Immuno-Oncology 360°

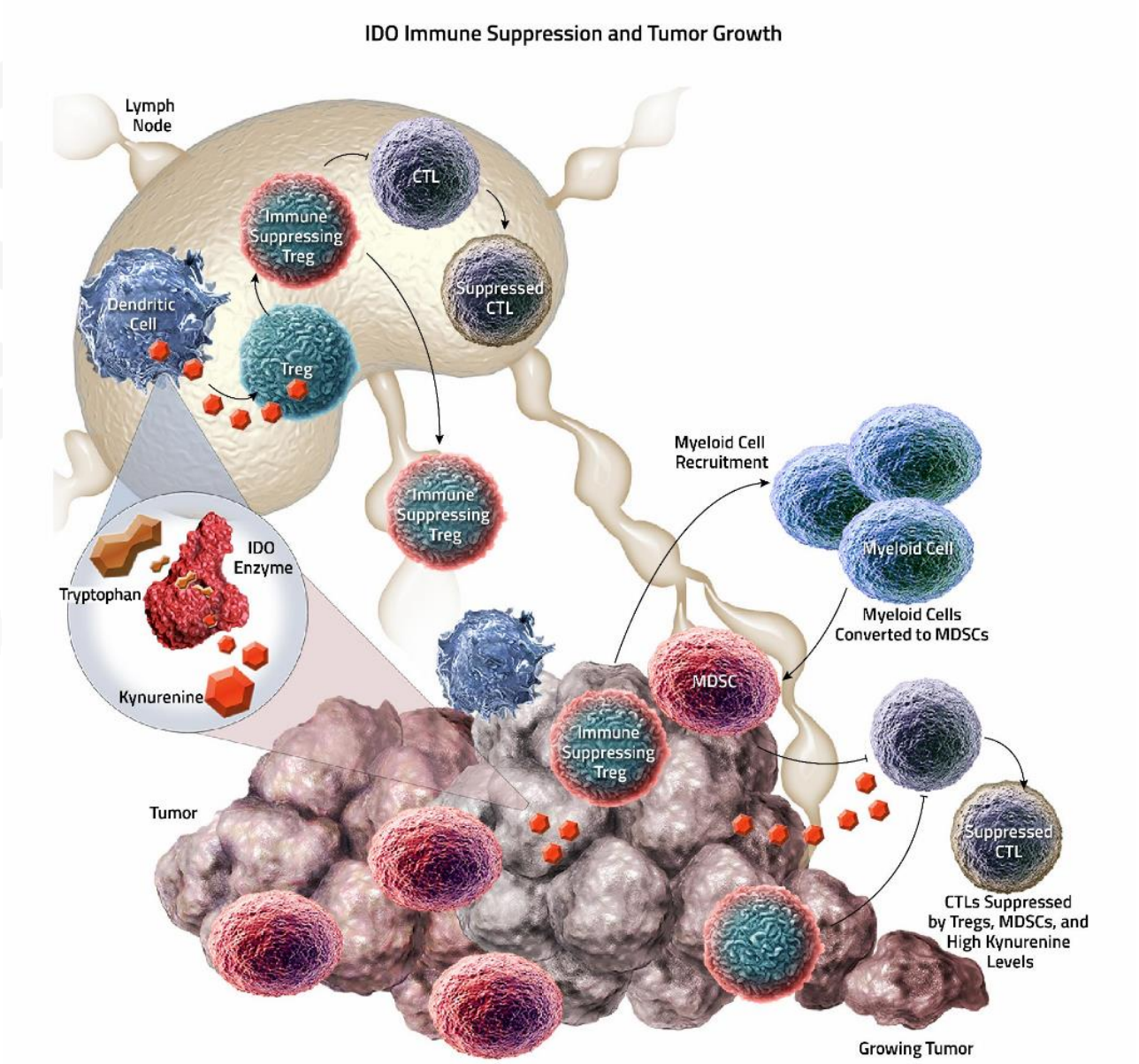
NewLink Genetics Corporation

NASDAQ: NLNK
February 2019

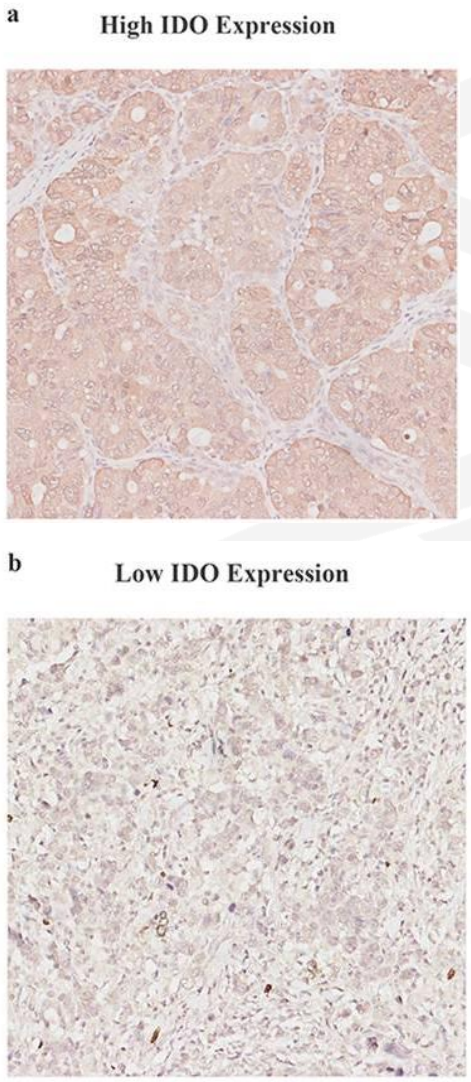
Cautionary Note Regarding Forward-Looking Statements

