

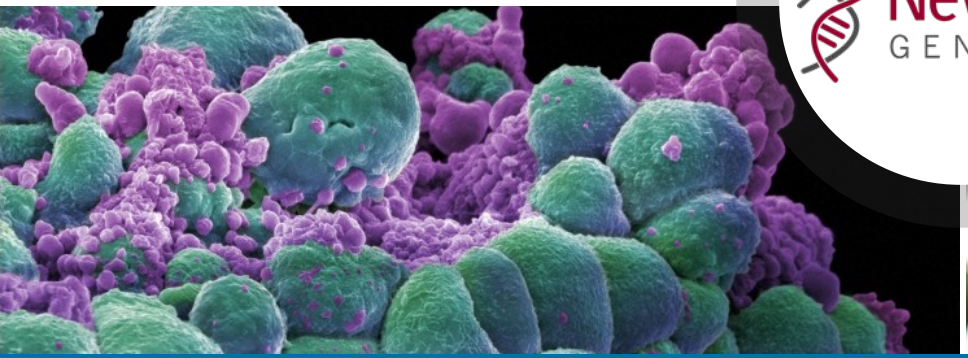


NewLink Genetics Corporation

Interim Analysis of the Phase 2 Clinical Trial of the IDO Pathway Inhibitor Indoximod in Combination With Pembrolizumab for Patients With Advanced Melanoma

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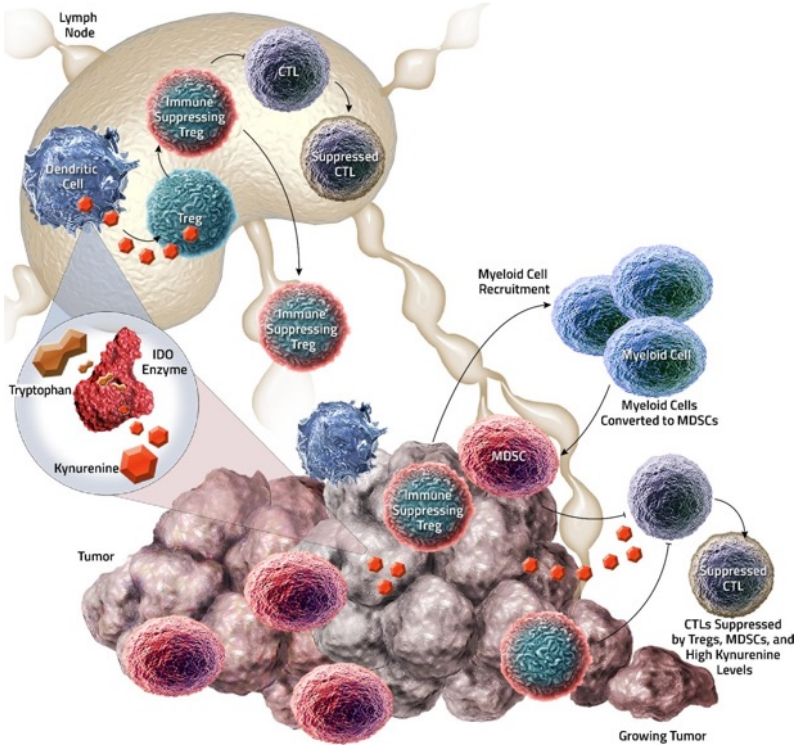
IDO Pathway and Cancer

Key Immuno-Oncology Target

- 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.

