Preliminary Antitumor and Immunomodulatory Activity of BMS-986205, an Optimized Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitor, in Combination With Nivolumab in Patients With Advanced Cancers

Jason J. Luke,[1] Karen Gelmon,[2] Russell K. Pachynski,[3] Jayesh Desai,[4] Victor Moreno,[5] Josep Tabernero,[6] Carlos A. Gomez-Roca,[7] Quincy Chu,[8] Paul Basciano,[9] Penny Phillips,[9] Li Zhu,[9] Zhaohui Liu,[9] Lillian L. Siu[10]

[1]University of Chicago Medical Center, Chicago, IL, USA; [2]University of British Columbia, BC Cancer Agency, Vancouver, BC, Canada; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia; [5]START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Institut Universitaire du Cancer, Oncopole, Toulouse, France; [8]Cross Cancer Institute, University of Alberta/Alberta Health Services, Edmonton, AB, Canada; [9]Bristol-Myers Squibb, Princeton, NJ, USA; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada

Presenter Disclosure Information

Jason J. Luke, MD, FACP

The following relationships exist related to this presentation

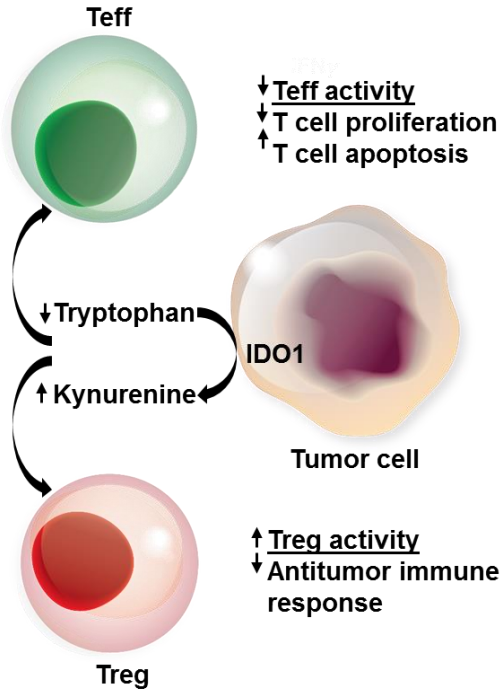
- Consultancy
  - 7 Hills, Actym, Amgen, Array, AstraZeneca, BeneVir, Bristol-Myers Squibb, Castle, EMD Serono, Gilead, Janssen, Merck, Novartis

- Support to institution
  - AbbVie, Boston Biomedical, Bristol-Myers Squibb, Celldex, Corvus, Delcath, Five Prime, Genentech, Immunocore, Incyte, Intensity, MedImmune, Macrogenics, Merck, Novartis, Pharmacyclics, Tesaro

- The University of Chicago is part of the BMS International Immuno-Oncology Network (II-ON)

IDO1 Plays a Pivotal Role in T-Cell Function and Immunosuppression

- IDO1 expression in tumors is associated with a decrease in immune cell tumor infiltration, an increase in regulatory T cells, and poor patient prognosis[1,2]
- IDO1 enzyme inhibits effector T-cell function through depletion of tryptophan and increasing production of immunosuppressive kynurenine[1]

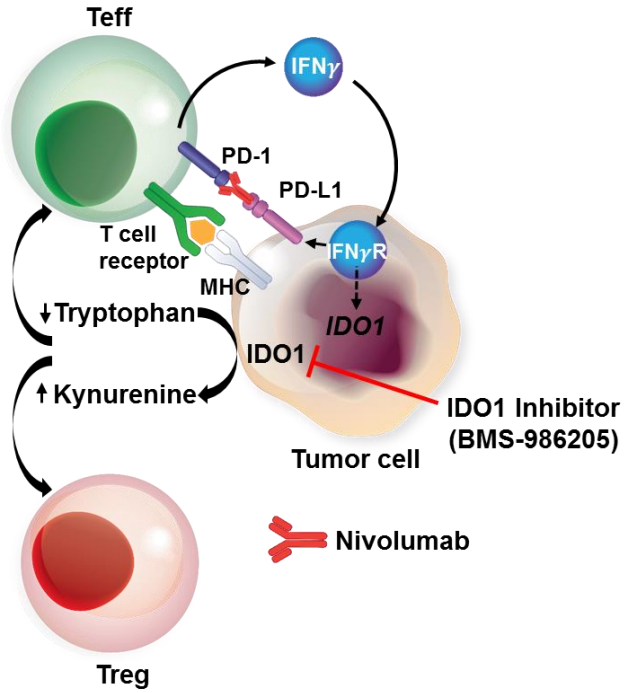


Adapted from Moon YW et al. *J Immunother Cancer*. 2015;3:51.
IFN = interferon; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death-1 ligand 1; Teff = effector T cell; Treg = regulatory T cell.