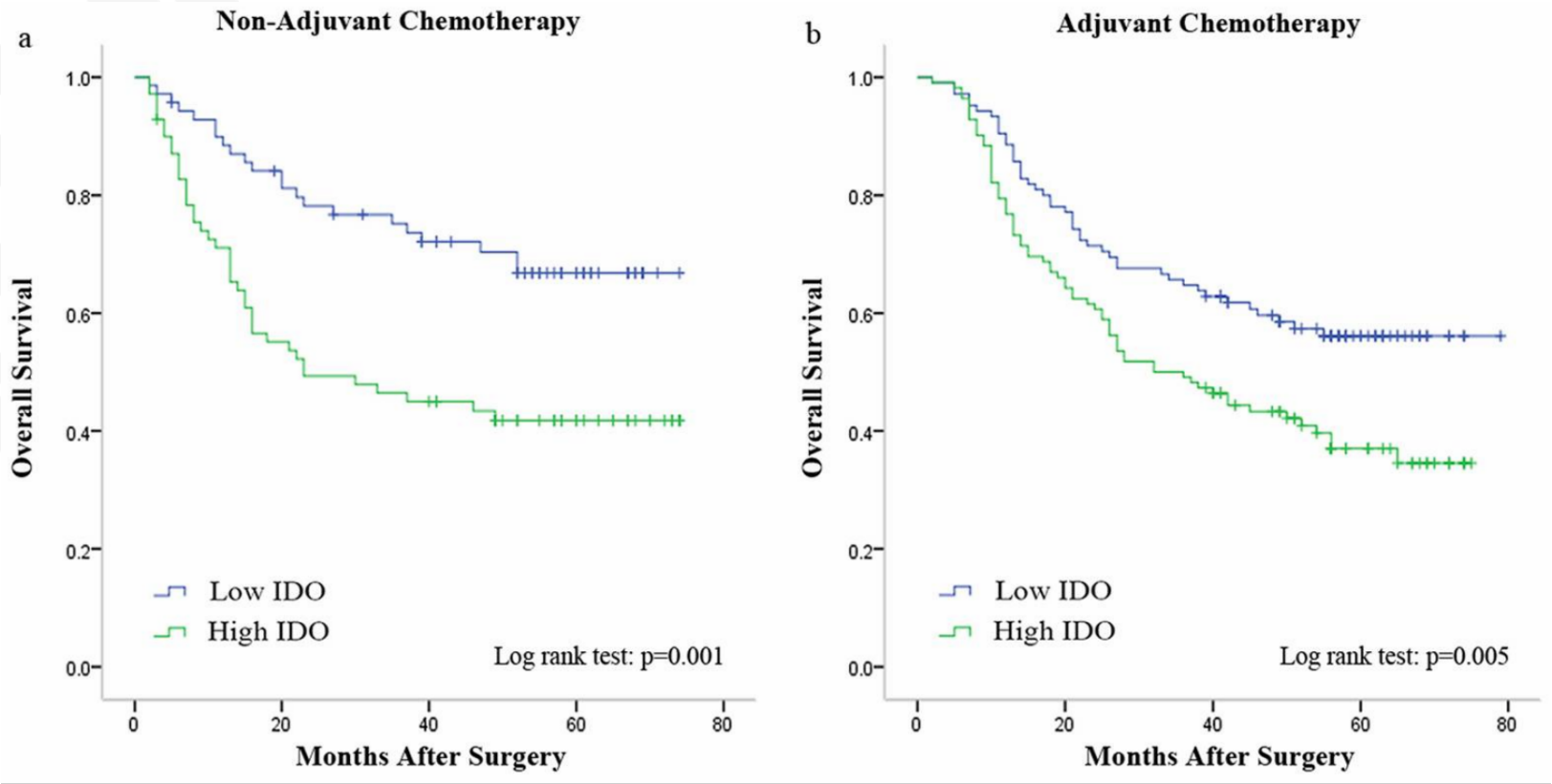
This presentation contains forward-looking statements of NewLink Genetics that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this presentation are forward-looking statements, within the meaning of The Private Securities Litigation Reform Act of 1995. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "target," "potential," "will," "could," "should," "seek" or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among others, statements about NewLink Genetics' financial guidance for 2018 and beyond; results of its clinical trials for product candidates; its timing of release of data from ongoing clinical studies; its plans related to execution of clinical trials; plans related to moving additional indications into clinical development; NewLink Genetics' future financial performance, results of operations, cash position and sufficiency of capital resources to fund its operating requirements; the effects of its organizational realignment, and any other statements other than statements of historical fact. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that NewLink Genetics makes due to a number of important factors, including those risks discussed in "Risk Factors" and elsewhere in NewLink Genetics' Annual Report on Form 10-K for the year ended December 31, 2017 and other reports filed with the U.S. Securities and Exchange Commission (SEC). The forward-looking statements in this presentation represent NewLink Genetics' views as of the date of this presentation. NewLink Genetics anticipates that subsequent events and developments will cause its views to change. However, while it may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. You should, therefore, not rely on these forward-looking statements as representing NewLink Genetics' views as of any date subsequent to the date of this presentation.

The IDO Pathway and Cancer



IDO expression correlates with poor survival



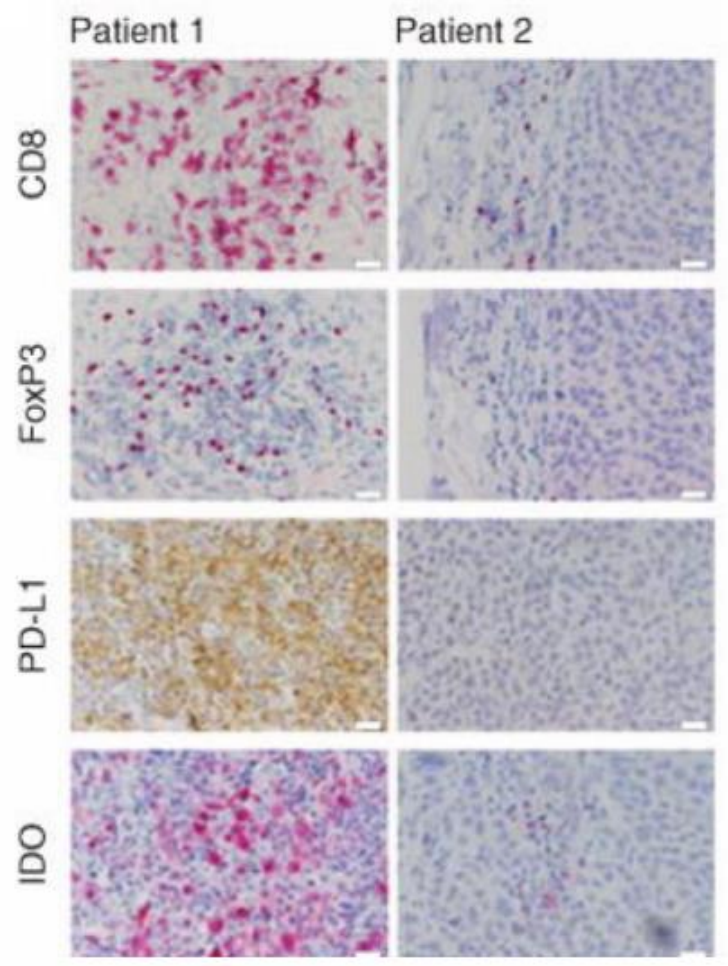


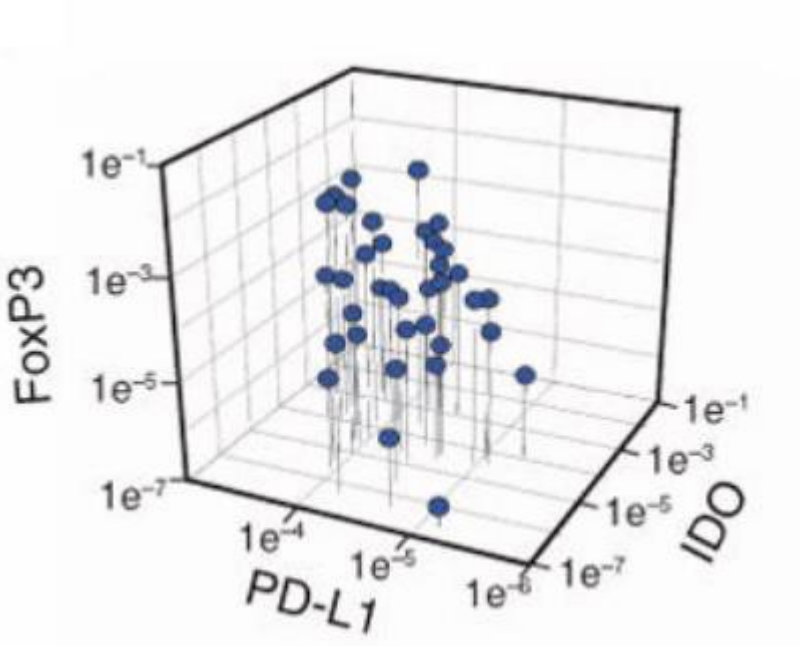
Data represent IDO staining (left) and overall survival (above) of patients with gastric adenocarcinoma. Similar correlation between IDO expression and survival exist in several types of cancer, including: breast cancer[1], non-small-cell lung cancer[2], head and neck cancer[3], and melanoma[4].

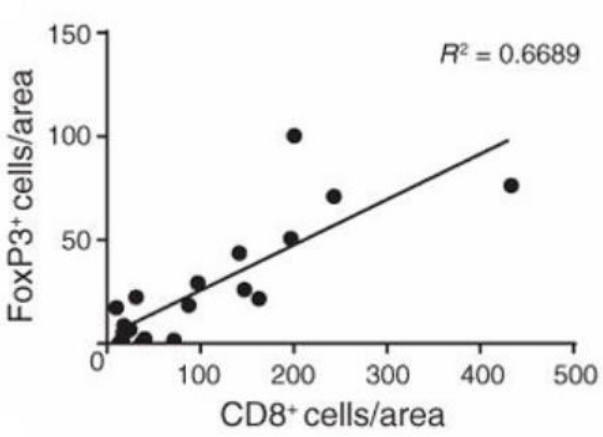
Liu, H. *et al. Sci. Rep.* **6**, 21319; doi: 10.1038/srep21319 (2016)..

