Selective IDO1 Inhibition: Pharmacodynamic and Antitumor Activity of INCB24360

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Presenter Disclosure Information

The following relationships exist related to this presentation:

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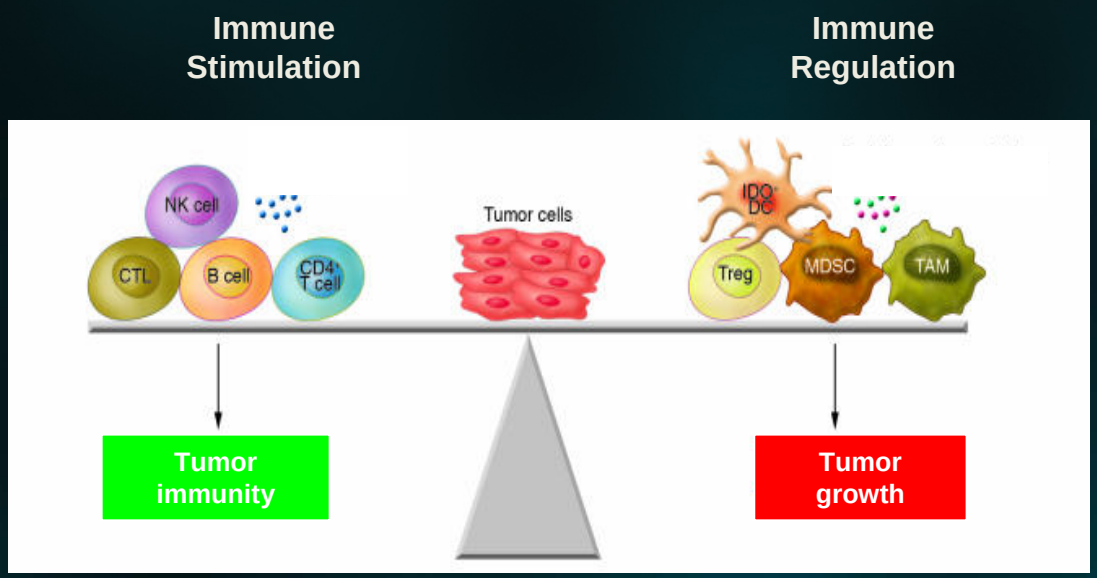
Negative Immune Regulation

All inflammatory and immune responses are accompanied and limited by the generation of feedback inhibition



Major players:

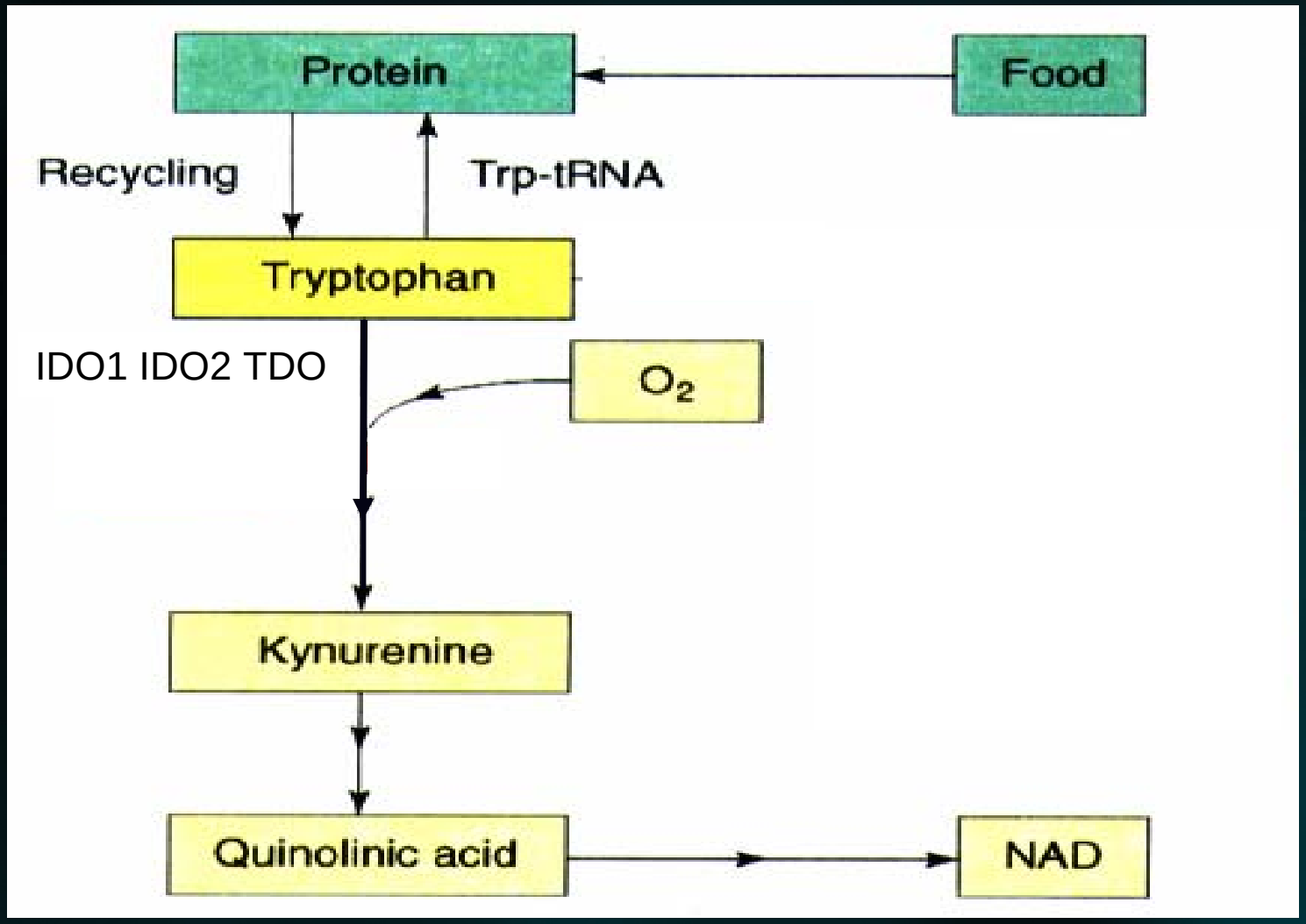
- Tregs
- Immunosuppressive cytokines
  - IL-10 and TGFβ
- Metabolic Enzymes
  - Arginase and IDO

