Immunotherapy for the Treatment of Brain Malignancies

Theodore S. Johnson, M.D., Ph.D.

Georgia Regents University Cancer Center
Cancer immunology, Inflammation and Tolerance (CIT) Program
Pediatric Immunotherapy Program

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Disclosures

- Theodore S. Johnson, M.D., Ph.D.
  - No relevant financial relationships exist with respect to this presentation
  - Off-label use of chemotherapy drugs will be discussed for pediatric patients

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Objectives

- Identify 3 immune checkpoint pathways that are being studied in brain cancer
- Discuss current clinical trials that use drugs to block immune checkpoints in patients with brain cancer
- Understand the concept of using combinatorial immune checkpoint blockade to treat brain cancer
- Discuss the concept of the Pediatric Piggyback Trial design

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What makes a viable tumor environment?

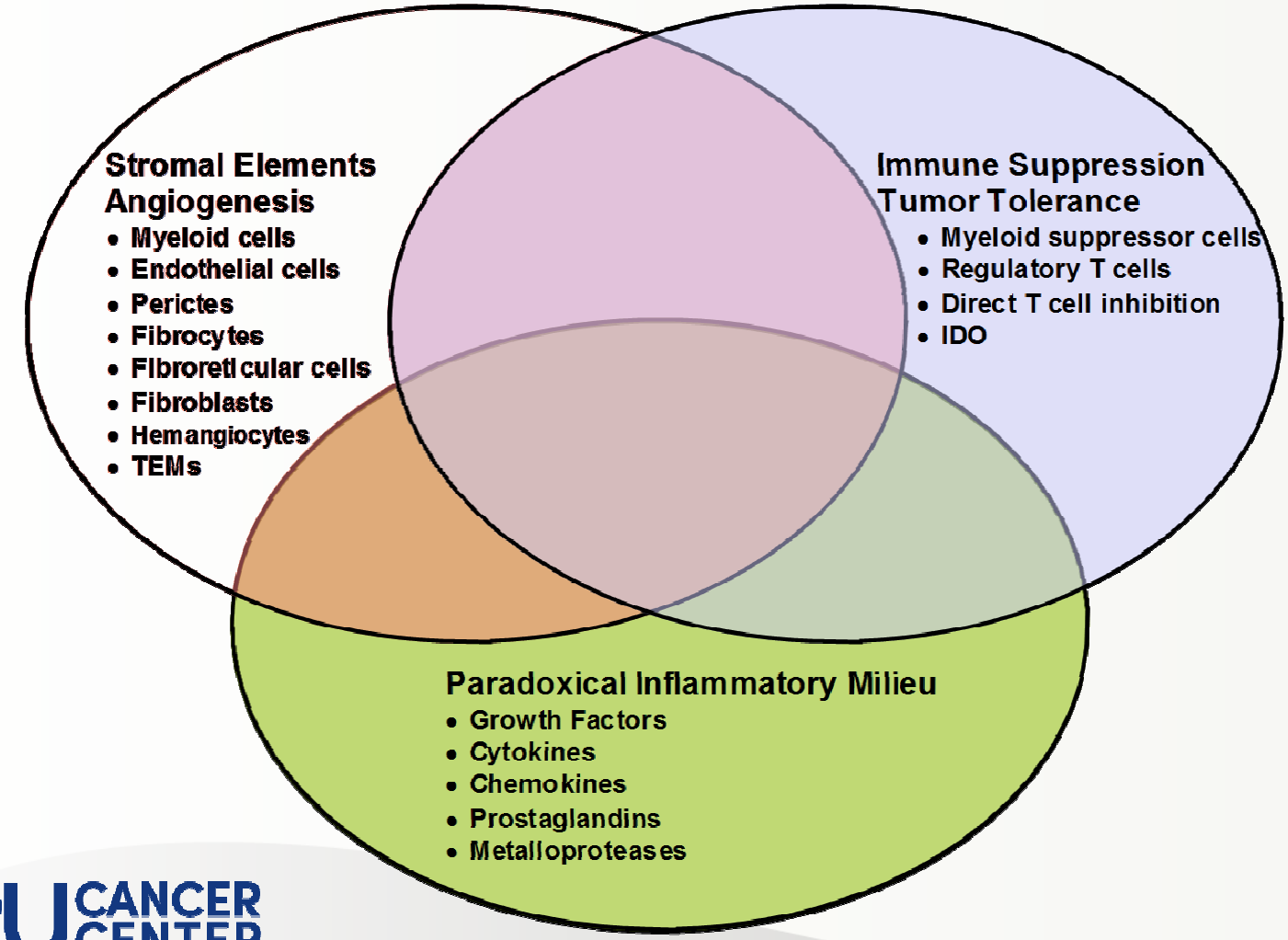

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Figure adapted from: Johnson, *et al*. Clinical and Developmental Immunology. 2012, 2012: 1-14.

What makes a viable tumor environment?

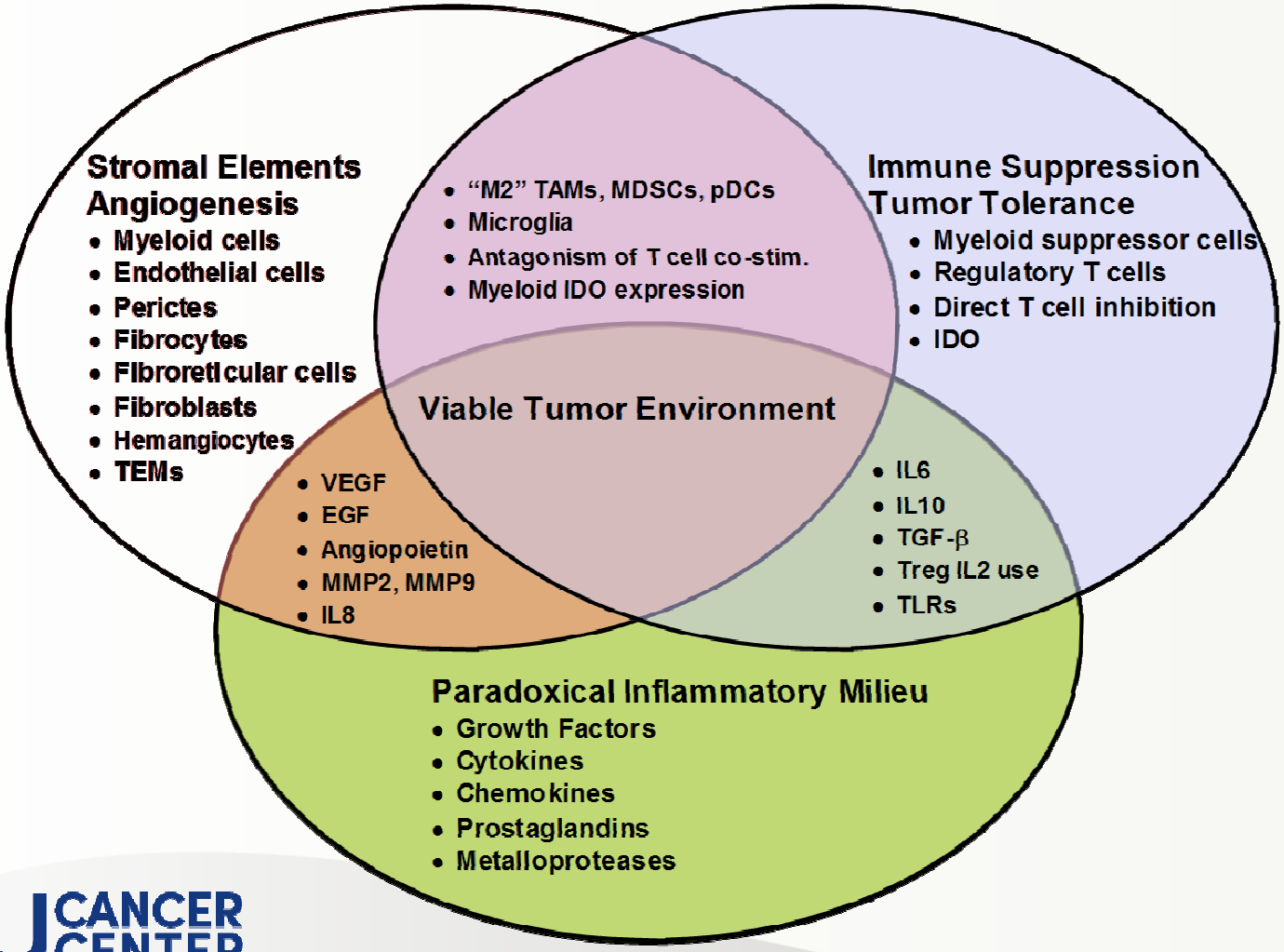

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Figure adapted from: Johnson, *et al*. Clinical and Developmental Immunology. 2012, 2012: 1-14.

