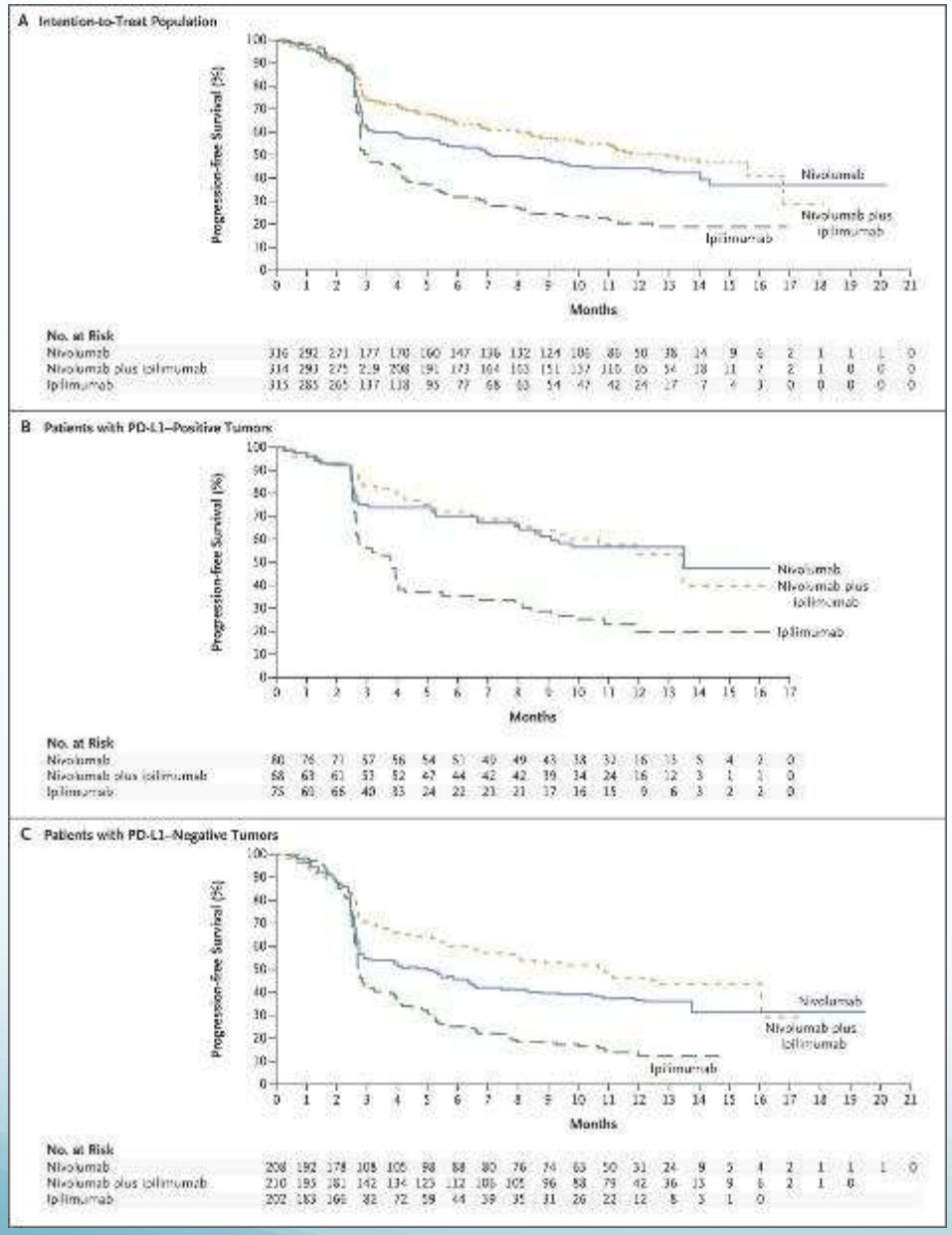
UCLA Jonsson Comprehensive Cancer Center

Treatments to Perturb the Tumor Microenvironment (TLR, IDO, Oncolytic Virus)

Siwen Hu-Lieskovan, MD, PhD

Disclosures

- Consulting Fees: Amgen, Novartis, Vaccinex
- Contracted Research: Pfizer, Plexxikon
- This presentation contains discussion of investigational use of products or use of products for non-FDA approved indications.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

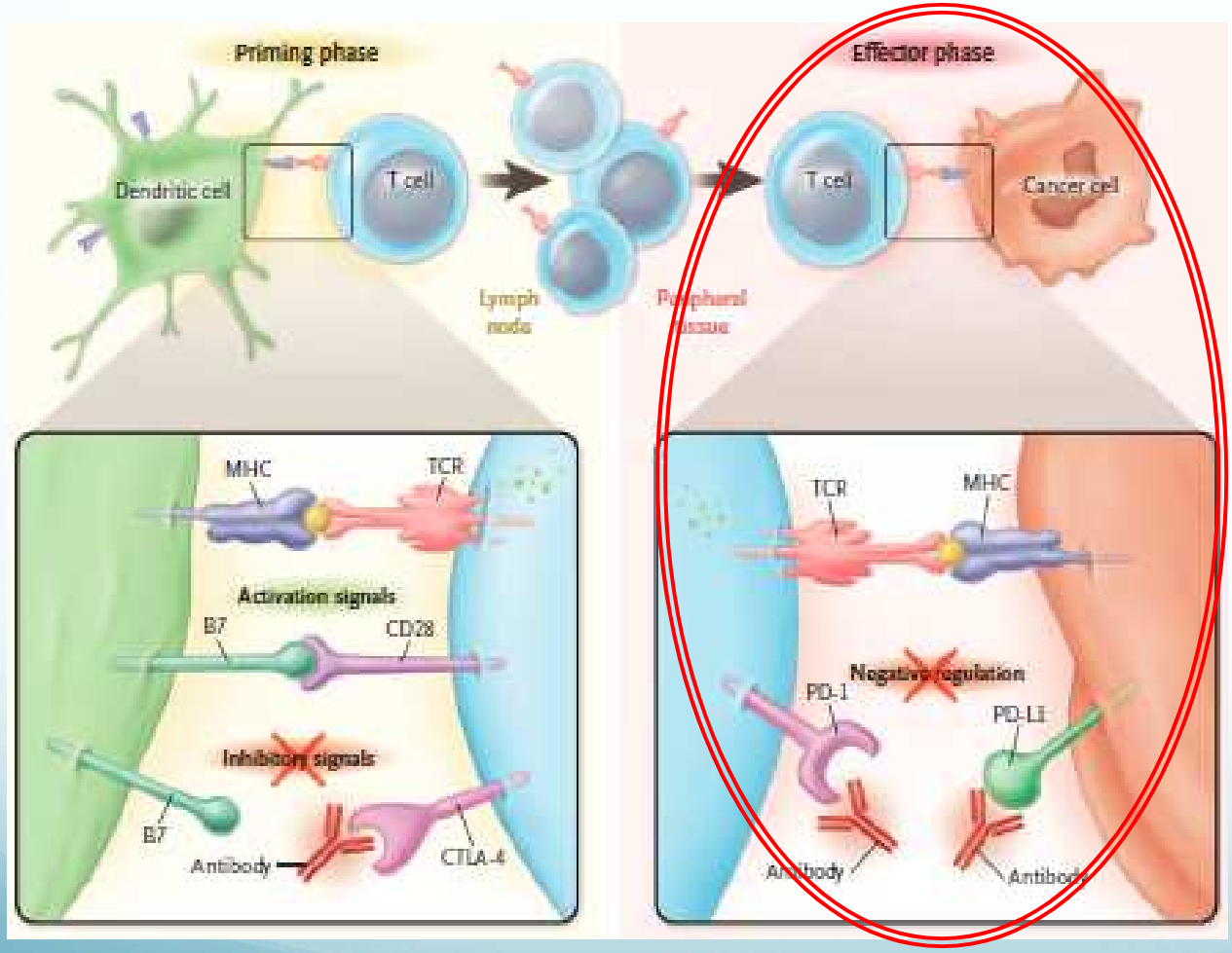
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

- Phase 3 study of combined NIVO+IPI in untreated melanoma:
  - Improved PFS with NIVO+IPI (11.5 months) or NIVO alone (6.9 months) vs. IPI alone (2.9 months)
  - **<u>ORR of 58% NIVO+IPI, 44% NIVO, 19% IPI</u>**
  - Grade 3/4 treatment-related AEs in 55% of patients (NIVO+IPI)

Larkin et al. N Engl J Med 2015;373:23–34.

Response to anti-PD-1/L1 based therapies reply on the patients' ability to mount a tumor specific response, which is then turned off by PD-1/PD-L1 engagements



When there is no pre-existing interferon-induced immune response in tumors then PD-1 blockade is unlikely to work.

Ribas, NEJM 2012; Jun 28; 366 (26): 2517-9

Innate and Adaptive Immunity

Innate immunity is the first line of host defense. Pathogens are detected by receptors that recognize molecular patterns widely expressed by microorganisms – such as DNA and RNA.

Innate responses are:

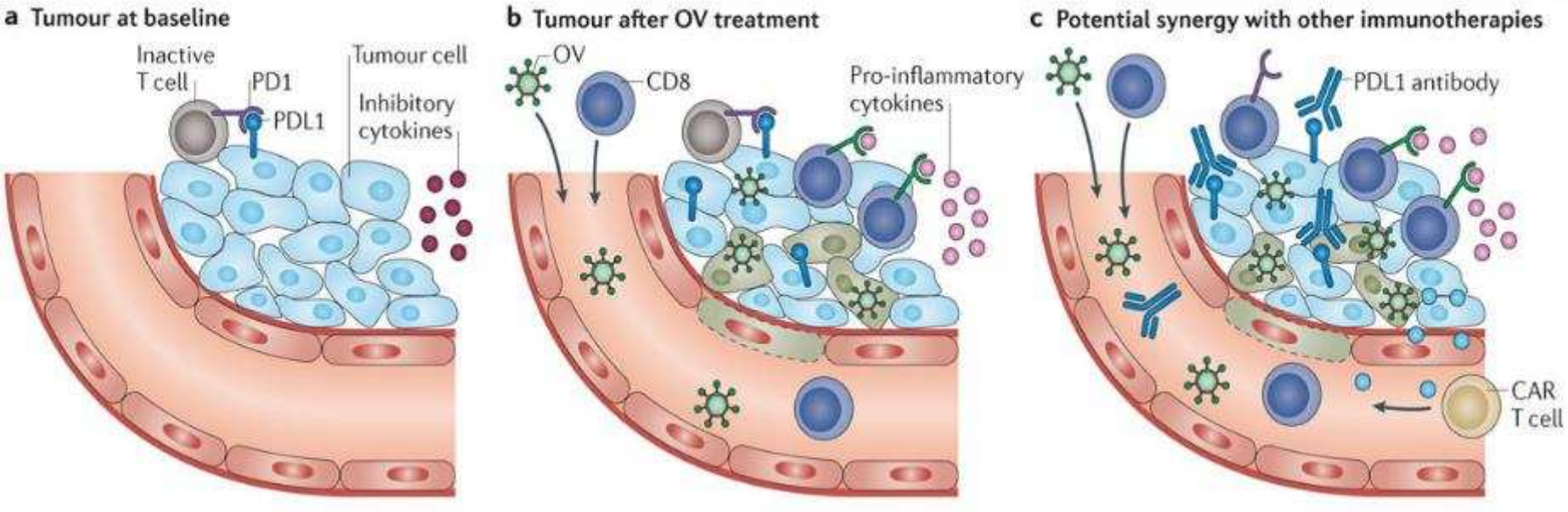
- Rapid (hours)
- Relatively non-specific
- Transient

Adaptive immunity describes responses of T and B lymphocytes. Pathogens are recognized by highly diverse and specific recognition receptors produced through rearrangement and mutation of genes within individual lymphocytes.