Many tumors appear to have subverted these mechanisms to suppress immunity

IDO1 – A Tryptophan Catabolizing Enzyme

- Converts tryptophan into kynurenine and other metabolites
  - Two other family members: TDO and IDO2
- Upregulated in response to IFN-γ during infection and tissue inflammation
- Predominantly expressed by antigen presenting cells
  - Tissue expression highest in gut, thymus, lung, placenta
- Plays an important role in the negative regulation of T cell responses
  - Low levels of tryptophan and high levels of kynurenine metabolites limit the proliferation of T cells
  - High IDO expression is associated with the induction of Tregs
  - Significant role in allogeneic fetal tolerance

Overview of Tryptophan Biochemistry



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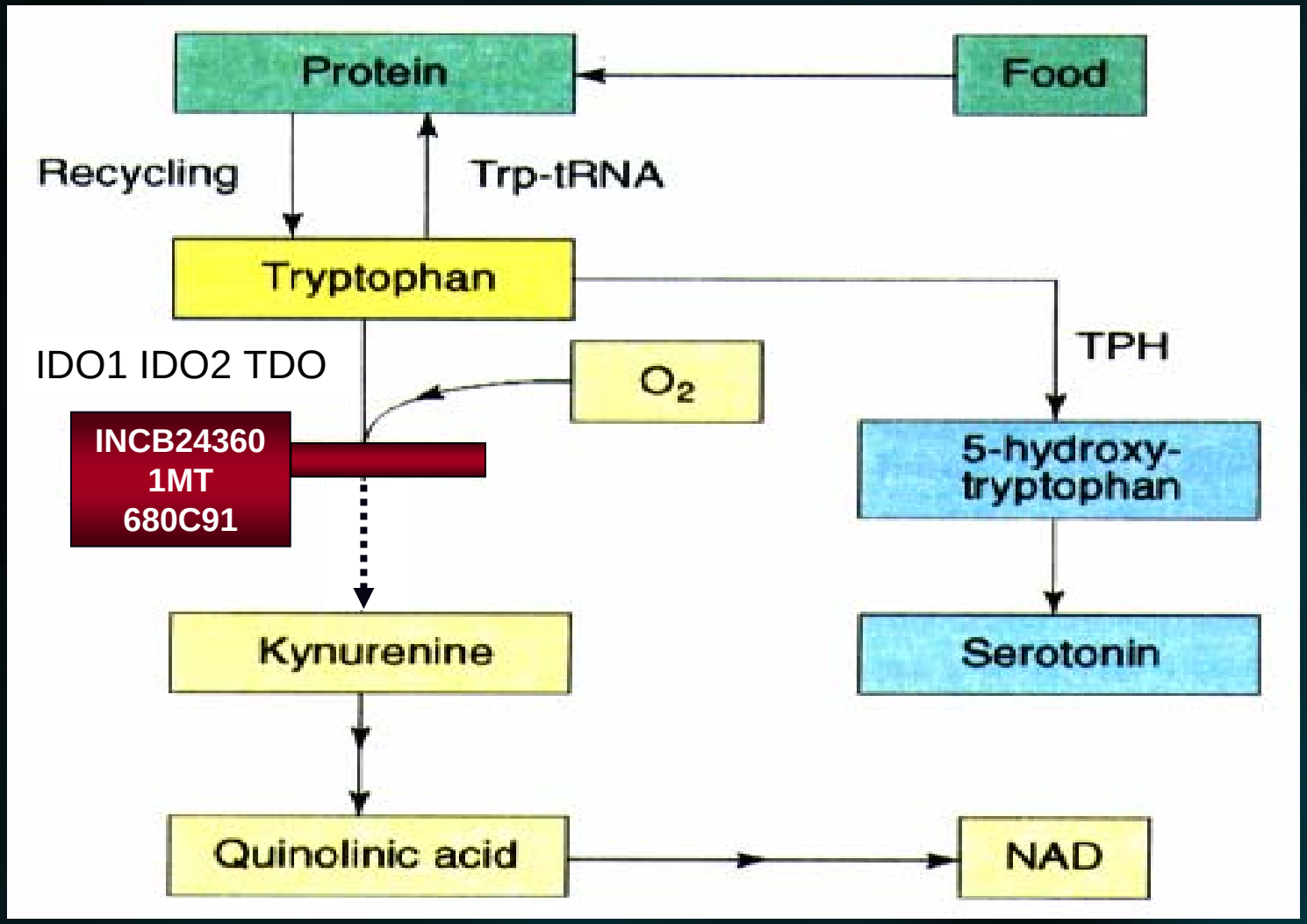