Specialized immunology of brain tumors

General peripheral tolerance

- T cell negative selection in thymus
- Natural (thymic) Tregs
- Acquired (adaptive) Tregs
- Local immunosuppression (IDO, TGF-β, IL10, CTLA-4, PD1)

CNS-specific privilege

- Reduced lymphatic transport to draining lymph nodes
- Lack of resident immunogenic APCs (dendritic cells)
- Specialized endothelium excludes naïve T cells
- Local immunosuppression by astrocytes and microglia

Tumor-induced immunosuppression (CNS and non-CNS)

- Local activation of natural Tregs
- Tumor-specific (adaptive) Tregs
- Local intratumoral immunosuppression
  - IDO
  - Arginase
  - TGF-β
  - IL10
  - CTLA-4
  - PD1/PD-L1
- Myeloid-derived suppressor cells
- Tolerogenic APCs
- Tolerogenic draining lymph nodes
- Quiescent vascular endothelium

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Figure adapted from: Johnson, *et al*. Clinical and Developmental Immunology. 2012, 2012: 1-14.

Targets for Immunotherapy

Immune checkpoint blockade		
IDO	inhibition	(small molecule)
CTLA-4	blockade	(antibody)
PD1/PDL1	blockade	(antibody)
Vaccine		
Tumor lysates		
Dendritic cell-based		
Antigen/peptide-based		
Viral delivery of DNA		
Heat shock protein-peptide complex		
GMCSF-assisted		
Adoptive lymphocyte transfer		
Autologous lymphocyte expansion/activation ex vivo		
Chimeric antigen receptor-modified (CAR) T cells		
Antibody-based therapy		
Biological pathway modifier		
Antigen-directed toxin delivery		
Antigen-directed radiopharmaceutical delivery		
Bispecific T cell engager (BiTE)		
Oncolytic virus therapy		
Adenovirus		
Herpes simplex virus		
Poliovirus		

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Table adapted from: P Fecci, *et al*. Clinical Cancer Research. 2014, 20: 5620.

Indoleamine 2,3-dioxygenase (IDO)

- IDO is the third of the known immune checkpoints
  - Along with the T cell checkpoints CTLA-4 and PD-1
- IDO is a natural endogenous molecular mechanism of immune suppression
  - IDO can impose *de novo* peripheral tolerance
- IDO is counter-regulatory
  - Induced by inflammation, but suppresses immune responses
- IDO regulates both adaptive and innate responses
  - suppresses effector T cells, activates Tregs
  - control of local inflammation, myeloid cell phenotype, etc.

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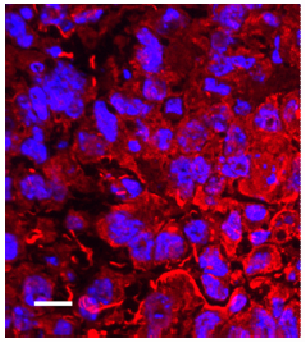
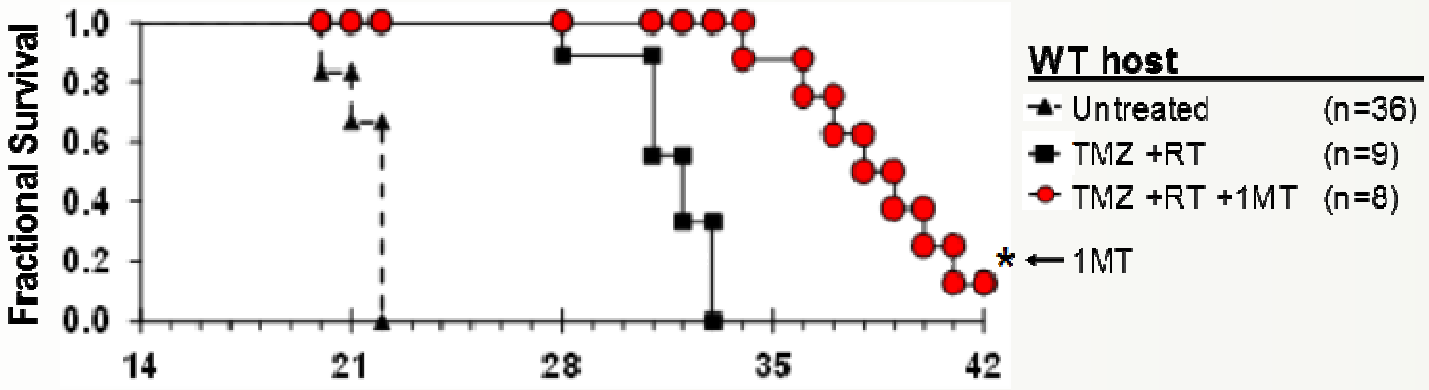
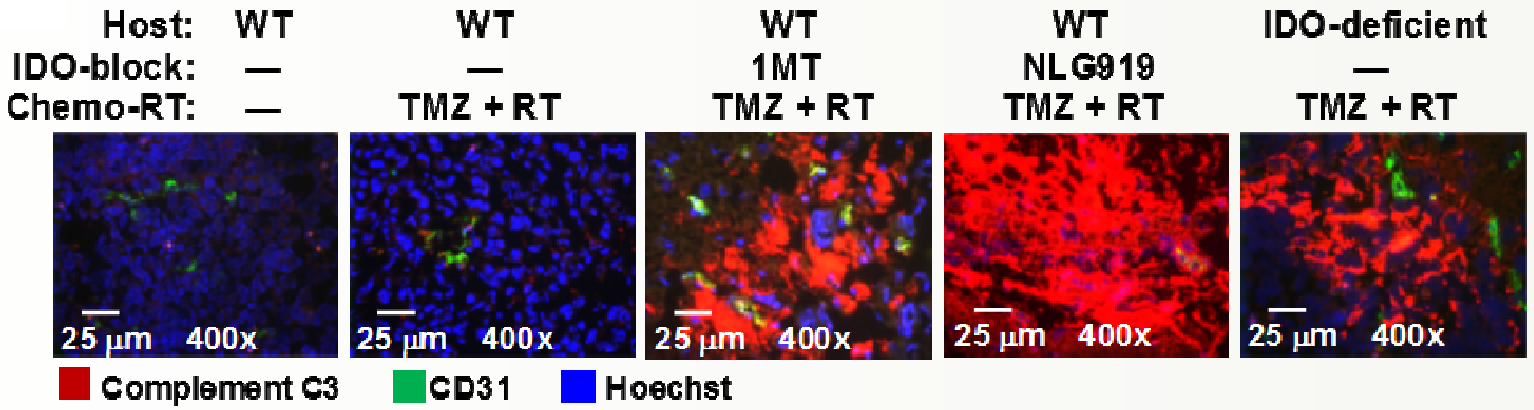
Animal model of glioblastoma: IDO blockade as a therapeutic strategy

