Anti-PD1 and Epacadostat vs IDO Inhibition: Lessons Learned

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NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

UPMC LIFE CHANGING MEDICINE

Disclosures past 3 years

- Updated disclosures available at: https://www.linkedin.com/in/jason-luke-11a38910/
- DSMB: Abbvie, Agenus, Amgen, Immutep, Evaxion
- Scientific Advisory Board: (no stock) 7 Hills, Affivant, Bright Peak, Exo, Fstar, Inzen, RefleXion, Xilio (stock) Actym, Alphamab Oncology, Arch Oncology, Duke Street Bio, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, physIQ, Pyxis, Saros, STipe, Tempest
- Consultancy with compensation: Abbvie, Agenus, Alnylam, Atomwise, Bayer, Bristol-Myers Squibb, Castle, Checkmate, Codiak, Crown, Cugene, Curadev, Day One, Eisai, EMD Serono, Endeavor, Flame, G1 Therapeutics, Genentech, Gilead, Glenmark, HotSpot, Kadmon, KSQ, Janssen, Ikena, Inzen, Immatics, Immunocore, Incyte, Instil, IO Biotech, Macrogenics, Merck, Mersana, Nektar, Novartis, Partner, Pfizer, Pioneering Medicines, PsiOxus, Regeneron, Replimmune, Ribon, Roivant, Servier, STINGthera, Synlogic, Synthekine
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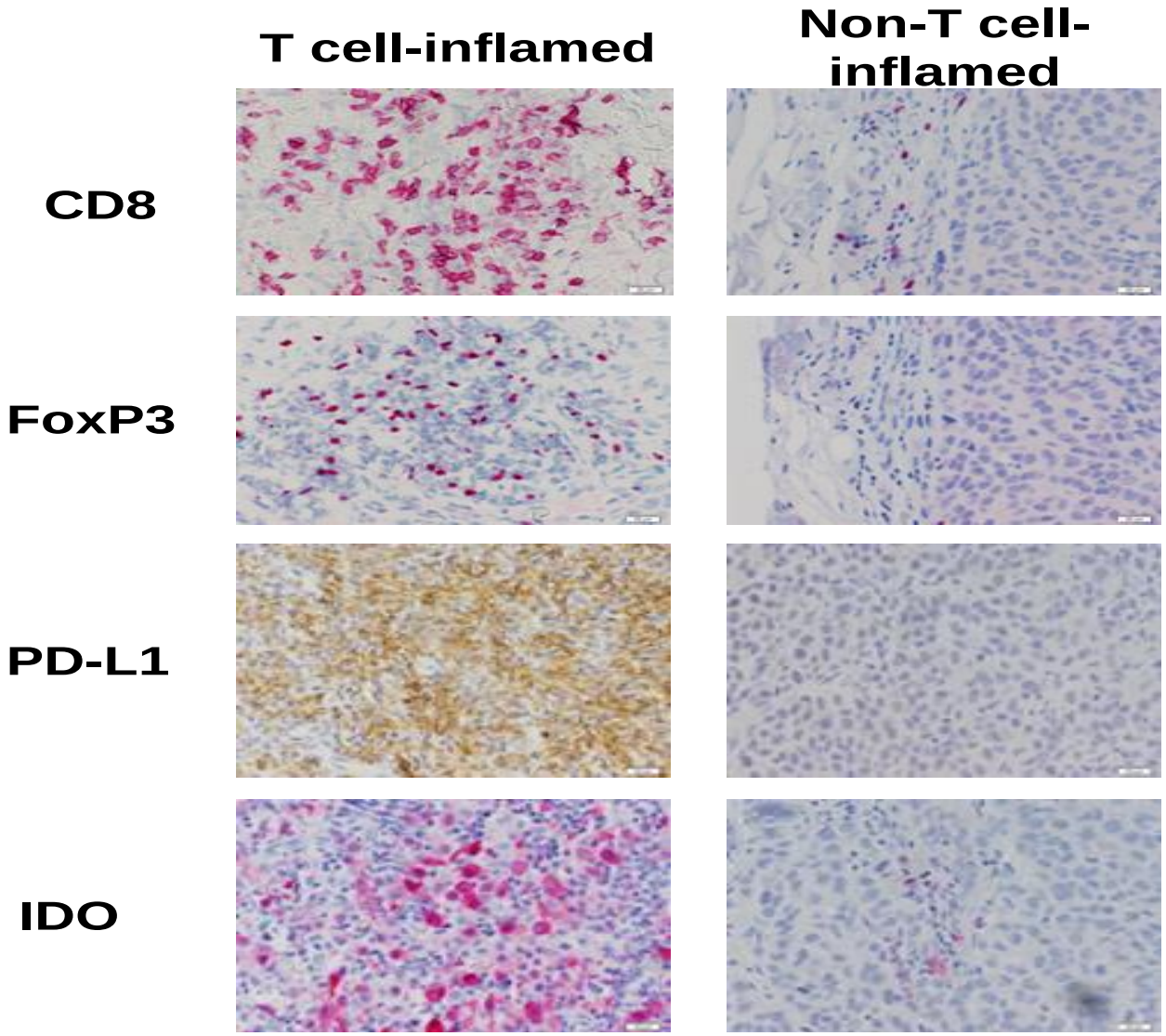
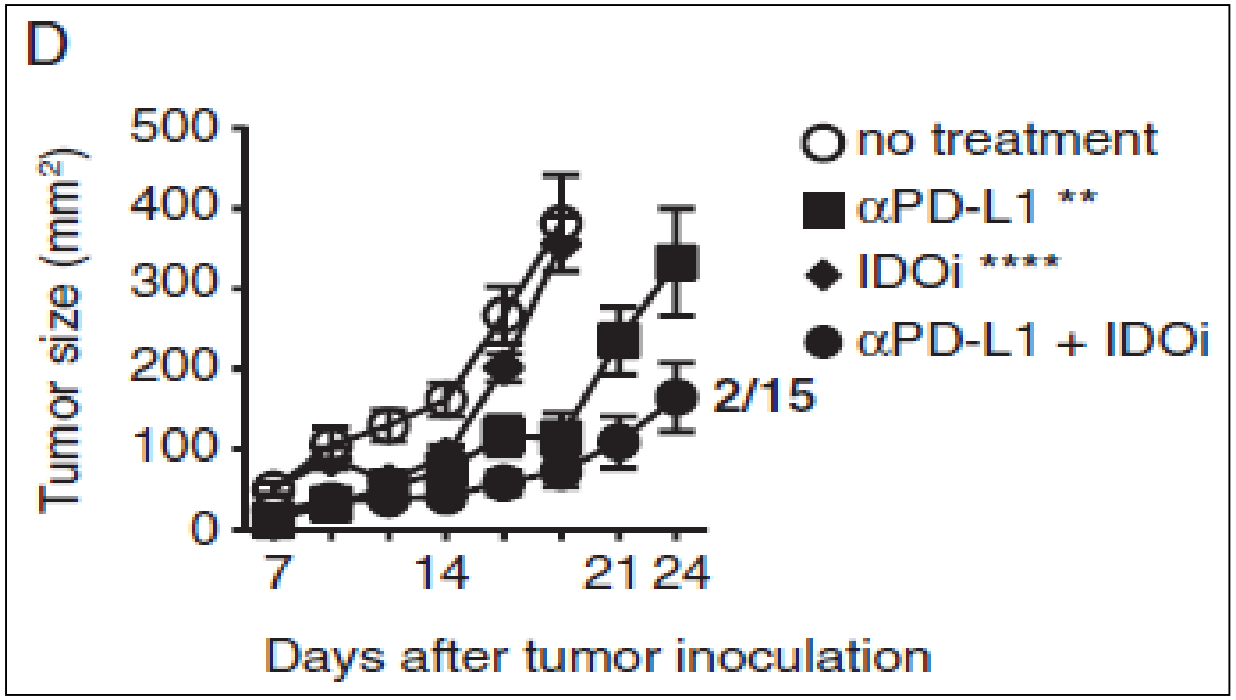
- Patents: (both provisional) Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)