1. Moon YW et al. *J Immunother Cancer.* 2015;3:51. 2. Godin-Ethier J et al. *Clin Cancer Res.* 2011;17:6985–6991.

IDO1 Plays a Pivotal Role in T-Cell Function and Immunosuppression

- IDO1 expression in tumors is associated with decrease in immune cell tumor infiltration, an increase in regulatory T cells, and poor patient prognosis[1,2]
- IDO1 enzyme inhibits effector T-cell function through depletion of tryptophan and increasing production of immunosuppressive kynurenine[1]
- IDO1 upregulation by IFNγ is enhanced by infiltrating effector T cells, and further upregulated by anti–PD-1 treatment (eg, nivolumab) in patients[3]
- BMS-986205 is a potent and selective inhibitor of IDO1, with a PK profile that supports QD dosing[4,5]



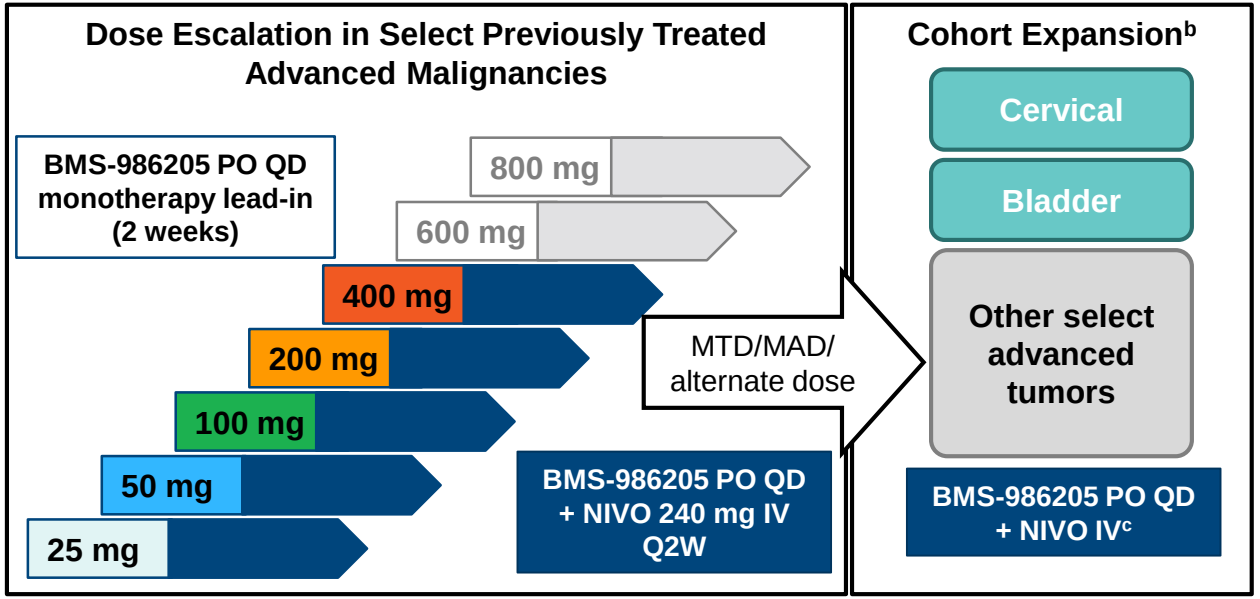
Adapted from Moon YW et al. *J Immunother Cancer*. 2015;3:51.
IFN = interferon; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death-1 ligand 1; Teff = effector T cell; Treg = regulatory T cell.

PK = pharmacokinetic.

1. Moon YW et al. *J Immunother Cancer.* 2015;3:51. 2. Godin-Ethier J et al. *Clin Cancer Res.* 2011;17:6985–6991. 3. Spranger S et al. *Sci Transl Med*. 2013;5:200. 4. Hunt J et al. AACR 2017: Oral presentation 4964. 5. Siu L et al. AACR 2017: Oral presentation CT116.

Phase 1/2a Trial of BMS-986205 + Nivolumab in Select Advanced Cancers (CA017-003)

- **Primary objectives:**
  - Safety, tolerability
  - DLTs, MTD, MAD, or alternate dose
  - Preliminary antitumor activity[a]
- **Secondary objectives:**
  - Pharmacokinetics (PK substudy)
  - Pharmacodynamics
  - Immunogenicity
- Prior immune checkpoint inhibitors and therapy targeting T-cell co-stimulation permitted



DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose; NIVO = nivolumab; PO QD = orally, once a day. ClinicalTrials.gov identifier: NCT02658890. [a] Cohort expansion only. [b] Expansion cohorts are ongoing. [c] BMS-986205 100 mg or 200 mg (including cervical and bladder cohorts) and NIVO 240 mg IV Q2W (including cervical and bladder cohorts) or 480 mg IV Q4W. Data cutoff: September 14, 2017. Additional cutoff for efficacy: October 13, 2017.