Adaptive responses are:

- Slow (days)
- Highly antigen-specific
- Long-lived and exhibit memory

Oncolytic Viruses



Nature Reviews Cancer **14**, 559–567 (2014)

- ✓ Direct tumor cell lyses
- ✓ Release of tumor antigen
- ✓ Attract dendritic cells
- ✓ Release of progeny virus
- ✓ Induce IFN response
- ✓ Up-regulation of PD-L1?

Immune-stimulatory Transgenes Encoded by Oncolytic Viruses

Transgenes	Vectors	Targets
GMCSF	• HSV-1 (REFS 18,25,89) • Vaccinia virus[9,22,90,91] • Adenovirus[92–94] • NDV[95] • Measles virus[96] • VSV[97]	Stimulates production of granulocytes and monocytes, promoting differentiation of monocytes into DCs for antigen presentation
FLT3L	• Adenovirus[98,99] • VSV[100]	Both conventional and plasmacytoid DCs, as well as NK cells
CCL3	Adenovirus[99]	Attracts polymorphonuclear leukocytes
CCL5	Adenovirus[101,102]	T cells (recruitment)
IL2	• HSV-1 (REF. 103) • NDV[95,104]	T cells (activation)
IL4	• Adenovirus[105] • HSV-1 (REF. 106)	T cells and B cells (replication and T_H2 skewing)
IL12	• Adenovirus[107,108] • HSV-1 (REFS 109,110) • VSV[111]	T cells and NK cells (activation)
IL15	• HSV-1 (REF. 112) • VSV[113] • Influenza A virus[114]	T cells and NK cells (activation)
IL18	• Adenovirus[107] • HSV-1 (REFS 115,116)	T cells and NK cells (activation)
IFNA1 or *IFNB1*	• Vaccinia virus[117] • Measles virus[118] • Adenovirus[119,120] • VSV[121]	APCs and T cells (enhanced T cell immunity)
IFNG	Adenovirus[122]	NK cells, T cells and macrophages (activation)
CD80 (encoding cell surface and soluble CD80)	• Adenovirus[106,123] • HSV-1 (REFS 115,116,124)	T cells (co-stimulation)
4-1BBL	• Adenovirus[125] • Vaccinia virus[126]	T cells (co-stimulation)
CD40L	• VSV[50] • HSV-1 (REF. 106)	T cells (co-stimulation)
Genes encoding heat shock proteins	Adenovirus[127,128]	APCs (delivery of peptides and activation)
IL12 and *4-1BBL*	Adenovirus[125]	Combined effects
IL18 and *CD80* (soluble)	HSV-1 (REF. 115)	Combined effects
IL12 and *CD80*	Adenovirus[109]	Combined effects
GMCSF and *CD80*	• Adenovirus[123] • HSV-1 (REF. 129)	Combined effects
IL12, *IL18* and *CD80* (soluble)	Adenovirus[109]	Combined effects

4-1BBL, 4-1BB ligand; APC, antigen-presenting cell; *CCL*, CC-chemokine ligand; *CD40L*, CD40 ligand; *CD80*, T lymphocyte activation antigen CD80; DC, dendritic cell; *FLT3L*, FMS-related tyrosine kinase 3 ligand; GMCSF, granulocyte–macrophage colony stimulating factor; HSV-1, herpes simplex virus 1; *IFN*, interferon; *IL*, interleukin; NDV, Newcastle disease virus; NK, natural killer; T_H2, T helper 2; VSV, vesicular stomatitis virus.

Nature Reviews Cancer **14**, 559–567 (2014)

Oncolytic Virus most advanced in clinical development

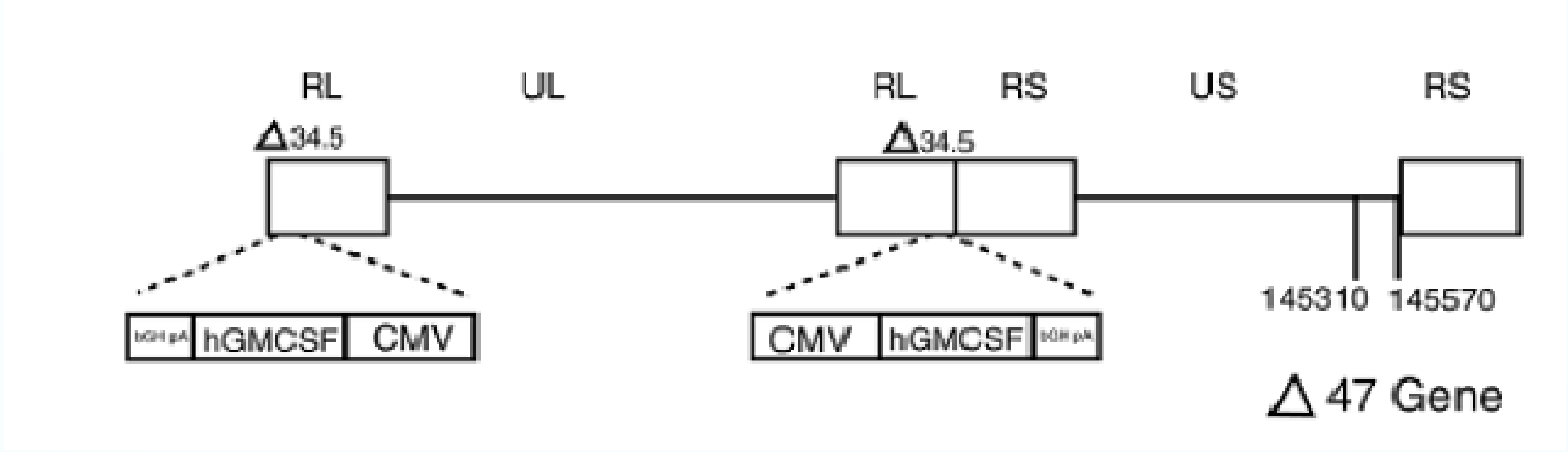
- Talimogene laherparepvec (T-VEC; **HSV**)
  Approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (NCT00769704)

- Pexastimogene devacirepvec (JX-594; **vaccinia virus**)
  Phase IIb trial for hepatocellular carcinoma (NCT01387555)

- Pelareorep (**reovirus**)
  Phase III in combination with chemotherapy in head and neck cancer (NCT01166542)

- H101 (a recombinant **adenovirus**)
  Approved for the treatment of head and neck cancer in China

T-VEC: A Modified HSV-1 Oncolytic Virus



- Deletion of virulent factor ICP34.5
  - Limits replication in normal cells, but replicates selectively in tumor cells
- Deletion of ICP47
  - Allows tumor antigen presentation
- Insertion of the human GM-CSF gene
  - Induce the recruitment and differentiation of DC precursors in and around the injected tumor

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ORIGINAL REPORT

Table 1. Baseline Demographic and Clinical Characteristics

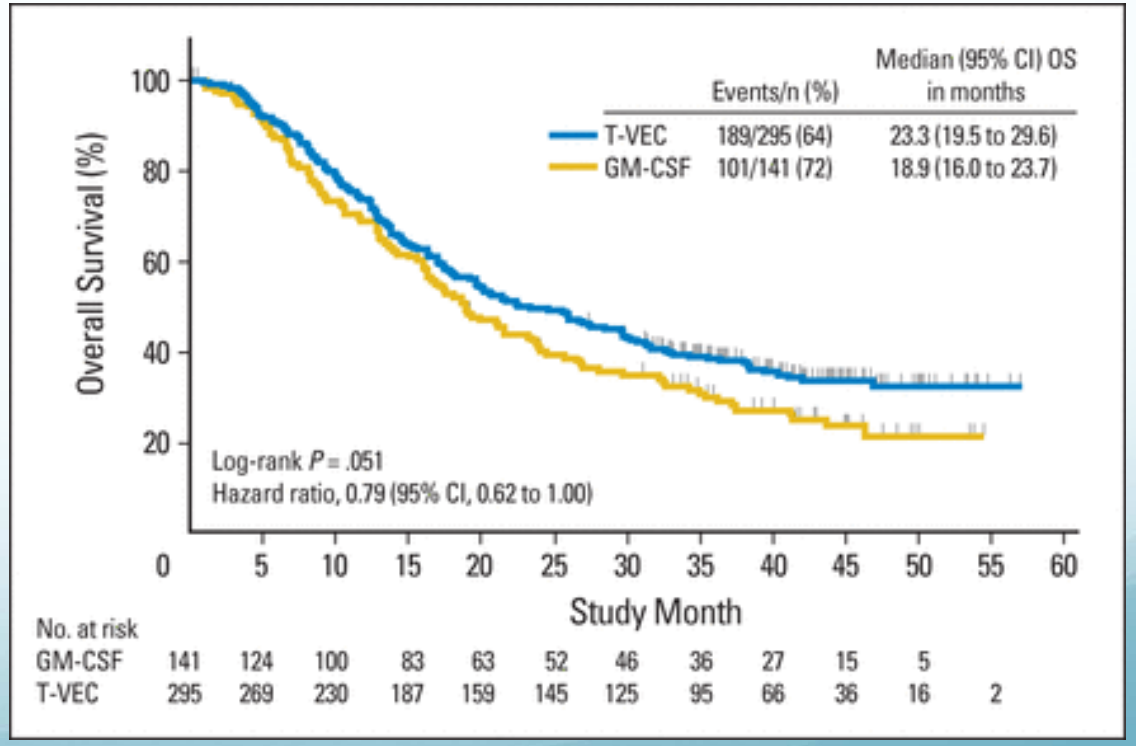
Characteristic	T-VEC (n = 295) No.	%	GM-CSF (n = 141) No.	%
Age, years				
Median	63		64	
Range	22 to 94		26 to 91	
< 65	152	52	72	51
≥ 65	143	48	69	49
Sex				
Male	173	59	77	55
Female	122	41	64	45
Disease substage				
IIIB	22	8	12	9
IIIC	66	22	31	22
IVM1a	75	25	43	30
IVM1b	64	22	26	18
IVM1c	67	23	29	21
Unknown	1	< 1	0	0
Line of therapy				
First	138	47	65	46
Second or later	157	53	76	54
ECOG performance status				
0	209	71	97	69
1	82	28	32	23
Unknown	4	1	12	9
LDH				
≤ ULN	266	90	124	88
> ULN	15	5	5	4
Unknown	14	5	12	9
HSV serostatus				
Positive	175	59	78	55
Negative	97	33	45	32
Unknown	23	8	18	13
BRAF status				
Mutation	46	16	23	16
Wild type	45	15	23	16
Unknown or missing	204	69	95	67