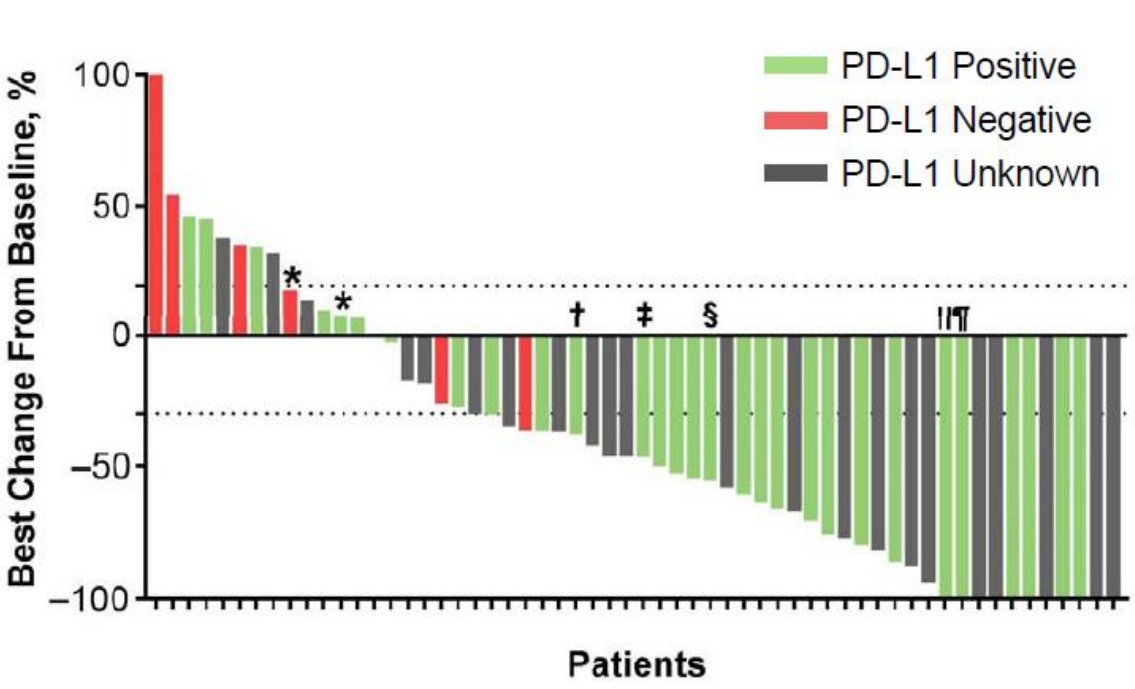
Translational and pre-clinical rationale for anti-PD1/L1 + IDO inhibitor appeared strong