Baseline Demographics

	Dose-Escalation Cohorts					All Treated Patients (N = 289)
	BMS-986205 25 mg + NIVO[a] (n = 7)	BMS-986205 50 mg + NIVO[a] (n = 10)	BMS-986205 100 mg + NIVO[a] (n = 12)	BMS-986205 200 mg + NIVO[a] (n = 18)	BMS-986205 400 mg + NIVO[a] (n = 6)	
Median age (range), years	54 (37–73)	58 (48–74)	61 (35–69)	56 (31–73)	59 (55–76)	**61** (18–92)
Gender, n (%)						
Male	1 (14.3)	5 (50.0)	3 (25.0)	8 (44.4)	3 (50.0)	**145** (50.2)
Female	6 (85.7)	5 (50.0)	9 (75.0)	10 (55.6)	3 (50.0)	**144** (49.8)
ECOG PS, n (%)						
0	4 (57.1)	5 (50.0)	4 (33.3)	6 (33.3)	1 (16.7)	**101** (34.9)
1	3 (42.9)	5 (50.0)	8 (66.7)	12 (66.7)	5 (83.3)	**176** (60.9)
Not reported	0	0	0	0	0	**12** (4.2)
Prior lines of therapy, n (%)						
1	1 (14.3)	1 (10.0)	4 (33.3)	5 (27.8)	1 (16.7)	**107** (37.0)
2	2 (28.6)	2 (20.0)	1 (8.3)	4 (22.2)	1 (16.7)	**56** (19.4)
3	2 (28.6)	2 (20.0)	0	3 (16.7)	2 (33.3)	**43** (14.9)
≥4	2 (28.6)	5 (50.0)	7 (58.3)	5 (27.8)	2 (33.3)	**60** (20.8)

[a] NIVO 240 mg Q2W. Data cutoff: September 14, 2017.

End of Treatment Disposition

	Dose-Escalation Cohorts					All Treated Patients (N = 289)
	BMS-986205 25 mg + NIVO[a] (n = 7)	BMS-986205 50 mg + NIVO[a] (n = 10)	BMS-986205 100 mg + NIVO[a] (n = 12)	BMS-986205 200 mg + NIVO[a] (n = 18)	BMS-986205 400 mg + NIVO[a,b] (n = 6)	
Median duration of therapy, weeks (min–max)[c]						
BMS-986205	10.0 (6–32)	12.0 (1–47)	8.7 (0–27)	6.0 (0–40)	8.9 (2–16)	**7.5** (0–47)
NIVO	10.0 (6–32)	12.0 (2–50)	9.0 (2–26)	6.5 (2–42)	7.0 (2–17)	**8.0** (2–50)
Continuing treatment, n (%)	0	0	0	2 (11.1)	1 (16.7)	**136** (47.1)
Completed treatment, n (%)[d]	1 (14.3)	2 (20.0)	1 (8.3)	2 (11.1)	0	**12** (4.2)
Treatment discontinuation, n (%)	6 (85.7)	8 (80.0)	11 (91.7)	14 (77.8)	5 (83.3)	**141** (48.8)
Reasons for discontinuation, n (%)						
Disease progression	5 (71.4)	6 (60.0)	5 (41.7)	10 (55.6)	5 (83.3)	**108** (37.4)
Study-drug toxicity	0	0	2 (16.7)	0	0	**4** (1.4)[e]
Death	0	0	0	0	0	**0**
AE unrelated to study drug	1 (14.3)	1 (10.0)	2 (16.7)	3 (16.7)	0	**18** (6.2)
Patient decision/withdrawal	0	1 (10.0)	1 (8.3)	0	0	**9** (3.1)
Other[f]	0	0	1 (8.3)	1 (5.6)	0	**2** (0.7)

[a] NIVO 240 mg Q2W. [b] One additional patient was discontinued during the mono lead-in phase due to Grade 2 increased AST. [c] Median duration of therapy is calculated from 286 patients who received combination BMS-986205 + NIVO. [d] Patients who have completed initial planned 24 weeks of treatment. [e] Treatment-related AEs leading to discontinuation: Grade 3 autoimmune hepatitis, Grade 4 autoimmune hepatitis, Grade 3 pneumonitis, Grade 2 uveitis. [f] Lost to follow-up/Noncompliance/Other/Not reported. Data cutoff: September 14, 2017.

sitc Society for Immunotherapy of Cancer

Dose-Escalation Phase: Final Results

	25 mg	50 mg	100 mg	200 mg	400 mg
# DLTs/ # DLT evaluable patients	0/7	0/8	1/9	3/12	2/4
DLTs			**Grade 3** • Autoimmune hepatitis	**Grade 3** • Fatigue and anemia leading to dose reduction • Anemia leading to dose reduction • AST and ALT elevations	**Grade 2** • Fatigue and anemia leading to dose reduction **Grade 3** • AST and ALT elevations