Mouse GL261







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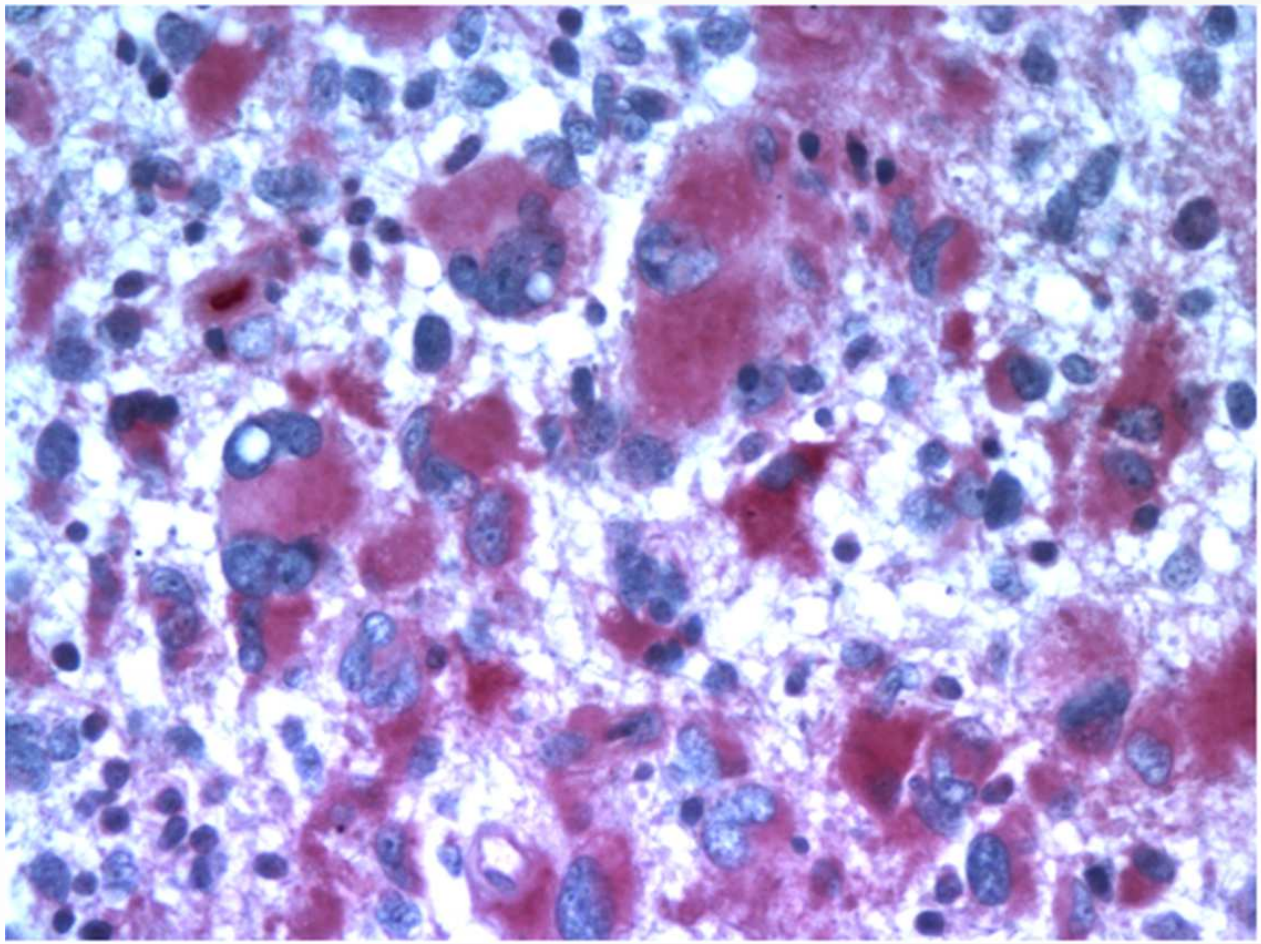
Figures adapted from: Li, *et al*. Journal for Immunotherapy of Cancer. 2014, 2: 21.

IDO expression in glioblastoma patients



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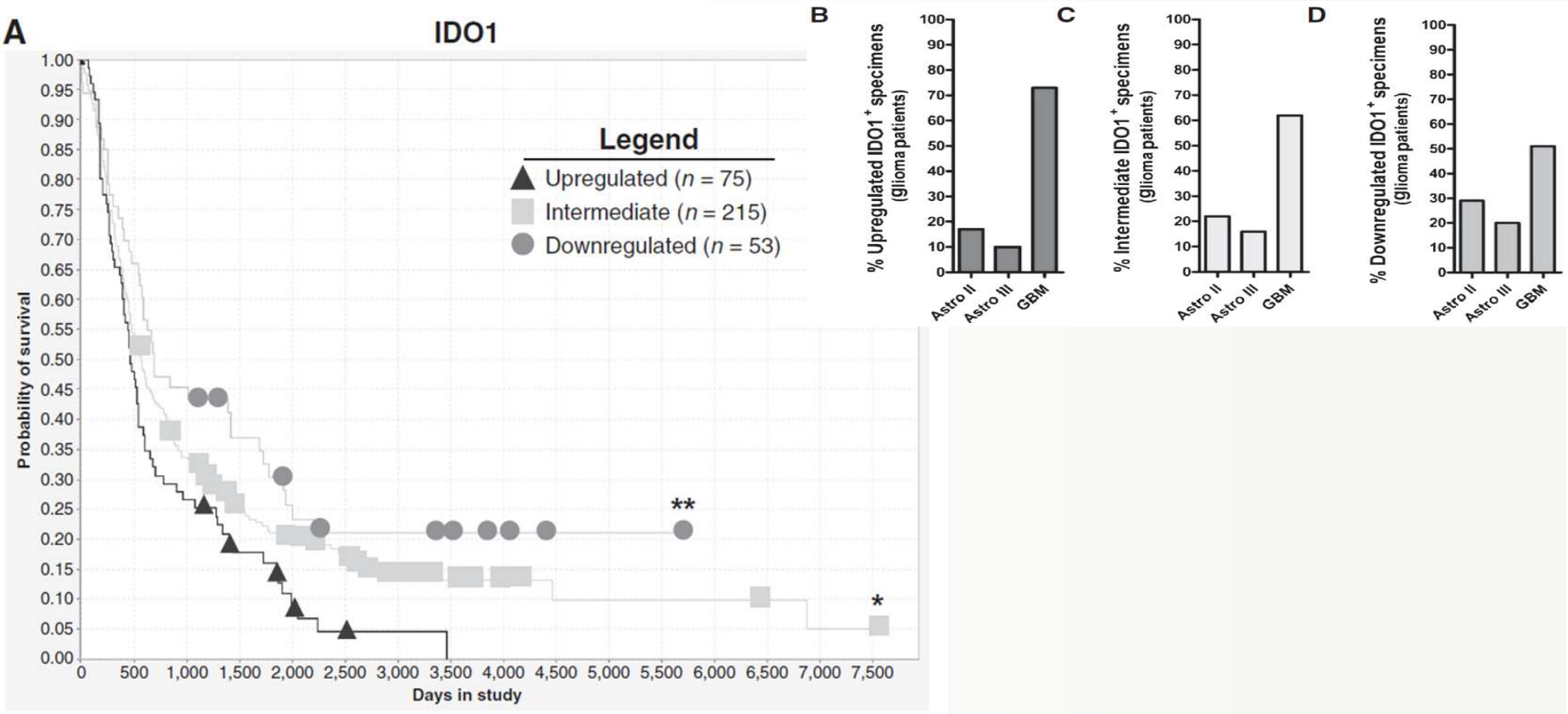
IDO levels in first biopsy correlate with poor outcome in glioma patients



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Figures adapted from: Wainwright, *et al*. Clinical Cancer Research. 2012, 18: 6110.