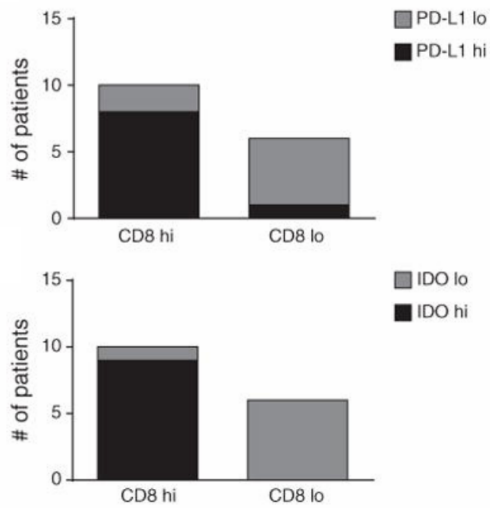
1 Front Immunol. 2018; 9: 724.
2 *Journal of Translational Medicine* (2018) 16:219.
3 *Aging* (Albany NY). 2019 Jan 22.
4 Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 3075-3075.

Immune responses against melanoma induce expression of regulatory proteins









CD8 infiltration into tumors correlates with FoxP3, PD-L1, and IDO expression

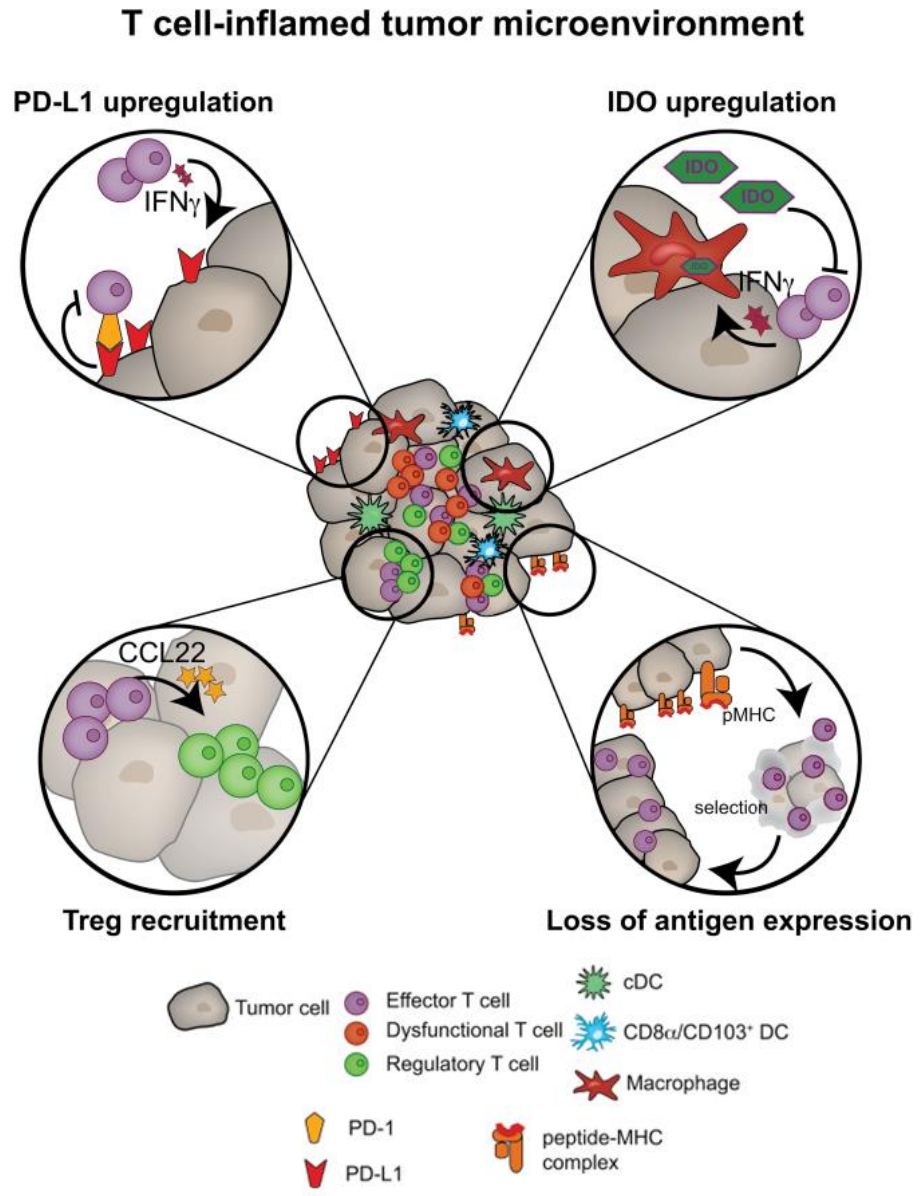
Sci Transl Med. 2013 Aug 28; 5(200): 200ra116.

Immune activation induces expression of counter-regulatory proteins in the tumor microenvironment

Anti-tumor immune responses result in CD8 T cell recruitment to the tumor microenvironment, as well as the activation of counter-regulatory mechanisms, including:

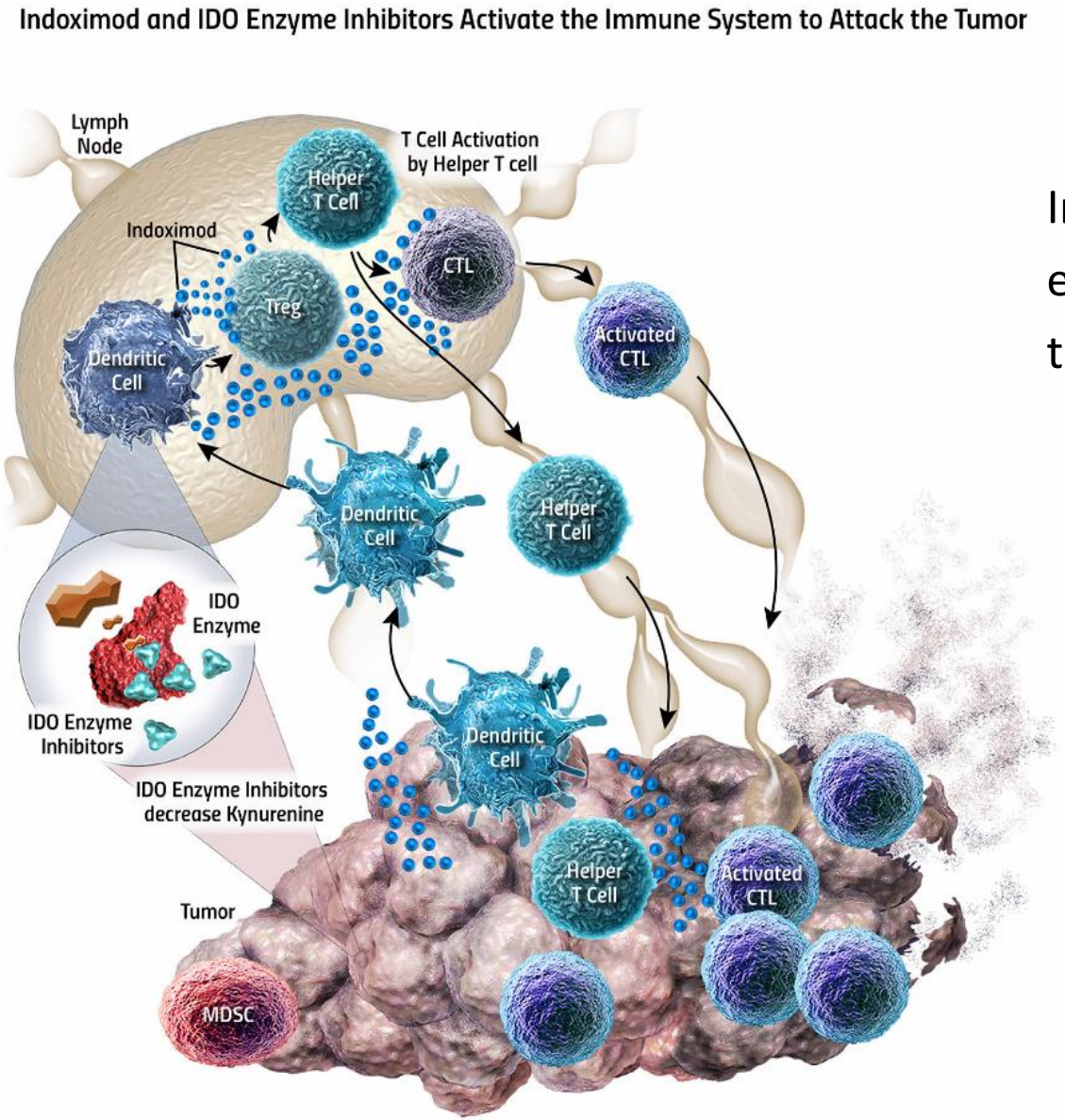
- The upregulation of PD-1 and PD-L1
- Upregulation and activation of IDO protein
- Recruitment of regulatory T cells (Treg)