- MTD established at 200 mg QD
- Recommended phase 2 dose established at 100 mg QD based on safety and pharmacodynamic profile

Treatment-Related Adverse Events (TRAEs)

	Any Grade	Grade 3	Grade 4
Patients with TRAEs, n (%)	**153** (53.5)	**30** (10.5)	**2** (0.7)
TRAEs in ≥10% of patients (any grade)[a]			
Fatigue	**39** (13.6)	**2** (0.7)	**0**
Nausea	**33** (11.5)	**1** (0.3)	**0**
Decreased appetite	**30** (10.5)	**1** (0.3)	**0**
Serious TRAEs	**16** (5.6)	**11** (3.8)	**2** (0.7)
TRAEs leading to BMS-986205 discontinuation	**7** (2.4)	**3** (1.0)	**1** (0.3)

- Includes all 286 patients who received at least 1 dose of BMS-986205 and NIVO
- No TRAEs resulted in death

[a] Other Grade 3/4 TRAEs occurring in ≥2 patients included increased AST in 5 patients (1.7%), increased ALT, anemia, and autoimmune hepatitis each in 4 patients (1.4%), and pneumonitis, hepatitis, hyponatremia, hypophosphatemia, and increased lipase each in 2 patients (0.7%). Grade 4 TRAEs were autoimmune hepatitis (n = 1) and acute hepatitis (n = 1) in patients receiving 100 mg BMS-986205 plus NIVO. Data cutoff: September 14, 2017.

sitc
Society for Immunotherapy of Cancer

Cohort Expansion: Baseline Demographics and End of Treatment Disposition

	Cervical (n = 22)	Bladder (n = 26)
Median age (range), years	53 (33–67)	66 (48–79)
Gender, n (%)		
Male	0	22 (84.6)
Female	22 (100)	4 (15.4)
ECOG PS, n (%)		
0	8 (36.4)	9 (34.6)
1	14 (63.6)	15 (57.7)
Not reported	0	2 (7.7)
Prior systemic therapy, n (%)	21 (95.5)[a]	26 (100)
Anti–PD-1/PD-L1	0	3 (11.5)
Other I-O	0	1 (3.8)
Prior lines of therapy, n (%)		
1	9 (40.9)	15 (57.7)
2	4 (18.2)	7 (26.9)
3	7 (31.8)	3 (11.5)
≥4	1 (4.5)	1 (3.8)
PD-L1 status[b]		
Positive	12 (54.5)	13 (52.0)
Negative	7 (31.8)	9 (36.0)
Not determined	3 (13.6)	3 (12.0)

	Cervical (n = 22)	Bladder (n = 26)
Median duration of therapy, weeks (min–max)		
BMS-986205	12.7 (1–29)	7.6 (0–36)
NIVO	13.3 (2–32)	8.0 (2–41)
Continuing treatment, n (%)	7 (31.8)	13 (50.0)
Completed treatment, n (%)	1 (4.5)	3 (11.5)
Treatment discontinuation, n (%)	14 (63.6)	10 (38.5)
Reasons for discontinuation, n (%)		
Disease progression	13 (59.1)	8 (30.8)
Study-drug toxicity	0	1 (3.8)
Death	0	0
AE unrelated to study drug	0	0
Patient decision/withdrawal	1 (4.5)	1 (3.8)
Other	0	0

[a] All patients received ≥1 line of prior therapy, previous adjuvant therapy as only prior therapy permitted for bladder cancer cohort. One patient with cervical cancer received 1 prior line of therapy but this was not reported prior to data cutoff. [b] Among evaluable patients; one bladder cancer patient without a post-treatment tumor assessment not included. PD-L1 status was validated using Dako anti–PD-L1 antibody clone 28-8. PD-L1 positive is ≥1% in tumor cells. Data cutoff: September 14, 2017.