1. A phase Ib/II study of the combination of indoximod and temozolomide for adult patients with temozolomide-refractory primary malignant brain tumors (NCT02052648)

Phase I: Indoximod (dose-escalation, PO BID on days 1-28), in combination with temozolomide (qDay on days 1-5), for patients 18-70 with progressive glioblastoma;

28 day cycles until disease progression or unacceptable toxicity

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Phase Ib results: indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

Table 2. Patient Demographic and Baseline Characteristics

Characteristic	Indoximod + TMZ (N = 12)
Gender, n (%)	
Female	5 (41.7)
Male	7 (58.3)
Race, n (%)	
White	9 (75.0)
Black/African American	3 (25.0)
Median age (range), years	48.5 (27-62)
Diagnosis	
GBM	10 (83.3)
Oligodendroglioma	1 (8.3)
Anaplastic astrocytoma	1 (8.3)

TMZ, temozolomide; GBM, glioblastoma multiforme.

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Table adapted from: Colman, *et al*. ASCO abstract. 2015.

Phase Ib results: indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

Table 3. Summary of AEs for Indoximod + TMZ (N = 12)

	Number of patients, n (%)		Number of patients, n (%)
Grade ≥3 AEs			
Fatigue	2 (17)	Vomiting	1 (8)
Hyperglycemia	1 (8)	Insomnia	1 (8)
Seizure	1 (8)	Extremity pain	1 (8)
Arm pain	1 (8)		
Treatment-related AEs*			
Nausea	4 (33)	Pruritus	1 (8)
Fatigue	2 (17)	Vomiting	1 (8)
Edema	1 (8)		

AE, adverse event; TMZ, temozolomide.

*All treatment-related AEs were grade 1 or 2 events except for fatigue, in which 1 patient had a grade 3 event.

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Table adapted from: Colman, *et al*. ASCO abstract. 2015.

Phase Ib results: indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

- The MTD for indoximod in combination with temozolomide was 1,200 mg PO BID
- One (8%) patient currently remains on therapy
- One (8%) patient showed an ongoing partial response after having exhibited stable disease for 10 months
- Four (33%) additional patients showed stable disease ranging from 4 to 11 months
- Among the 5 patients with responses better than progressive disease, 4 (80%) had a diagnosis of GBM

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Adapted from: Colman, *et al*. ASCO abstract. 2015.

Phase Ib results: indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

- One (8%) patient showed a partial response after having exhibited stable disease for 10 months
  - 42-year-old African American woman with a left fronto-parietal GBM
    - Unable to have definitive surgical resection due to location of tumor
    - Treated initially with standard chemoradiotherapy (60 Gy over 6 weeks with temozolomide [75 mg/m2/day]) followed by maintenance temozolomide
  - Progressive disease documented after 5 cycles of maintenance temozolomide
    - Subsequently, treated with single-agent bevacizumab
  - GBM progressed again 6 months later and bevacizumab was stopped

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  - Progressive disease documented after 5 cycles of maintenance temozolomide
    - Subsequently, treated with single-agent bevacizumab
  - GBM progressed again 6 months later and bevacizumab was stopped
  - Treated with indoximod + temozolomide
    - Stable disease with slow but modest reduction in tumor size over 10 months
    - Partial Response was achieved by RANO criteria after 12 months of therapy

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Adapted from : Colman, *et al*. ASCO abstract. 2015.

Phase Ib results: indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

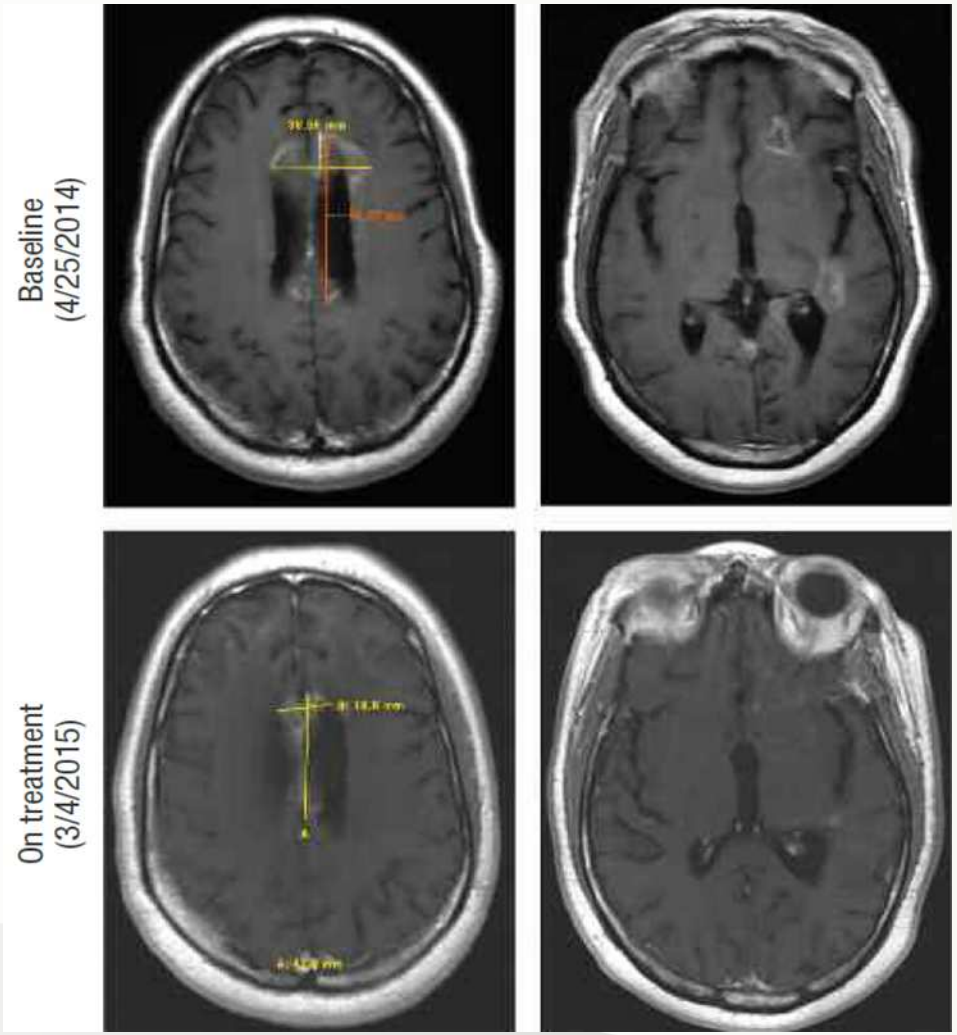

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Figure adapted from: Colman, *et al*. ASCO abstract. 2015.

Phase II:
indoximod + temozolomide for refractory primary malignant brain tumors (NCT02052648)

- 28-day cycles until disease progression or toxicity
- Currently enrolling relapsed/refractory glioblastoma patients 16-70 years of age in 3 cohorts:
  - Indoximod (days 1-28) + temozolomide (days 1-5)
  - Indoximod + temozolomide and bevacizumab (q2 weeks)
    - patients who progressed while on bevacizumab
  - Indoximod + temozolomide and stereotactic radiosurgery
    - patients with GBM who may benefit from tumor debulking

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Adapted from : Colman, *et al*. ASCO abstract. 2015.

