Combined inhibition of the IDO and PD-1 pathways improves the response rate for patients with advanced melanoma

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CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference
Mainz, Germany
09/09/2017

Disclosure Information

I have the following financial relationships to disclose:

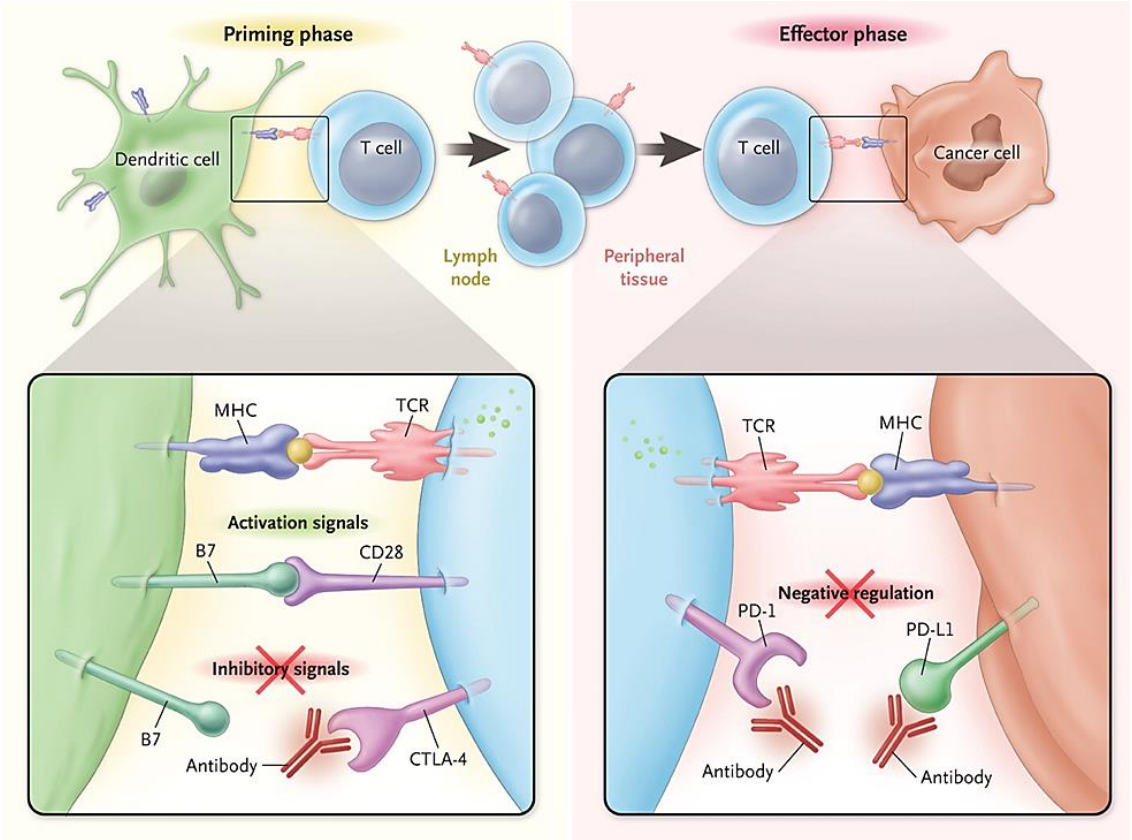
- Advisory Board: Amgen, Roche Diagnostics, Novartis, Eisai, Castle Bioscience

- Grant/research support from: The presenter's institution received research support from NewLink Genetics for the purpose of this study

I will be discussing the use of the investigational agent indoximod.

T-Cell Activation, Proliferation, and Function

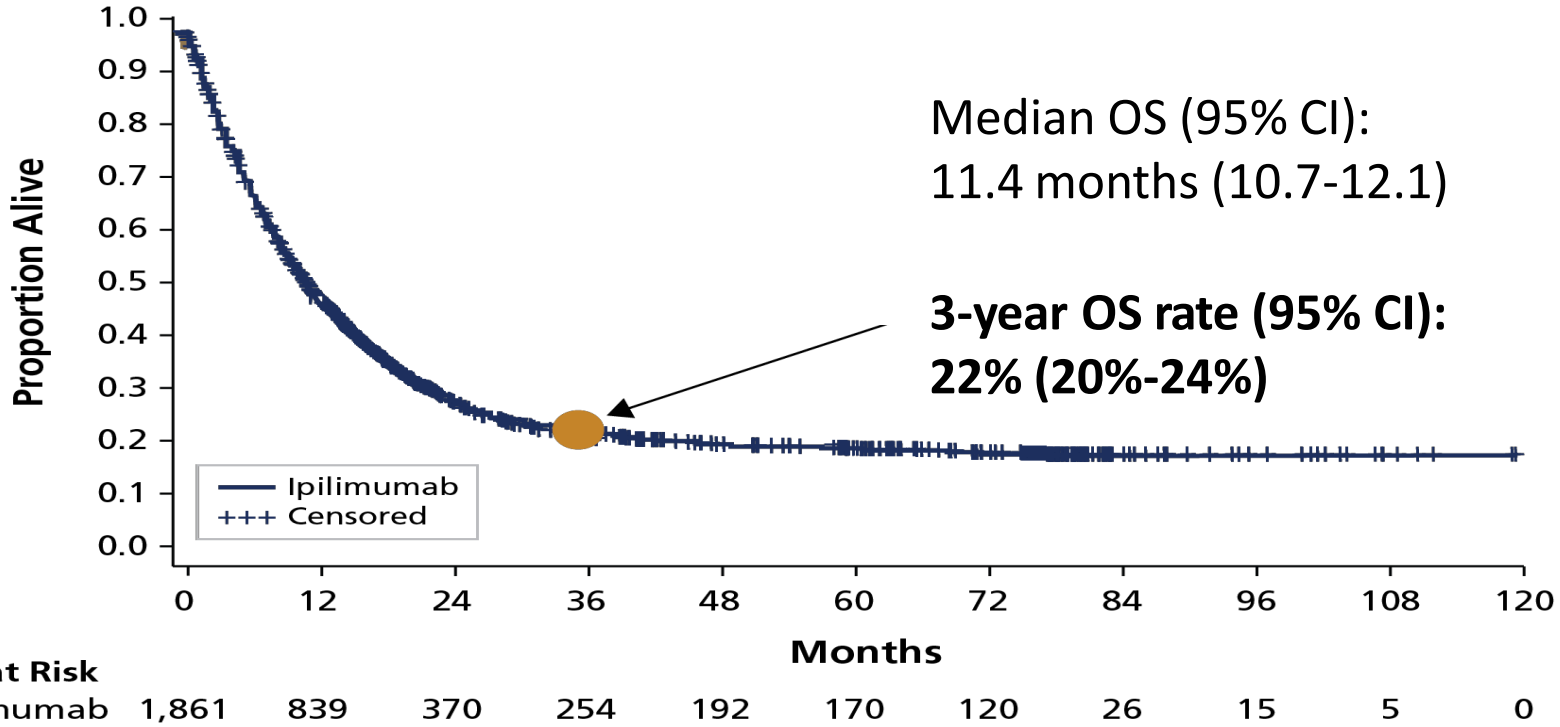
Controlled by Multiple Agonist and Antagonist Signals



Ribas A. *N Engl J Med*. 2012;366(26):2517-2519.

The CTLA-4 Experience

Primary Analysis of Pooled OS Data on Ipilimumab in 1,861 Patients[1]



Median OS (95% CI):
11.4 months (10.7-12.1)

3-year OS rate (95% CI):
22% (20%-24%)

CTLA-4, cytotoxic T-lymphocyte associated protein 4; OS, overall survival; CI, confidence interval.

[1]Schadendorf D, et al. Presented at: European Cancer Congress; September 27-October 1, 2013; Amsterdam, Netherlands. Abstract 24.