sitc Society for Immunotherapy of Cancer

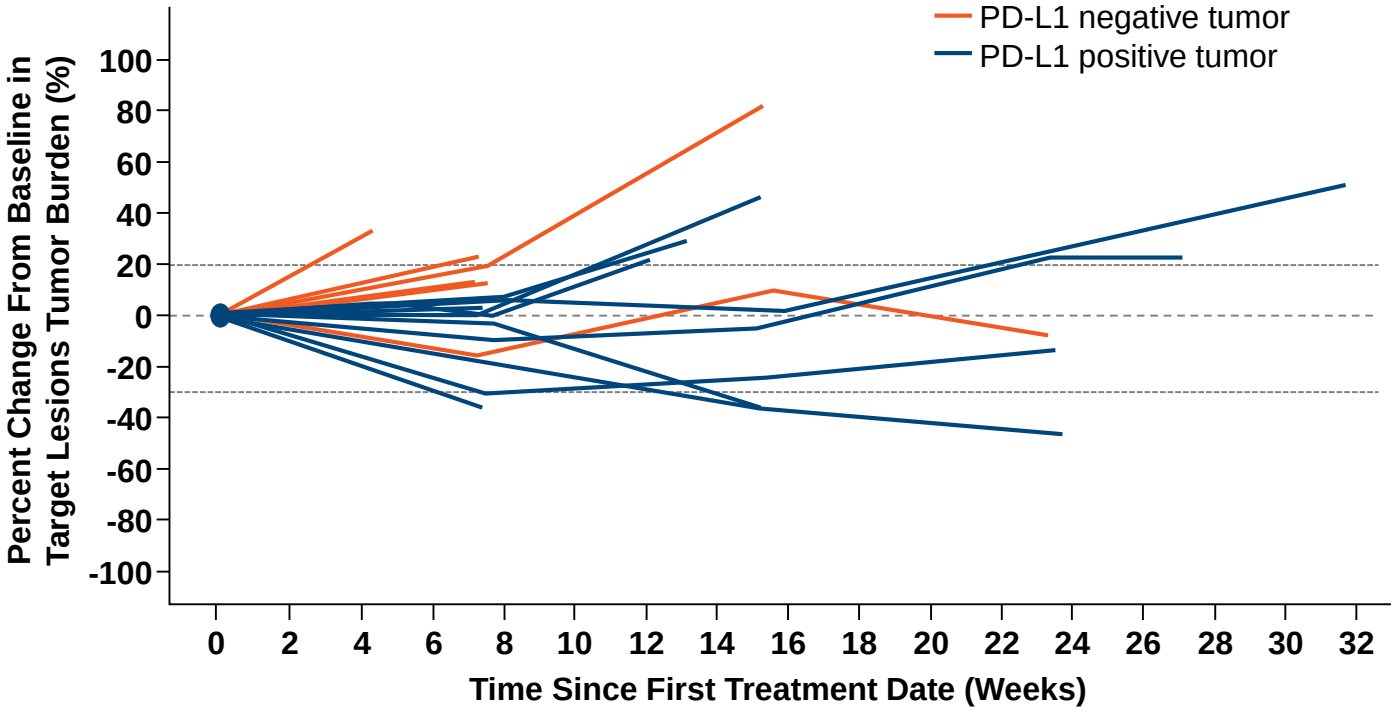
Cervical Cancer Cohort: Best Overall Response

	All Patients (n = 22)	1 Prior Line of Therapy (n = 11)	≥2 Prior Lines of Therapy (n = 11)	PD-L1 Positive (n = 12)	PD-L1 Negative (n = 7)
Best overall response[a], n (%)					
Complete response	0	0	0	0	0
Partial response[b]	3 (13.6)	2 (18.2)	1 (9.1)	3 (25.0)	0
Stable disease	11 (50.0)	6 (54.5)	5 (45.5)	6 (50.0)	3 (42.9)
Progressive disease	6 (27.3)	2 (18.2)	4 (36.4)	1 (8.3)	4 (57.1)
Death prior to disease assessment/unable to determine	2 (9.1)	1 (9.1)	1 (9.1)	2 (16.6)	0
Objective response rate[c], % (95 % CI)	**13.6** (2.9, 34.9)	**18.2** (2.3, 51.8)	**9.1** (0.2, 41.3)	**25.0** (5.5, 57.2)	**0** (0.0, 41.0)
Disease control rate[d], % (95% CI)	**63.6** (40.7, 82.8)	**72.7** (39.0, 94.0)	**54.5** (23.4, 83.3)	**75.0** (42.8, 94.5)	**42.9** (9.9, 81.6)

[a] Tumor assessment by RECIST v1.1, investigator assessed, every 8 weeks. [b] 1 patient with a PD-L1 positive tumor who received ≥2 prior lines of therapy had a confirmed partial response. [c] Complete responses + partial responses (confirmed and unconfirmed). [d] Complete responses + partial responses (confirmed and unconfirmed) + stable disease. Data cutoff: October 13, 2017.

sitc Society for Immunotherapy of Cancer

Cervical Cancer Cohort: Tumor Burden of Target Lesions



Includes patients who have at least 1 reported on-treatment tumor assessment and known PD-L1 status. Tumor assessment by RECIST v1.1, investigator assessed, every 8 weeks. Data cutoff: October 13, 2017.