Pediatric Piggyback Trial Design

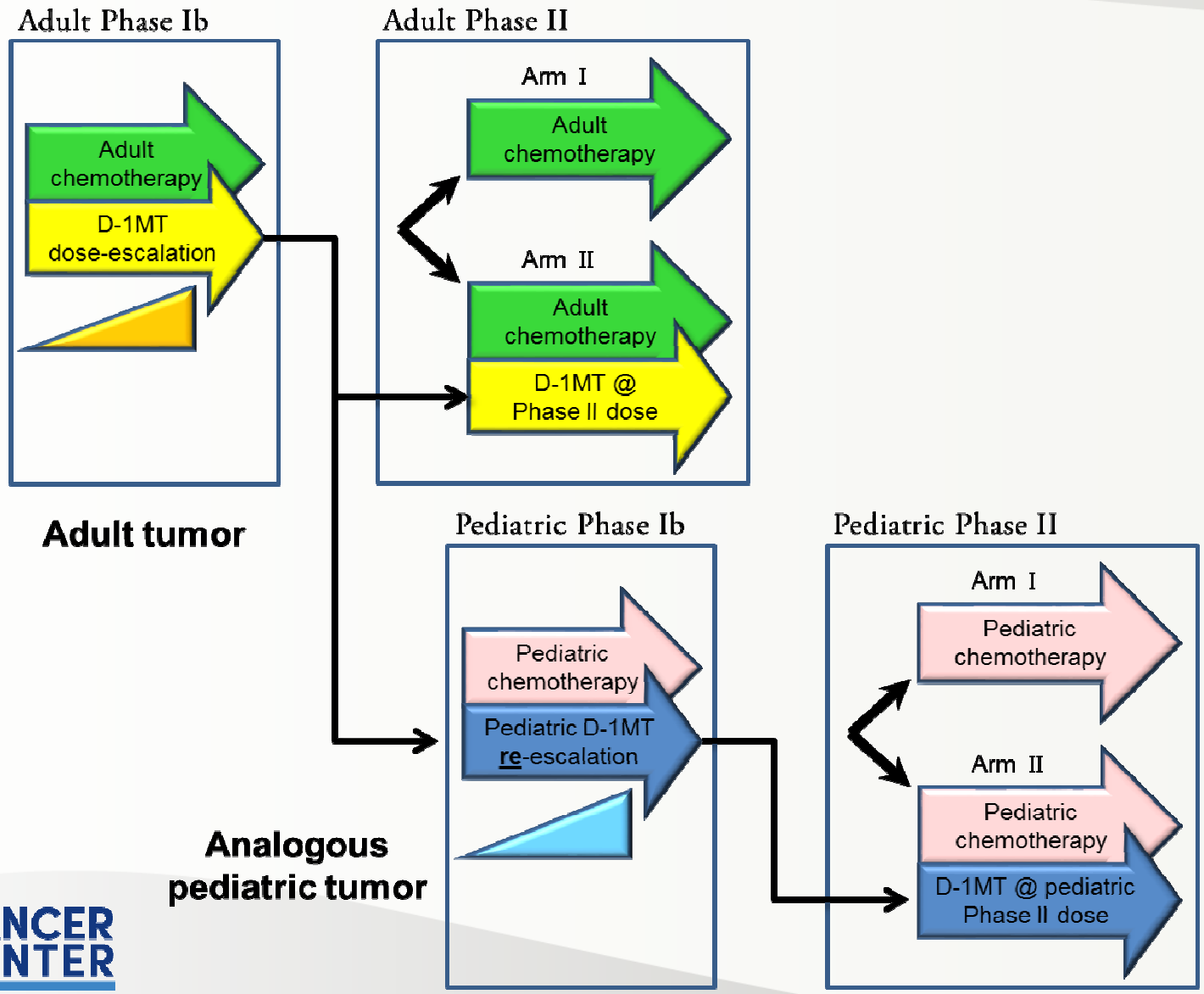

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Figure courtesy of David Munn, MD

Advantages of the Pediatric Piggyback Trial Design

- The linked adult toxicity data provides a measure of protection for the pediatric cohort
- The incremental cost to drug companies is not large
- Foundations or institutions can fund the pediatric component at modest cost

  ... thus leveraging the larger adult infrastructure

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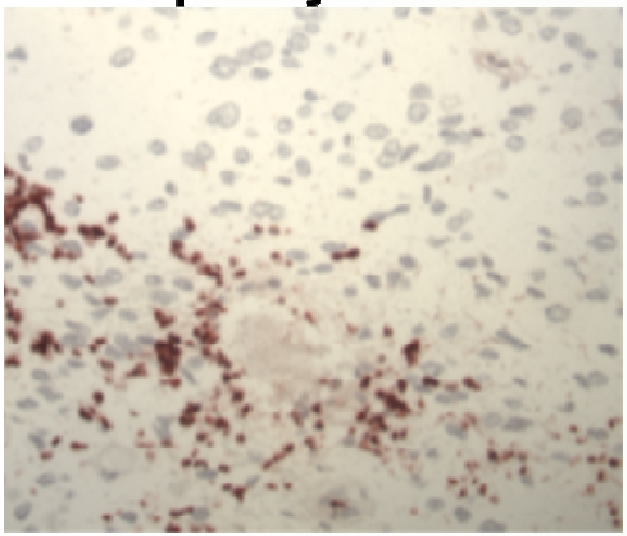
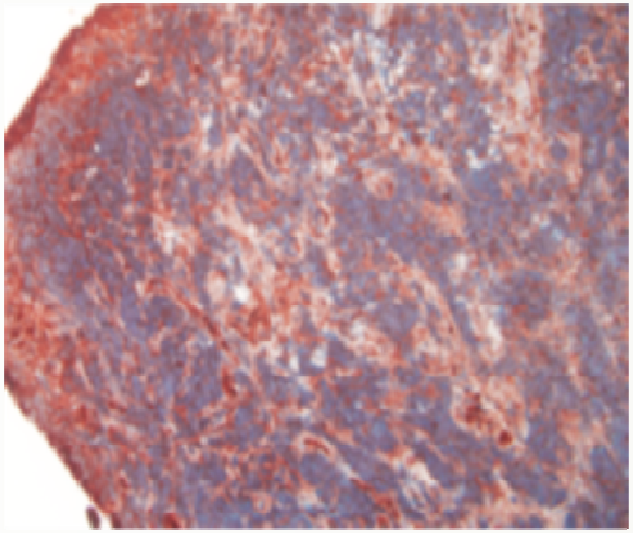
IDO expression in pediatric brain tumors

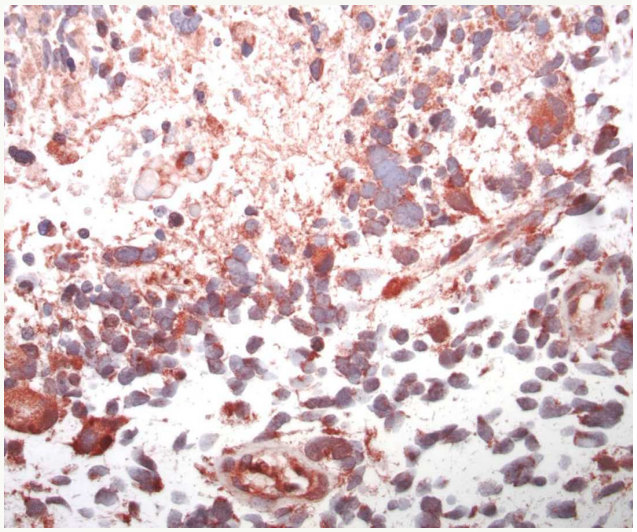
Ependymoma



Medulloblastoma



Glioblastoma



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2. Phase I trial of indoximod in combination with temozolomide-based therapy for children with progressive primary brain tumors (NCT02502708)

- 28-day cycles x 12 planned cycles, until disease progression or unacceptable toxicity
- Relapsed/refractory brain tumor patients age 3-21 years enroll in one of 3 groups:

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2. Phase I trial of indoximod in combination with temozolomide-based therapy for children with progressive primary brain tumors (NCT02502708)

Group 1: Indoximod (dose-escalation, PO BID on days 1-28), plus temozolomide (qDay on days 1-5), for children with progressive brain tumors ("Core Regimen")

Group 2: Indoximod (RP2D) plus temozolomide "Core Regimen" for pediatric patients with progressive brain tumors

(expansion cohorts)

- Group 2a: High-grade glioma
- Group 2b: Ependymoma
- Group 2c: Medulloblastoma

Group 3: Indoximod (dose-escalation), in combination with up-front conformal radiation therapy, for children with progressive brain tumors, followed by "Core Regimen" Maintenance therapy