3-Year Survival Follow Up

Anti–PD-1 Antibodies From Phase 1 Studies in Melanoma

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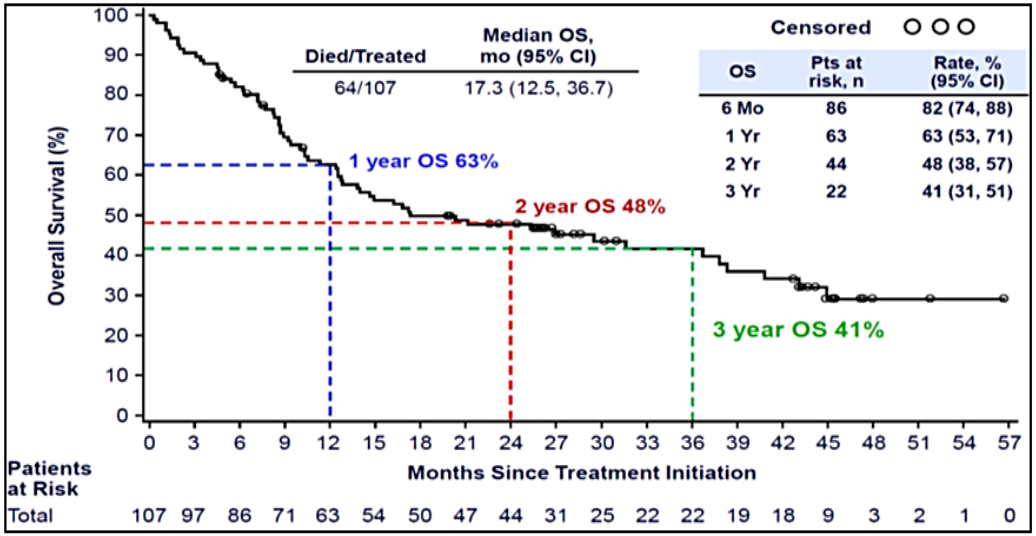
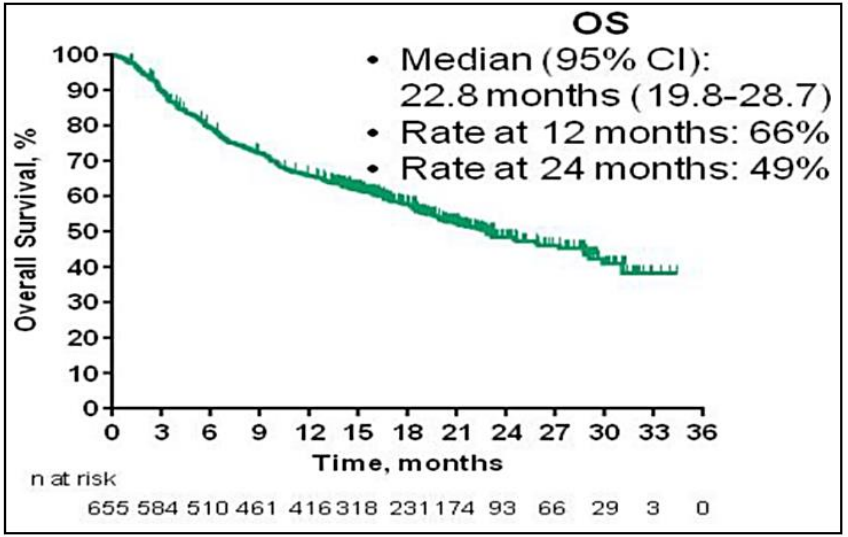
Nivolumab[1]



Pembrolizumab[2]



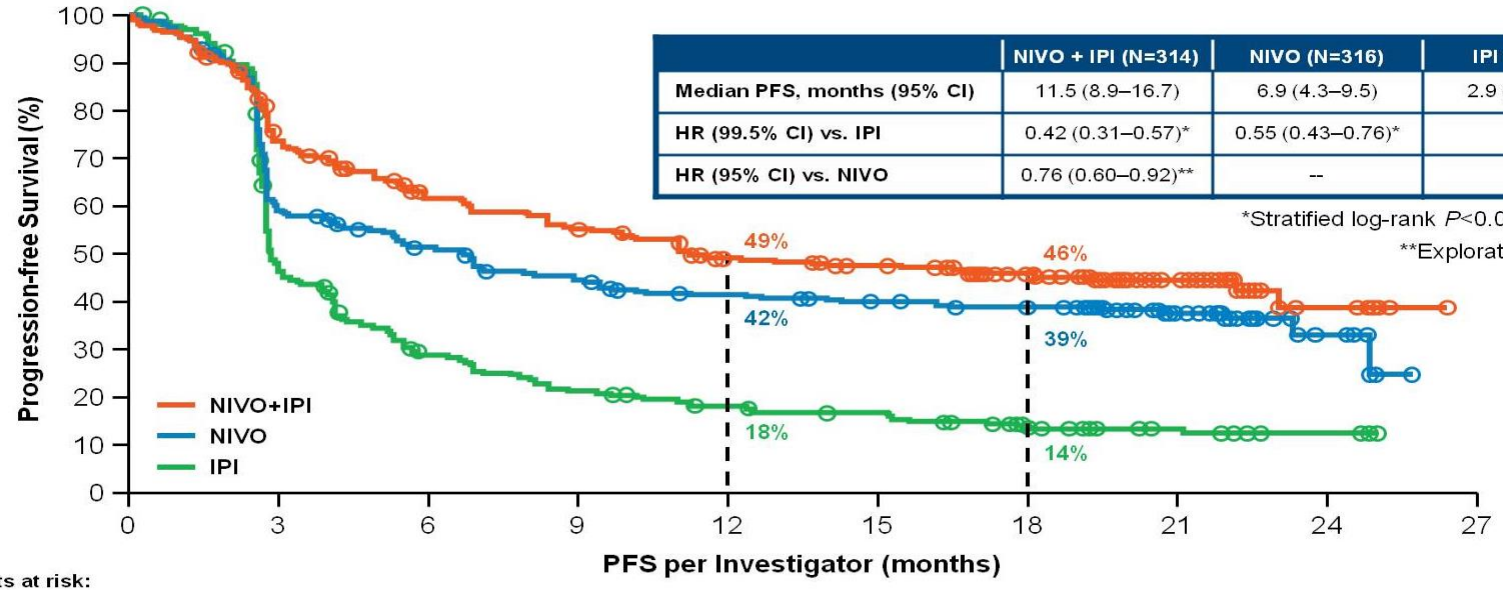
PD-1, programmed cell death protein 1; OS, overall survival; CI, confidence interval.

[1]Hodi FS, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2014; Chicago, Illinois, USA. Abstract 9002.

[2]Daud A, et al. Presented at: ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois, USA. Abstract 9005.

Progression-Free Survival With Nivolumab + Ipilimumab

Intent-to-Treat Population in Melanoma



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

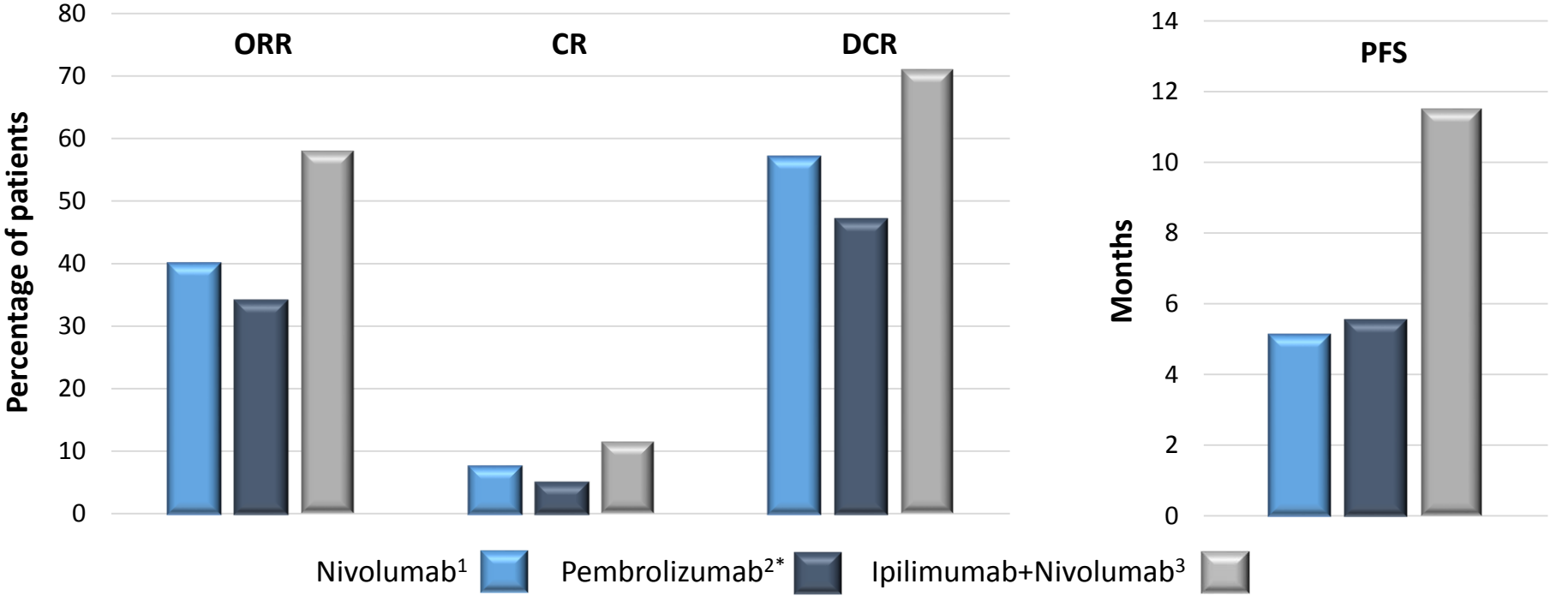
Database lock Nov 2015

PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

Wolchok JD, et al. Presented at: ASCO Annual Meeting; June 3-7, 2016; Chicago, Illinois, USA. Abstract 9505.