IDO Expression in Various Tumor Types

Tumor	IDO+ Tumor Samples	>50% IDO+ Cells	10-50% IDO+ Cells	<10% IDO+ Cells
Prostate	11/11	7	3	1
Colorectal	10/10	5	3	2
Pancreatic	10/10	8	2	0
NSCLC	9/11	1	1	7
Ovarian	8/10	0	3	5
Renal Cell	5/10	0	1	4
Melanoma	11/25	0	0	11

Uyttenhove, Nature Med, 2003

Elevated kynurenine levels in urine of patients with breast, prostate, bladder cancer and leukemia

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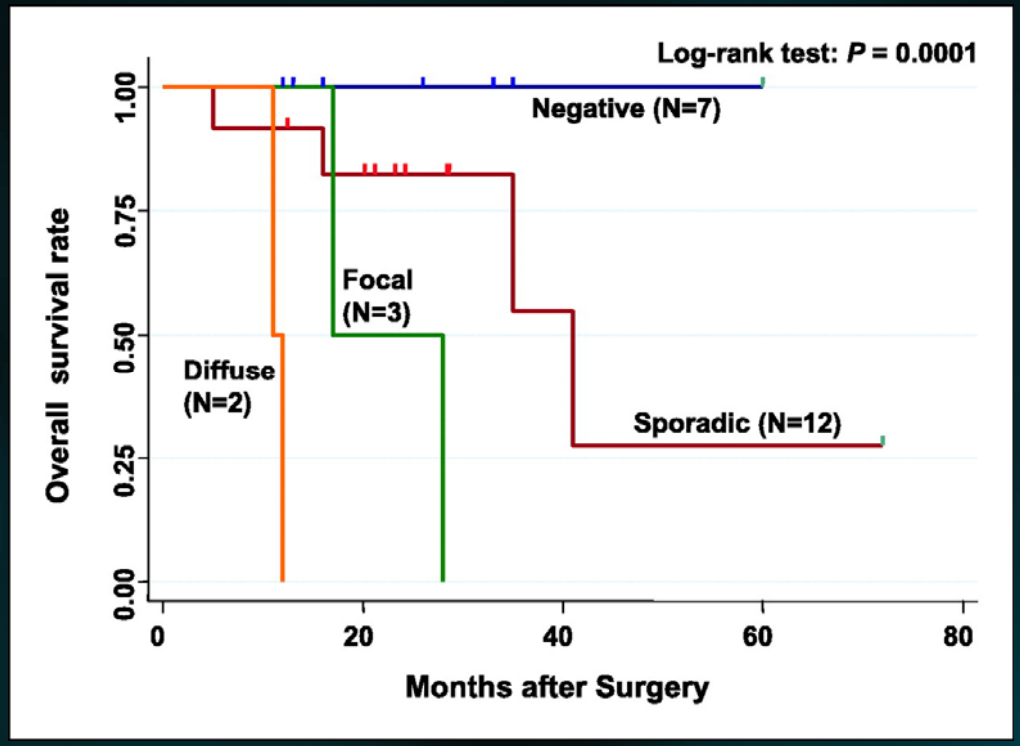
IDO1 Is A Marker Of Poor Prognosis

IDO1 expression in human tumors is associated with decreased survival

- Ovarian
- Melanoma
- Colon
- Pancreatic
- Endometrial
- Oral squamous cell carcinoma

Kaplan-Meier survival curves in ovarian cancer based on IDO staining



Okamoto et al. Clin Cancer Res 2005;11:6030-39

IDO1 Inhibitor Identification Strategy

Through a directed medicinal chemistry effort, identify a potent, selective, orally bioavailable IDO1 inhibitor that would:

- Reduce kynurenine levels both *in vitro* and *in vivo*
- Not impact TDO metabolic activity
- Allow for enhanced activation of the immune system
- Control the growth of tumors, alone and in combination regimens
- Meet ADME and safety criteria to allow safe dosing in humans