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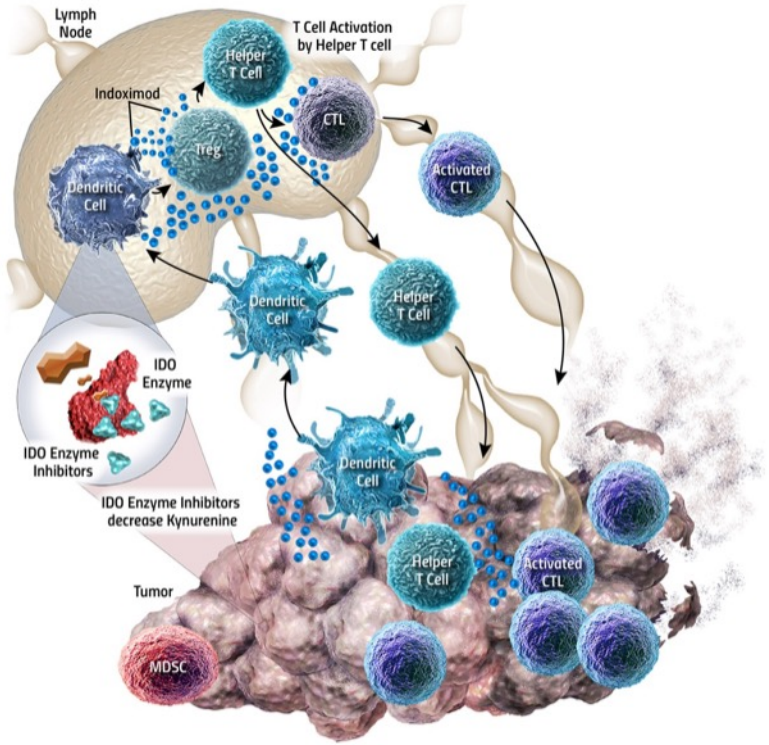
Targeting the IDO Pathway

Two Distinct Strategies for Inhibiting the IDO Pathway

- GDC-0919 and epacadostat
  - Direct IDO enzymatic inhibitors, block tryptophan metabolism[1,2]
- Indoximod
  - Acts directly on immune cells to reverse IDO pathway–mediated suppression
- Available data indicate similar activity with both approaches[3]



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]Mautino M. AACR 2013. Abstract 5023.

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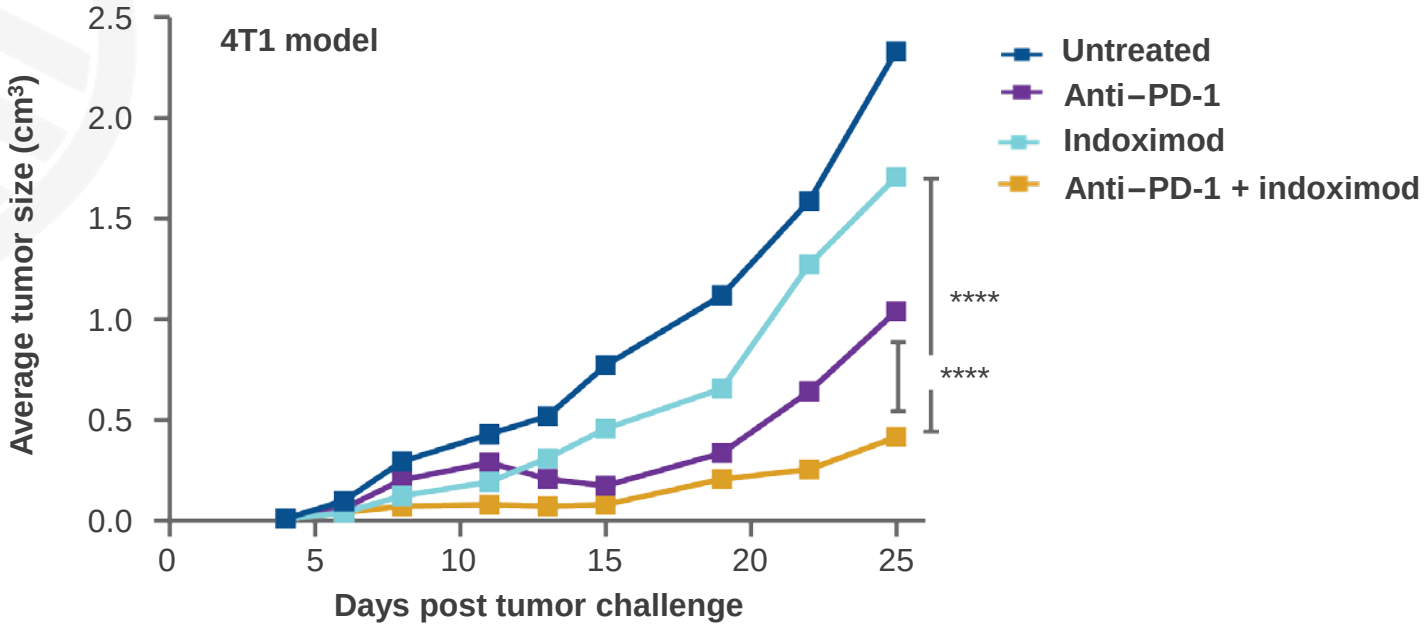
Indoximod Plus Anti–PD-1

Synergistic Activity in Preclinical Model



These data provide the scientific basis for the current trial design

PD-1, programmed cell death 1.