NOTE. Distribution of randomization stratification factors is shown in Appendix, Table A1.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; LDH, lactate dehydrogenase; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

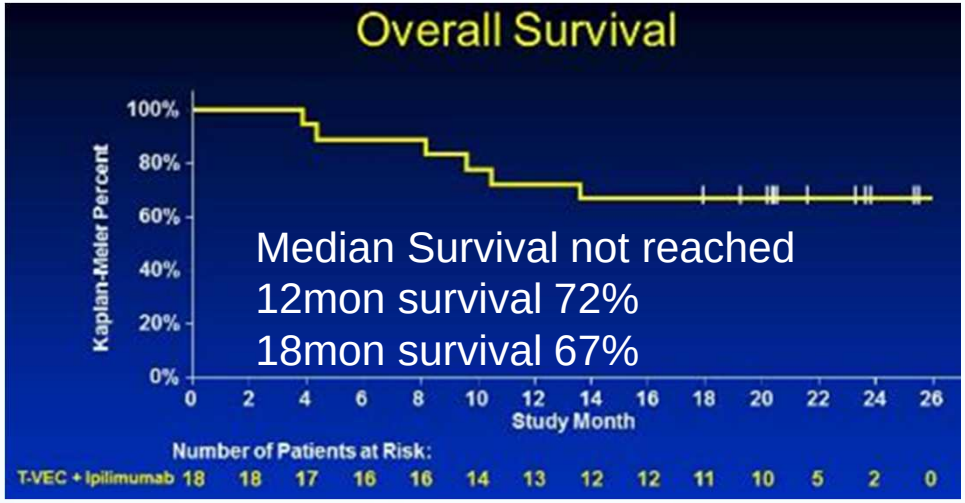
Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin

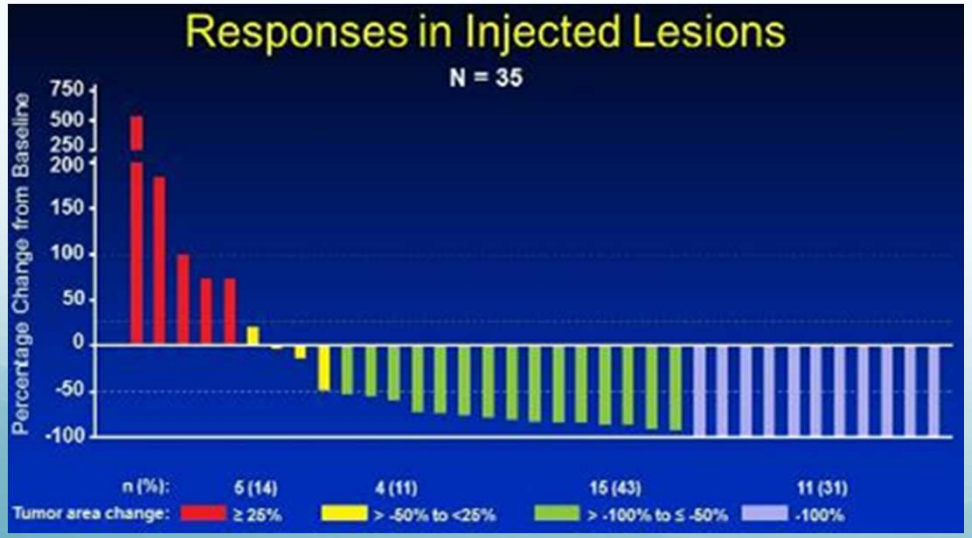


T-VEC Efficacy and Safety

- **OPTiM study (005-05)**:
  - Phase 3, T-VEC vs GM-CSF, melanoma stage IIIB to IV, 436 patients (292 with T-VEC)
  - **DRR (primary endpoint): 16%** vs 2% ($p<0.0001$)
  - **ORR: 26%** vs 5.7%
  - Median OS: 23 vs 19 months (HR 0.79, P=0.07)
- Nine trials (427 patients) have been conducted to test T-VEC safety.
  - **Relatively low toxicity**, mostly flu-like symptoms and injection site reactions.
  - No fatal AE was directly related to T-VEC

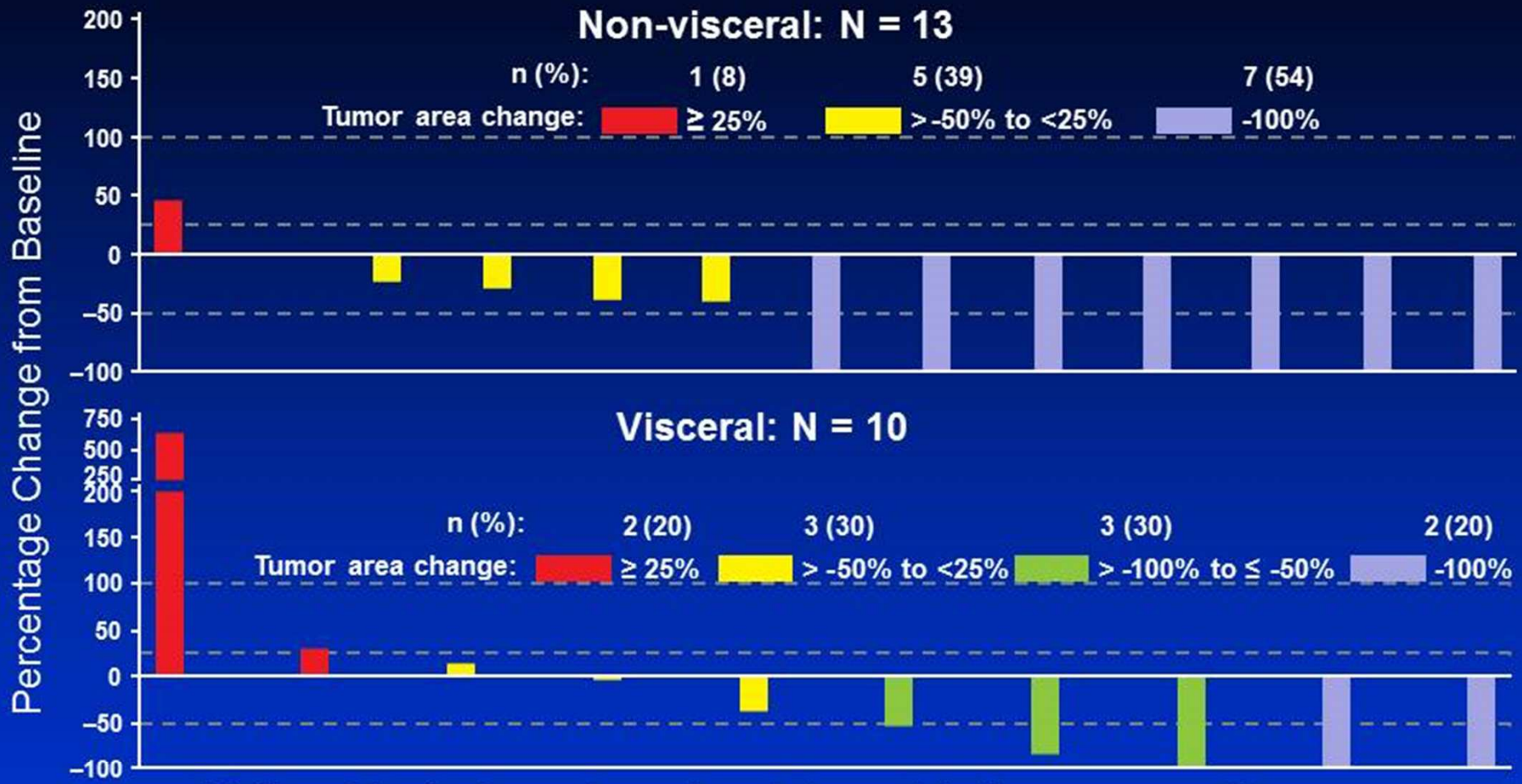
Phase Ib T-VEC+ipi in Treatment Naïve stage IIIB-IV Melanoma





Preferred Term	Total N (%)	Grade 3 N (%)
Any event	19 (100)	5 (26)
Any attributed to T-VEC	17 (90)	3 (16)†
Any attributed to ipilimumab	15 (80)	3 (16)†
Chills	11 (58)	-
Fatigue	11 (58)	1 (5)
Pyrexia	11 (58)	1 (5)
Nausea	9 (47)	2 (11)
Rash	9 (47)	-
Diarrhea	8 (42)	1 (5)
Headache	8 (42)	-
Pruritis	8 (42)	-
Decreased appetite	4 (21)	-
Hyperglycemia	4 (21)	-
Vomiting	4 (21)	1 (5)
ALT increased	3 (16)	-
Back pain	3 (16)	1 (5)
Influenza-like illness	3 (16)	1 (5)
Pain	3 (16)	-
Vision blurred	3 (16)	-