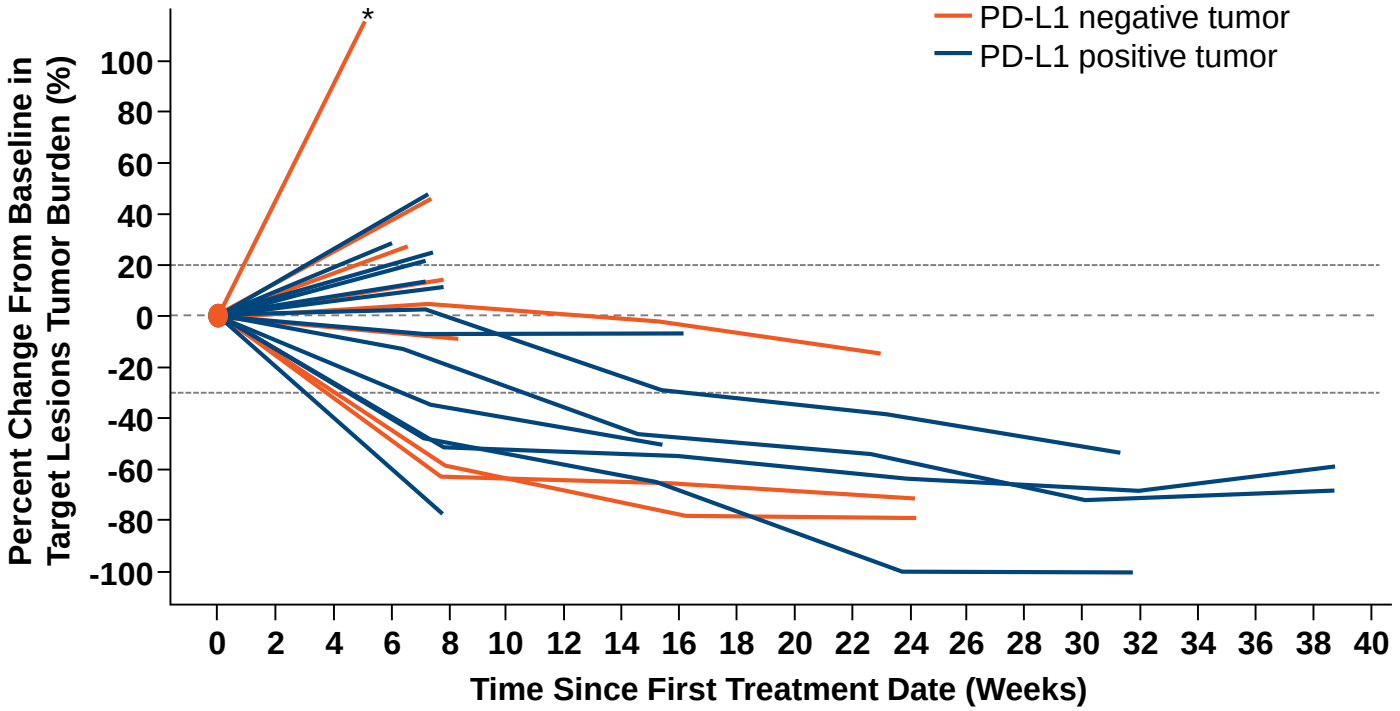
Bladder Cancer Cohort: Best Overall Response

	All Patients (n = 25) [a]	1 Prior Line of Therapy (n = 15)	≥2 Prior Lines of Therapy (n = 10)	PD-L1 Positive (n = 13)	PD-L1 Negative (n = 9)
Best overall response[b], n (%)					
Complete response	0	0	0	0	0
Partial response[b]	8 (32.0)	6 (40.0)	2 (20.0)	6 (46.2)	2 (22.2)
Stable disease	3 (12.0)	0	3 (30.0)	2 (15.4)	1 (11.1)
Progressive disease	13 (52.0)	9 (60.0)	4 (40.0)	5 (38.5)	5 (55.6)
Death prior to disease assessment	1 (4.0)	0	1 (10.0)	0	1 (11.1)
Objective response rate[c], % (95 % CI)	**32.0** (14.9, 53.5)	**40.0** (16.3, 67.7)	**20.0** (2.5, 55.6)	**46.2** (19.2, 74.9)	**22.2** (2.8, 60.0)
Disease control rate[d], % (95% CI)	**44.0** (24.4, 65.1)	**40.0** (16.3, 67.7)	**50.0** (18.7, 81.3)	**61.5** (31.6, 86.1)	**33.3** (7.5, 70.1)

[a] One patient without a post-treatment tumor assessment not included. [b] Tumor assessment by RECIST v1.1, investigator assessed, every 8 weeks. 7 patients had a confirmed partial response: 5 had received 1 prior line of therapy and 2 had received ≥2 prior lines of therapy; 5 had PD-L1 positive tumors and 2 had PD-L1 negative tumors. [c] Complete responses + partial responses (confirmed and unconfirmed). [d] Complete responses + partial responses (confirmed and unconfirmed) + stable disease. Data cutoff: October 13, 2017.