Holmgaard RB. January 13, 2014.

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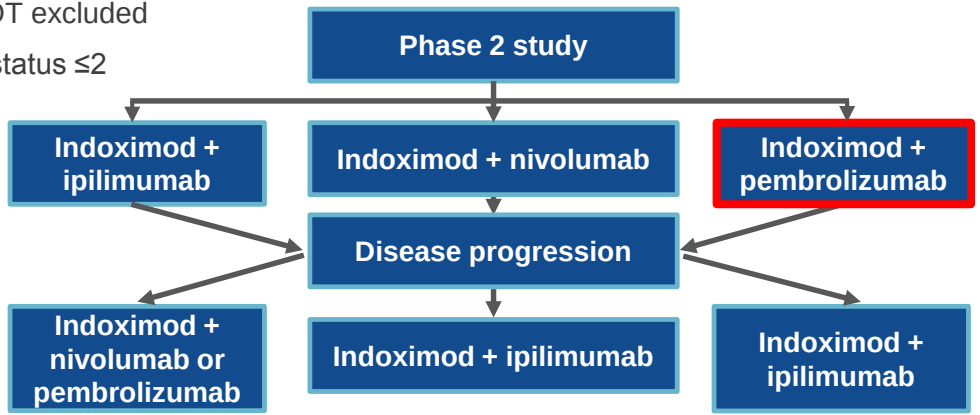
NLG2103 Study Design

Phase 2: Indoximod Plus Checkpoint Inhibitors in 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
  - Ocular melanoma NOT excluded
  - 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.

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Phase 2 Interim Analysis Cohort

Indoximod Plus Pembrolizumab in 60 Evaluable Patients With Advanced Melanoma

- Indoximod 1200 mg PO BID + pembrolizumab 2 mg/kg IV q3w
- 102 patients enrolled as of March 2017
  - 94 patients received pembrolizumab
  - 8 patients received nivolumab or ipilimumab
- 60 of 94 evaluable patients (≥1 on-treatment image at data cut-off, January 2017)

PO, orally; BID, twice a day; IV, intravenously; q3w, every 3 weeks; q8w, every 8 weeks.

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Baseline Demographic and Clinical Characteristics

Characteristic	Indoximod + Pembrolizumab (n = 60)
Median age (range), y	62.3 (27-88)
Male, n (%)	40 (67)
Race/ethnicity, n (%)*	
White, non-Hispanic	59 (98)
LDH above ULN, n (%)	15 (25)
Disease stage, n (%)	
III	8 (13)
IV	52 (87)
M1a	9 (15)
M1b	13 (22)
M1c	30 (50)

Characteristic	Indoximod + Pembrolizumab (n = 60)
ECOG PS, n (%)	
0	44 (73)
1	16 (27)
Primary site, n (%)	
Cutaneous	40 (67)
Ocular	9 (15)
Non-ocular†	11 (18)
Prior therapy, n (%)	
Radiation	13 (22)
Systemic therapy	15 (25)
None	32 (53)

*One patient declined to answer.
†Includes mucosal, primary of unknown origin, and primary location not reported.
LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group performance status.
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Phase 2 Interim Results

Indoximod Plus Pembrolizumab Response Rates*

n (%)	All patients (n = 60)	Cutaneous/non-ocular† (n = 51)
ORR	**31 (52)**	**30 (59)**
CR	6 (10)	6 (12)
PR	25 (42)	24 (47)
SD	13 (22)	11 (22)
DCR	**44 (73)**	**41 (80)**
PD	16 (27)	10 (20)

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

†Includes mucosal, primary of unknown origin, and primary location not reported.