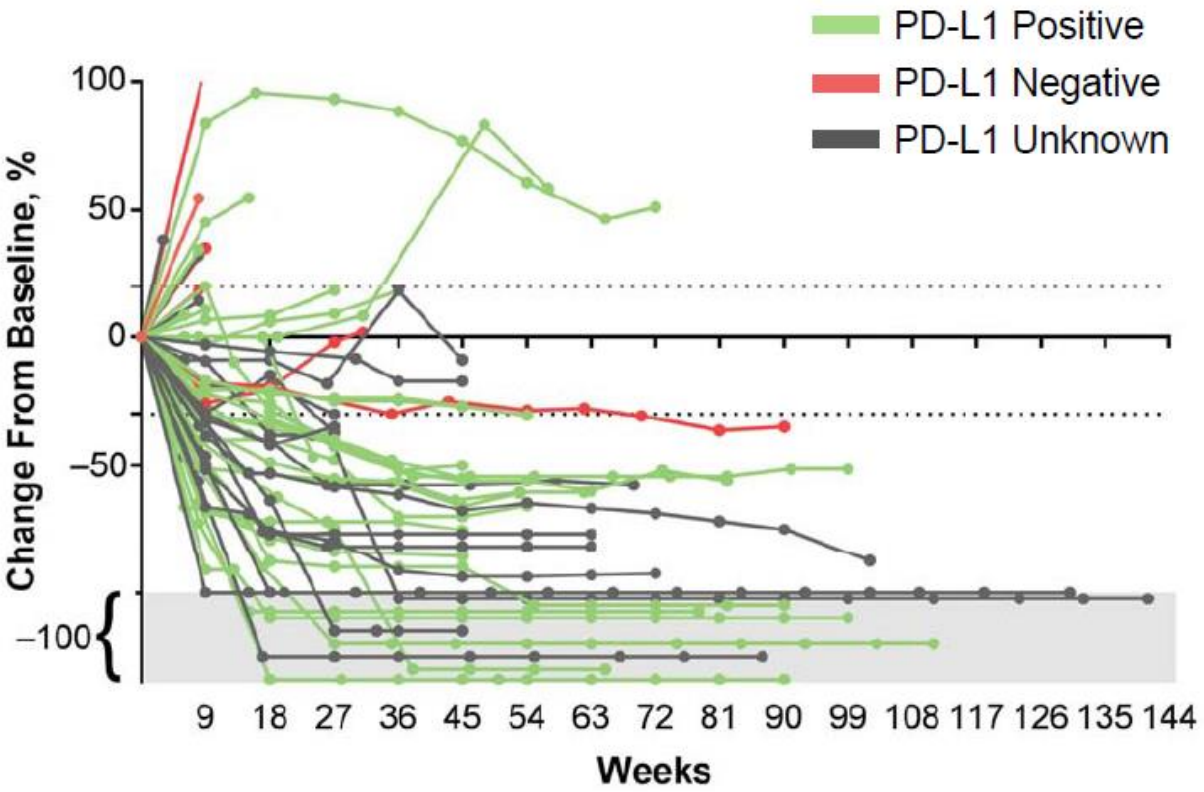




Spranger *et al., Science Trans. Med.* 2013; Spranger *et al. J Immunother*

Phase 2 Epacadostat + Pembrolizumab in Melanoma



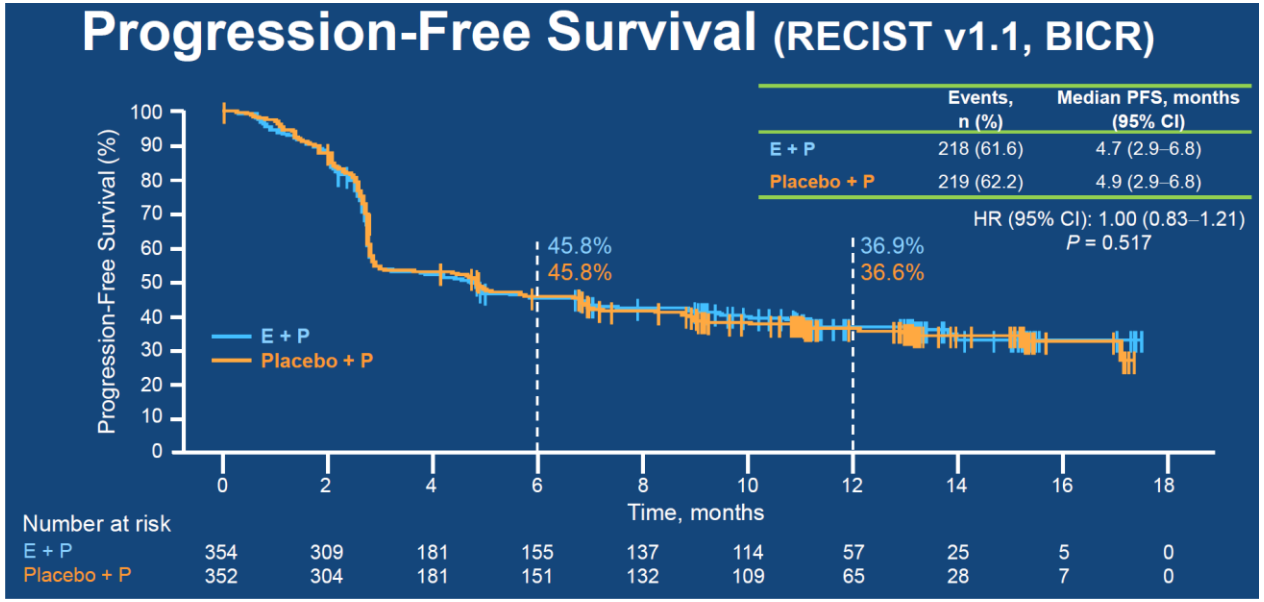


Hamid et al. ESMO 2017

ECHO-301: Pembro vs Pembro+epacadostat

Long et al. ASCO 2018; Lancet Onc. 2019

Progression-Free Survival (RECIST v1.1, BICR)



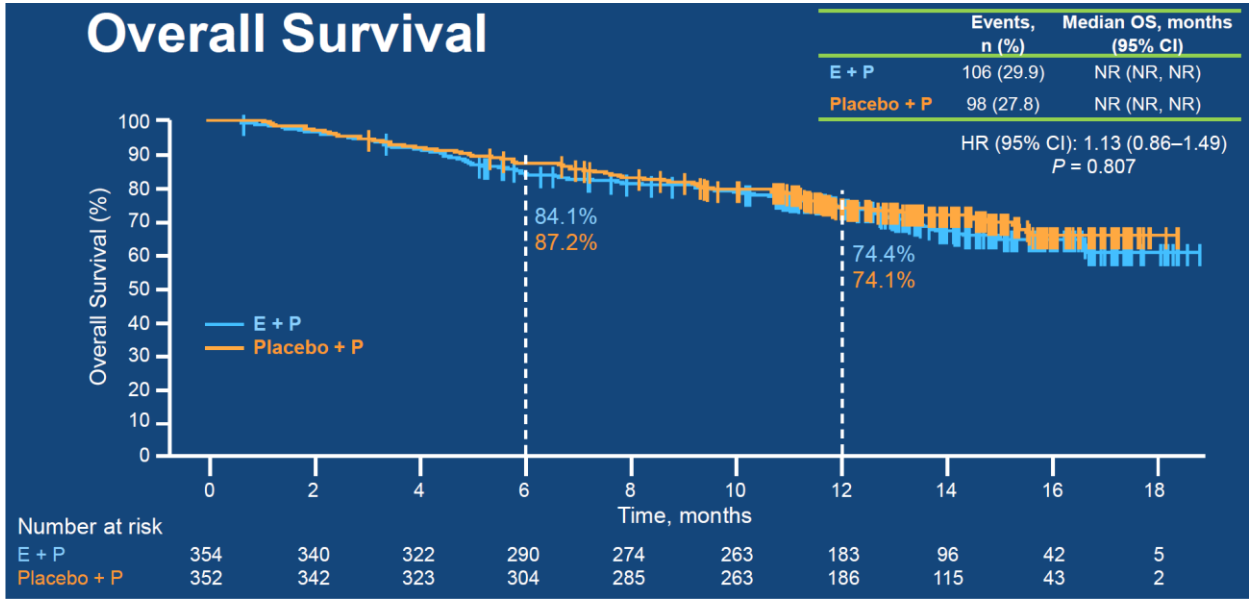
	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517