INCB24360 identified as the clinical candidate

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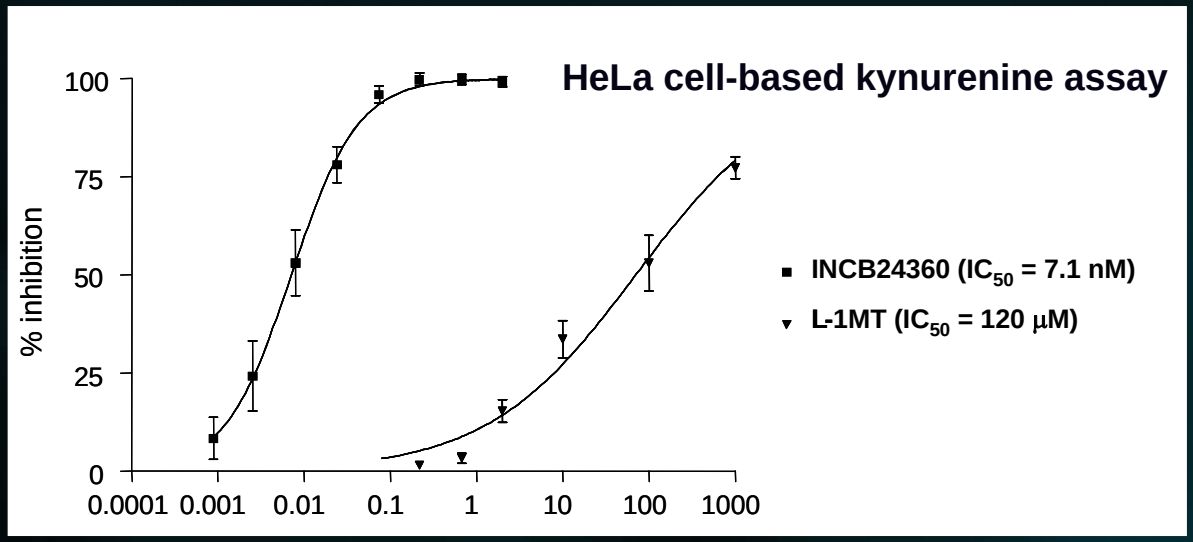
INCB24360: A Potent and Highly Selective IDO1 Inhibitor