Indoximod counters these mechanisms, making it a strong candidate for pairing with other inhibitors of the PD-1/PD-L1 pathway checkpoint



Adapted from: *International Immunology*, Volume 28, Issue 8, 1 August 2016, Pages 383–391

Indoximod disrupts the influence of IDO pathway in cancer

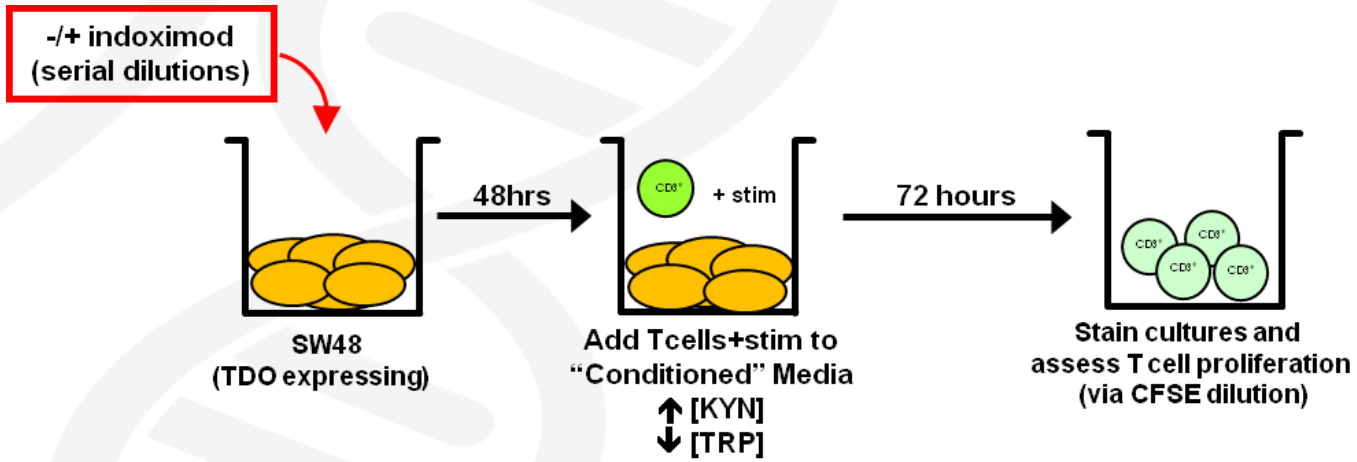


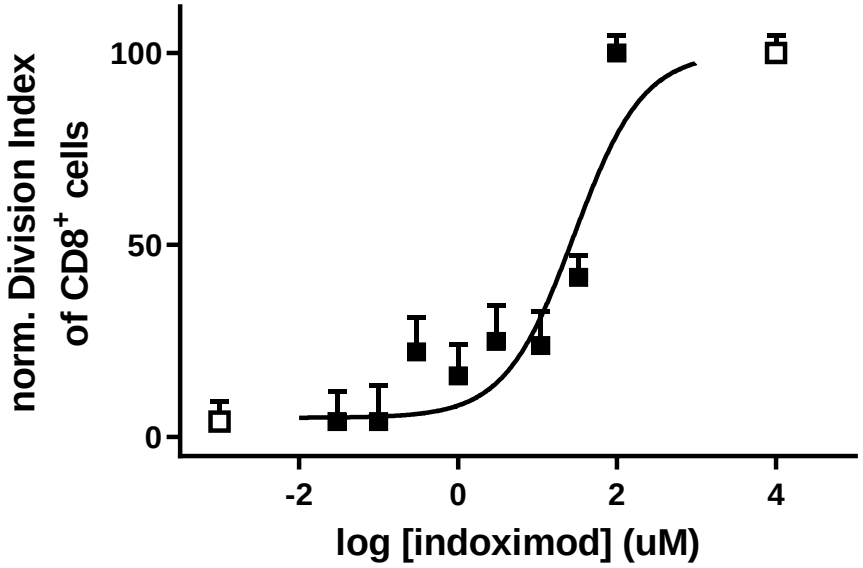
Indoximod reverses the immunosuppressive effects of low tryptophan and high kynurenine that result from IDO activity by:

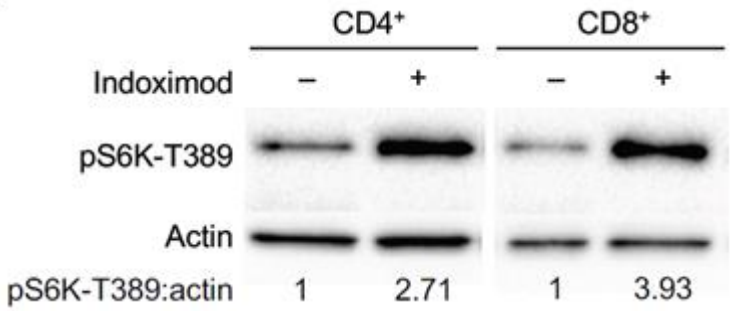
- Reversing the effects of low tryptophan by increasing proliferation of effector T cells
- Driving differentiation into T helper cells vs regulatory T cells
- Downregulating IDO expression in dendritic cells