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

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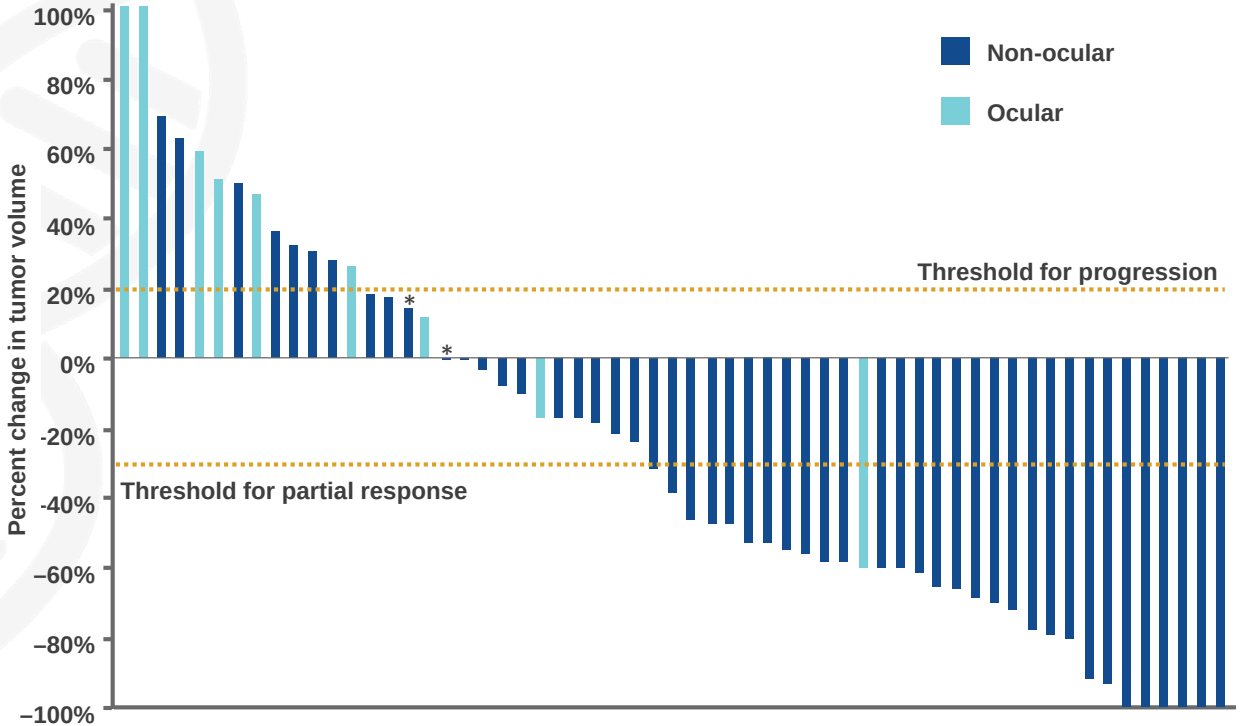
Best Response by Patient

Distinct Difference in Non-ocular Versus Ocular Patients



*Stable disease of primary lesion; new non-target lesions classified patients as progressive disease.

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.

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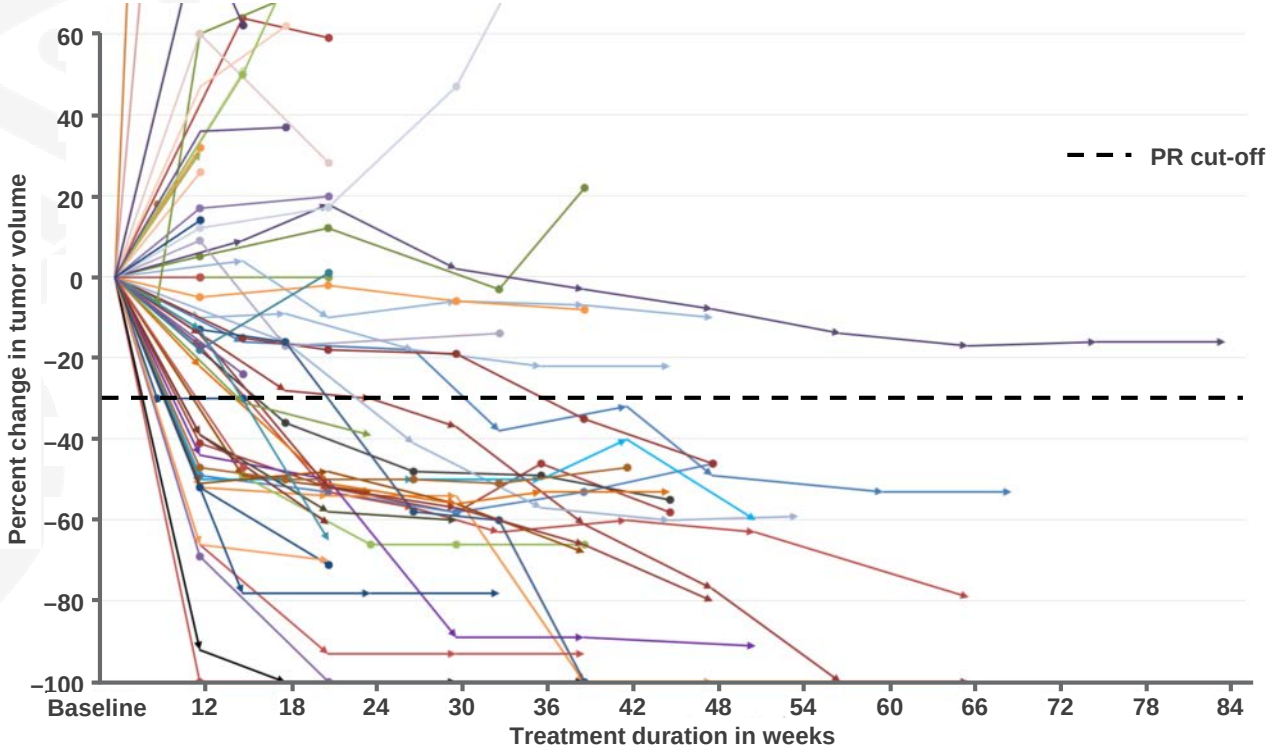
Change in Tumor Volume Over Time