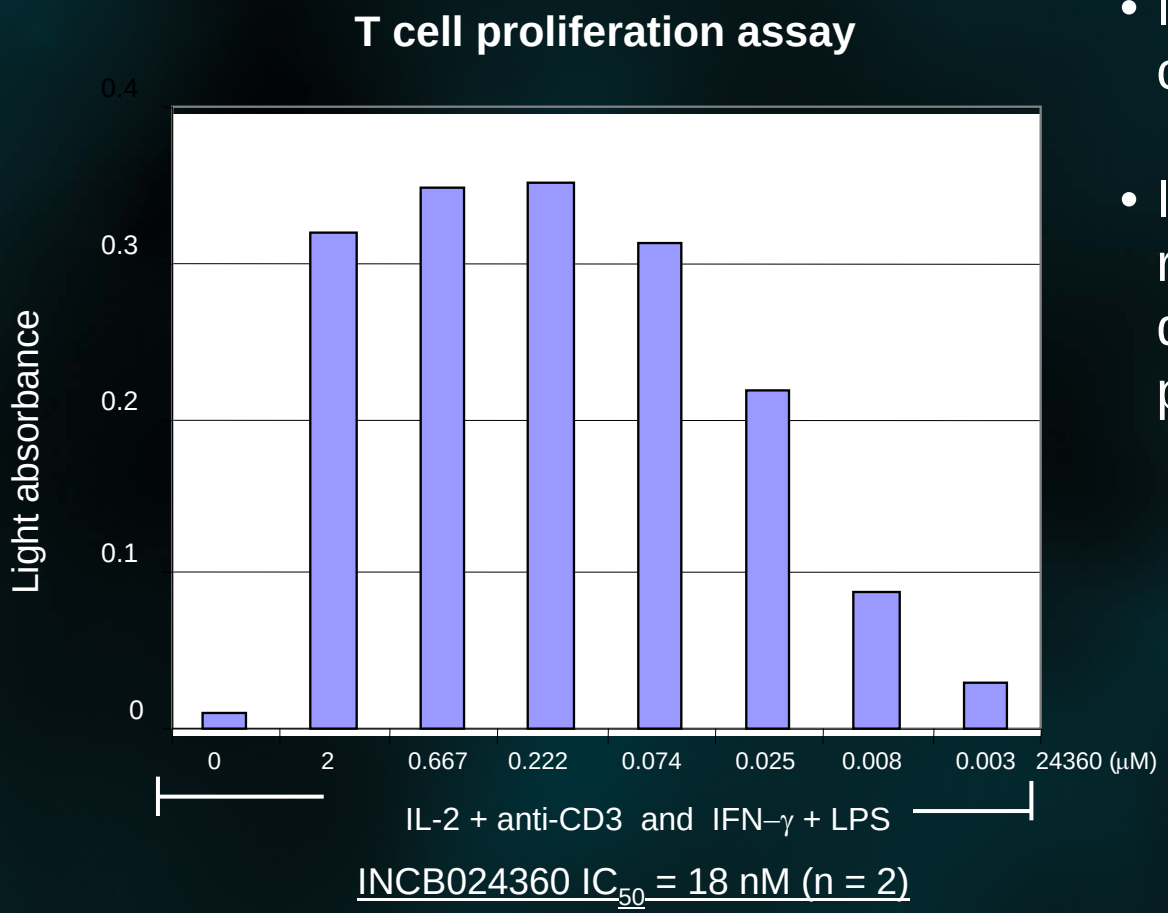


Assay	Cell type	IC_{50} ± SD (nM)
Tryptophan to kynurenine conversion	HeLa	7.1 ± 0.6 (n=56)
	Human dendritic cells (DCs)	12.7 ± 1.1 (n=3)
	HEK293/MSR-human IDO1	15.0 ± 3.3 (n=4)
	HEK293/MSR-mouse IDO1	52.4 ± 15.7 (n=8)
	HEK293/MSR-mouse IDO2	>5,000 (n=8)
	HEK293/MSR-human TDO	>10,000 (n=2)
Tryptophan transport	THP-1	>30,000 (n=2)

INCB24360 (10 μM) exhibits little activity against a panel of 50 GPCRs, ion channels, transporters and enzymes

Liu et al Blood 2010

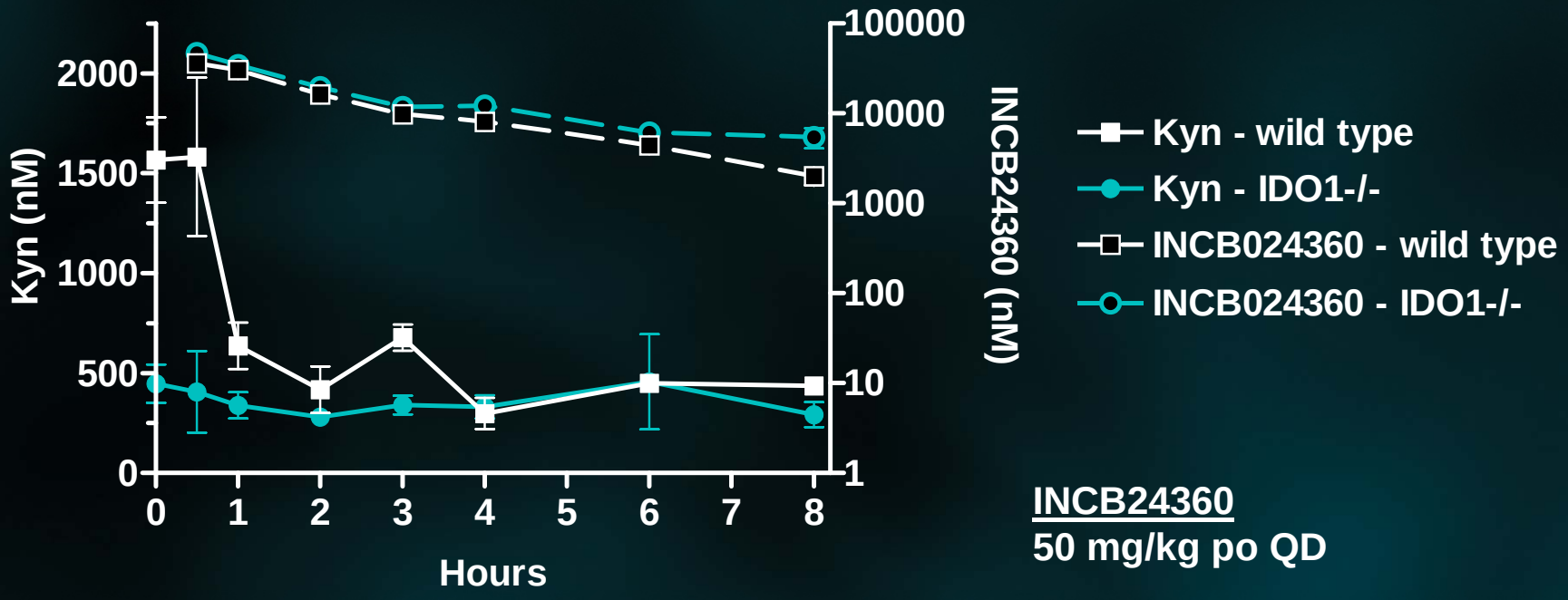
IDO1 Inhibition By INCB24360 Modulates T Cell Responses *in vitro*



- IDO1^{+} dendritic cells block T cell proliferation *in vitro*
- INCB024360 treatment reverses inhibition and dose-dependently promotes T cell proliferation
  - Similar effects on proliferation observed in CD4+, CD8+ and NK cells
  - Results in significant increases in IFN-γ production

Liu et al Blood 2010

INCB24360 Reduces Kyn Levels In Wild Type Mice To Levels Present In IDO1$^{-/-}$ Mice