Number at risk

E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

Overall Survival



	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807

Number at risk

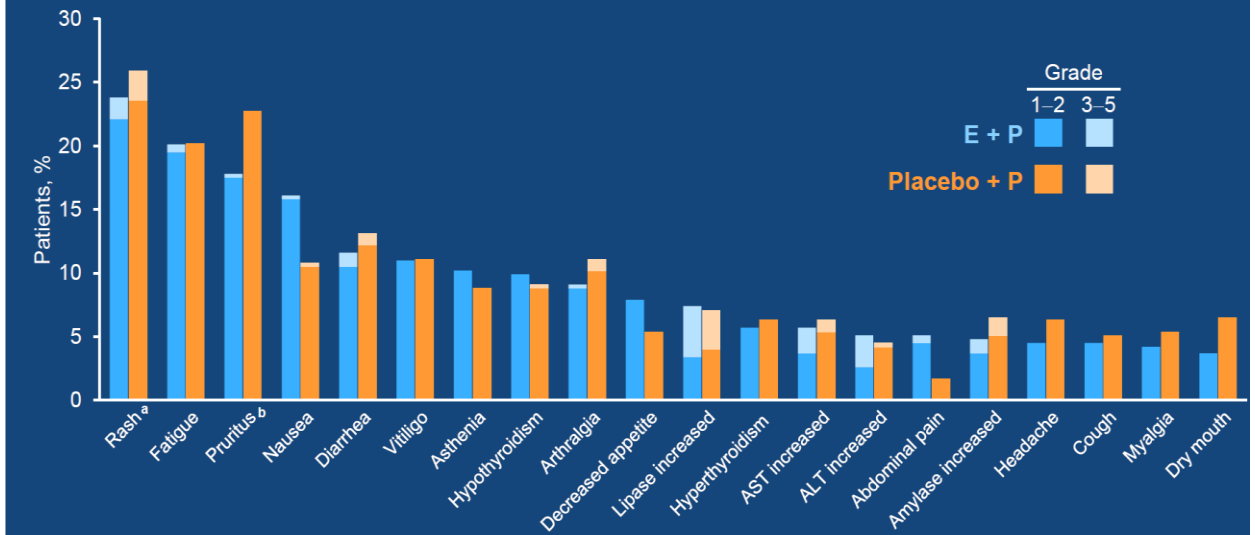
E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

Best Objective Response (RECIST v1.1, BICR)

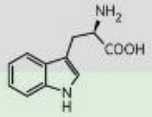
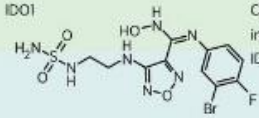
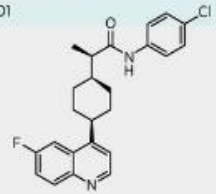
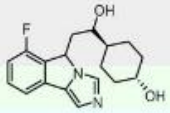
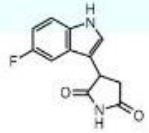
Response, n (%)	Epacadostat + Pembrolizumab (n=354)	Placebo + Pembrolizumab (n=352)
ORR	**121 (34.2)**	**111 (31.5)**
CR	14 (4.0)	15 (4.3)
PR	107 (30.2)	96 (27.3)
SD	59 (16.7)	68 (19.3)
DCR (CR+PR+SD)	180 (50.8)	179 (50.9)
PD	151 (42.7)	150 (42.6)
Non-CR/Non-PD	10 (2.8)	9 (2.6)
Not available or evaluable[a]	13 (3.7)	14 (4.0)
Median DOR (range), months	NR (0.0+ to 14.7+)	NR (0.0+ to 15.0+)

Treatment-Related Adverse Events

≥5% in Any Treatment Group



Trp–Kyn pathway inhibitors (previously…) in development

Drug	Company	Target	Structure	Mechanism	Dosing	Human IDO1 enzymatic assay (IC_{50})	Human IDO1 cell-based assay (IC_{50})	Human TDO enzymatic activity	Phase of development
Indoximod	NewLink	Trypto-phan mimetic		Stimulates mTOR kinase to reduce T-cell autophagy (49)	1200 mg BID (77)		>2.5 mM (HeLa cells) (46) -30 uM (Human DCs)	Nonselective	III
Epacadostat	Incyte	IDO1		Competitive inhibition of IDO1 (46)	100 mg BID (59)	72 nM (46)	7–23 nM (46)	>100-fold (46)	III
BMS986205	Bristol-Meyers Squib	IDO1		Irreversible inhibition of IDO1 (78)	150 mg QD (79)		1 nM (HEK293 cells) 2 nM (IFNγ-stimulated HeLa cells) (44)	>100-fold (44) >2 uM in HEK293 cells	III
Navoximod	NewLink	IDO1		Noncompetitive inhibition of IDO1	50–800 mg BID (80)	28 nM (82)	75 nM (81)	10–20-fold (78)	Ib
PF-06840003	iTeos	IDO1		Noncompetitive inhibition of IDO1 (82)	250–500 mg BID (83)	120 nM (82)	1100 nM (82)	>100-fold (82)	I
KHK2455	Kyowa Hakko Kirin	IDO1	Not available	Competitive inhibition, apo-conformation (84)	1 mg QD (85)		14 nM (84)	>100-fold (84)	I
RG70099	Roche	IDO1/TDO	Not available	Competitive inhibition	Unspecified	16 nM (69)	12 nM (69)	6-fold (69)	Preclinical
IOM-E	Merck	IDO1	Not available	Unknown	Unspecified		100 nM (70)	>100-fold (70)	Preclinical
IOM-D	Merck	IDO1/TDO	Not available	Unknown	Unspecified		365 (70)	10 nM (70)	Preclinical

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Labadie, Bao, Luke. *Clin Cancer Res*. 2019

Why did epacadostat fail?

- **Were the populations between phase I/II and III different?**
- **Lack of monotherapy activity?**
- **Was the dose too low?**
- **Was the potency too low (incomplete KYN suppression in tumor)?**
- **Is IDO1 an inadequate target for therapeutic suppression of the pathway?**

Labadie, Bao, Luke. *Clin Cancer Res*. 2019

Populations from epacadostat phase 2 & 3 trials

Variable	Total (N=65)
Median (range) age, y	65 (28–93)
Men, n (%)	45 (69)
White, n (%)	61 (94)
ECOG PS, n (%)	
0	50 (77)
1	15 (23)
M stage, n (%)	
M0	5 (8)
M1a/b	24 (37)
M1c	36 (55)
Common sites of metastases, n (%)	
Lung	38 (59)
Lymph nodes	34 (52)
Liver	26 (40)
Skin or subcutaneous tissue	18 (28)
CNS	4 (6)
Bone	3 (5)
Pancreas	3 (5)
Other	29 (45)
BRAF status, n (%)	
Positive	19 (29)
Negative	44 (68)
Unknown	2 (3)
Lactate dehydrogenase level, n (%)	
Normal	40 (62)
Elevated	24 (37)
Unknown	1 (2)
Prior radiation treatment, n (%)	12 (19)
Prior systemic therapy,* n (%)	
No therapy	46 (71)
Adjuvant therapy	10 (15)
1 line of therapy for advanced disease	11 (17)
Unknown	1 (2)
PD-L1 expression, n (%)	
Positive (≥1%†)	34 (52)
Negative (<1%)	8 (12)
Unknown	23 (35)