- Patients who may benefit from tumor debulking

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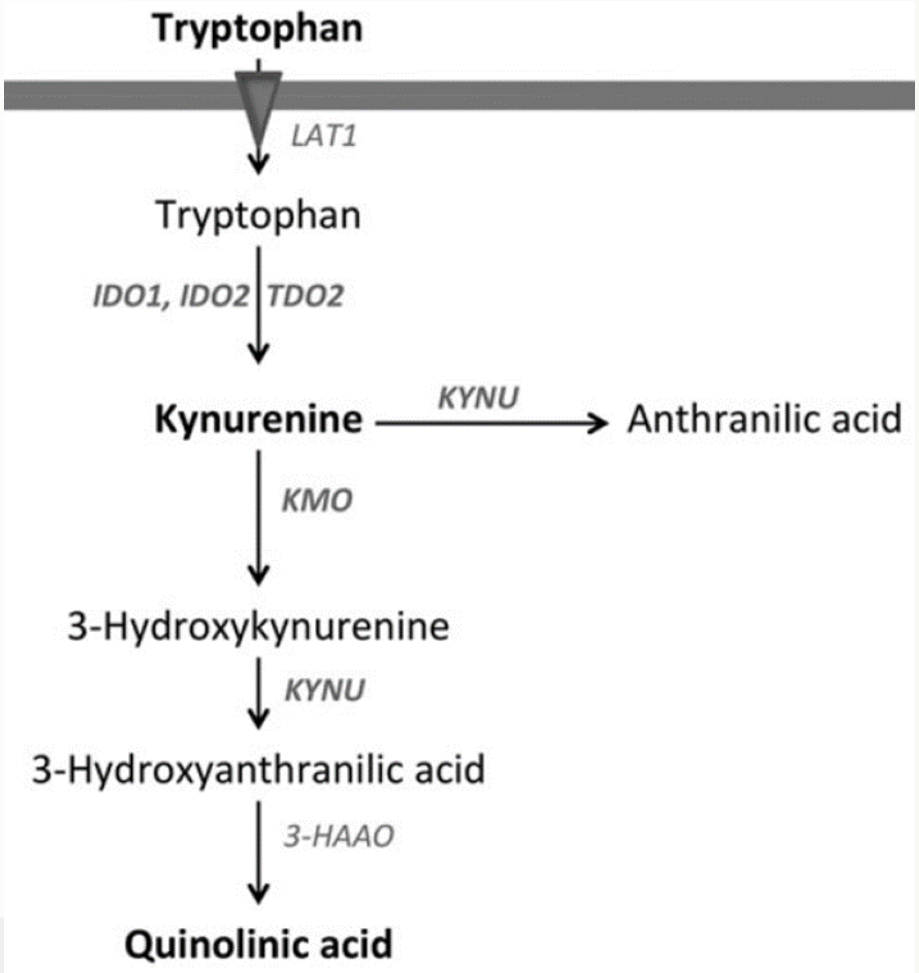
Assessment of IDO activity *in vivo*: α-[^{11}C]-methyl-L-tryptophan PET avidity



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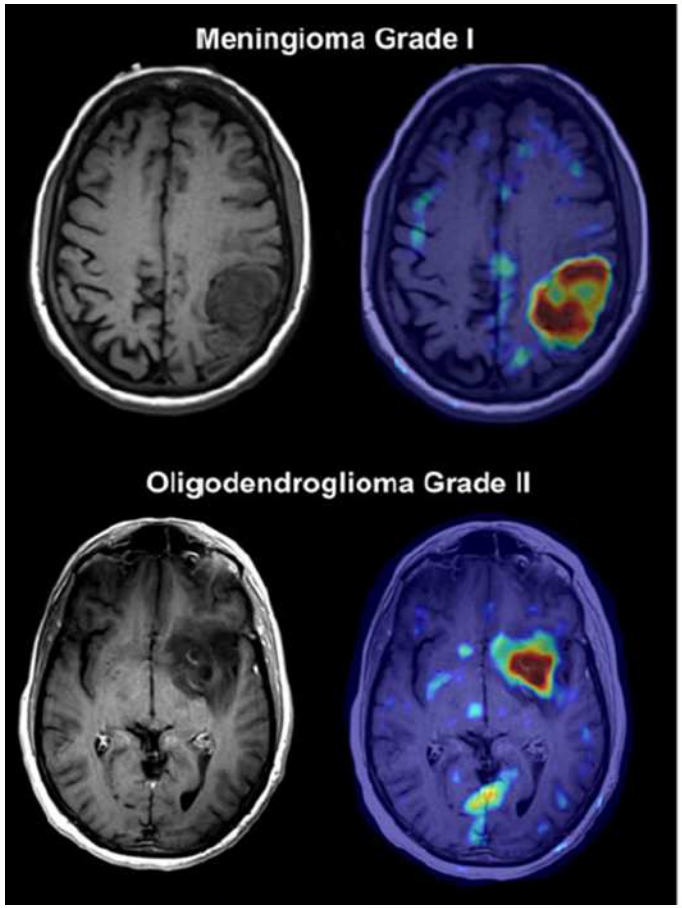
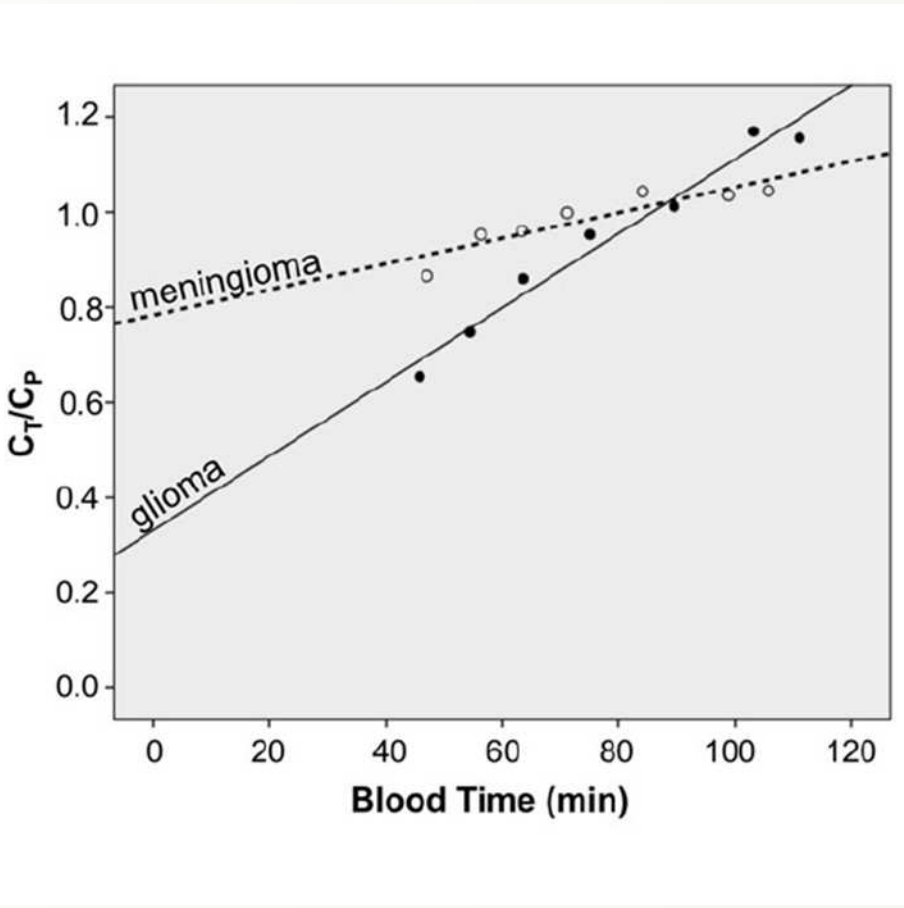
Figures adapted from: Bosnyak, *et al*. Neuro-oncology. 2015, 17: 1284.