Currently Approved Checkpoint Therapy Efficacy Results

Substantial Remaining Unmet Need in Metastatic Melanoma



[*]Data are for Q2W regimen.

ORR, objective response rate; CR, complete response; DCR, disease control rate; PFS, progression-free survival.

[1]Robert C, et al. *N Engl J Med*. 2015;372(4):320-330; [2]Robert C, et al. *N Engl J Med*. 2015;372(26):2521-2532; [3]Larkin J, et al. *N Engl J Med*. 2015;373(1):23-34.

Safety Summary

Nivolumab + Ipilimumab in Melanoma

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued nivolumab + ipilimumab due to treatment-related AEs achieved a response

AE, adverse event.
*One reported in the nivolumab group (neutropenia) and one in the ipilimumab group (colon perforation).
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IDO Pathway and Cancer

Key Immuno-Oncology Target

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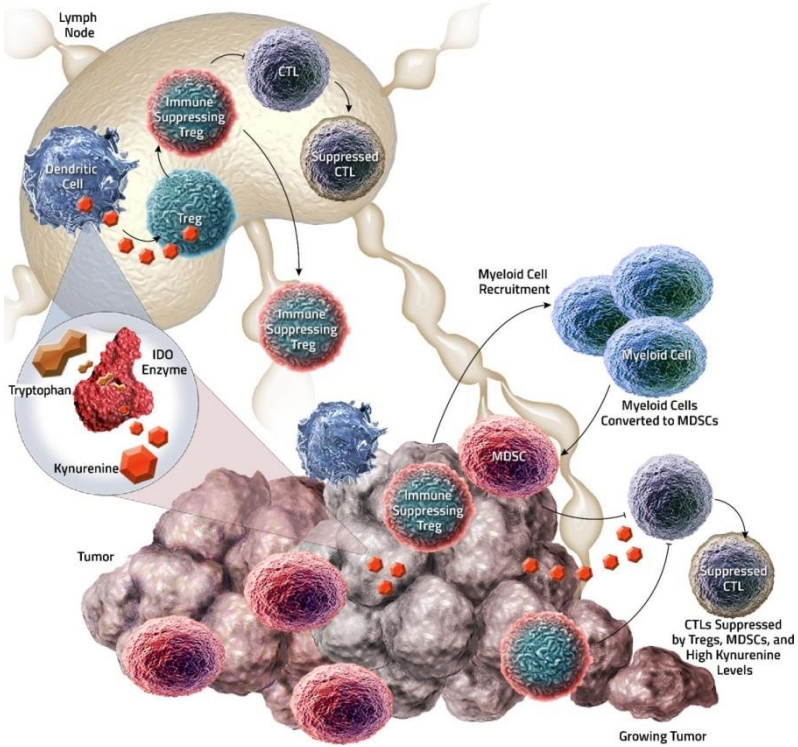
- IDO (indoleamine 2,3-dioxygenase): intracellular enzyme that regulates immune response by degrading tryptophan to kynurenine[1]
- IDO pathway activity results in a shift of the ratio of tryptophan (↓) to kynurenine (↑)[1]
- This shift in ratio signals a suppressive phenotype rather than an activated antitumor phenotype[1]
- Tumors hijack the IDO pathway, a normal part of the immune system, to facilitate immune escape[2]



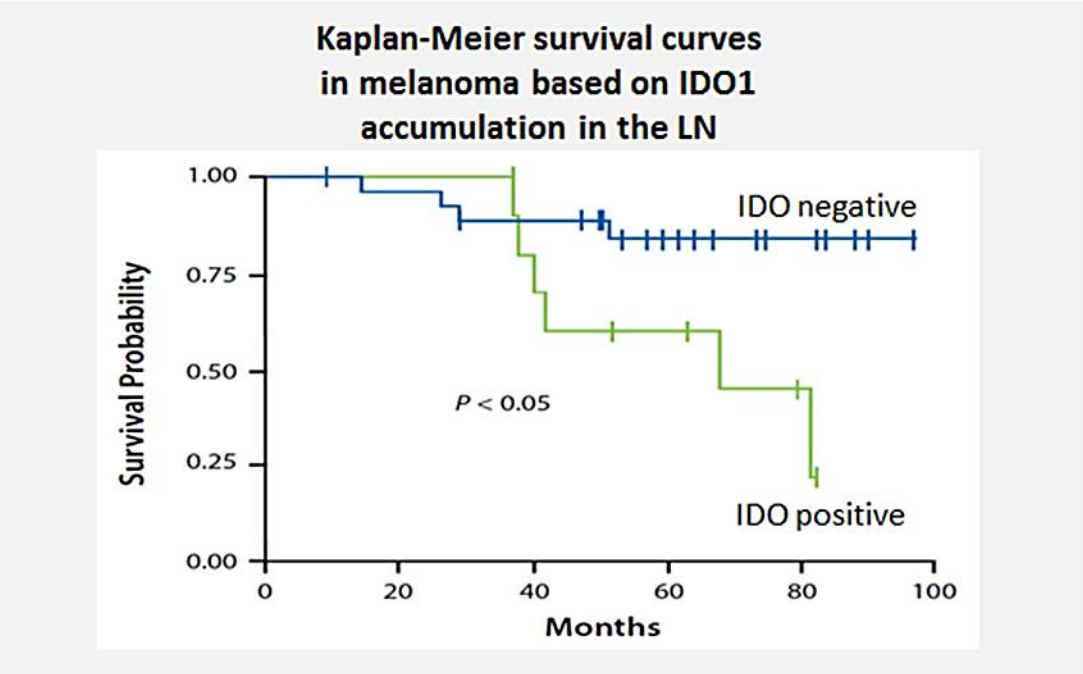
Treg, regulatory T cell; IDO, indoleamine 2,3-dioxygenase; MDSC, myeloid-derived suppressor cell; CTL, cytotoxic T lymphocyte.

[1]Metz R. *Oncoimmunology*. 2012;1(9):1460-1468. [2]Johnson TS. *Immunol Invest*. 2012;41(6-7):765-797.

IDO1 Expression in Various Tumor Types

Associated With Poor Patient Outcome

- IDO1 is highly expressed in multiple tumor types
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - Colorectal cancer
  - Glioblastoma
  - Squamous cell carcinoma
  - Endometrial carcinoma
  - DLBCL
  - RCC
  - TCC
  - TNBC



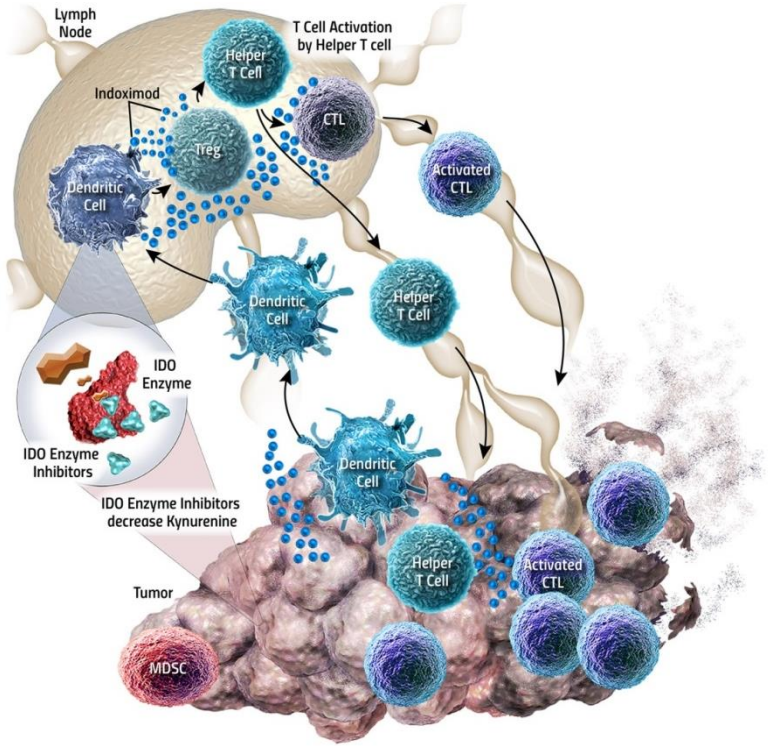
IDO, indoleamine 2,3-dioxygenase; LN, lymph node; NSCLC, non-small cell lung cancer; DLBCL, diffuse large B-cell lymphoma; RCC, renal cell carcinoma; TCC, transitional cell carcinoma; TNBC, triple-negative breast cancer.