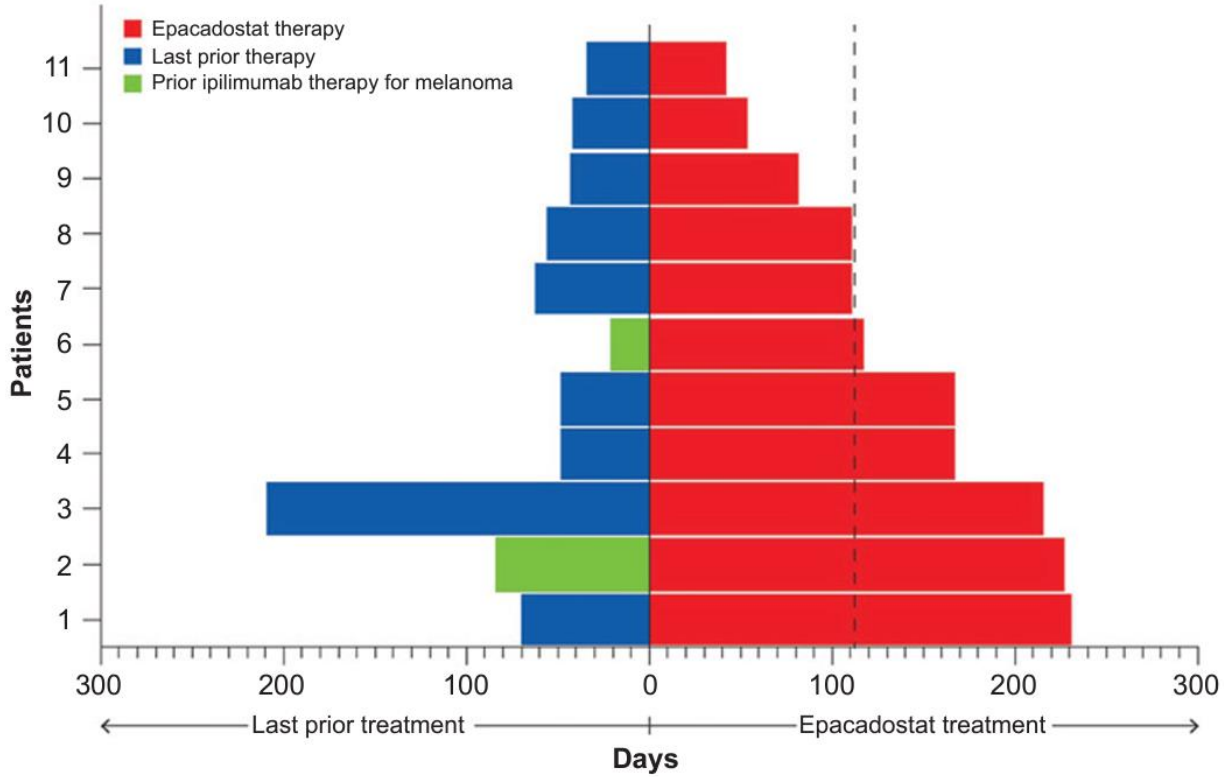
Baseline Characteristics

Patients, n (%)	Epacadostat + Pembrolizumab (n=354)	Placebo + Pembrolizumab (n=352)
Age, median (range), y	64 (20–88)	63 (23–91)
Male	217 (61.3)	206 (58.5)
ECOG PS		
0	261 (73.7)	267 (75.9)
1	93 (26.3)	85 (24.1)
Lactate dehydrogenase >ULN	123 (34.7)	113 (32.1)
>ULN but <2X ULN	99 (28.0)	93 (26.4)
≥2x ULN	24 (6.8)	20 (5.7)
M1c disease	228 (64.4)	214 (60.8)
Treated brain metastasis	19 (5.4)	14 (4.0)
Prior adjuvant/neoadjuvant therapy	34 (9.6)	23 (6.5)
Prior lines of therapy for advanced disease		
1	47 (13.3)	37 (10.5)
≥2	1 (0.3)	5 (1.4)

Hamid et al. ESMO 2017
Long et al. ASCO 2018

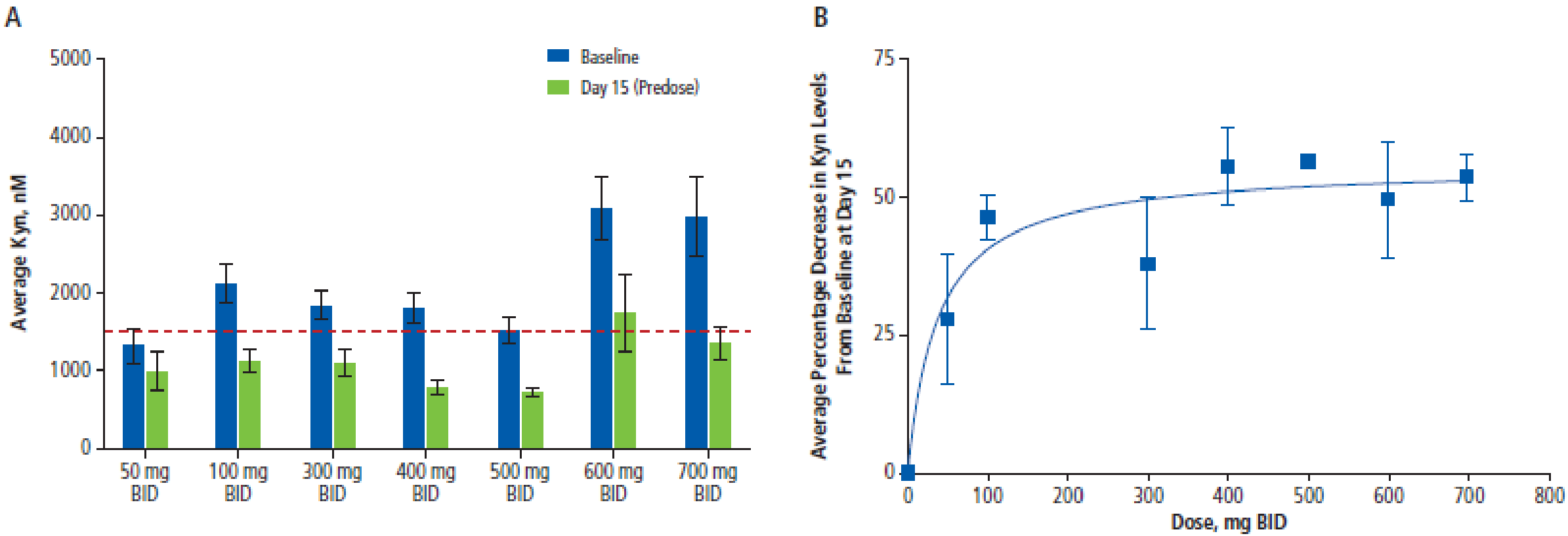
Lack of monotherapy activity?