sitc
Society for Immunotherapy of Cancer

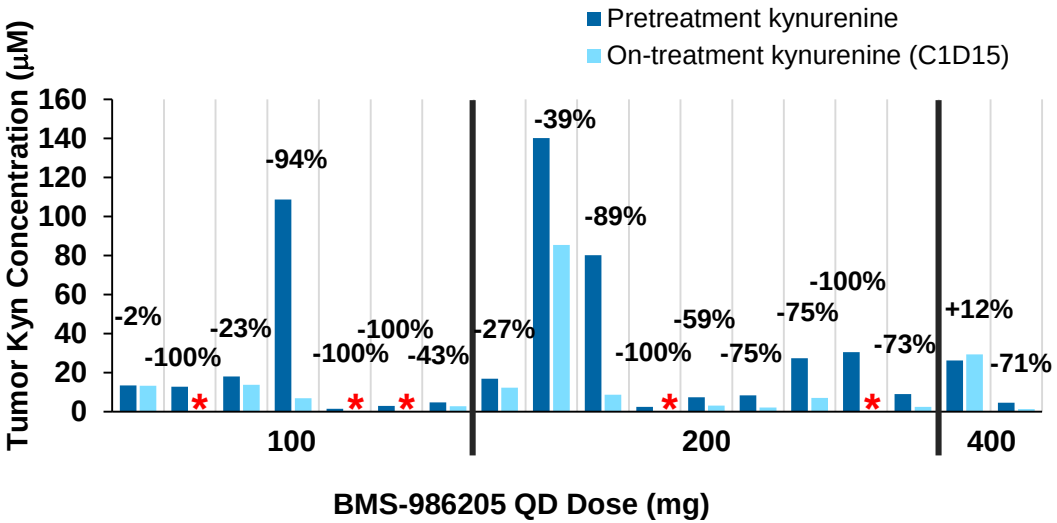
Bladder Cancer Cohort: Tumor Burden of Target Lesions



Includes patients who have at least 1 reported on-treatment tumor assessment and known PD-L1 status. Tumor assessment by RECIST v1.1, investigator assessed, every 8 weeks. * Denotes patient with >100% increase. Data cutoff: October 13, 2017.

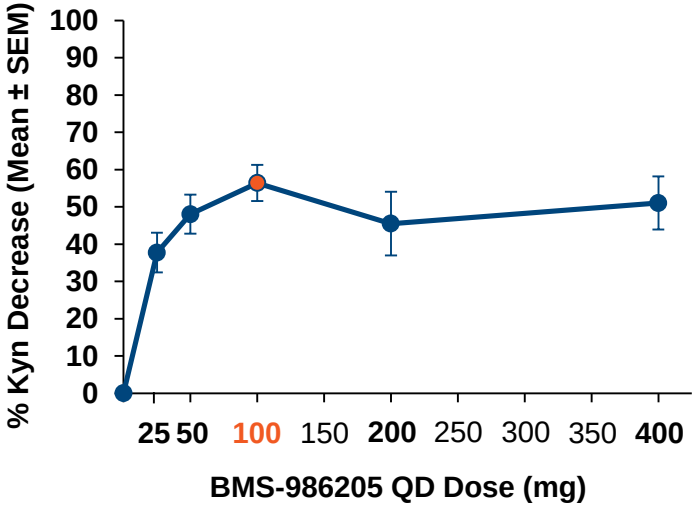
BMS-986205 Plus NIVO Decreased Tumoral and Serum Kynurenine Levels

Tumoral Kynurenine Concentration



* Denotes samples below the lower limit of quantitation.

