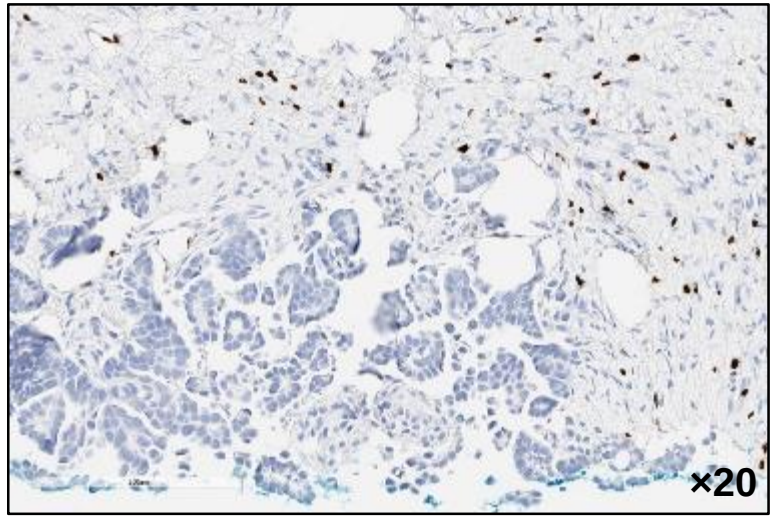
72-year-old female patient with ovarian adenocarcinoma

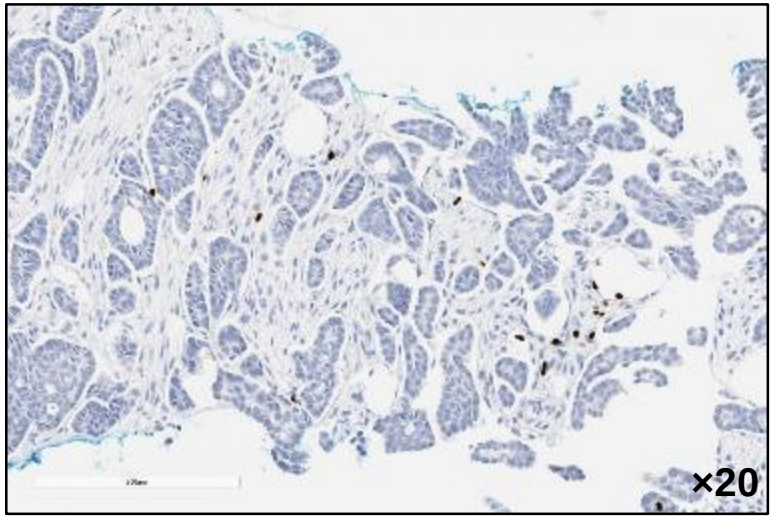
- Patient received prior surgery and chemotherapy (carboplatin and paclitaxel)