n (%)	Total (*N* = 52)
Complete response	0
Partial response	0
Stable disease	18 (34.6)
Progressive disease	22 (42.3)
Not evaluable	12 (23.1)



Beatty *et al. Clin Can Res.* 2017

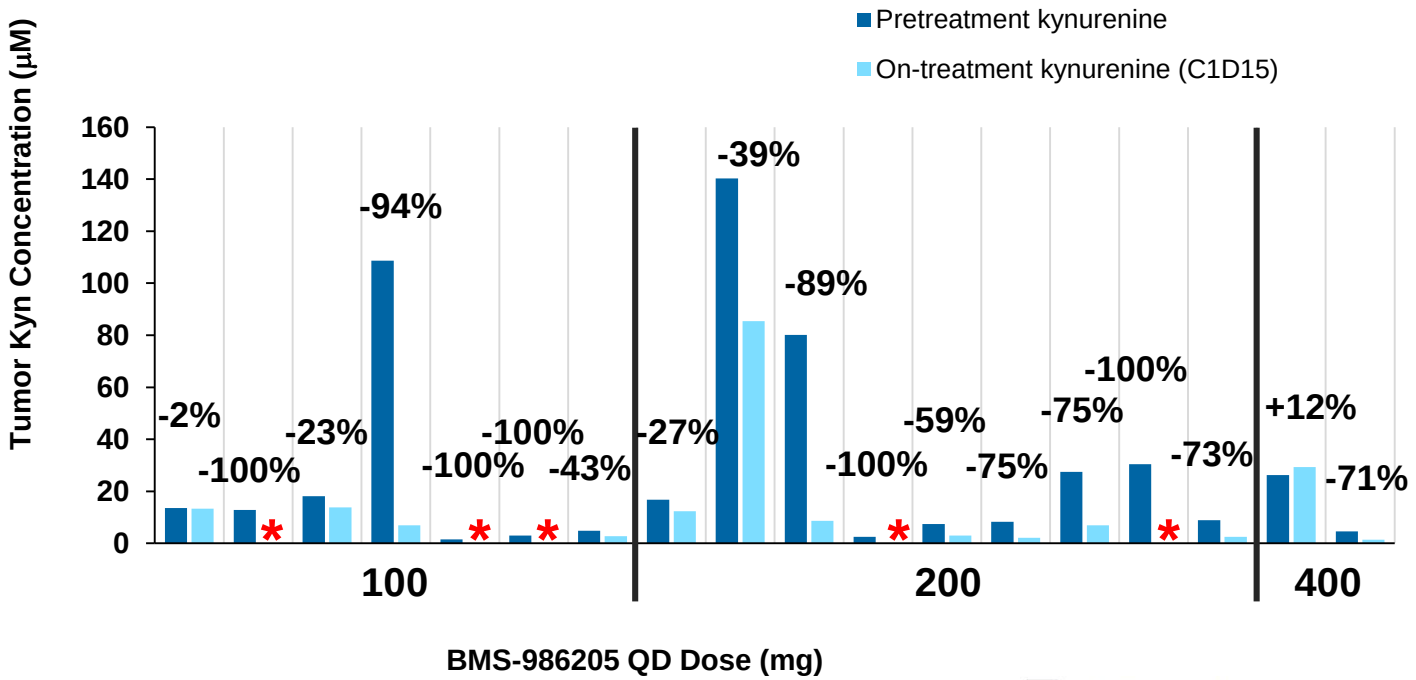
PK:PD studies of epacadostat were inadequate to support a therapeutic association of suppression of tumor kynurenine & response