Munn DH, et al. *J Clin Invest*. 2004;114(2):280-290.

Targeting the IDO Pathway

Two Distinct Strategies for Inhibiting the IDO Pathway

- Indoximod
  - Acts directly on immune cells to reverse IDO pathway-mediated suppression
- Epacadostat, navoximod, and BMS-986205
  - Direct IDO enzymatic inhibitors, block tryptophan metabolism[1-3]
- Available clinical data indicate similar activity with both approaches

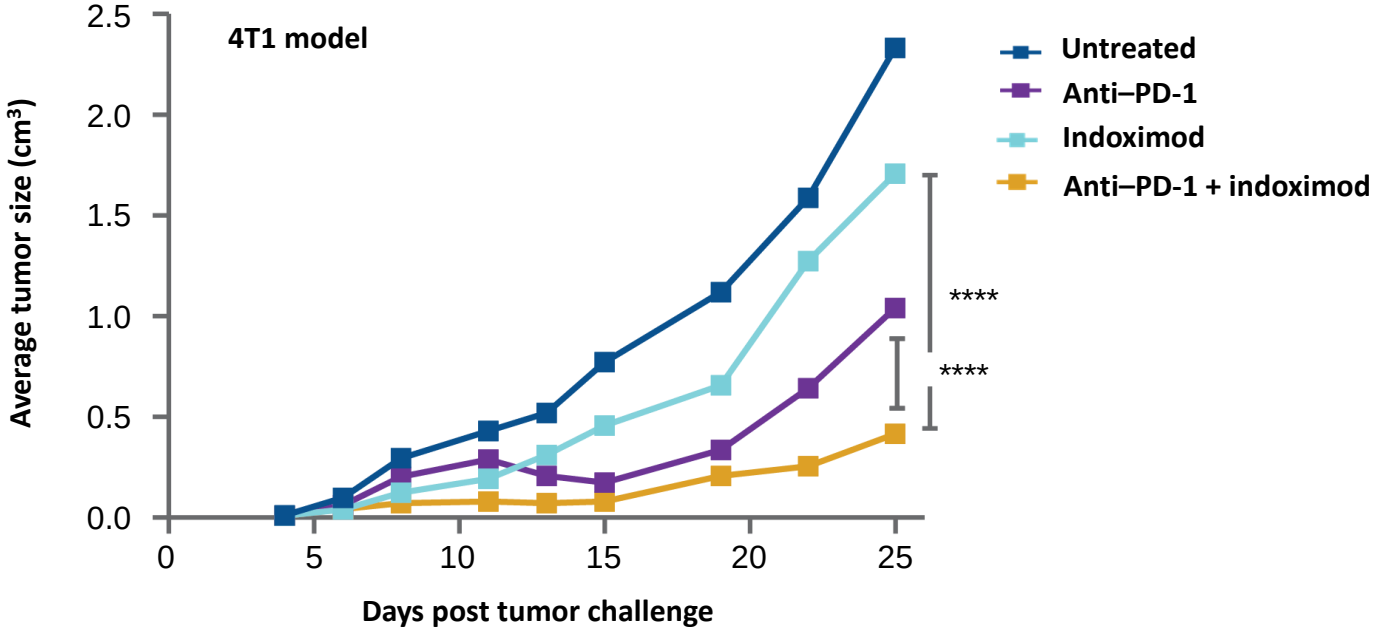


IDO, indoleamine 2,3-dioxygenase; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; CTL, cytotoxic T lymphocyte.

[1]Mautino M. AACR 2013. Abstract 491. [2]Jochems C. *Oncotarget*. 2016;7(25):37762-37772. [3]Siu LL. AACR 2017. Abstract CT116.

Indoximod Plus Anti–PD-1

Synergistic Activity in Preclinical Model



These data provide the scientific basis for the current trial design

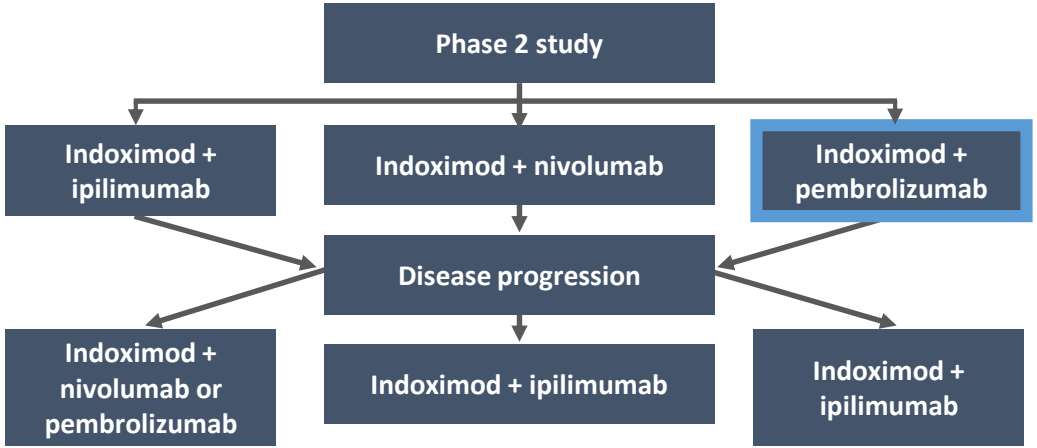
PD-1, programmed cell death protein 1.
Courtesy to Holmgaard RB. January 13, 2014.

Phase 2 Study Design (NLG2103)

Indoximod Plus Checkpoint Inhibitors in Advanced Melanoma

- Open-label, single-arm study
- Primary endpoint: objective response rate
- Key eligibility criteria
  - Unresectable stage III or IV advanced melanoma
  - No systemic treatment, including RT, in the previous 28 days
  - ECOG performance status ≤2

- Indoximod 1200 mg PO BID + approved standard of care checkpoint inhibitors
- Treatment until toxicity or disease progression
- Imaging at Week 12, then Q8W
- Change to second checkpoint allowed at first progression, indoximod continues



RT, radiation therapy; ECOG, Eastern Cooperative Oncology Group; PO, orally; BID, twice a day; Q8W, every 8 weeks.

Phase 2 Results in Advanced Melanoma

Indoximod Plus Pembrolizumab

- Interim Phase 2 results were presented at AACR Plenary Session 2017[1]
  - Encouraging response rates observed
  - Treatment regimen was well tolerated
- Updated Phase 2 efficacy results are presented here
  - Longer term follow up period
  - Continued improvement over time observed
  - Treatment remains well tolerated

[1]Zakharia Y, et al. Oral presentation Plenary Session at: 107th Annual Meeting of the American Association for Cancer Research (AACR); April 1-5, 2017; Washington, DC. Abstract CT117.

Baseline Demographic and Clinical Characteristics

Indoximod Plus Pembrolizumab for Advanced Melanoma

Characteristic	n = 51*
Median age (range), y	62.9 (27-88)
Male, n (%)	34 (67)
Race/ethnicity, n (%)	
White, non-Hispanic†	50 (98)
LDH above ULN, n (%)	12 (24)
Disease stage, n (%)	
III	8 (16)
IV	43 (84)
M1a	9 (18)
M1b	13 (25)
M1c	21 (41)

Characteristic	n = 51*
ECOG PS, n (%)	
0	38 (75)
1	13 (25)
Primary site, n (%)	
Cutaneous	40 (78)
Mucosal or primary unknown	11 (22)
Prior therapy, n (%)	
Radiation	9 (18)
Systemic therapy	14 (27)
None	28 (55)

LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Excludes uveal melanoma patients.
†One patient declined to answer.