Responses in Uninjected Non-visceral and Visceral Lesions



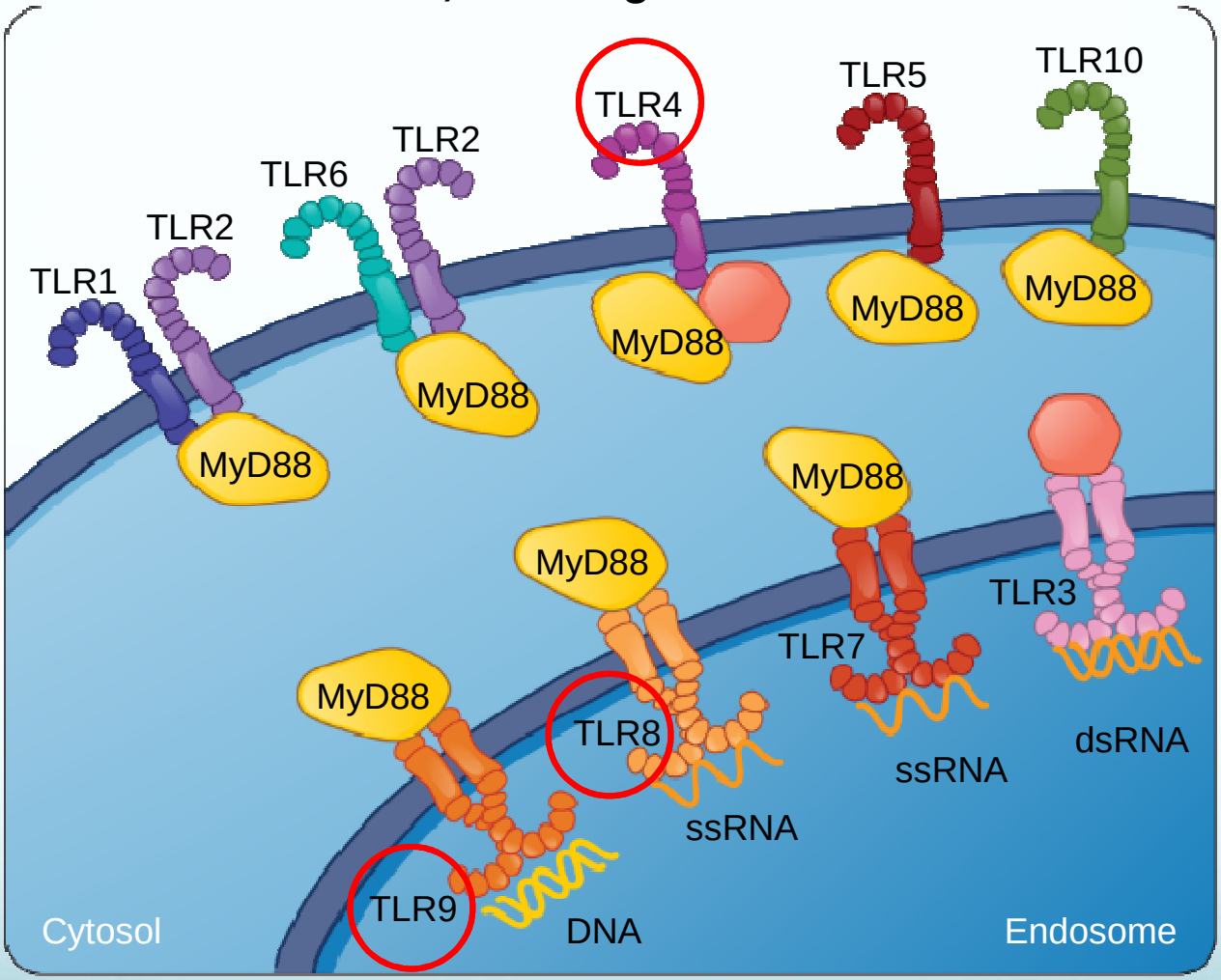
- Both uninjected non-visceral and visceral lesions regressed
- 52% of uninjected index lesions regressed ≥ 50%
- 39% completely regressed

Clinical Development of T-VEC for Cancer

- A Phase 1b/3, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresected,Stage IIIB to IVM1c Melanoma (MASTERKEY-265) **NCT02263508**
- A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma **NCT02211131**
- A Phase 1, Multicenter, Open-label Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Liver Tumors **NCT02509507**

TLRs are Key Recognition and Signaling Receptors for Innate Immunity

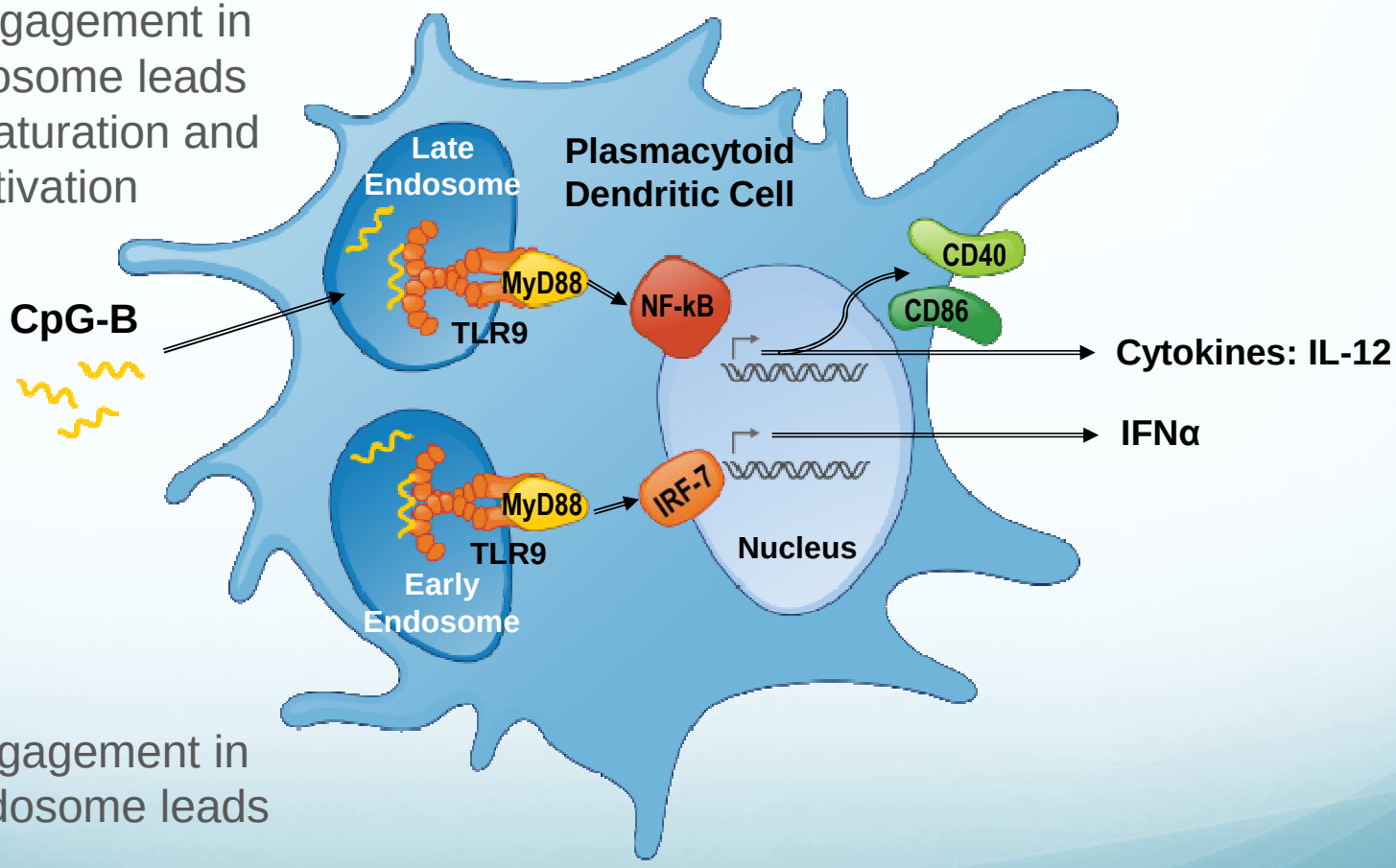
G100, TLR4 agonist



TLR8 agonist Motolimod/VTX-2337
TLR 7/8 agonist, MEDI9197
TLR9 agonist, SD-101

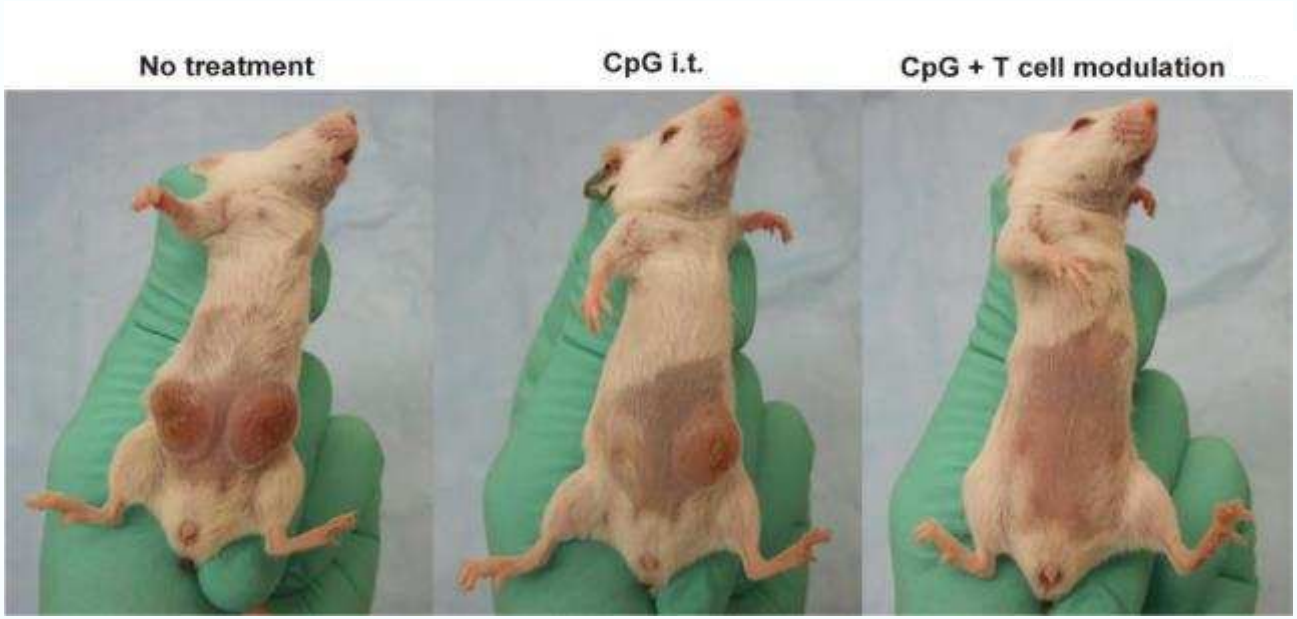
TLR9 Engagement in Different Cellular Compartments Activates Different Functional Responses