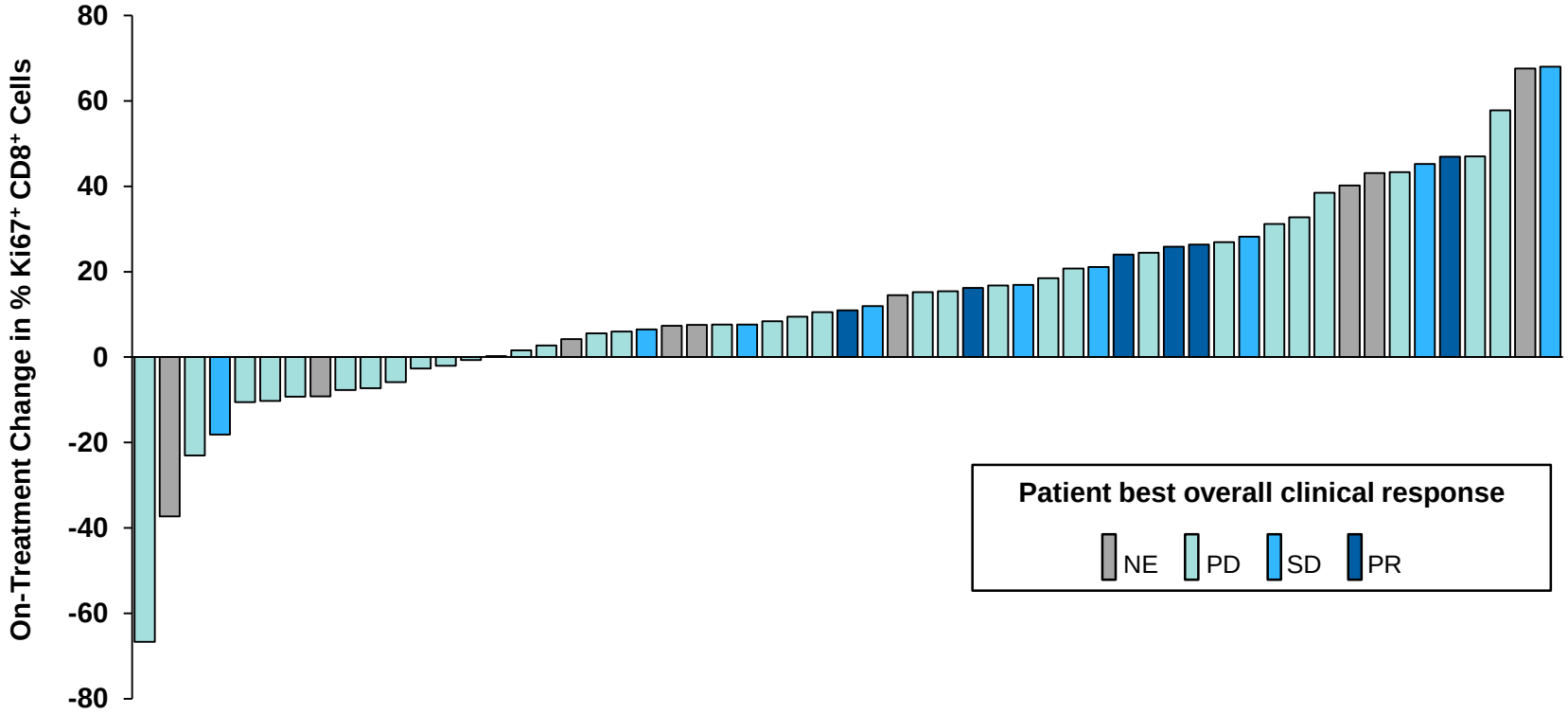
Serum Kynurenine



- Tumoral kynurenine was reduced across all doses including in tumors with high baseline kynurenine

Kyn = kynurenine.

BMS-986205 Plus NIVO Increased Tumoral Proliferating (Ki67+) CD8+ T Cells



NE = non-evaluable; PD = progressive disease; PR = partial response; SD = stable disease. Data cutoff: October 13, 2017.

Summary and Conclusions

- BMS-986205 is a potent and selective inhibitor of IDO1
- Combination of BMS-986205 and nivolumab demonstrated a favorable safety profile in heavily pretreated patients
  - Grade 3/4 TRAEs occurred in 11% of patients
  - No treatment-related deaths were reported
- Antitumor activity observed in patients with advanced cancers
  - ORR of 14% and DCR of 64% in advanced cervical cancer, with ORR of 25% in PD-L1 positive patients
  - ORR of 32% and DCR of 44% in advanced bladder cancer, with ORR of 46% in PD-L1 positive patients
- BMS-986205 at the recommended phase 2 dose in combination with nivolumab reduced serum kynurenine levels by ~60%
- Increase in tumoral proliferating $CD8^+$ T cells in on-treatment biopsies was observed
- These data support the ongoing evaluation of BMS-986205 in combination with nivolumab in patients with advanced cancers

DCR = disease control rate; ORR = objective response rate.

Acknowledgments

- The patients and families who made this trial possible
- The clinical study teams who participated in this trial
- Bristol-Myers Squibb (Princeton, NJ) and Ono Pharmaceutical Company, Limited (Osaka, Japan)
- The study was supported by Bristol-Myers Squibb
- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Stuart Rulten, of Spark Medica Inc. (USA), funded by Bristol-Myers Squibb

Investigators

Canada

Quincy Chu
Karen Gelmon
Wilson Miller
Lillian Siu

Spain

Emiliano Calvo
Victor Moreno Garcia
Josep Tabernero

Italy

Filippo de Braud
Giuseppe Curigliano
Luca Gianni
Armando Santoro

Australia

Victoria Atkinson
Matteo Carlino
Jayesh Desai
Anthony Joshua
Georgina Long
Benjamin Markman
Michael Millward

United States of America

Olatunji Alese
Scott Antonia
Rodolfo Bordoni
Diwakar Davar
Martin Gutierrez
Jason Luke
Daruka Mahadevan
Anthony Olszanski
Russell Pachynski
Sandip Patel
William Sharfman
Dale Shepard
Ulka Vaishampayan

France

Philippe Cassier
Brigitte Dréno
Carlos Alberto Gomez-Roca
Christophe Le Tourneau
Caroline Gaudy-Marqueste
Franck Morschhauser
Andreea Varga

Poland

Iwona Lugowska

sitc
Society for Immunotherapy of Cancer