Update on Response*

Indoximod Plus Pembrolizumab for Advanced Melanoma

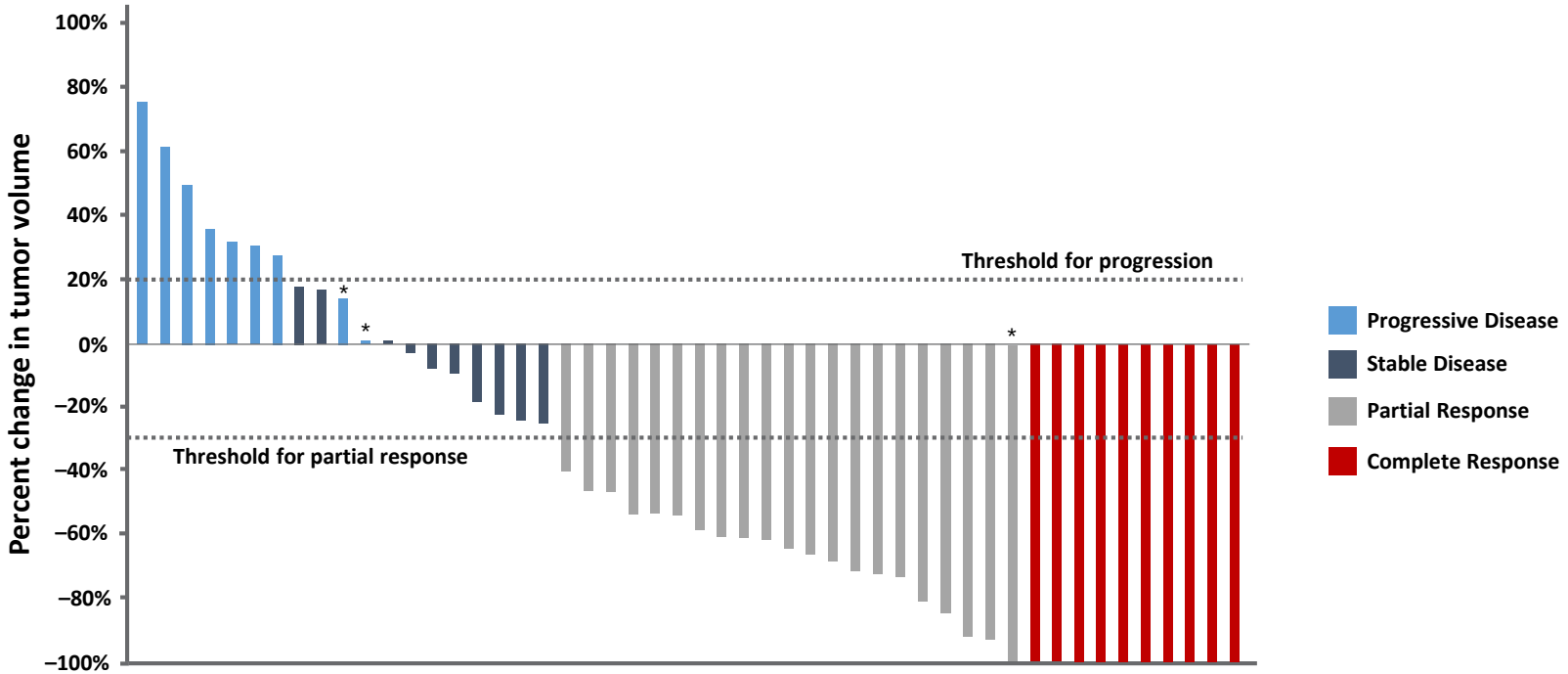
n = 51	n (%)
ORR	**31 (61)**
CR	10 (20)
PR	21 (41)
SD	10 (20)
DCR	**41 (80)**
PD	10 (20)

ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; PD, progressive disease.

*Based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 by site report.

Best Response by Patient With Advanced Melanoma

Significant Depth of Response

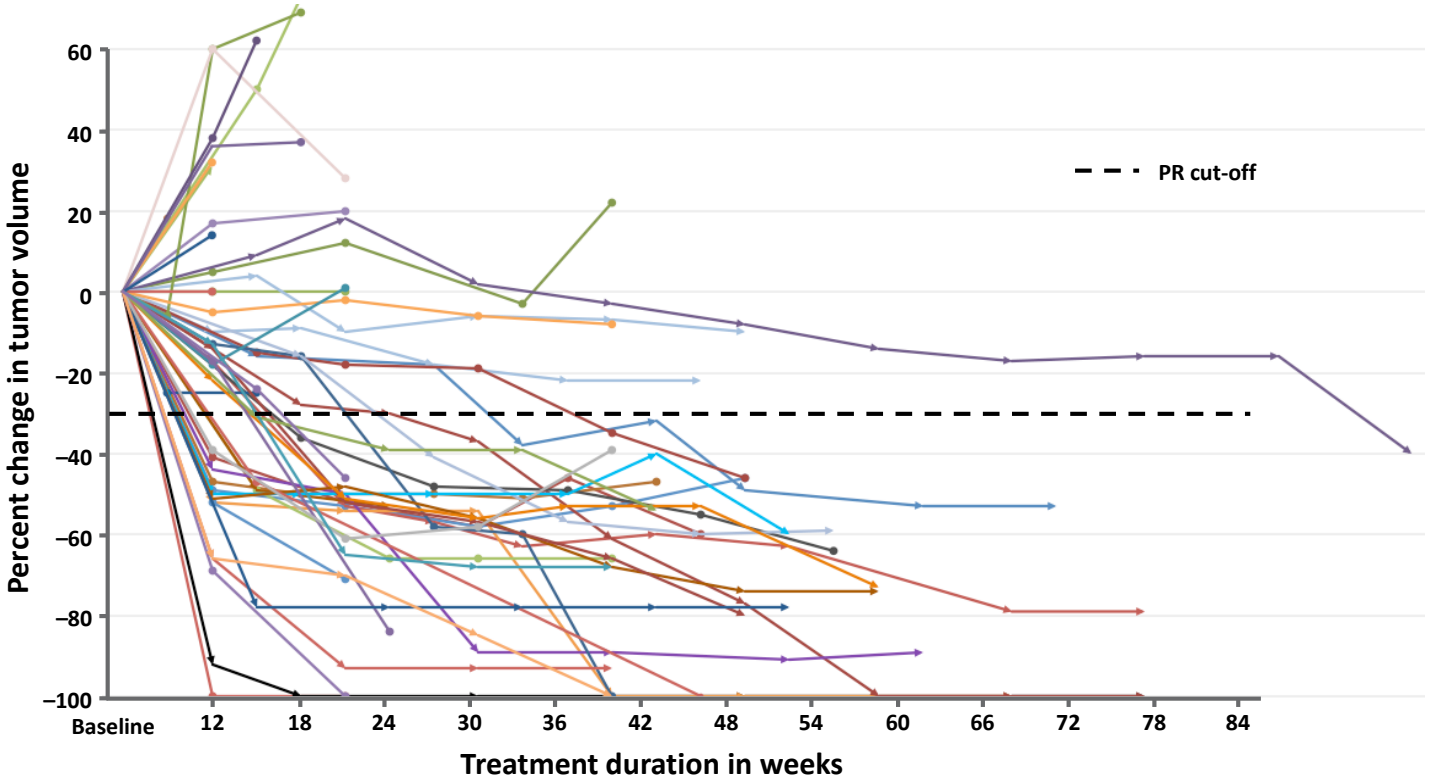


*Patients that progressed due to new non-target lesions.

Note: 1 patient was unevaluable for response due to pleural effusion/collapsed left lung; the patient progressed based on several new non-target lesions.