- TLR9 engagement in late endosome leads to DC maturation and T cell activation



- TLR9 engagement in early endosome leads to IFN-α

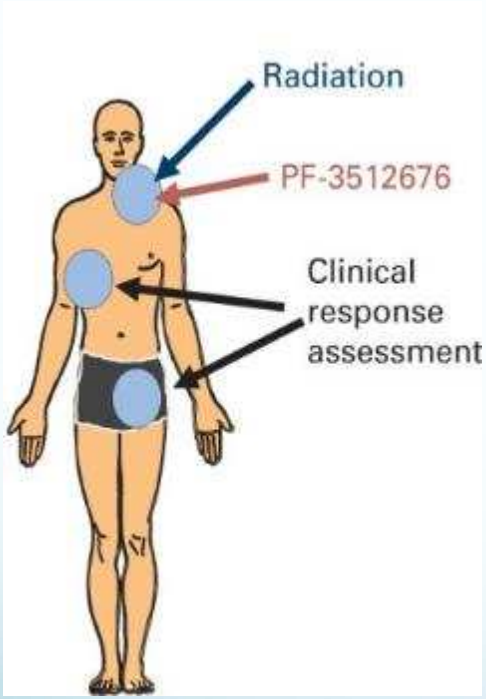
Intratumoral CpG Enhances Checkpoint Inhibitory Antibodies in Mouse Tumor Models



- Intratumoral CpG causes regression only in injected tumor
- Combination with checkpoint inhibitors (OX40 and ipilimumab) leads to immune mediated regression of uninjected tumor

Houot and Levy, Blood (2009) 113:3546

Intratumoral Administration of CpG in Humans



Brody, Levy et al (2010) J Clin Onc 28:4324.

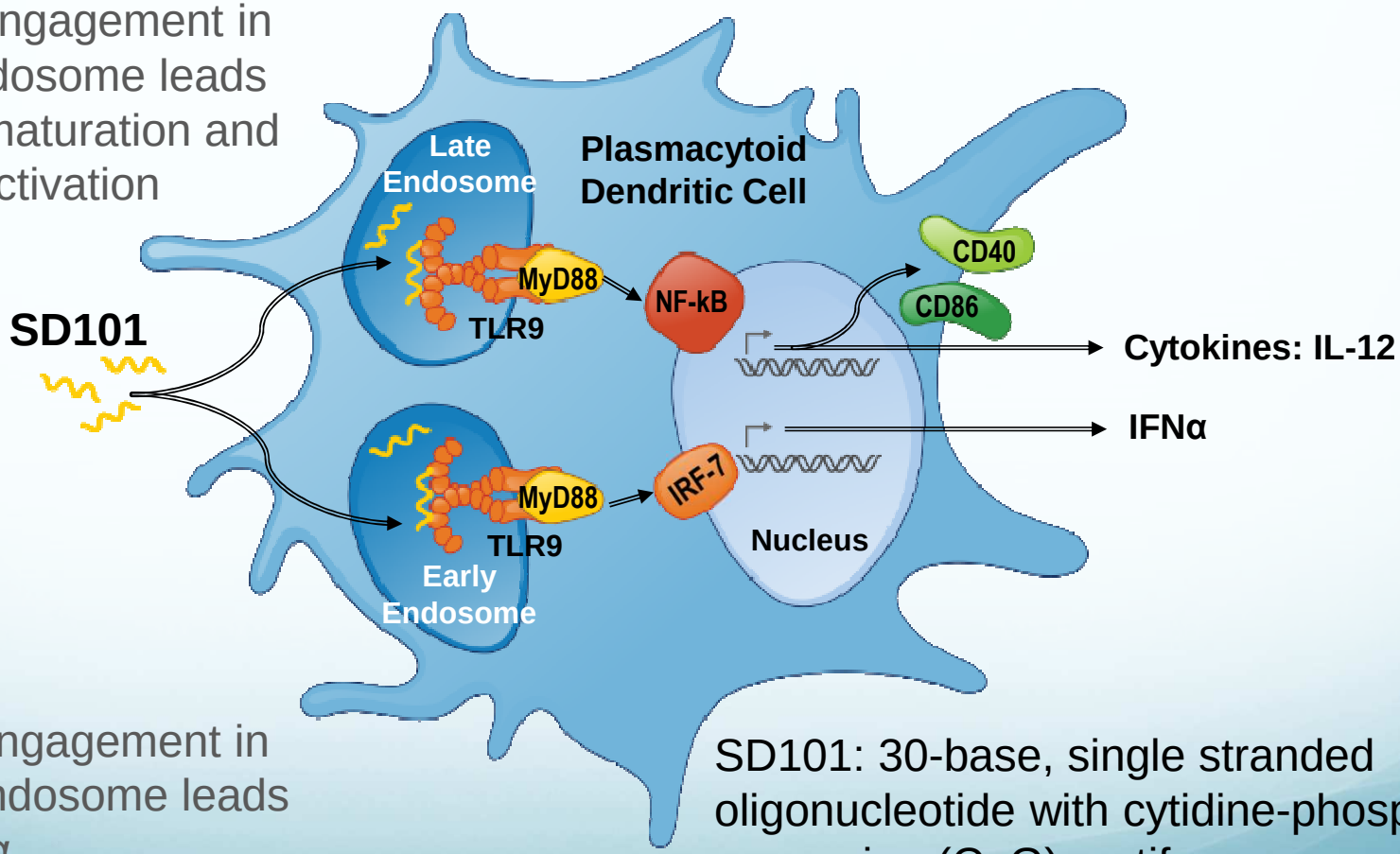
- Grade III/IV Lymphomas, multiple treatment failures
- Local irradiation + intratumoral “B-Class” CpG
- 4/15 responses in untreated sites, including 1 CR
- Induction of tumor-reactive CD8+ T cells in many patients

Kim, Levy et al (2012) Blood 119:355.

- Cutaneous T cell lymphoma (MF), ≥ 1 treatment failures
- Local irradiation + intratumoral “B-Class” CpG
- 5/15 partial responses in untreated sites
- Treg cells reduced in injected site

SD-101: “C” Class CpG Providing Potent Stimulation of Both TLR9 Signaling Pathways

- TLR9 engagement in late endosome leads to DC maturation and T cell activation

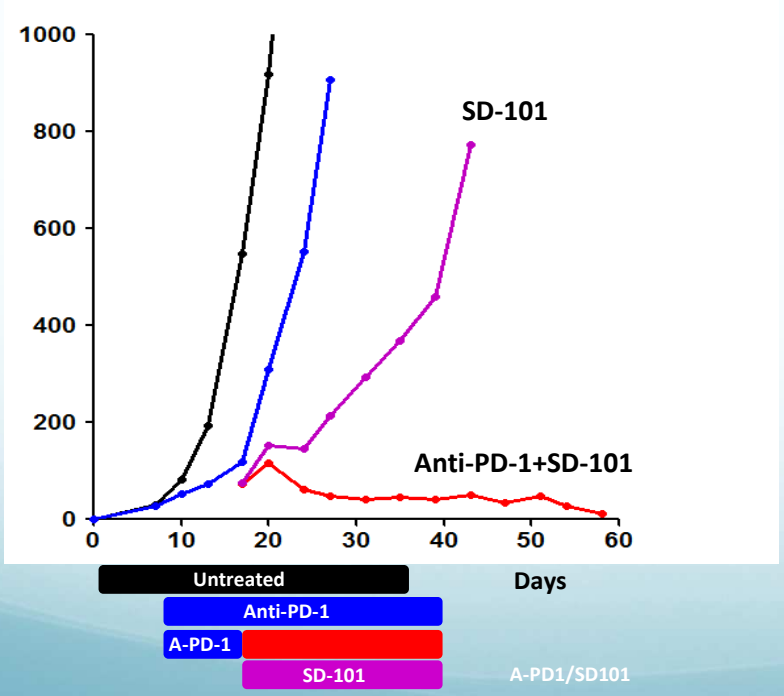


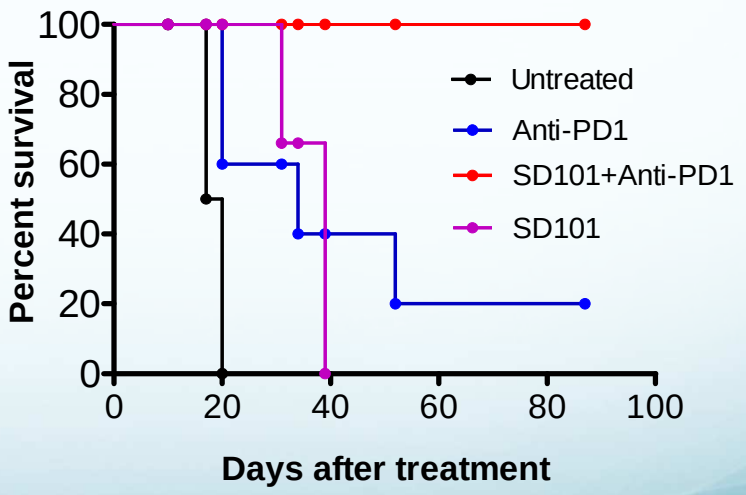
- TLR9 engagement in early endosome leads to IFN-α

SD101: 30-base, single stranded oligonucleotide with cytidine-phospho-guanosine (CpG) motifs on a phosphorothioate backbone