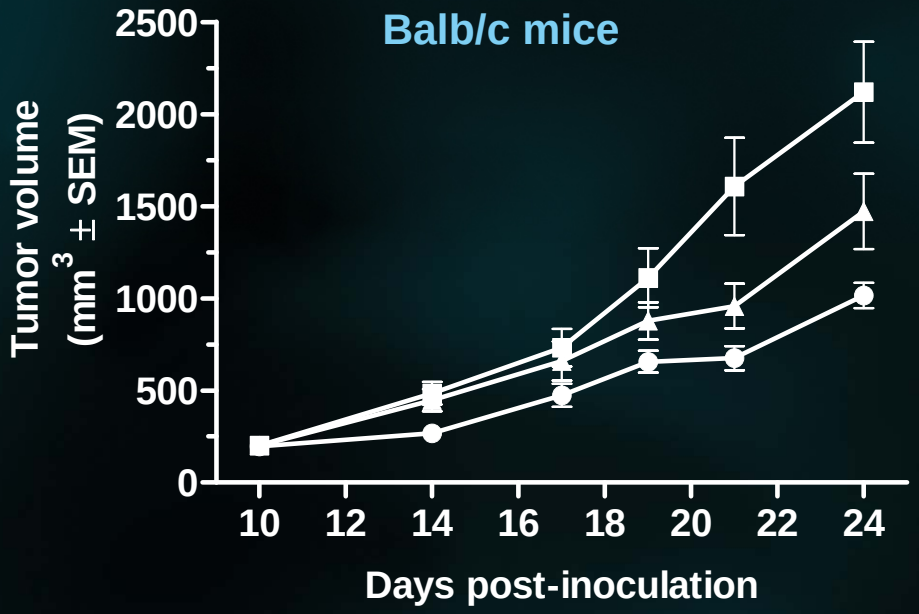


Kyn inhibition observed in multiple species

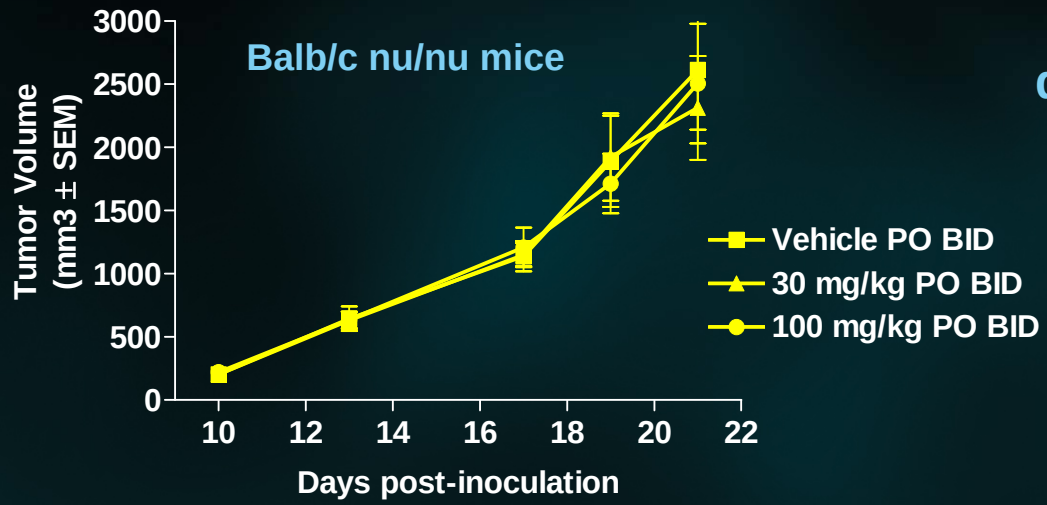
In tumor-bearing mice, decreased kyn levels observed in plasma, tumor and LN