Change in Tumor Volume Over Time

Durable and Ongoing Responses

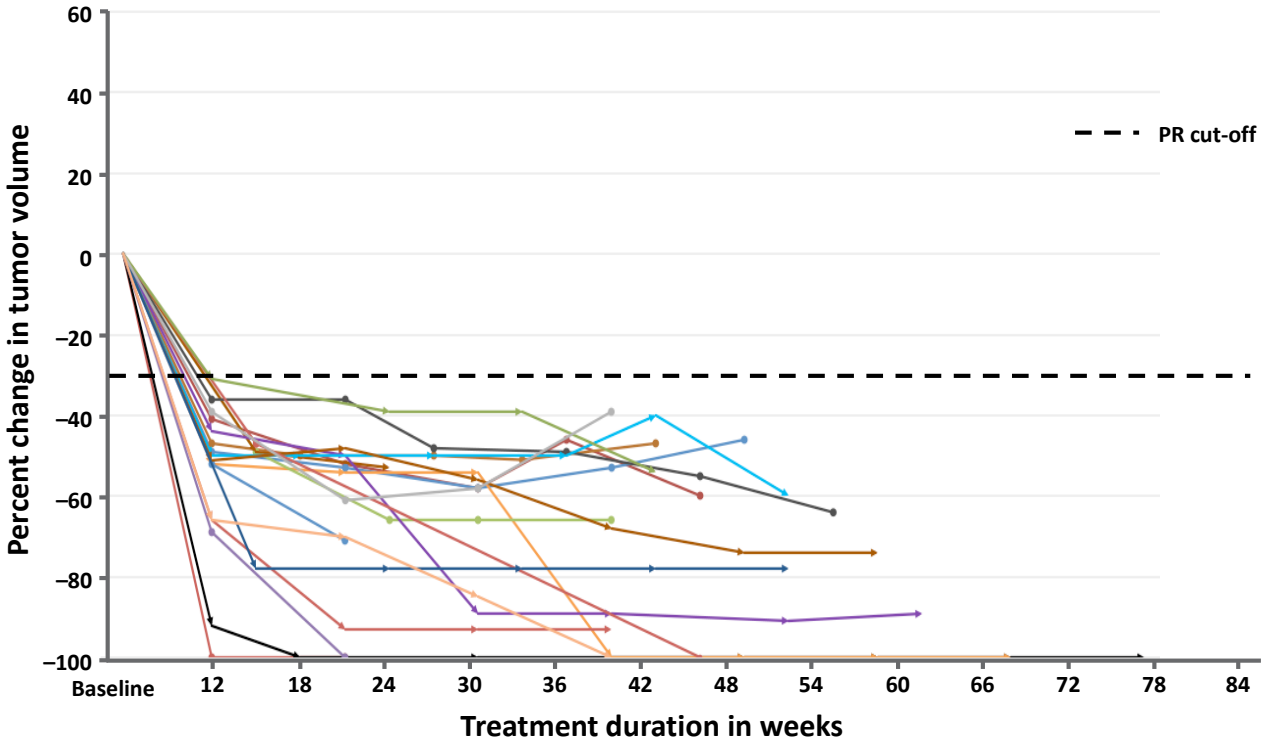


PR, partial response.

Note: 1 patient was unevaluable for response due to pleural effusion/collapsed left lung; the patient progressed based on several new non-target lesions at Week 13.

Change in Tumor Volume Over Time

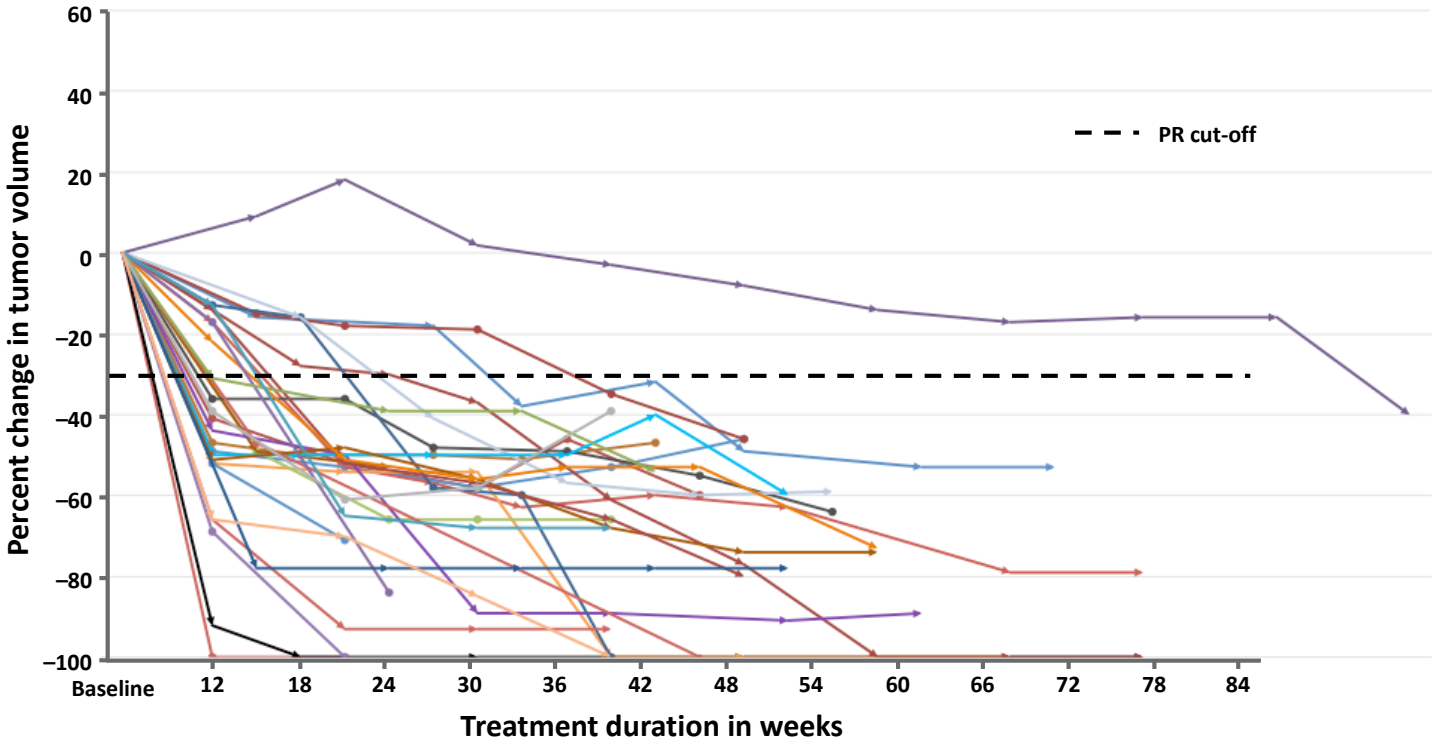
Early Partial and Complete Responses at 12 Weeks



PR, partial response.

Change in Tumor Volume Over Time

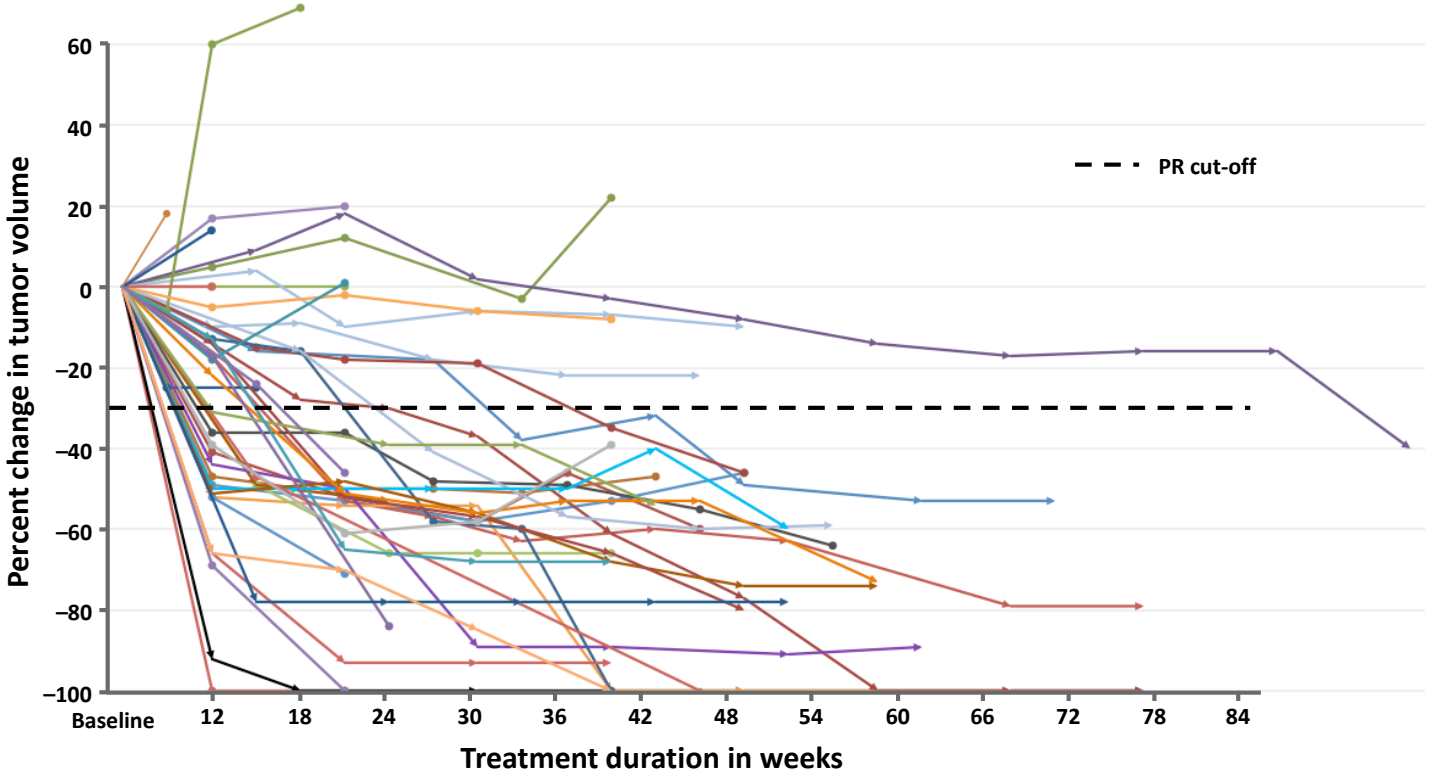
Delayed Responses Observed in Some Patients



PR, partial response.