Indoximod restores T cell proliferation in IDO- or TDO-conditioned cultures

Stimulation of CD8+ T cell proliferation Trp-depleted media





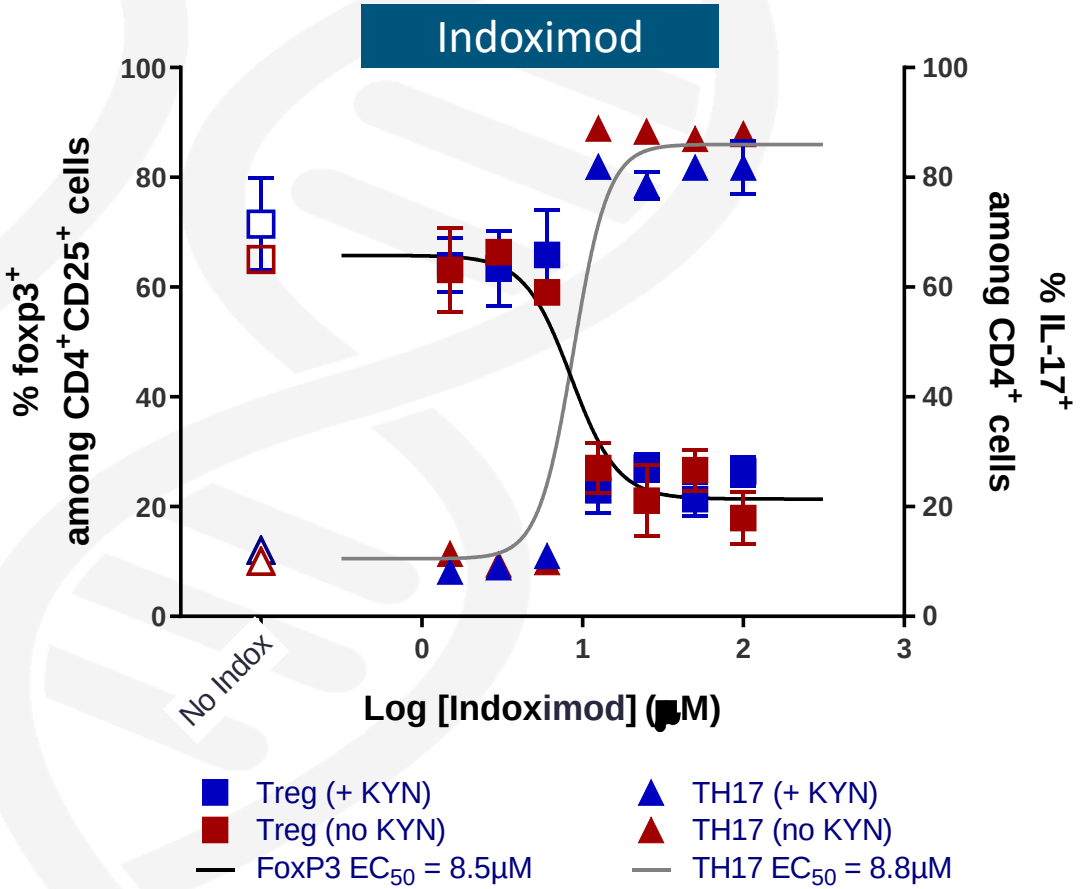


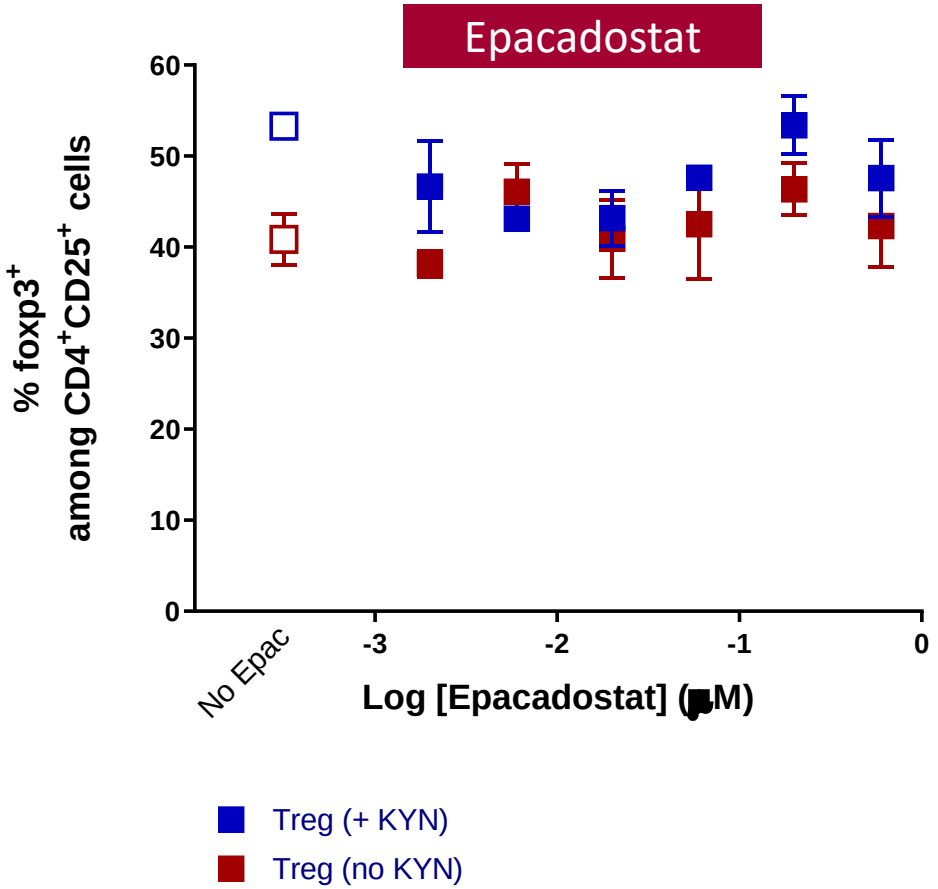
Indoximod restores T cell proliferation *in vitro* by activating mTOR

Adapted from: Brincks EL, *et al*. AACR 2018. Abstract 3753.

Indoximod vs Epacadostat: A Different Mechanism of Action

Indoximod Drives Differentiation of Helper vs Regulatory T Cells

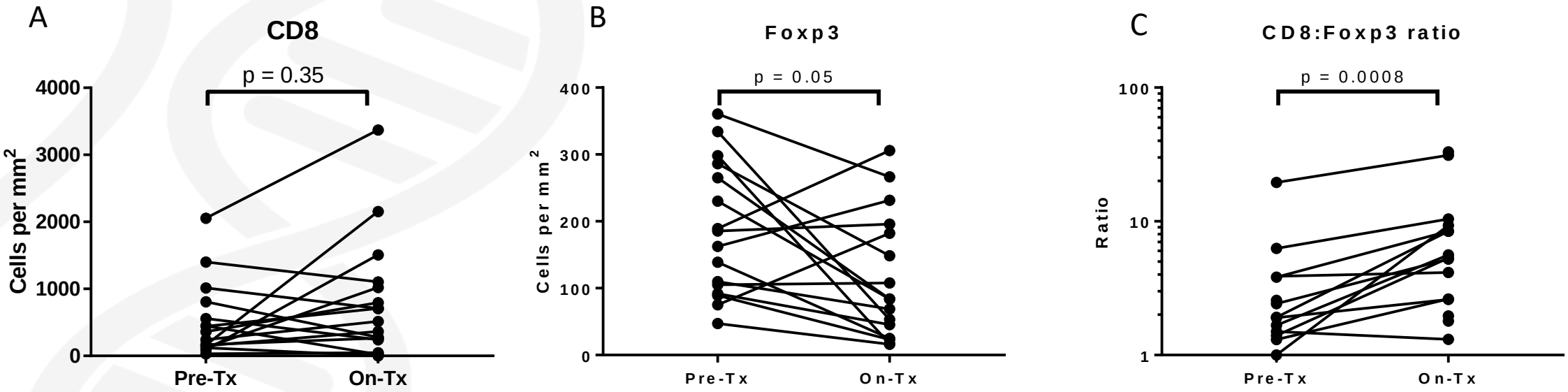




Indoximod reduces T-regs and increases effector T-cells

Brincks EL, *et al*. AACR 2018. Abstract 3753.

Treg decreased and CD8:Foxp3 ratio was increased in tumors of patients treated with indoximod + gemcitabine/nab-paclitaxel