Koblish et al Mol Can Ther 2010

INCB24360 Controls CT26 Tumor Growth Only In Immunocompetent Mice



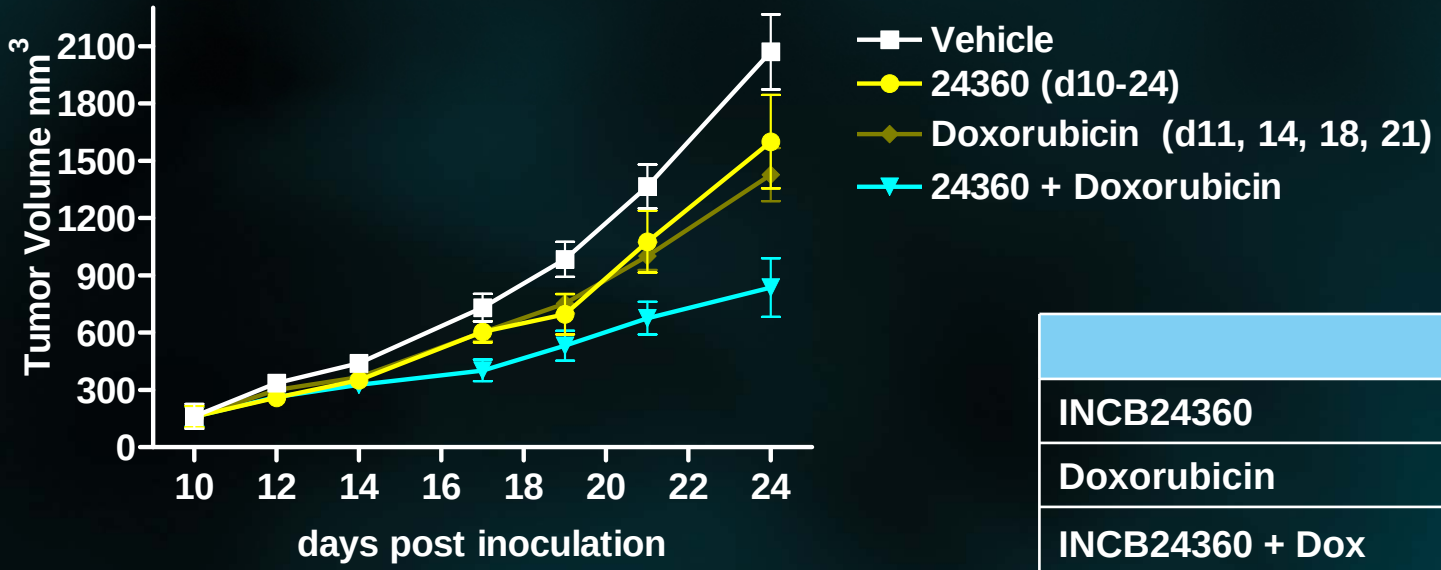
Dose (mg/kg)	TGC (Day 21)	Hours (per 24h) >50% inh of Kyn
30	46%	~16
100	66%	~24



Associated with increased T cell percentages and activity and decreased percentage of Tregs

Koblish et al Mol Can Ther 2010

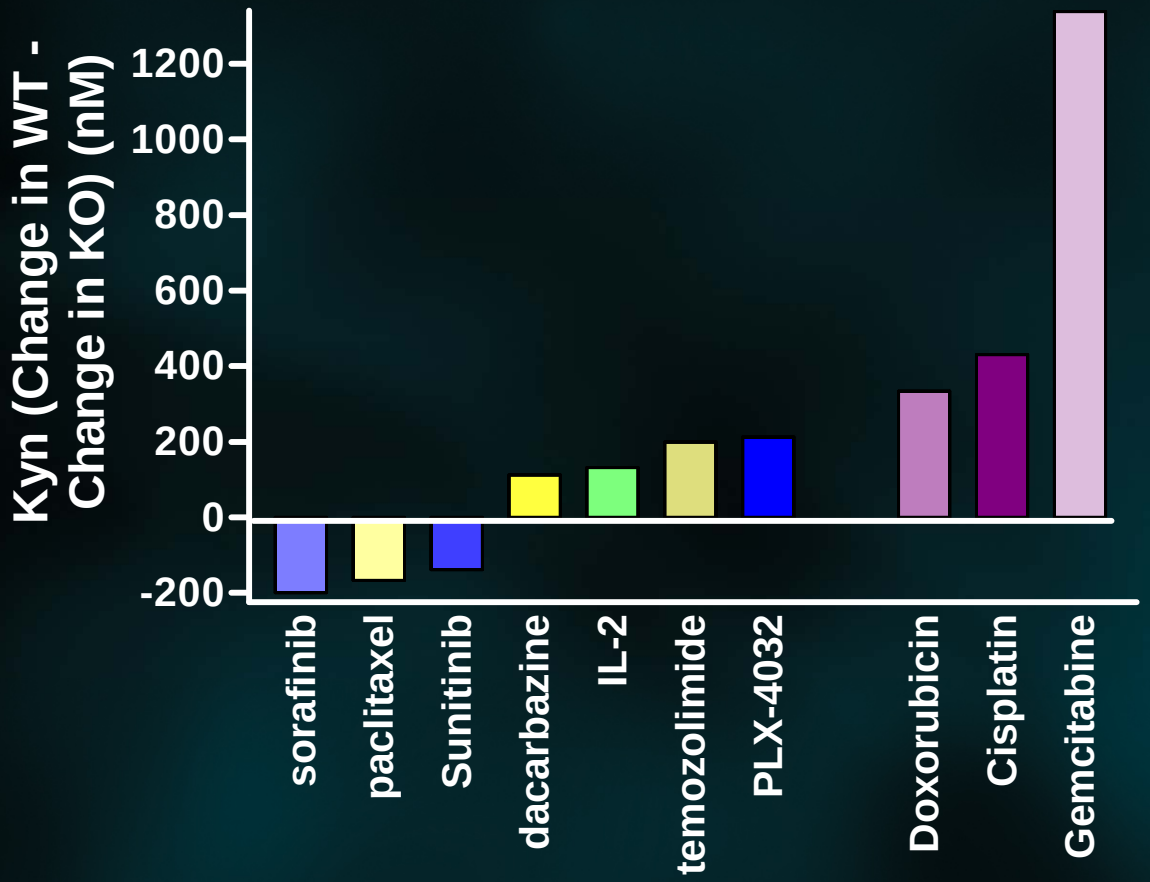
INCB24360 Enhances Doxorubicin Activity In CT26 Tumors