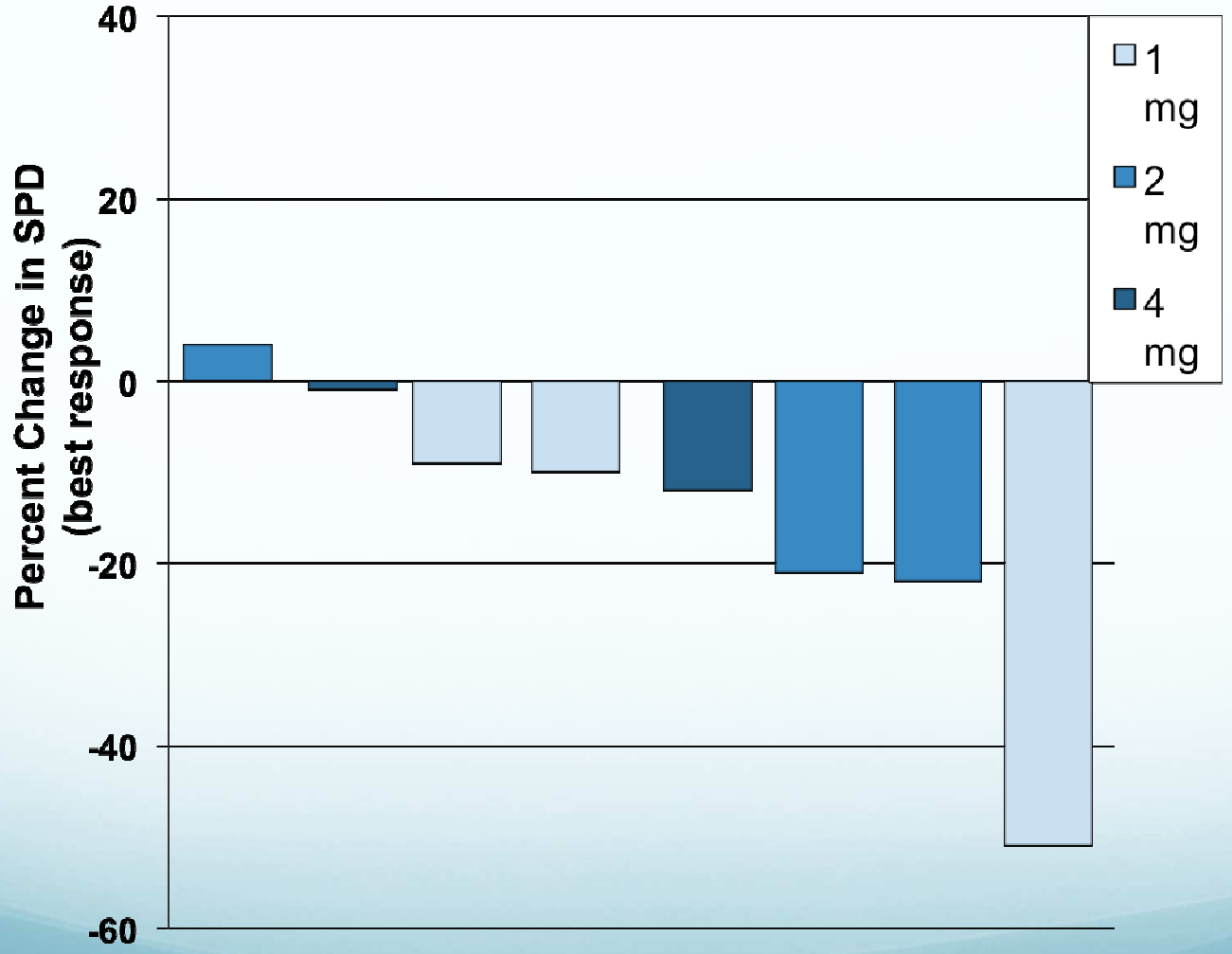
Preclinical Studies Provide Support for Combining SD-101 with Checkpoint Inhibitors

- Intratumoral SD-101 with continued anti-PD-1 treatment reverses tumor escape from anti-PD-1 therapy and leads to long-term, immune-mediated control of tumor growth





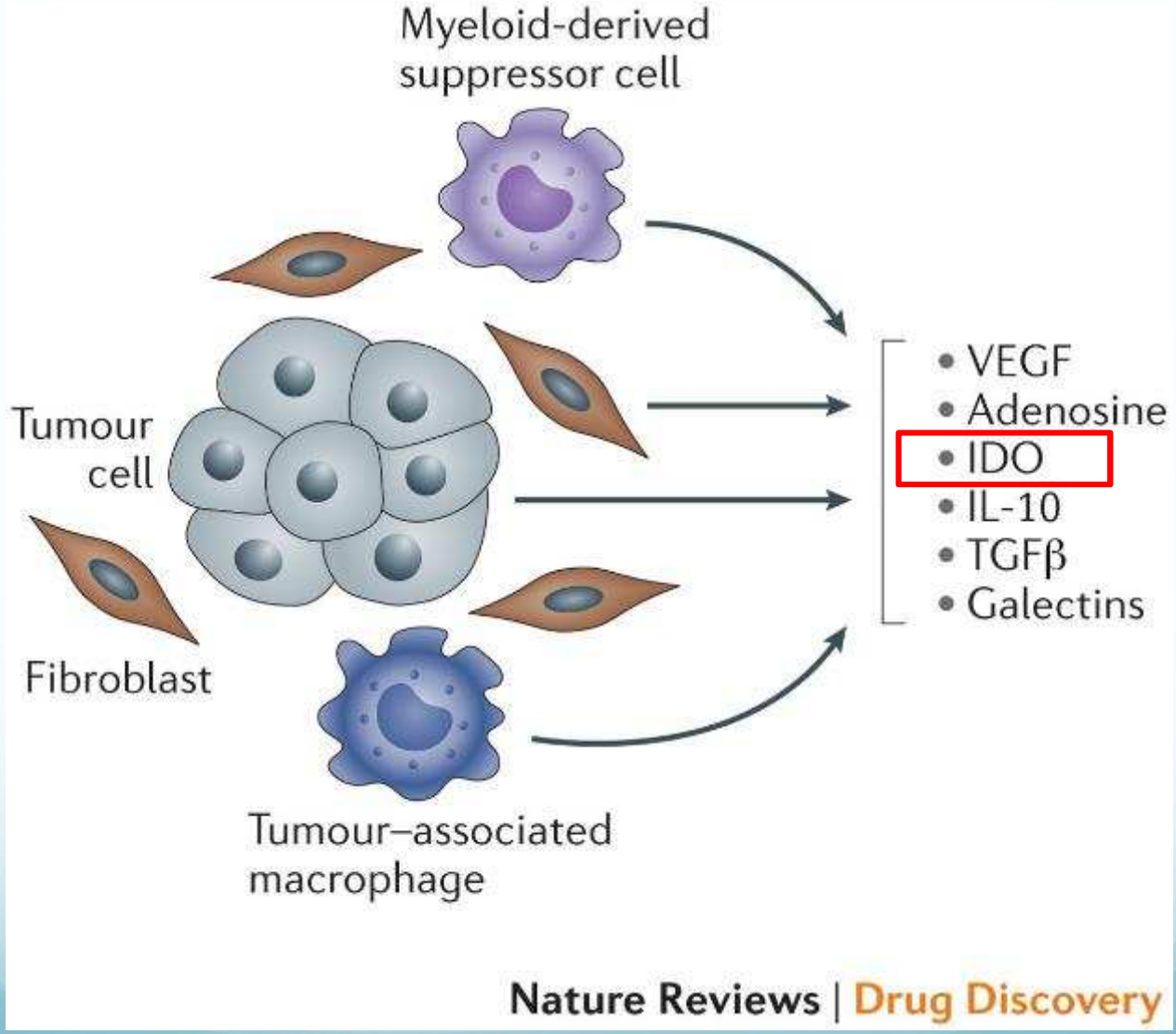
Phase 1/2 Study in Untreated Indolent Lymphoma Patients



Clinical Development of SD-101 for Cancer

- Multicenter Phase 1/2 trial of intratumoral SD-101 plus pembrolizumab in metastatic melanoma **NCT02521870**
- A Phase 1/2, Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma **NCT02266147**
- A Phase I/II Study of Intratumoral Injection of SD-101, an Immunostimulatory CpG, and Intratumoral Injection of Ipilimumab, an Anti-CTLA4 Monoclonal Antibody, in Combination With Local Radiation in Low-Grade B-Cell Lymphomas **NCT02254772**

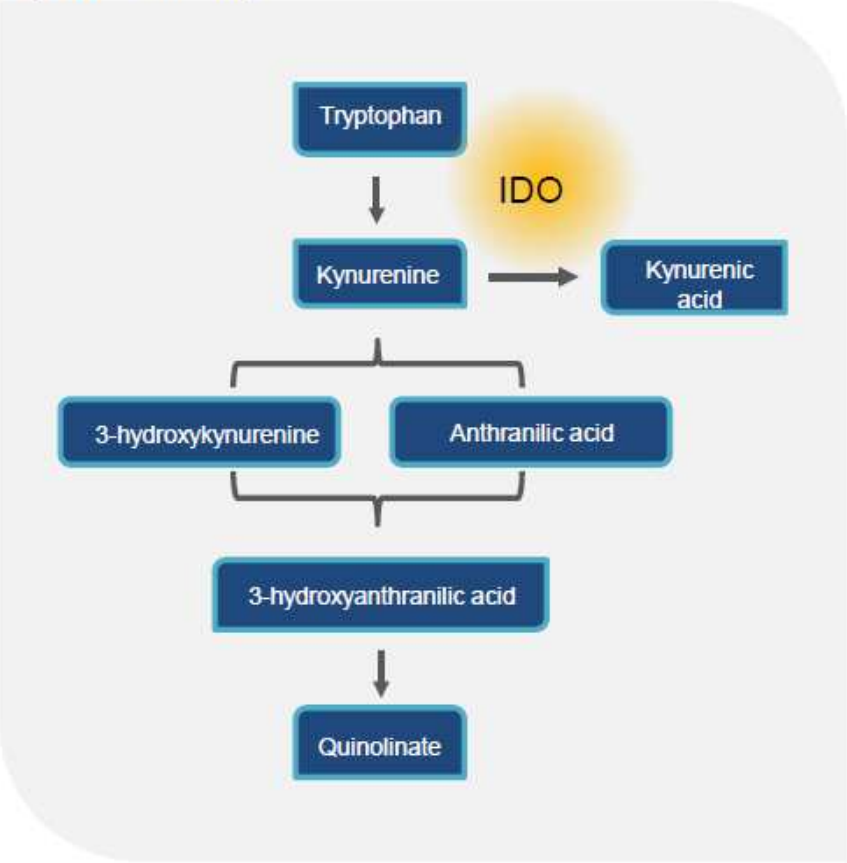
Tumor Immune-suppressive Microenvironment