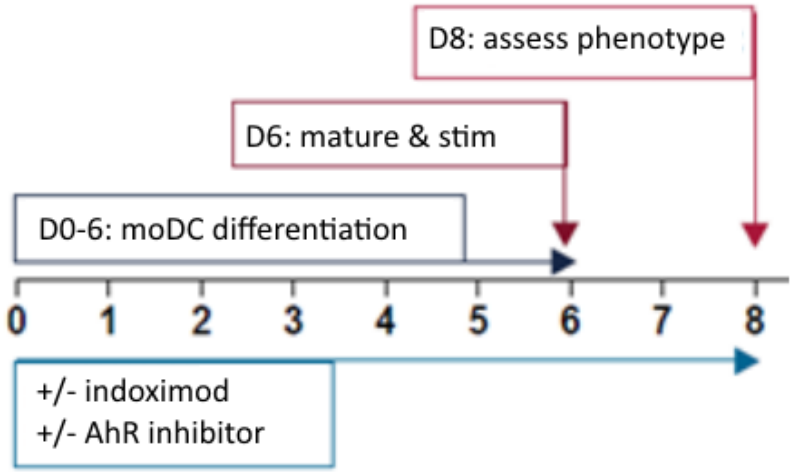


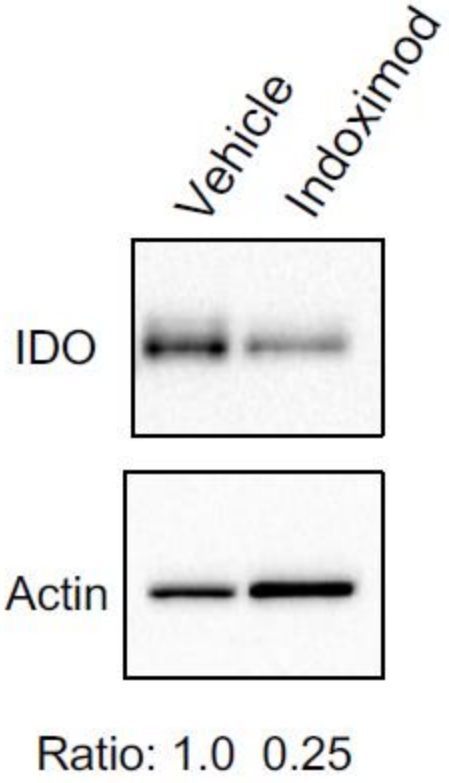
With immunohistochemistry studies, paired analysis of quantification for CD8 (A) and Foxp3 (B) cell infiltrates into tumor tissue seen at baseline and post-treatment, and paired analysis of ratio of CD8 to Foxp3 cells (C) in baseline and post-treatment biopsies are shown.

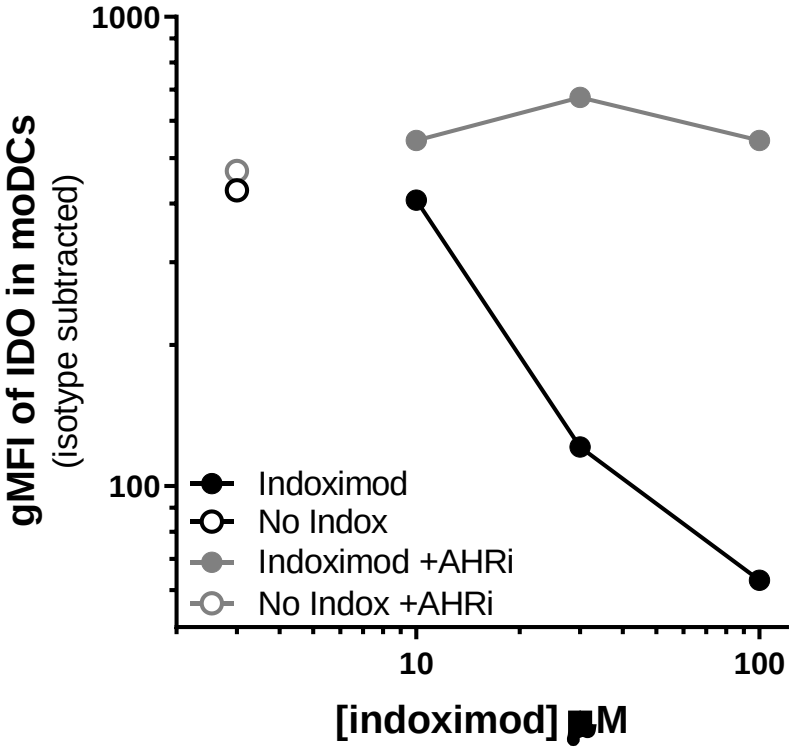
Indoximod therapy shifts the CD8:Treg ratio in the TME

Yu J, Rossi GR, et.al. SITC 2018; abstract P706

Modulation of IDO expression in moDCs by indoximod





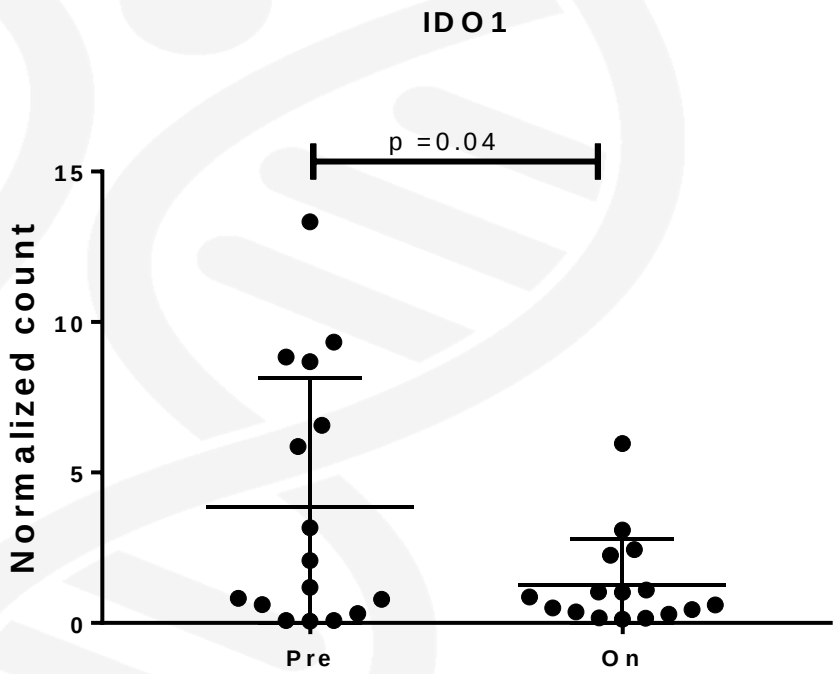


NOTE: decreased expression of IDO in moDC corresponded with indoximod-driven decreases in KYN production in moDC cultures and indoximod-induced increase of T cell proliferation in MLR assays.

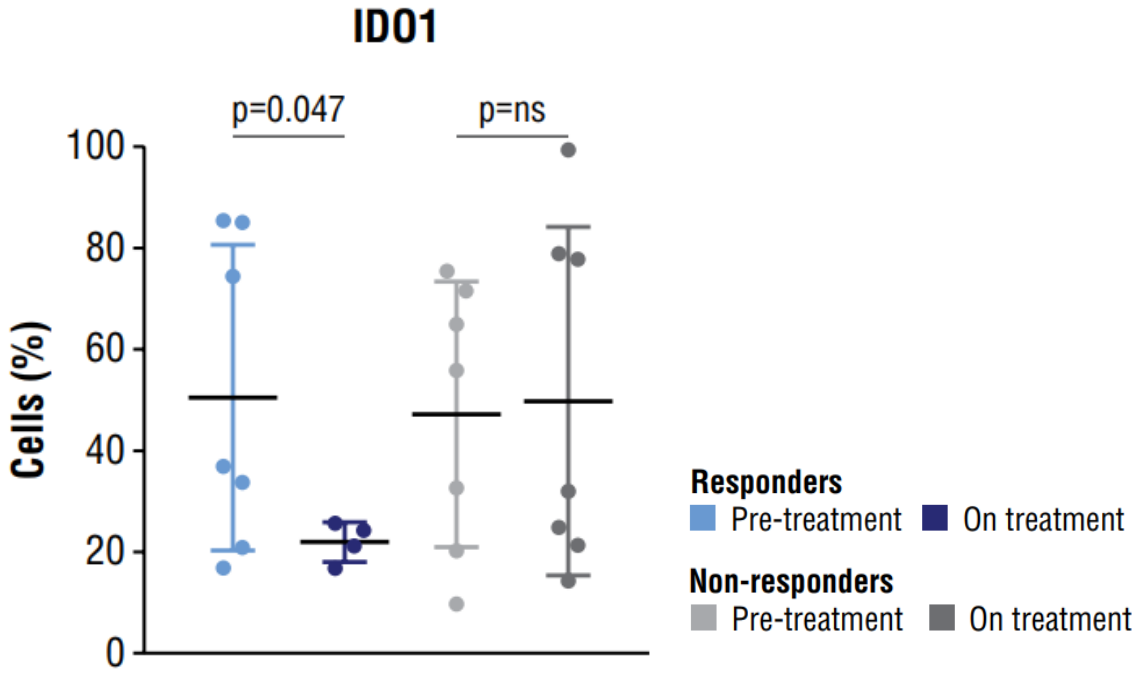
Indoximod blocks IDO expression and function in CD83+ moDC via AHR

Adapted from: Brincks EL, *et al*. AACR 2018. Abstract 3753.