Assessment of IDO activity *in vivo*: α-[^{11}C]-methyl-L-tryptophan PET avidity





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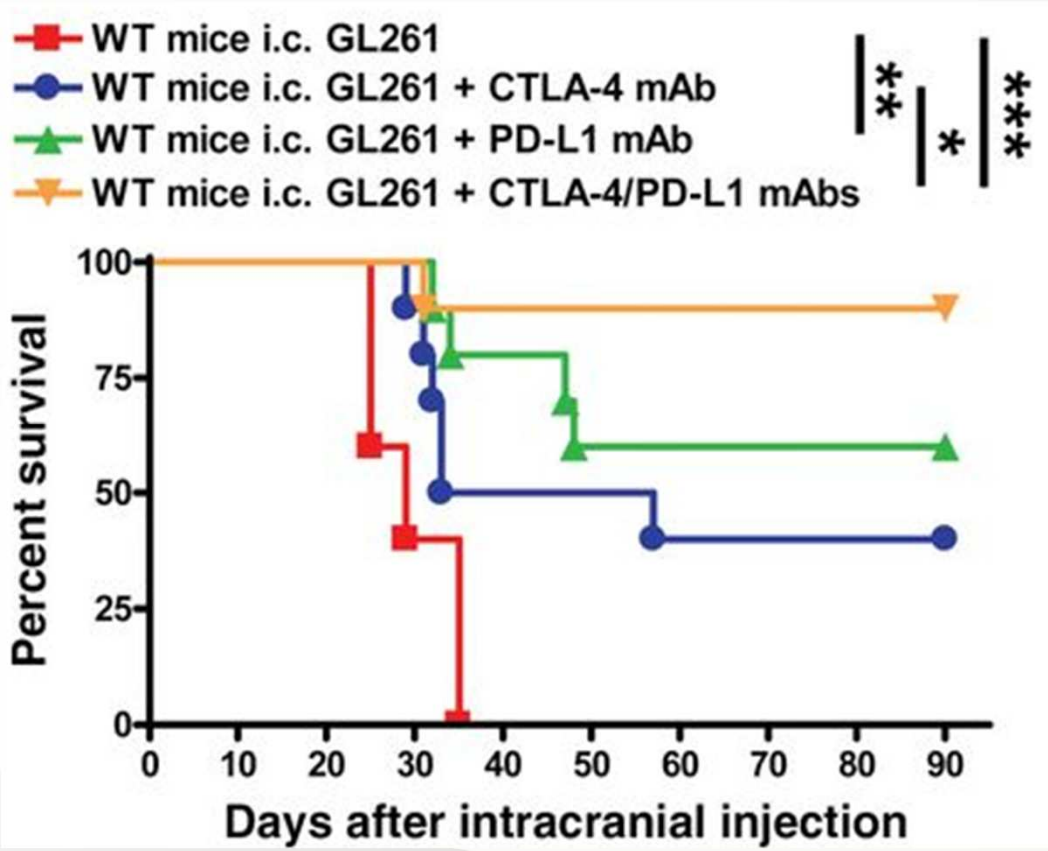
Immune checkpoint blockade and combinatorial checkpoint blockade



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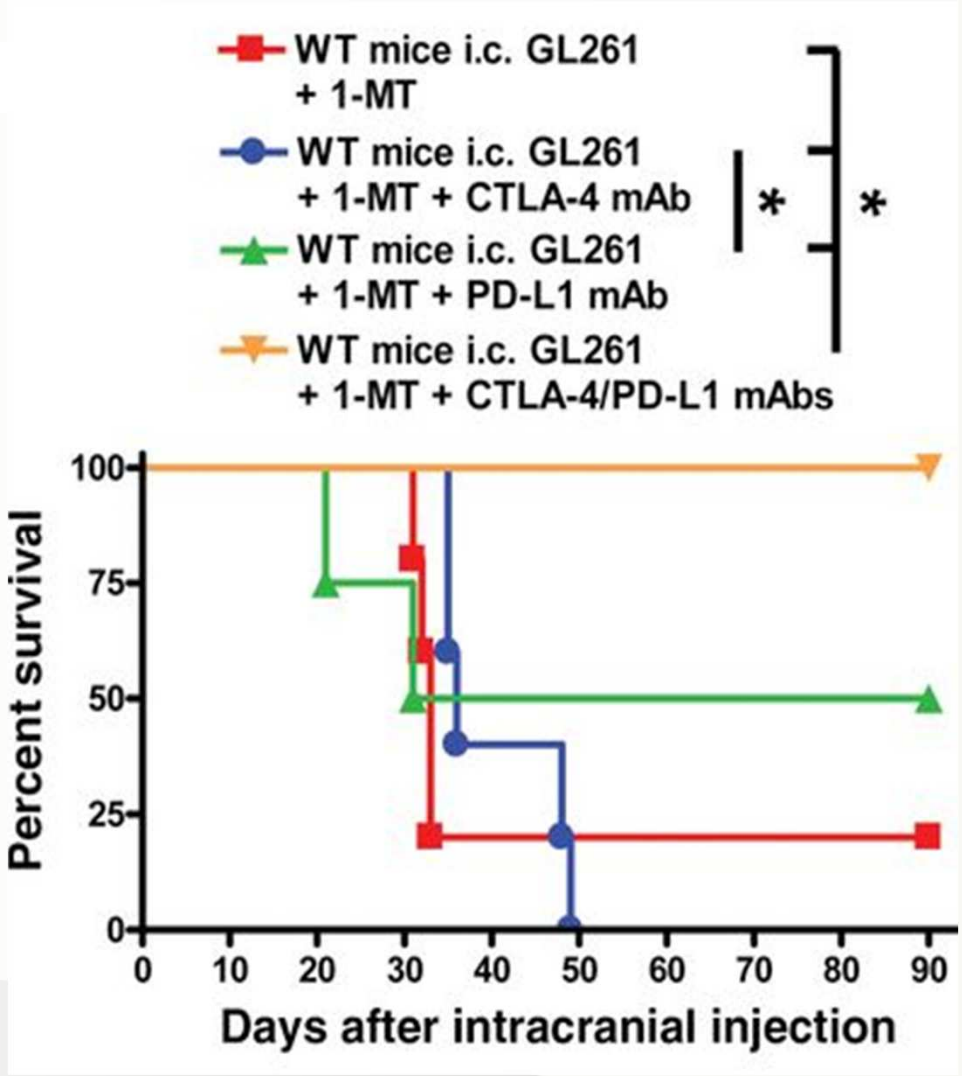
Figures adapted from: Wainwright, *et al*. Clinical Cancer Research. 2014, 20: 5290.

Immune checkpoint blockade and combinatorial checkpoint blockade



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Figures adapted from: Wainwright, *et al*. Clinical Cancer Research. 2014, 20: 5290.