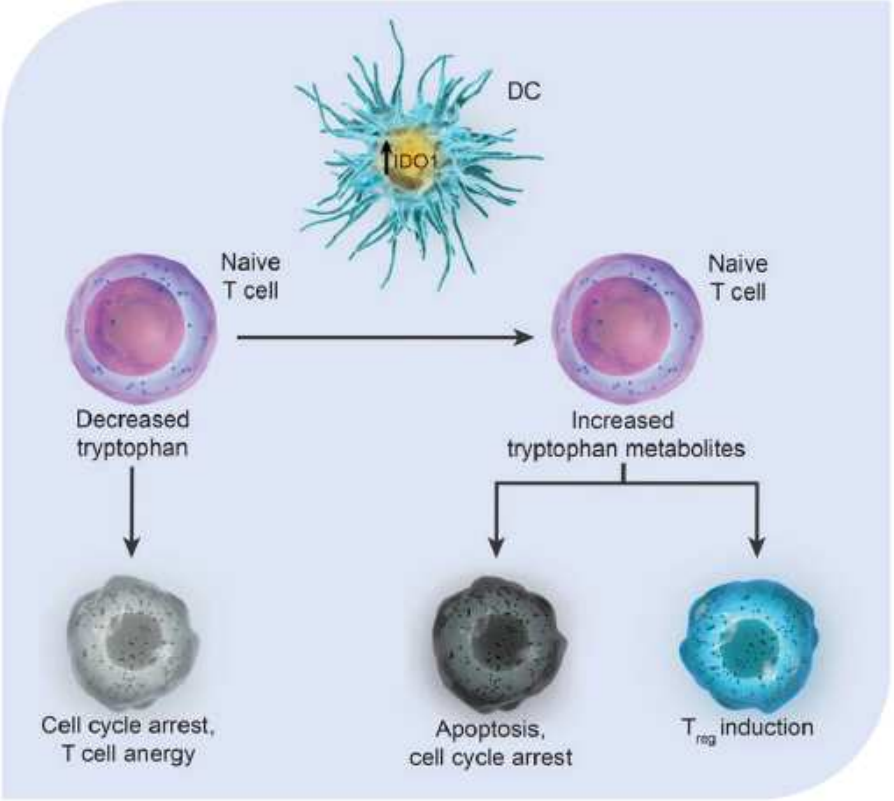
Nature Reviews Drug Discovery **14**, 561–584 (2015)

IDO in Normal Physiology

IDO catalyzes the rate-limiting step in degradation of tryptophan to kynurenine[1,2]



Depletion of cellular tryptophan levels and accumulation of downstream metabolites potentially mediates immune-suppressive effects[1,2]



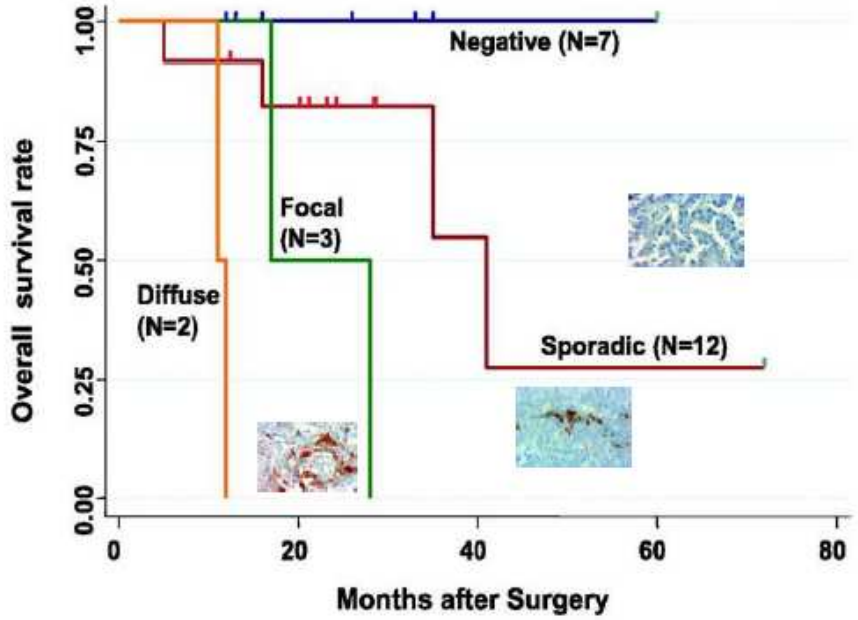
DC=dendritic cell; IDO=indoleamine 2,3-dioxygenase 1; T_{reg}=regulatory T cell.

1. Munn DH, Mellor AL. *J Clin Invest*. 2007;117:1147-1154; 2. Curti A et al. *Blood*. 2009;113:2394-2401.

IDO1 Expression Is Associated with Poor Outcome in Several Tumor Types[1]

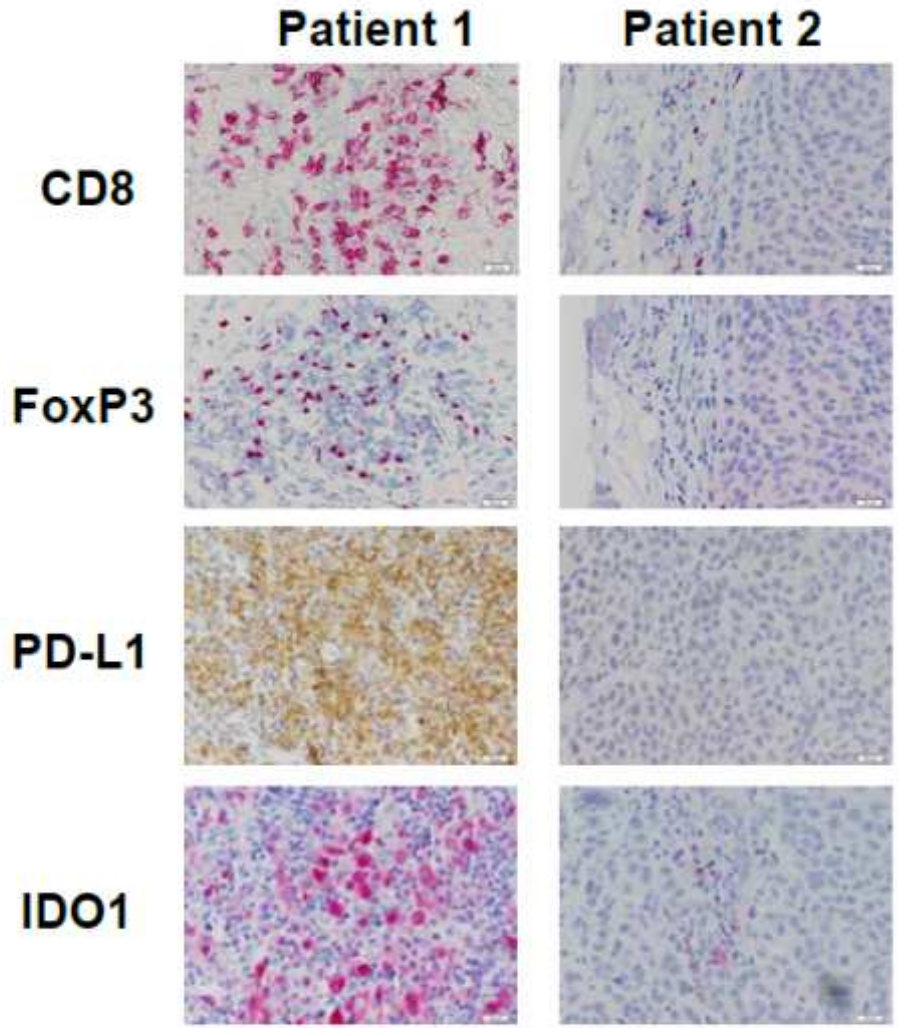
- IDO1 is highly expressed in multiple tumor types:[2]
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - Colorectal cancer
  - Glioblastoma
  - Squamous cell carcinoma
  - AML
  - Endometrial carcinoma
  - DLBCL
  - MDS

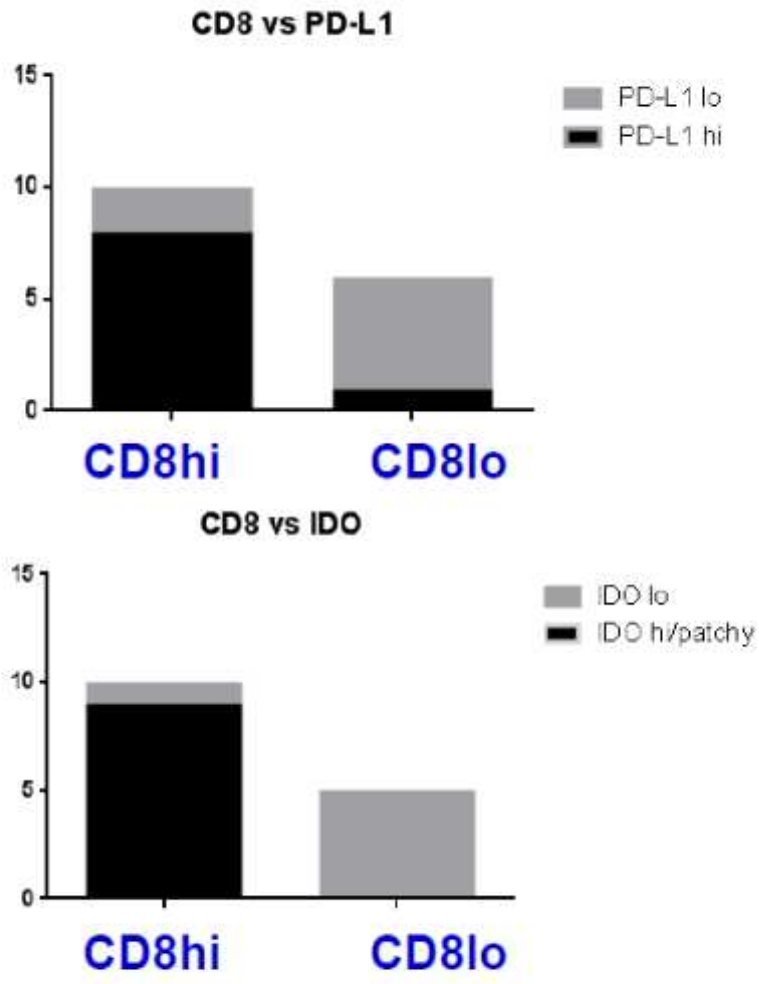
Kaplan-Meier survival curves in ovarian cancer based on IDO1 staining[3]



1. Gostner JM et al. *Expert Opin Ther Targets*. 2015;19:605–615; 2. Uyttenhove C et al. *Nat Med*. 2003;9:1269–1274; 3. Okamoto A et al. *Clin Can Res*. 2005;480:161–172.