Indoximod downregulates IDO expression the tumor microenvironment



- Pancreatic cancer patients treated with indoximod + gemcitabine/nab-paclitaxel
- IDO gene expression in TME tissue at baseline and post-treatment.



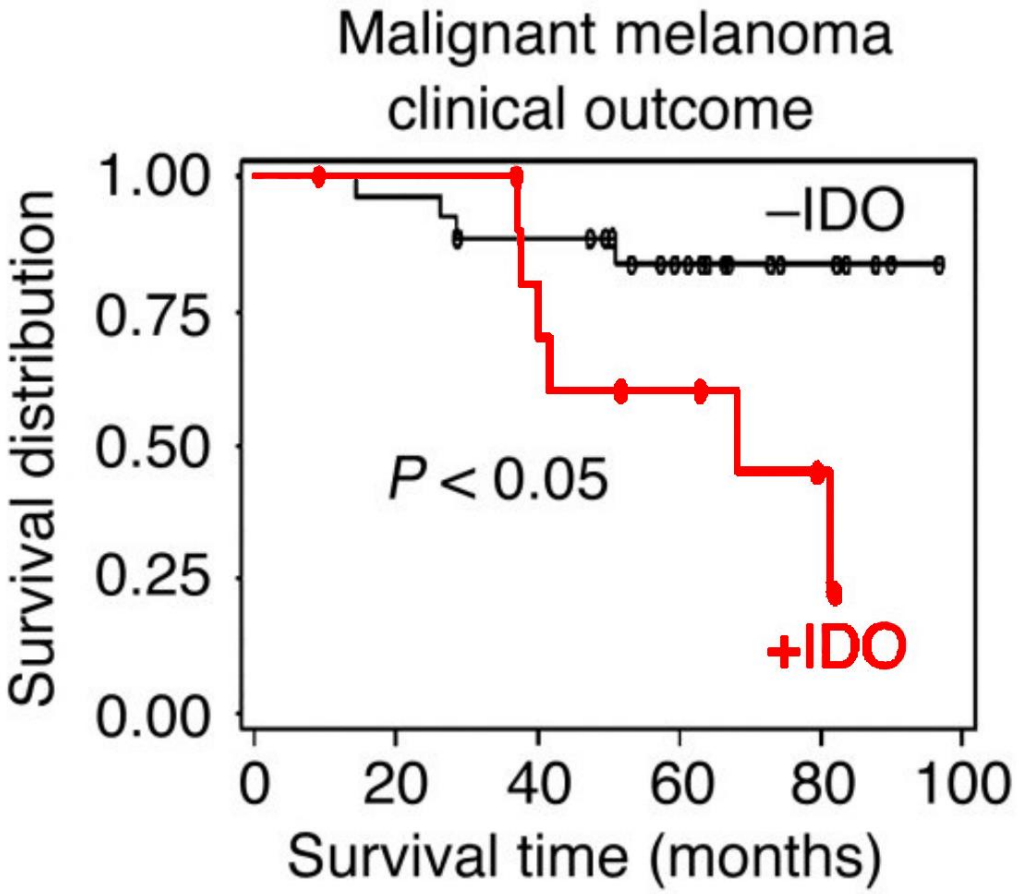
- Melanoma patients treated with indoximod + pembrolizumab
- IDO protein expression in TME was significantly reduced in patients responding to therapy when comparing baseline to post-treatment.

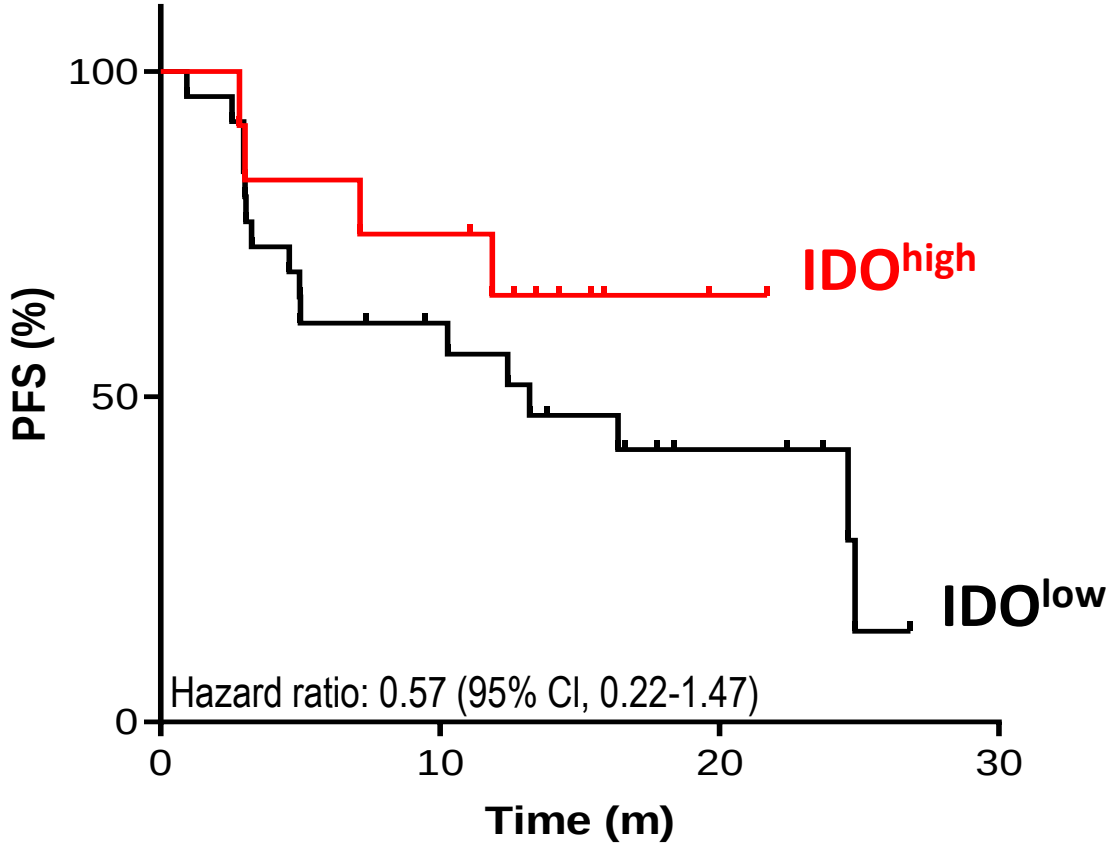
Treatment significantly downregulates IDO1 expression in the tumor microenvironment