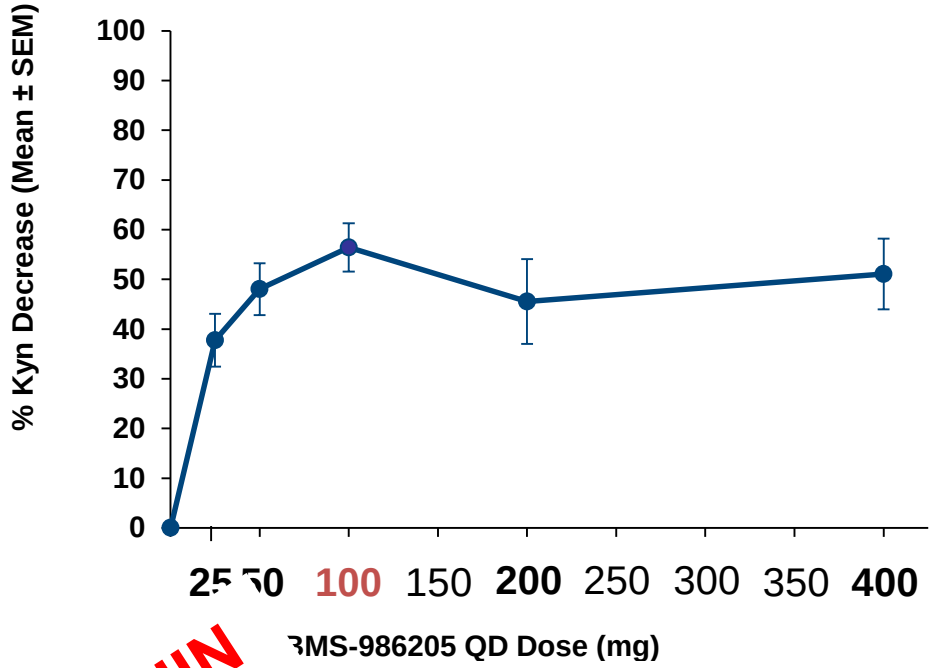
Beatty *et al. Clin Can Res.* 2017

BMS-986205 Plus NIVO Decreased Tumoral and Serum Kyn Levels

Tumoral Kynurenine Concentration



Serum Kynurenine

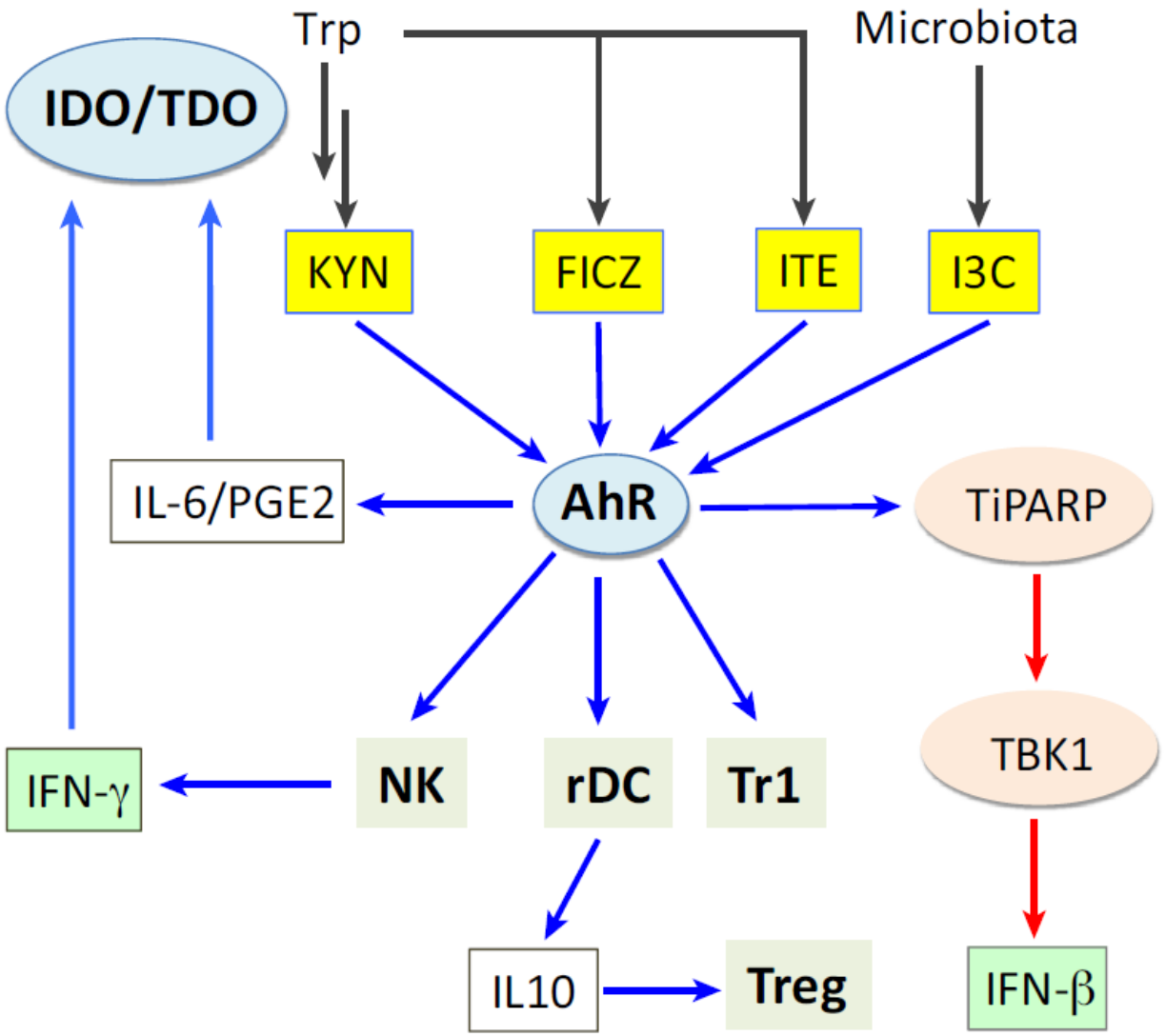


* Denotes samples below the lower limit of quantitation.

Kyn = kynurenine.

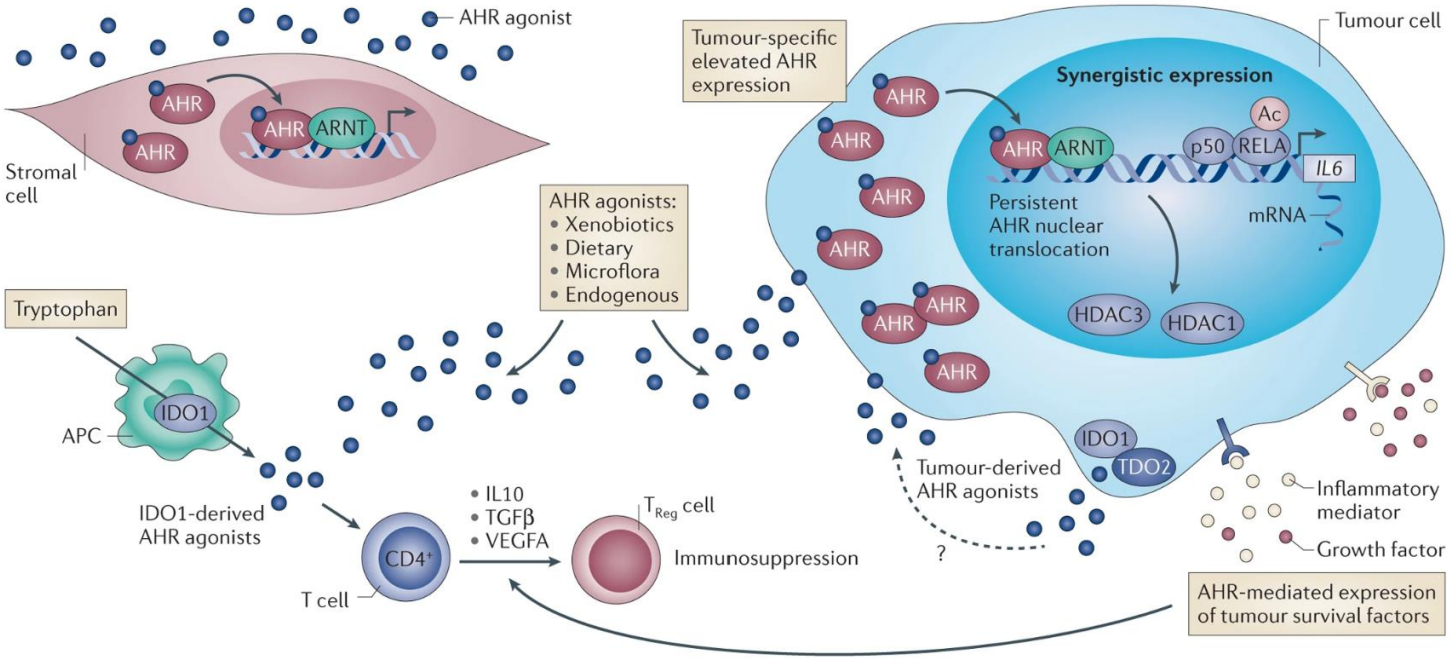
DISCONTINUED WITHIN DAYS OF ECHO-301!!!

Is the Aryl Hydrocarbon Receptor (AHR) the dominate immunoregulatory node?