Change in Tumor Volume Over Time

Extended Clinical Benefit



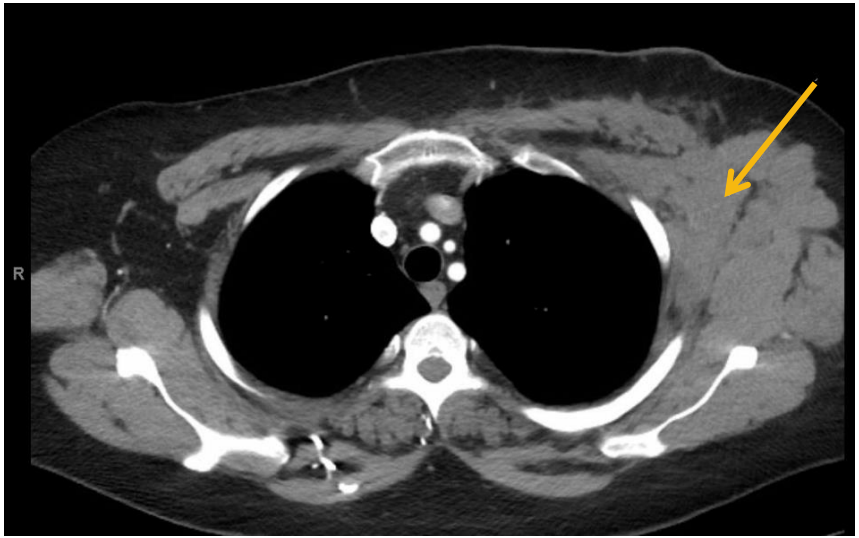
PR, partial response.

Dramatic Responses in Advanced Melanoma

Indoximod Plus Pembrolizumab

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care

Before treatment
(October 2015)



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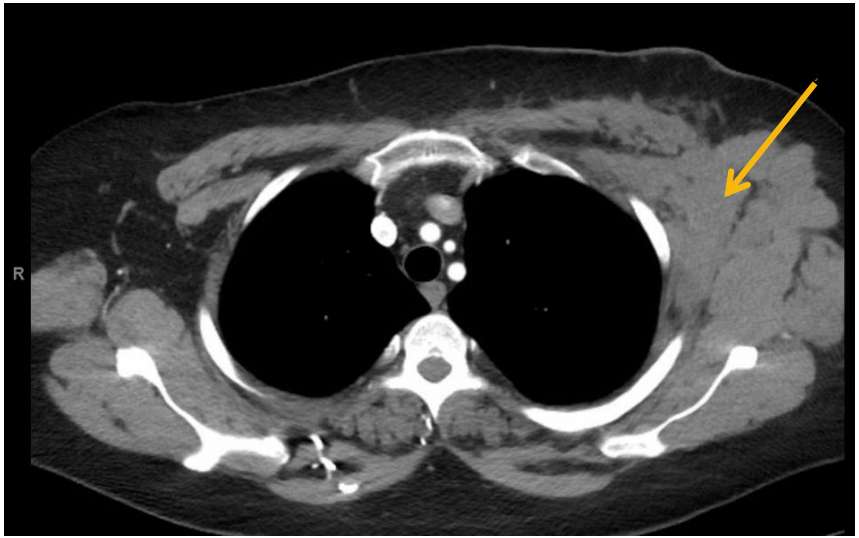
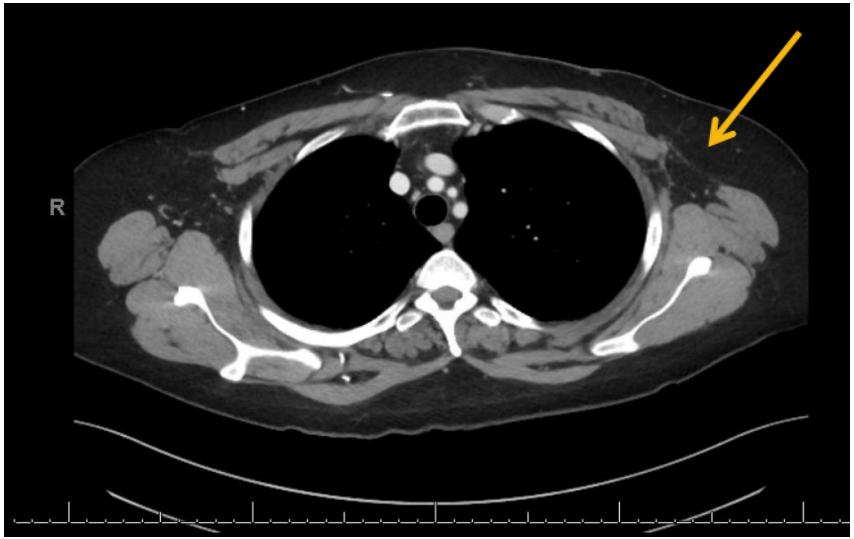
(October 2015)



After treatment
(September 2017)



Progression-Free Survival in Advanced Melanoma

Improvement on Current Standard of Care

	All patients (n = 51)
Kaplan Meier PFS (months)	12.9
6-month PFS rate	71%
12-month PFS rate	56%

PFS, progression-free survival.

Most Commonly Observed Adverse Events*

Generally Well Tolerated With Limited Grade 3 and 1 Grade 4† Adverse Event

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University of Iowa Health Care

AE, n (%)‡ n = 60§	Any grade	Grade ≤2	Grade 3
Fatigue	36 (60)	35 (58)	1 (2)
Headache	20 (33)	20 (33)	0 (0)
Nausea	19 (32)	19 (32)	0 (0)
Arthralgia	17 (28)	17 (28)	0 (0)
Diarrhea	17 (28)	16 (26)	1 (2)
Pruritus	16 (26)	16 (26)	0 (0)
Rash	14 (24)	13 (22)	1 (2)
Cough	13 (22)	13 (22)	0 (0)
Anemia	10 (17)	10 (17)	0 (0)
Constipation	10 (17)	10 (17)	0 (0)
Vomiting	10 (17)	9 (15)	1 (2)
Dec. Appetite	10 (17)	9 (15)	1 (2)

AE, n (%)‡ n = 60§	Any grade	Grade ≤2	Grade 3
Hyperglycemia	10 (17)	9 (15)	1 (2)
Dizziness	10 (17)	9 (15)	1 (2)
Insomnia	9 (15)	9 (15)	0 (0)
Dyspnoea	7 (12)	7 (12)	0 (0)
Hypertension	7 (12)	6 (10)	1 (2)
Back Pain	6 (10)	5 (8)	1 (2)
Pain in Extremity	6 (10)	5 (8)	1 (2)
Weight Loss	5 (8)	4 (7)	1 (2)
Hypocalcaemia	4 (7)	3 (5)	1 (2)
Fall	4 (7)	3 (5)	1 (2)
Hypophosphataemia	3 (5)	1 (2)	2 (3)

AE, adverse event.

*Regimen consists of full single-agent dose for each agent. †One Grade 4 pulmonary embolism not attributed to indoximod occurred.

‡Occurring in ≥10% of patients or any Grade 3/4, regardless of attribution. §Safety data from 9 uveal melanoma patients included.

Serious Adverse Events

Possible Attribution to Indoximod

- SAEs possibly related to indoximod were reported in 4 patients
  - Grade 3: arthritis, gastritis, hearing impairment
  - Grade 2: interstitial nephritis
- SAEs (arthritis, hearing impairment, rash) led to discontinuation in 3 patients
- No treatment-related deaths were reported

SAE, serious adverse event.