Yu J, Rossi GR, et.al. SITC 2018; abstract P706

Yu J, Rossi GR, et.al. SITC 2018; abstract P142

Indoximod improves the prognosis of melanoma patients with IDO-high phenotype



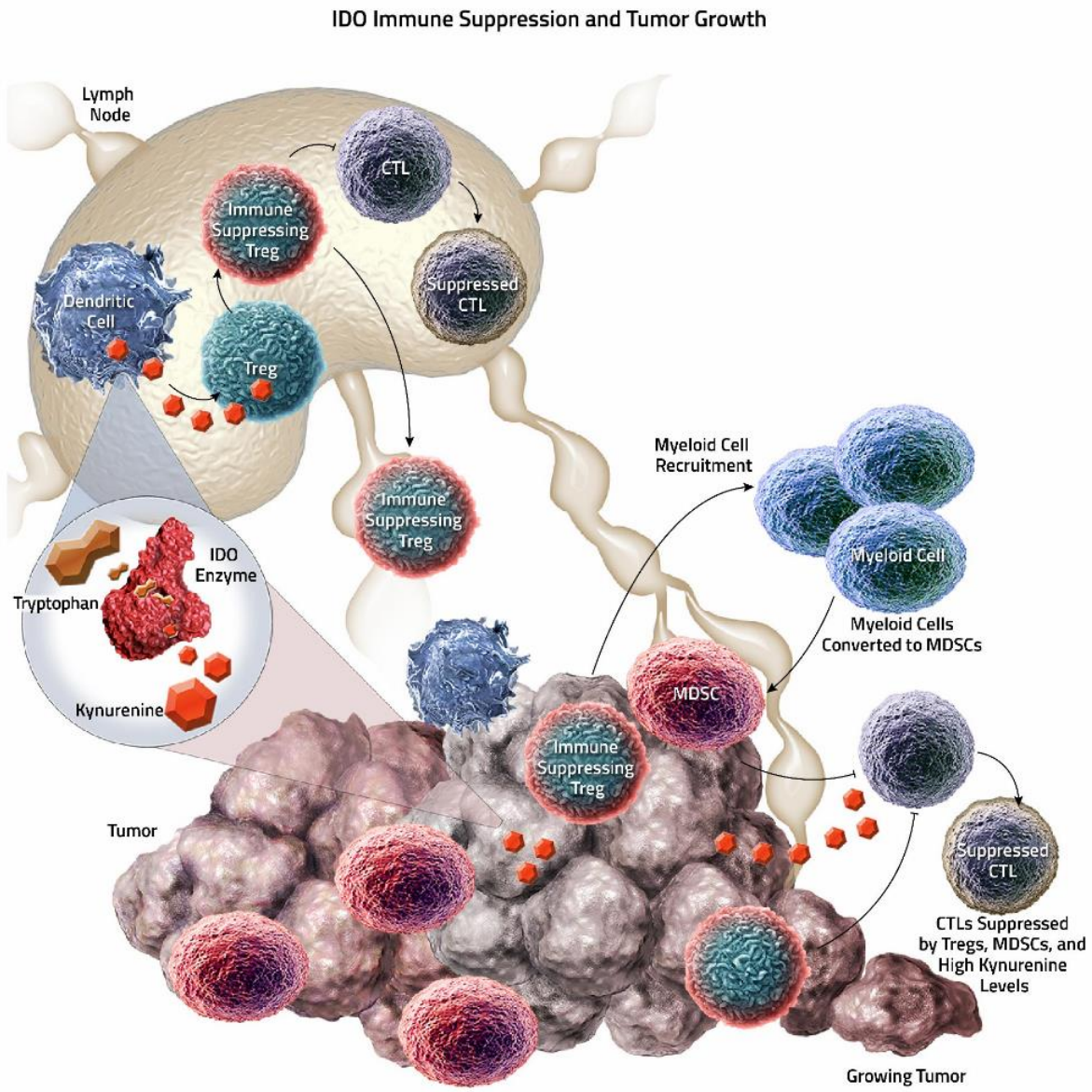


Indoximod reverses the poor prognosis of the IDO-high phenotype in melanoma

Adapted from: J Clin Invest. 2004;114(2):280-290.

Yu J, Rossi GR, et.al. SITC 2018; abstract P142

The IDO Pathway and Cancer



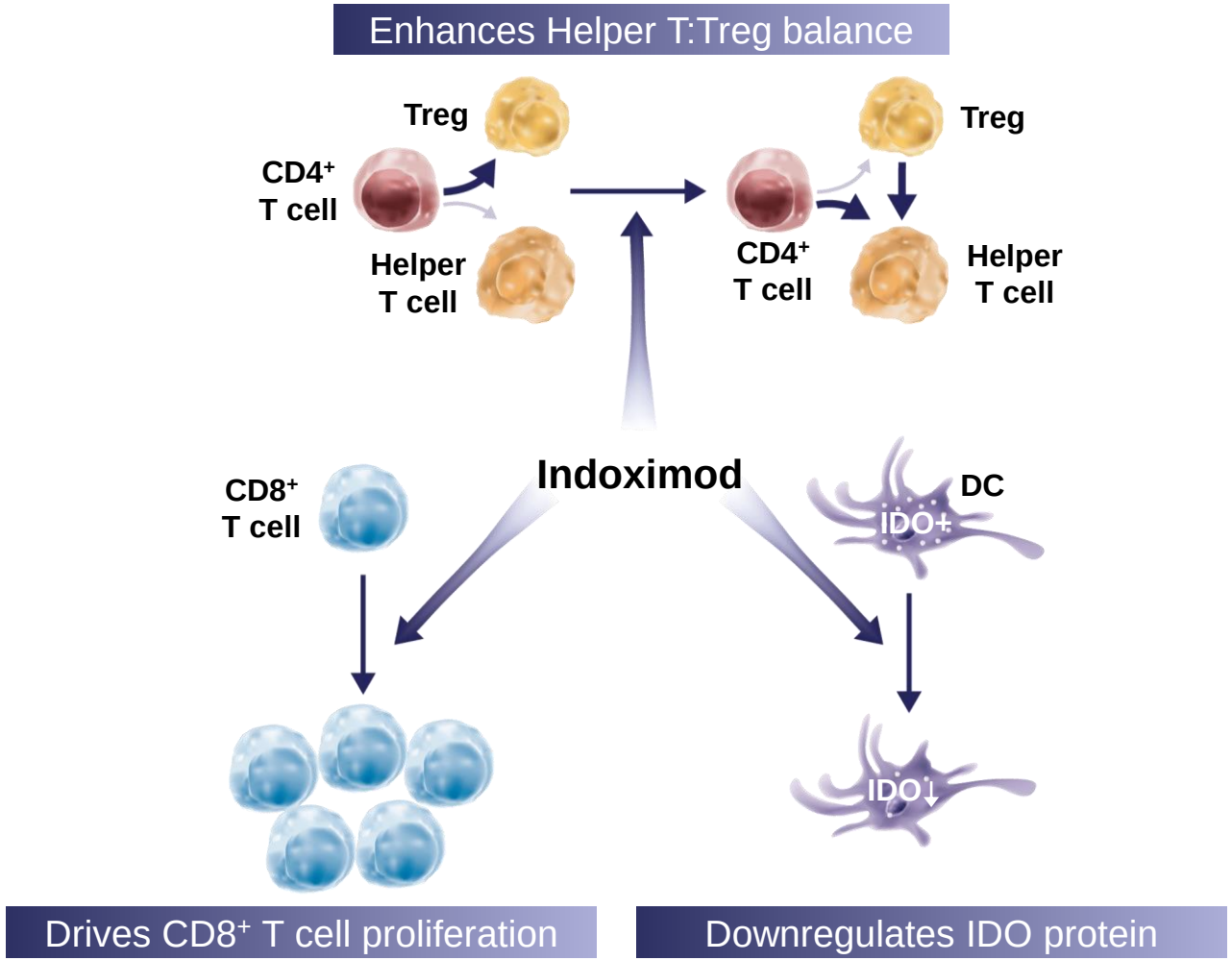
Inflammation in the TME induces IDO expression and function.

IDO activity creates an immuno-suppressive environment, hindering anti-tumor responses via:

- Localized depletion of Trp, which limits effector T cell function
- Production of Kyn, which stimulates induction and activation of Treg
- Promotion of PD-1expression by effector T cells

Indoximod Mechanism of Action

- Indoximod is an orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of low tryptophan and high kynurenine that result from IDO activity
- Indoximod has immunostimulatory effects involving 4 main cell types: $CD8^+$ T cells, $CD4^+$ T helper cells, T regulatory cells, and dendritic cells
  - Indoximod reverses the effects of low tryptophan by increasing proliferation of effector T cells
  - Indoximod drives differentiation into T helper cells vs regulatory T cells
  - Indoximod downregulates IDO expression in dendritic cells



Differentiating indoximod from other IDO inhibitors

- Indoximod directly modulates expression and function of IDO protein in monocyte-derived dendritic cells

- Indoximod activity on IDO expression in DCs and differentiation of CD4 T cells appears to be mediated by AHR (a transcription factor that regulates IDO1, foxp3, rorc, and other genes):
  - In dendritic cells by modulating IDO protein expression and function
  - In CD4 T cells by inducing the differentiation of TH-17 helper cells rather than regulatory T cells