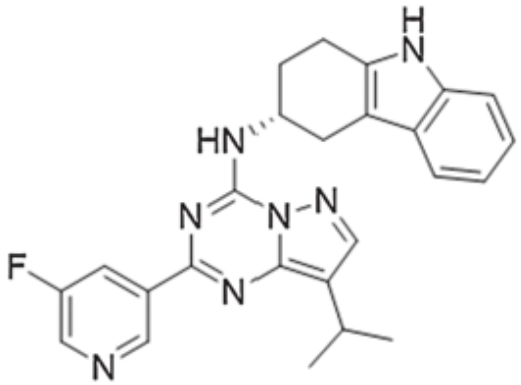


Cheong and Sun. *Trends in Pharm Sci*. 2017

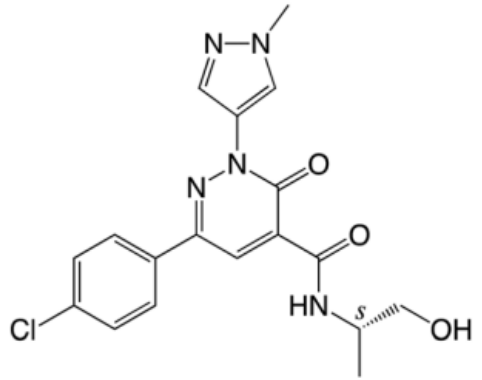
AHR inhibitors in development



IK-175 - Ikena



BAY 2416964 - Bayer



Murray *et al. Nature Reviews Cancer*. 2014
McGovern *et al. Mol Cancer Ther*. 2022
Sanchez-Martin *et al*. SITC. 2021

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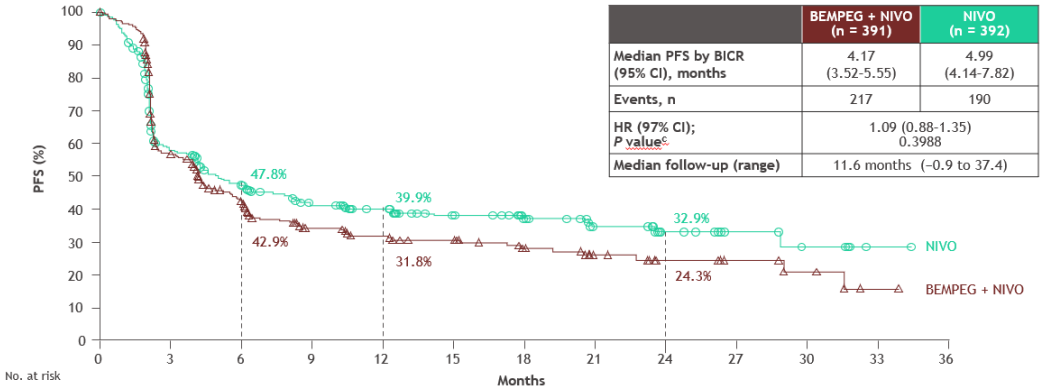
Disciples of the epacadostat school

Bempegaldesleukin (BEMPEG) + NIVO vs NIVO PFS

- There was no significant difference in PFS with the combination of BEMPEG + NIVO and NIVO monotherapy



	BEMPEG + NIVO (n = 391)	NIVO (n = 392)
Median PFS by BICR (95% CI), months	4.17 (3.52-5.55)	4.99 (4.14-7.82)
Events, n	217	190
HR (97% CI); *P* value[c]	1.09 (0.88-1.35) 0.3988	
Median follow-up (range)	11.6 months (~0.9 to 37.4)	

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IDERA PHARMACEUTICALS ANNOUNCES RESULTS FROM ILLUMINATE-301 TRIAL OF TILSOTOLIMOD + IPILIMUMAB IN ANTI-PD-1 REFRACTORY ADVANCED MELANOMA

– Objective Response Rate Endpoint Not Met –

EXTON, Pa., March 18, 2021 (GLOBE NEWSWIRE) -- Idera Pharmaceuticals, Inc. (Nasdaq: IDRA; the "Company") today is announcing that ILLUMINATE-301, the Company's pivotal registration trial of tilsotolimod in combination with ipilimumab versus ipilimumab alone in patients with anti-PD-1 refractory advanced melanoma, did not meet its primary endpoint of objective response rate (ORR). Idera is evaluating its next steps regarding continuation of the trial toward its overall survival (OS) endpoint, which includes evaluating the full data set when it is available. The Company also plans to

Diab *et al.* ESMO. 2022; Idera Press Release 2021

Conclusions

- **IDO1 is an IFN-ɣ linked enzyme that is clearly immuno-suppressive but of unclear therapeutic value**
- **Epacadostat had poor drug properties and no translational data informs the failure of ECHO-301**
- **Me too-ism on display in IDO inhibitor development**
- **IO is not magic and principals of drug development still apply**
  - **Vigorous preclinical testing, PK/PD relationships, Single agent activity, Translational evidence to support proof of concept, Randomization**

Acknowledgements

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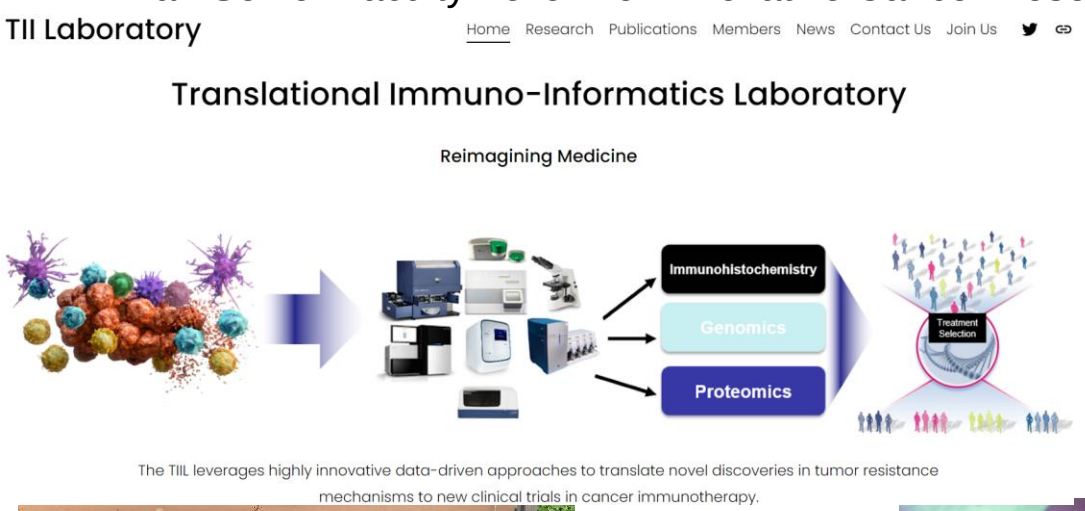
- NIH P50CA254865-01A1
- UPMC Hillman Developmental Award P30CA047904-32
- Sy Holzer Endowed Immunotherapy Research Fund Award
- Hillman Senior Faculty Fellow for Innovative Cancer Research



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