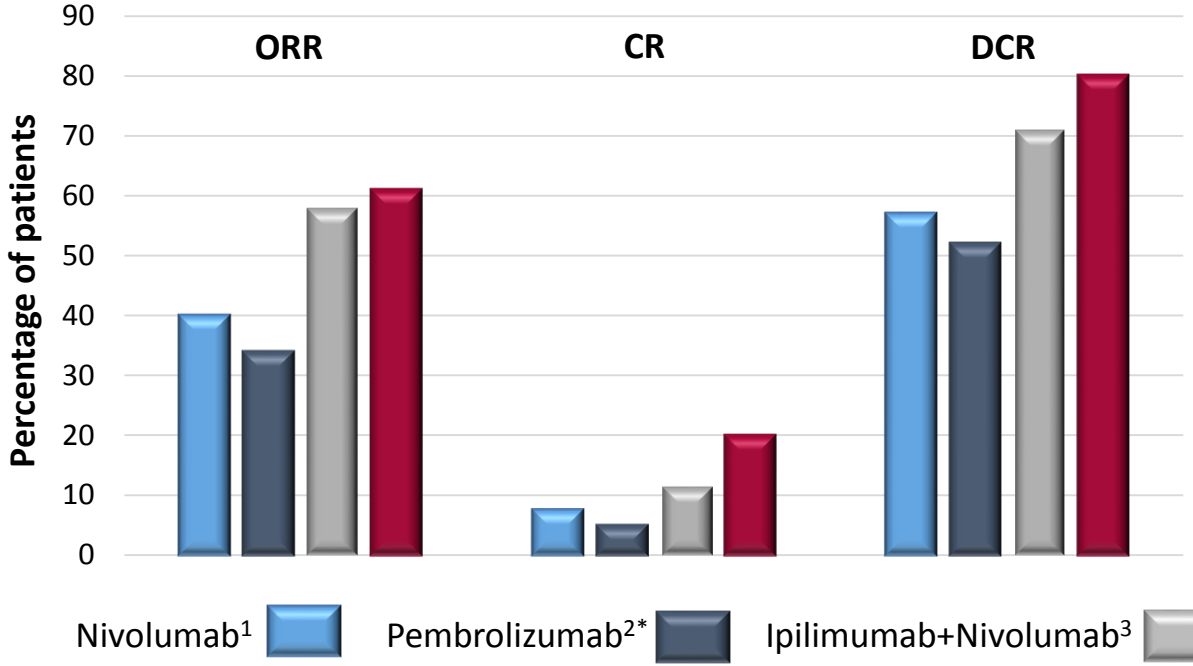
Summary

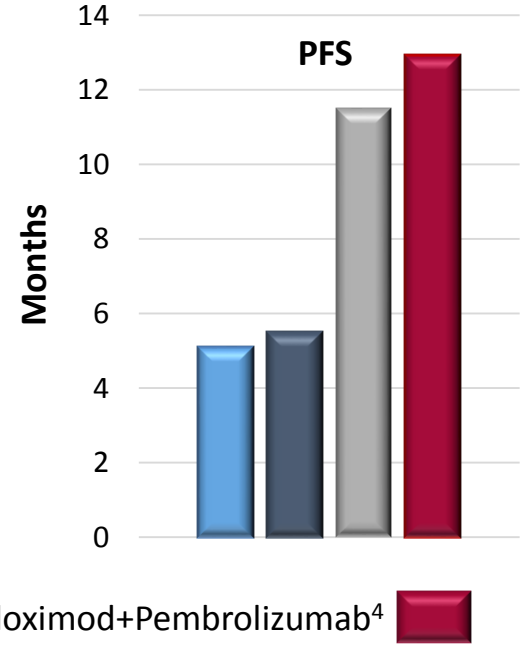
- Indoximod inhibits the IDO pathway, a key immuno-oncology target
- The combination of indoximod plus pembrolizumab demonstrated an ORR of 61%, a CR rate of 20%, and a DCR of 80% in melanoma patients
- PFS was 12.9 months, and the rate of 12-month PFS was 56% with indoximod plus pembrolizumab
- The combination of indoximod plus pembrolizumab was generally well tolerated and comparable to reported data for pembrolizumab alone

IDO, indoleamine 2,3-dioxygenase; ORR, objective response rate; CR, complete response; DCR, disease control rate; PFS, progression-free survival.

Indoximod Plus PD-1 Response and Survival in Advanced Melanoma

Potential to Improve Outcomes Without Added Toxicity of Ipilimumab + Nivolumab





Nivolumab[1] Pembrolizumab[2*] Ipilimumab+Nivolumab[3] Indoximod+Pembrolizumab[4]

[*]Data are for Q2W regimen.

PD-1, programmed cell death protein 1; ORR, objective response rate; CR, complete response; DCR, disease control rate; PFS, progression-free survival.

[1]Robert C, et al. *N Engl J Med*. 2015;372(4): 320-330. [2]Robert C, et al. *N Engl J Med*. 2015;372(26): 2521-2532. [3]Larkin J, et al. *N Engl J Med*. 2015;373(1):23-34.

[4]Zakharia Y. Oral presentation at: International Cancer Immunotherapy Conference, September 6-9, 2017; Frankfurt, Germany.

IDO Inhibitors in Clinical Development

Multiple Ongoing Clinical Studies

Agent	Phase	Clinical trials
Epacadostat	3	• Phase 3 epacadostat + pembrolizumab for melanoma (ECHO-301) • Phase 2 combination studies for advanced tumors
Indoximod	2	• Phase 2 indoximod + checkpoint inhibitors for melanoma (NLG2103) • Phase 2 combination studies for advanced tumors
BMS-986205	1/2	• Phase 1/2 combination studies in advanced tumors
Navoximod (GDC-0919)	1	• Phase 1 navoximod for solid tumors • Phase 1 navoximod + atezolizumab
Indoximod prodrug (NLG802)	1	• Phase 1 NLG802 for solid tumors
KHK2455	1	• Phase 1 KHK2455 ± mogamulizumab (anti-CCR4) for solid tumors
PF-06840003	1	• Phase 1 PF-06840003 for malignant gliomas

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IDO, indoleamine 2,3-dioxygenase; CCR4, CC chemokine receptor 4.

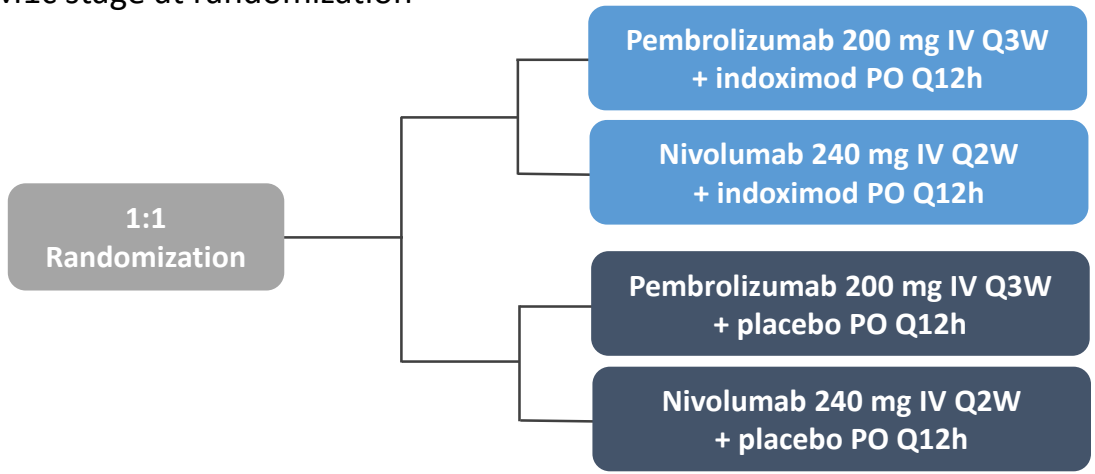
Indoximod Plus PD-1 Inhibitors

Phase 3 Pivotal Study Design

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care

Two-arm, randomized, double-blind, placebo-controlled, fixed-dose study

- Randomization stratified by:
  - Choice of checkpoint inhibitor (pembrolizumab or nivolumab)
  - BRAF status (positive/negative)
  - M1c stage at randomization



Study powered to support the co-primary endpoints:

- PFS
- OS

PD-1, programmed cell death protein 1; BRAF, B-Raf proto-oncogene, serine-threonine kinase; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks; PO, orally; Q12h, every 12 hours; PFS, progression-free survival; OS, overall survival.

Acknowledgments

- The patients and their families
- Investigators and collaborators:
  - David Munn
  - Mohammed Milhem
  - Olivier Rixe
  - Samir Khleif
  - Robert McWilliams
  - Montaser Shaheen
  - Joseph Drabick
  - Kenneth Grossmann
- Members of clinical trial teams
- NewLink Genetics for their support of this study