PD1/PDL1 pathway blockade

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3. A randomized phase III open label study of nivolumab versus bevacizumab, and multiple phase I safety cohorts of nivolumab or nivolumab in combination with ipilimumab for glioblastoma (NCT02017717)

- Histologically confirmed Grade IV malignant glioma
- Cohorts 1, 1b, and 2:
  - Any recurrence of GBM
  - Previous treatment with radiotherapy and temozolomide
- Cohort 1c:
  - First diagnosis of GBM with resectable disease
- Cohort 1d:
  - First diagnosis of GBM with resectable disease, unmethylated MGMT

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3. Multiple phase I safety cohorts of nivolumab or nivolumab with ipilimumab for glioblastoma (NCT02017717)

- Experimental Arm N: Nivolumab
  - Cohorts 1, 1c, 1d:
    - Nivolumab 3mg/kg intravenously q2 weeks until disease progression or unacceptable toxicity

- Experimental Arm N + I: Nivolumab + Ipilimumab
  - Cohort 1:
    - Nivolumab 1mg/kg + Ipilimumab 3mg/kg intravenously q3 weeks x 4 doses, then Nivolumab 3mg/kg q2 weeks until progression or toxicity
  - Cohort 1b:
    - Nivolumab 3mg/kg + Ipilimumab 1mg/kg intravenously q3 weeks x 4 doses, then Nivolumab 3mg/kg q2 weeks thereafter until progression or toxicity

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3. Randomized phase III open label study of nivolumab versus bevacizumab for recurrent glioblastoma (NCT02017717)

- Experimental Arm N: Nivolumab
  - Cohort 2:
    - Nivolumab 3mg/kg intravenously q2 weeks until disease progression or unacceptable toxicity

- Comparator Arm B: Bevacizumab
  - Cohort 2:
    - Bevacizumab 10 mg/kg intravenously q2 weeks until disease progression or unacceptable toxicity

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4. A phase I and open label, randomized, controlled phase II study testing the safety, toxicities, and efficacy of MK-3475 (pembrolizumab) in combination with MRI-guided laser ablation in recurrent malignant gliomas (NCT02311582)

- Unequivocal evidence of tumor progression as documented by biopsy or brain MRI scan per RANO criteria
- Proscriptive prior chemo-radiotherapy requirements
- Phase I:
  - Histologically confirmed grade III or IV malignant glioma
  - Candidate for MLA based on the size, location, and shape of the recurrent tumor
    - Surgical resection/debulking prior to MLA is allowed per standard of care
- Phase II:
  - Histologically confirmed grade IV malignant glioma (GBM)
  - Candidate for surgical resection/debulking followed by MLA treatment of residual tumor based on the size, location, and shape of the recurrent tumor

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4. A phase I and open label, randomized, controlled phase II study testing the safety, toxicities, and efficacy of MK-3475 in combination with MRI-guided laser ablation in recurrent malignant gliomas (NCT02311582)

- Phase I: MK-3475 + MLA
  - MK-3475 (dose-escalation) q3 weeks until progression or unacceptable toxicity
  - MLA will take place no more than 2 weeks after the first dose of MK-3475

- Phase II: MK-3475
  - MK-3475 (RP2D) will be given once prior to surgical debulking and again q3 weeks beginning 3 weeks after surgical debulking

    MK-3475 + MLA
  - MK-3475 (RP2D) will be given once prior to surgical debulking and again q3 weeks beginning no more than 1 week after MLA (if applicable).

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5. Phase II study to evaluate the clinical efficacy and safety of MEDI4736 in patients with glioblastoma (NCT02336165)

- This is an open-label, non-randomized, multicenter Phase 2 study of MEDI4736 with three non-comparative cohorts:
- Cohort A:
  - Newly diagnosed unmethylated MGMT GBM will receive MEDI4736 every 2 weeks in combination with standard radiotherapy
- Cohort B:
  - Bevacizumab-naïve patients with recurrent GBM will receive MEDI4736 every 2 weeks as monotherapy
- Cohort C:
  - Bevacizumab-refractory patients with recurrent GBM will receive MEDI4736 every 2 weeks in combination with continued bevacizumab

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PD1/PDL1 pathway blockade open for pediatric patient enrollment

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6. A phase I/II clinical trial of CT-011 (pidilizumab) in diffuse intrinsic pontine glioma and relapsed glioblastoma multiforme (NCT01952769)

- Age: 3-90 years
- Study location: Jerusalem
- Diagnosis:
  - Imaging diagnosis of diffuse intrinsic pontine glioma (DIPG)
  - Glioblastoma (GBM arm has filled accrual)

- Pidilizumab (CT-011) q2 weeks, until disease progression or a serious adverse event

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7. Phase I pembrolizumab in treating younger patients with recurrent, progressive, or refractory high-grade gliomas or diffuse intrinsic pontine gliomas (NCT02359565)

- Age: 1-21 years
- Diagnosis:
  - Histologically confirmed recurrent, progressive or refractory non-brainstem high-grade glioma
  - Imaging or histological diagnosis of diffuse intrinsic pontine glioma (DIPG) that is recurrent, progressive, or refractory
- Excludes patients previously treated with immune checkpoint blockade
- Pembrolizumab (using recommended adult dose) q21 days x 34 courses, in the absence of disease progression or unacceptable toxicity

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Combinatorial checkpoint blockade

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3. Phase I safety cohorts of nivolumab or nivolumab with ipilimumab for glioblastoma (NCT02017717)

- Cohorts 1 and 1b:
  - Recurrent glioblastoma
  - Previous treatment with radiotherapy and temozolomide
- Experimental Arm N: Nivolumab
  - Cohort 1:
    - Nivolumab 3mg/kg intravenously q2 weeks until disease progression or unacceptable toxicity
- Experimental Arm N + I: Nivolumab + Ipilimumab
  - Cohort 1:
    - Nivolumab 1mg/kg + Ipilimumab 3mg/kg intravenously q3 weeks x 4 doses, then Nivolumab 3mg/kg q2 weeks until progression or toxicity
  - Cohort 1b:
    - Nivolumab 3mg/kg + Ipilimumab 1mg/kg intravenously q3 weeks x 4 doses, then Nivolumab 3mg/kg q2 weeks thereafter until progression or toxicity

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8. Phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma (NCT02311920)

- Histologically proven diagnosis of glioblastoma or gliosarcoma
- Must have:
  - a unifocal tumor confined to the supratentorial compartment,
  - and achieve a gross total or near gross total resection
- Excludes prior vaccine-based immunotherapy

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8. Phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma (NCT02311920)

Following standard up-front temozolomide/radiation:

- Arm 1: Ipilimumab with temozolomide
  - Temozolomide 5 day course repeats every 28 days for up to 6 courses;
  - ipilimumab q4 weeks x 4 courses, then q3 months for 4 courses
- Arm 2: Nivolumab with temozolomide
  - Temozolomide 5 day course repeats every 28 days for up to 6 courses;
  - nivolumab q2 weeks x 64 weeks
- Arm 3: Ipilimumab and nivolumab with temozolomide
  - Temozolomide 5 day course repeats every 28 days for up to 6 courses;
  - ipilimumab q4 weeks x 4 courses;
  - nivolumab q2 weeks x 64 weeks

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Checkpoint blockade with DC vaccine

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9. Phase I study of nivolumab with DC vaccines for recurrent brain tumors (NCT02529072)

- First or second recurrence of WHO Grade III or IV glioma or astrocytoma in surgically accessible areas with prior histologic diagnosis
- Bevacizumab-naïve
- Radiation Therapy with ≥ 45 Gray (Gy) tumor dose, completed ≥ 8 weeks prior to study entry

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9. Phase I study of nivolumab with DC vaccines for recurrent brain tumors (NCT02529072)

Nivolumab plus hCMV pp65-LAMP mRNA-pulsed autologous DCs

- Group 1:
  - Nivolumab q2 weeks x 6 doses,
  - then surgery,
  - then nivolumab and vaccine q2 weeks x 4 vaccines,
  - then nivolumab q2 weeks and monthly vaccine x 4 more vaccines,
  - then nivolumab q2 weeks until progression
- Group 2:
  - Nivolumab q2 weeks x 3 doses,
  - then nivolumab and vaccine q2 weeks x 4 vaccines,
  - then surgery,
  - then nivolumab q2 weeks and monthly vaccine x 4 more vaccines,
  - then nivolumab q2 weeks until progression

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Summary and future directions

- Substantial preclinical data supports conducting clinical studies for brain cancer patients, using checkpoint blockade to target these pathways:
  - IDO
  - CTLA4
  - PD1 and PDL1
- Synergy may be achievable by combining immune checkpoint blockade with surgery, radiation therapy, laser ablation, chemotherapy, or other inflammatory treatments
- Synergy may be achievable by using combinatorial immune checkpoint therapy to target different pathways
- The Pediatric Piggyback Trial design allows pediatric trials to open while adult trials are still ongoing, once the adult dosing and toxicity data are available

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