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.

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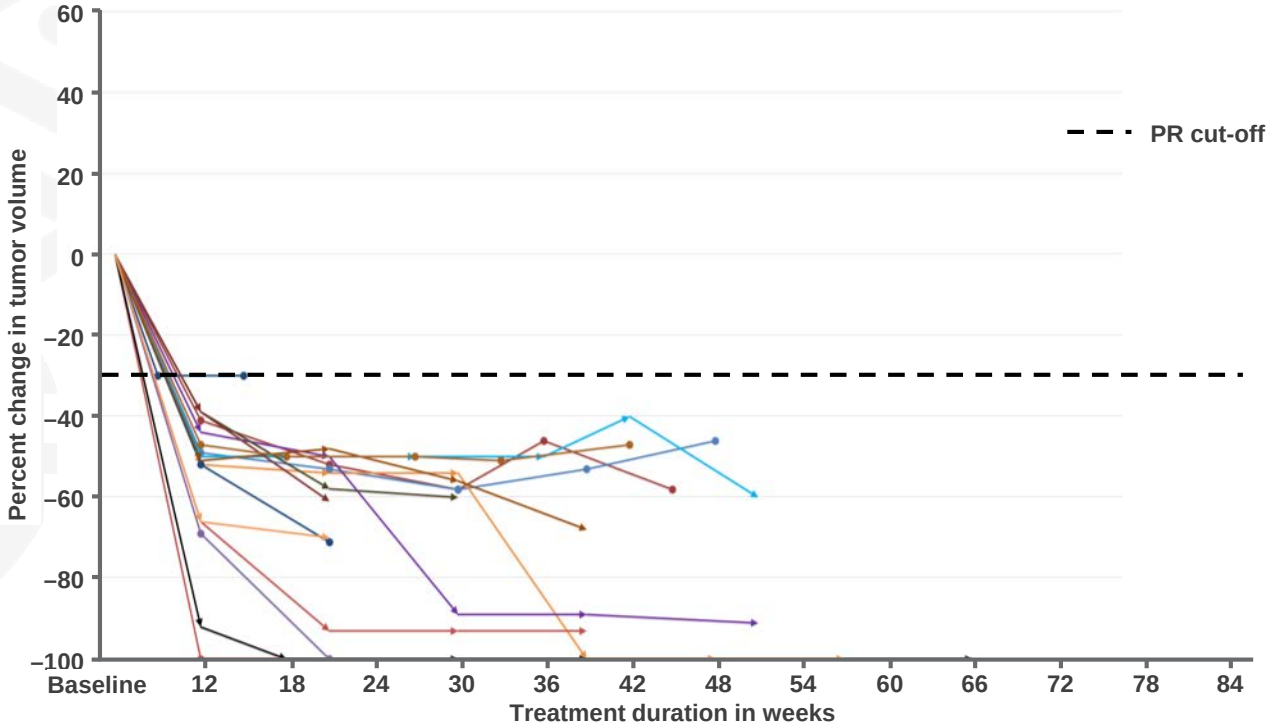
Change in Tumor Volume Over Time

Early Partial and Complete Response at 12 Weeks



PR, partial response.