	TGI (%, d24)
INCB24360	25%
Doxorubicin	33%
INCB24360 + Dox	65%

Similar data have been obtained with gemcitabine and cisplatin

Chemotherapy induced Kyn generation correlates with enhanced efficacy in combination studies



24 hours, naïve mice

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INCB 24360-101 Phase 1 Study

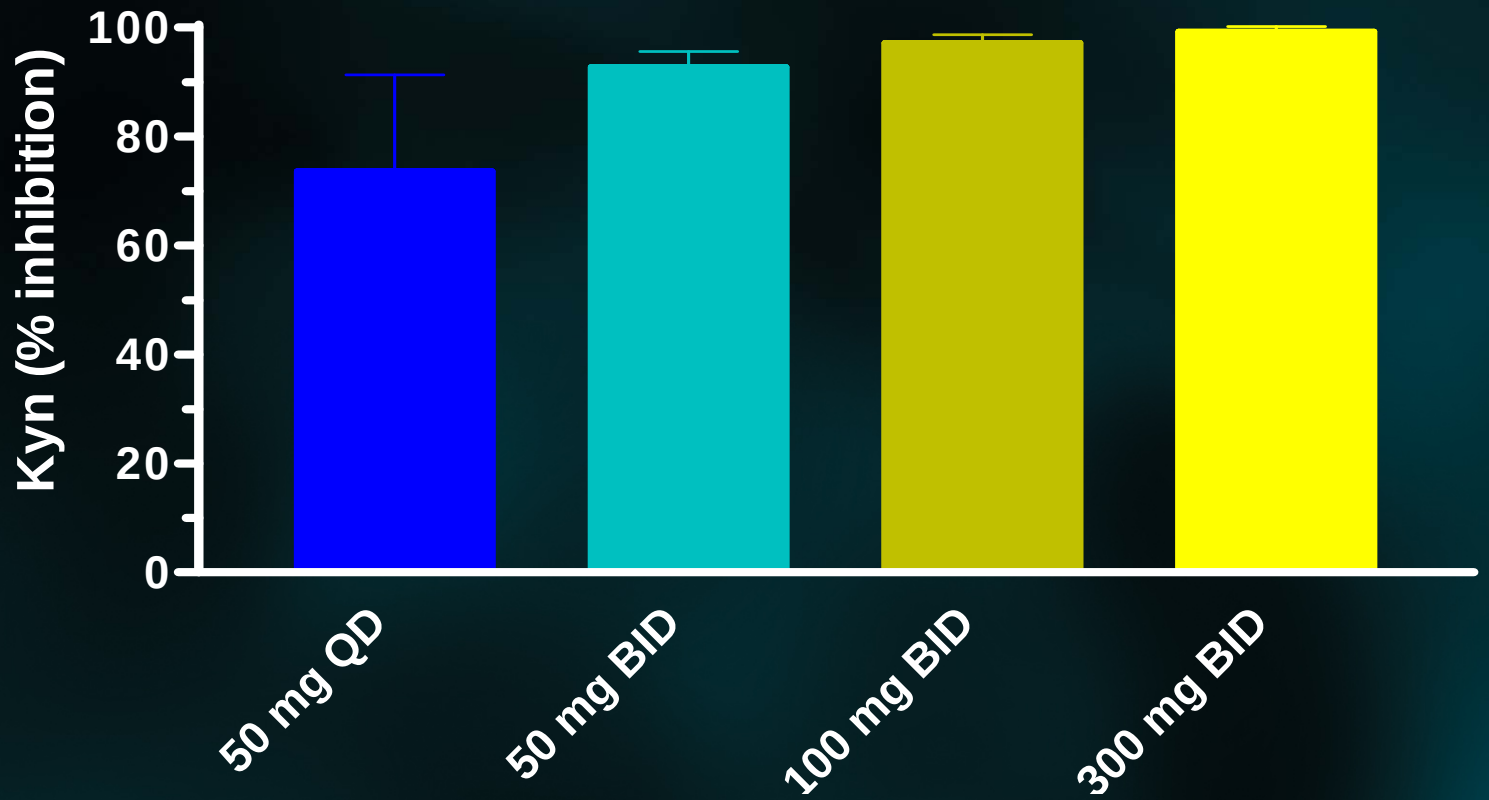
Basic study design

- Non-randomized, open-label, single agent dose escalation in advanced cancers (all tumor types) to assess safety and tolerability and to determine the maximum tolerated dose
- Safe Starting Dose of 960 mg, first cohort received 50 mg
- Endpoints to include:
  - Characterization of the pharmacokinetics of INCB24360
  - Analysis of PD markers
    - IDO whole blood assay and plasma tryptophan/kynurenine ratio
    - Markers of immune cell activation
    - Markers of inflammation
    - Correlation of effects with IDO1 expression in primary biopsy
  - Evidence of anti-tumor activity

INCB24360 inhibits Kyn generation in patients

Day 15 PD:

- Dose dependent PD effect
- Consistent PD profile observed in all subjects in a cohort
- PD effects are consistent with the PK profile



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