Baseline | **On treatment**





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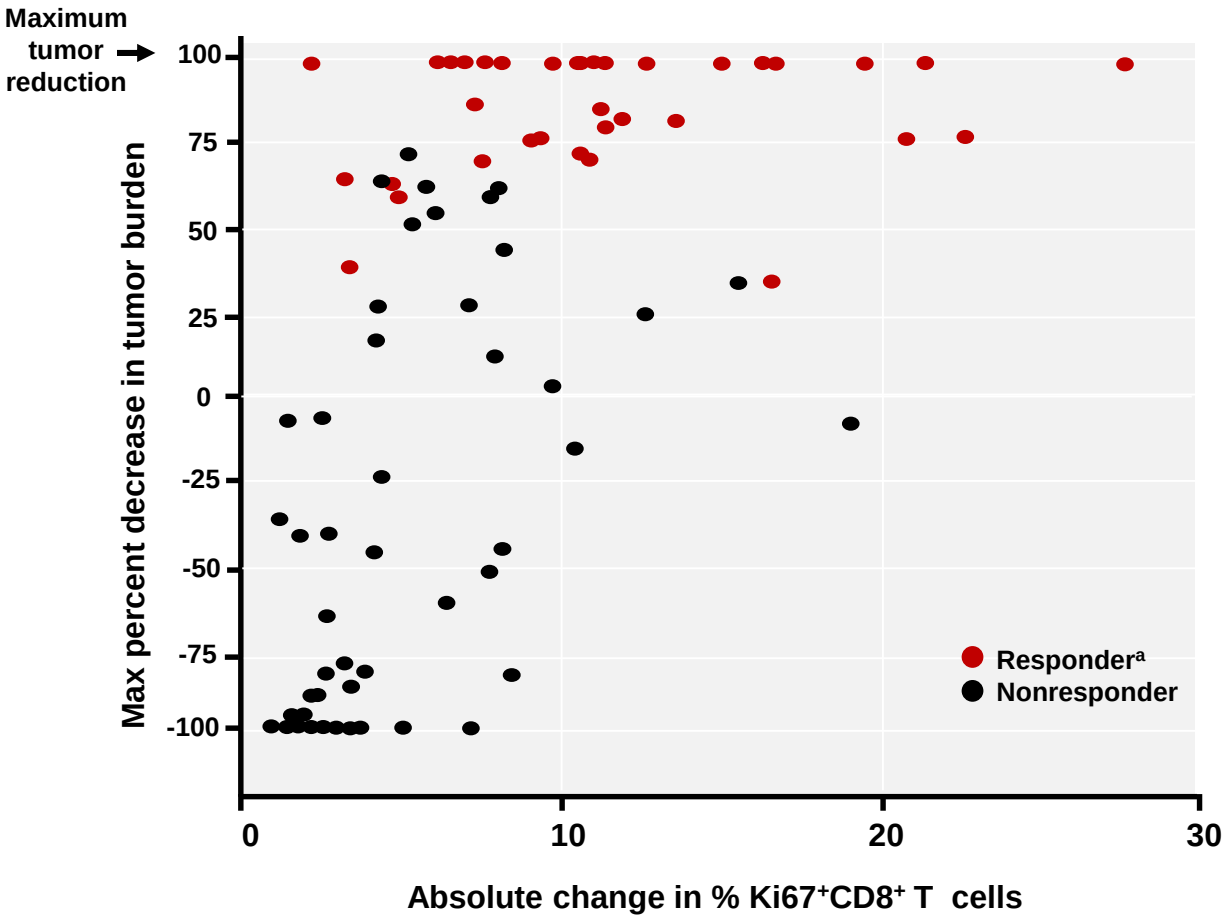
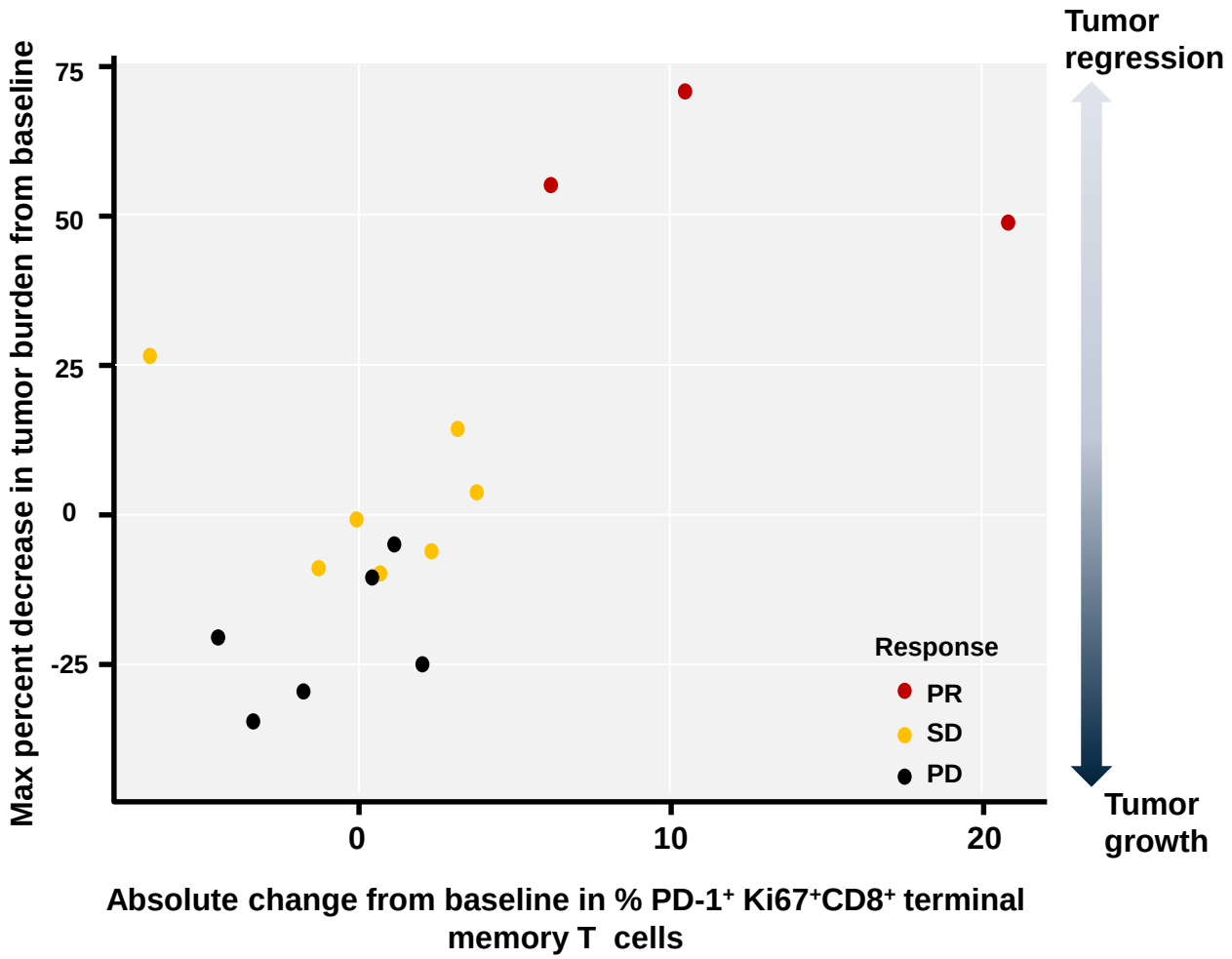
Consistent With Preclinical Results, Antitumor Activity Correlates With Increased Proliferating Ki67+ CD8+ T Cells

Preclinical results

Ki67+ CD8+ (day 12)
Tumor volume (day 20)



Clinical results[b]



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[a]"Responders" were classified as mice with tumor volume <100 mm^3 on day 20; [b]the clinical flow data are shown only for patients with available samples

PD = progressive disease; PR = partial response; SD = stable disease

Conclusions

- The OX40 agonist, BMS-986178, with or without nivolumab, was well tolerated, with no evidence of additive toxicity over nivolumab monotherapy
- The combination demonstrated linear PK with dose-related increase in exposure
- Pharmacodynamic activity was observed, with increased proliferation of $CD8^+$ T cells and decreased $FOXP3^+$ cells in tumors
- These data support the effect of this combination and its further evaluation

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Investigators

USA

Richard Carvajal
Martin Gutierrez
Anthony Olszanski

Canada

Quincy Chu
Michael Ong
Anna Spreafico

Spain

Victor Moreno Garcia
Elena Garralda
Ignacio Melero
Maria Ochoa de Olza
Jose Manuel Trigo Perez
Mariano Provencio

The Netherlands

Kimberley Heinhuis
Jan Schellens
Filip De Vos

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