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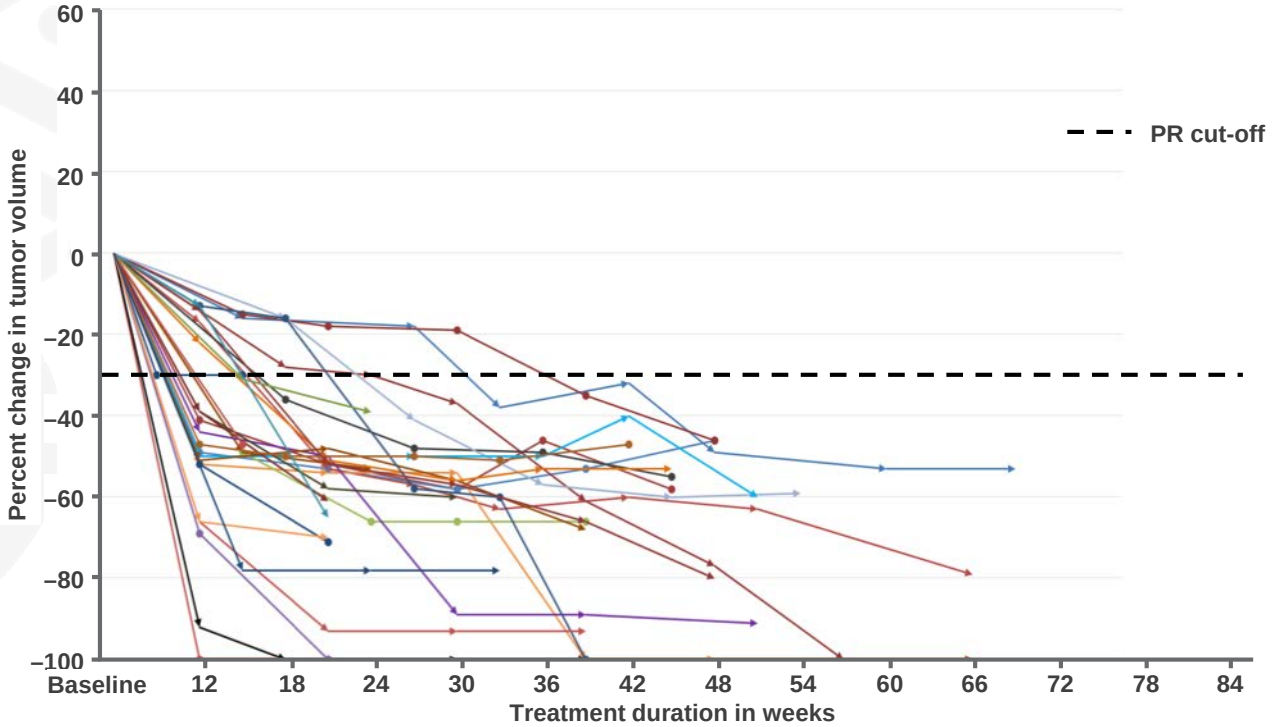
Change in Tumor Volume Over Time

Delayed Responses Observed in some Patients



PR, partial response.

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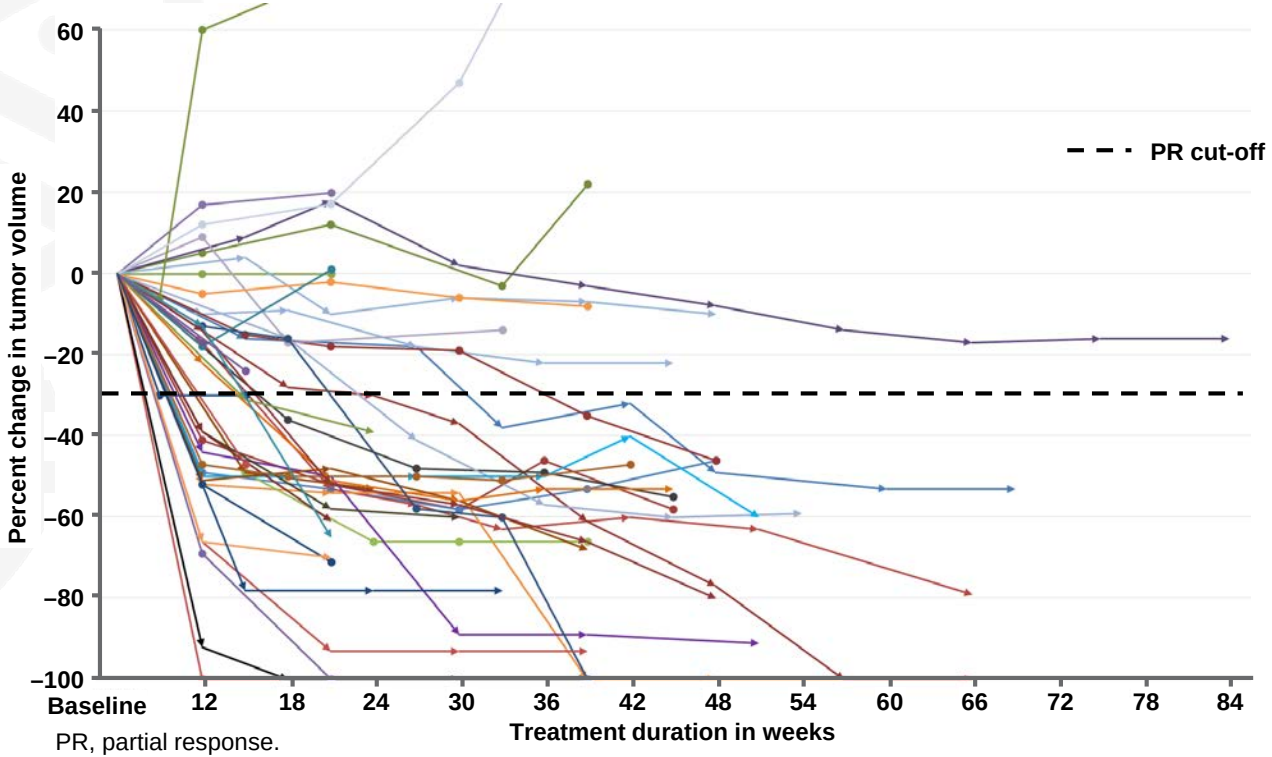
Change in Tumor Volume Over Time

Extended Clinical Benefit



PR, partial response.

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Most Commonly Observed Adverse Events*

Combination Therapy Generally Well Tolerated

	Indoximod + pembrolizumab (n = 60)		
AE, n (%)*	**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 (23)	13 (21)	1 (2)
Cough	13 (21)	13 (21)	0 (0)

AE, adverse event.
*Occurring in ≥20% of patients, regardless of attribution.
†No grade 4 or grade 5 events were reported.
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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.

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Immune-mediated Adverse Events
Regardless of Attribution to Indoximod

- Limited immune-mediated AEs reported
  - Relevant reported AEs included dermatitis (n = 2), hypothyroidism (n = 2), pneumonitis (n = 2), colitis (n = 1), gastritis (n = 1), nephritis (n = 1)
- Elevated lab values reported in 12 patients (3 patients had >1 lab value elevated)
  - Alanine aminotransferase (n = 2), amylase (n = 1), aspartate aminotransferase (n = 2), alkaline phosphatase (n = 4), creatinine (n = 4), lipase (n = 2)

AE, adverse event.

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Summary

Indoximod Plus Pembrolizumab in Advanced Melanoma

- Indoximod inhibits the IDO pathway, a key immuno-oncology target
- The ORR for the entire study cohort was 52%
- The combination of indoximod plus pembrolizumab demonstrated an ORR of 59% and a DCR of 80% in patients with cutaneous and non-ocular advanced melanoma
- The combination of indoximod plus pembrolizumab was generally well tolerated and comparable to reported data for pembrolizumab alone
- Indoximod is being evaluated in combination studies across multiple solid tumors and hematologic malignancies
- These data support phase 3 development of indoximod plus pembrolizumab for the treatment of advanced melanoma

IDO, indoleamine 2,3-dioxygenase; ORR, objective response rate; DCR, disease control rate.

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