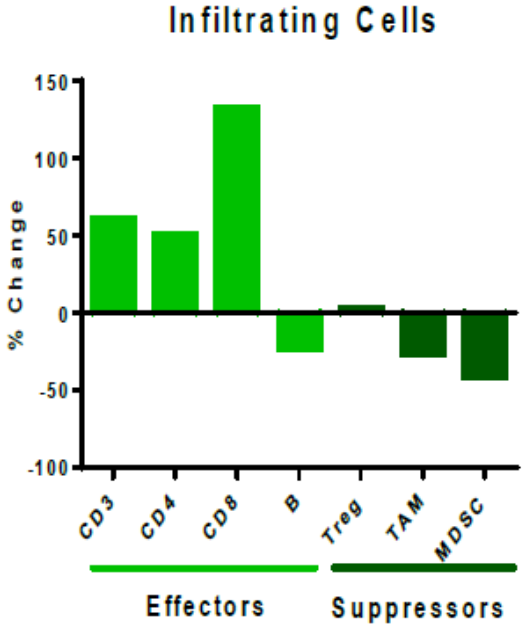
Presence of Tregs and Expression of PD-L1 and IDO1 are Associated with a CD8+ T Cell Infiltrate

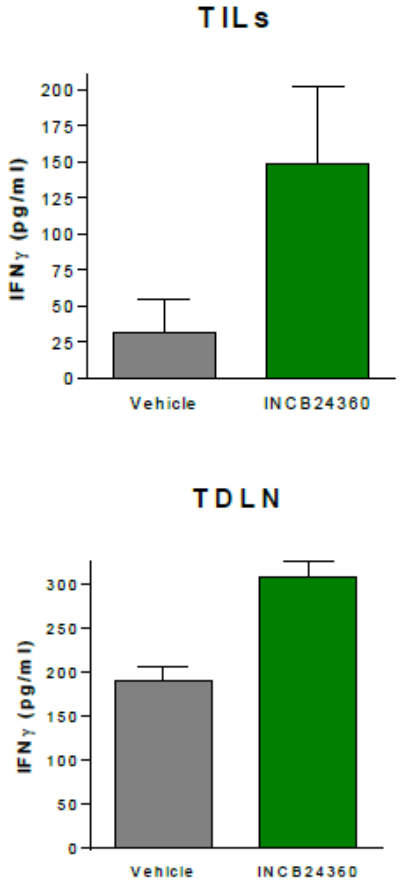




Spranger S et al. *Sci Transl Med.* 2013;5:200ra116.

Reduction In Kyn Correlates With Increases In Lymphocyte Numbers and Responsiveness

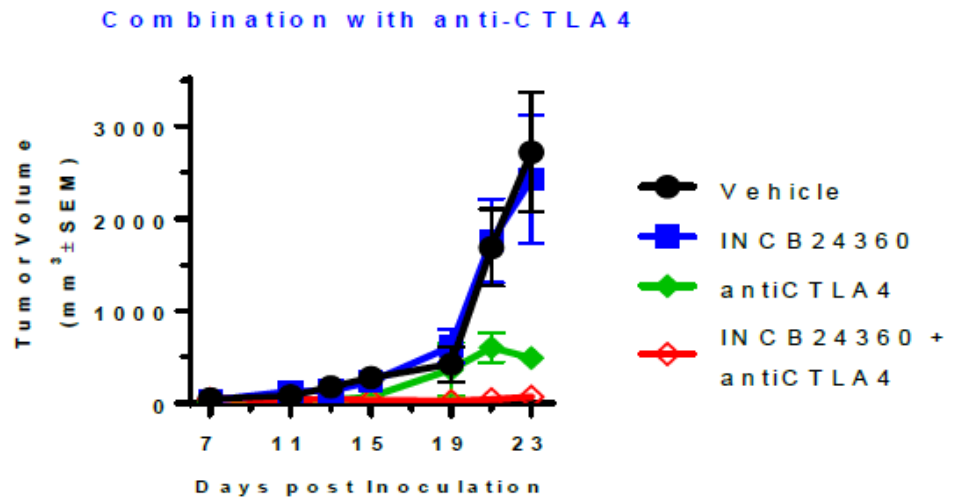


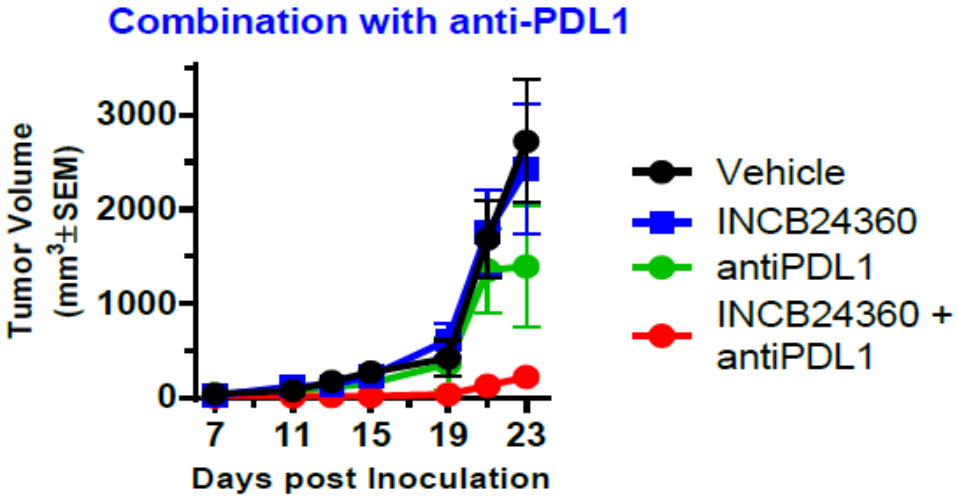


- IDO1 inhibitor leads to increased numbers of TILs and decreased Tregs in tumors
- Enhanced IFN-γ secretion from TILs observed following IDO1 inhibitor treatment

Koblish et al. AACR poster no. 1336, 2015

Combination Inhibition is Synergistic in Preclinical Models





Spranger S et al. *JITC*. 2014;2:1–14.

Compound(s) Dosed	TGI (Day 24)
INCB024360	11%
anti-CTLA4	82%
INCB24360 + anti-CTLA4	97%
anti-PDL1	49%
INCB024360 + anti-PD-L1	92%

- INCB024360 strongly synergizes with anti-CTLA4 and anti-PDL1 mAbs in a B16-SIY melanoma model
- Major biological effect was restoration of IL-2 production and proliferation of CD8+ T cells already present within the tumor microenvironment

Abstract 3025
Presented at the 2013 Annual Meeting of the
American Society of Clinical Oncology
Chicago, IL, May 31-June 4, 2013

Phase 1 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Oral Inhibitor of Indoleamine 2,3-dioxygenase (IDO1) INCB024360 in Patients With Advanced Malignancies

Gregory L Beatty,[1] Peter J O'Dwyer,[1] Jason Clark,[2] Jack G Shi,[2] Robert C Newton,[2] Richard Schaub,[2] Janet Maleski,[2] Lance Leopold,[2] Thomas F. Gajewski[3]

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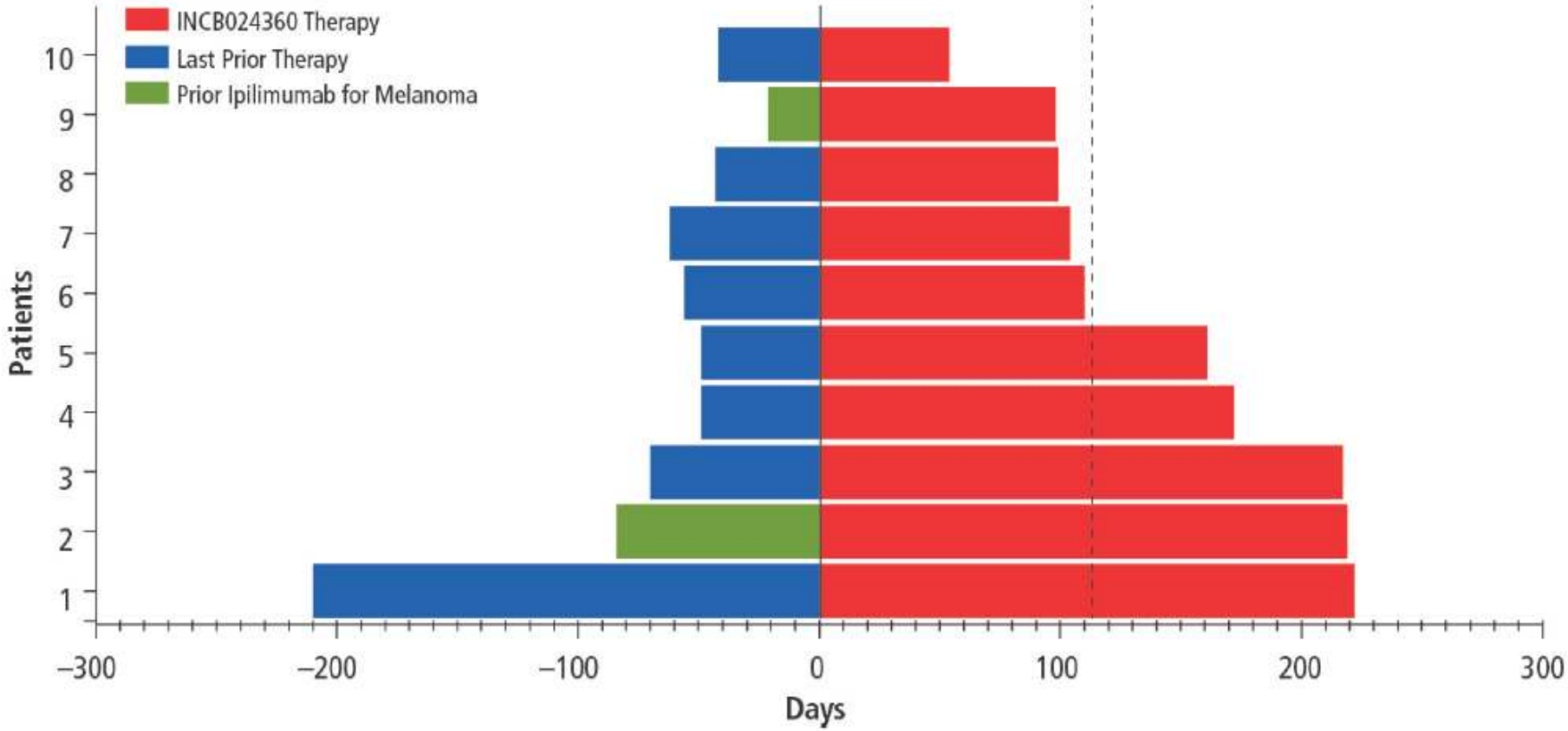
Treatment Duration

- In 10 patients the duration of INCB024360 therapy exceeded that of the last prior therapy, including ipilimumab in 2 patients with melanoma

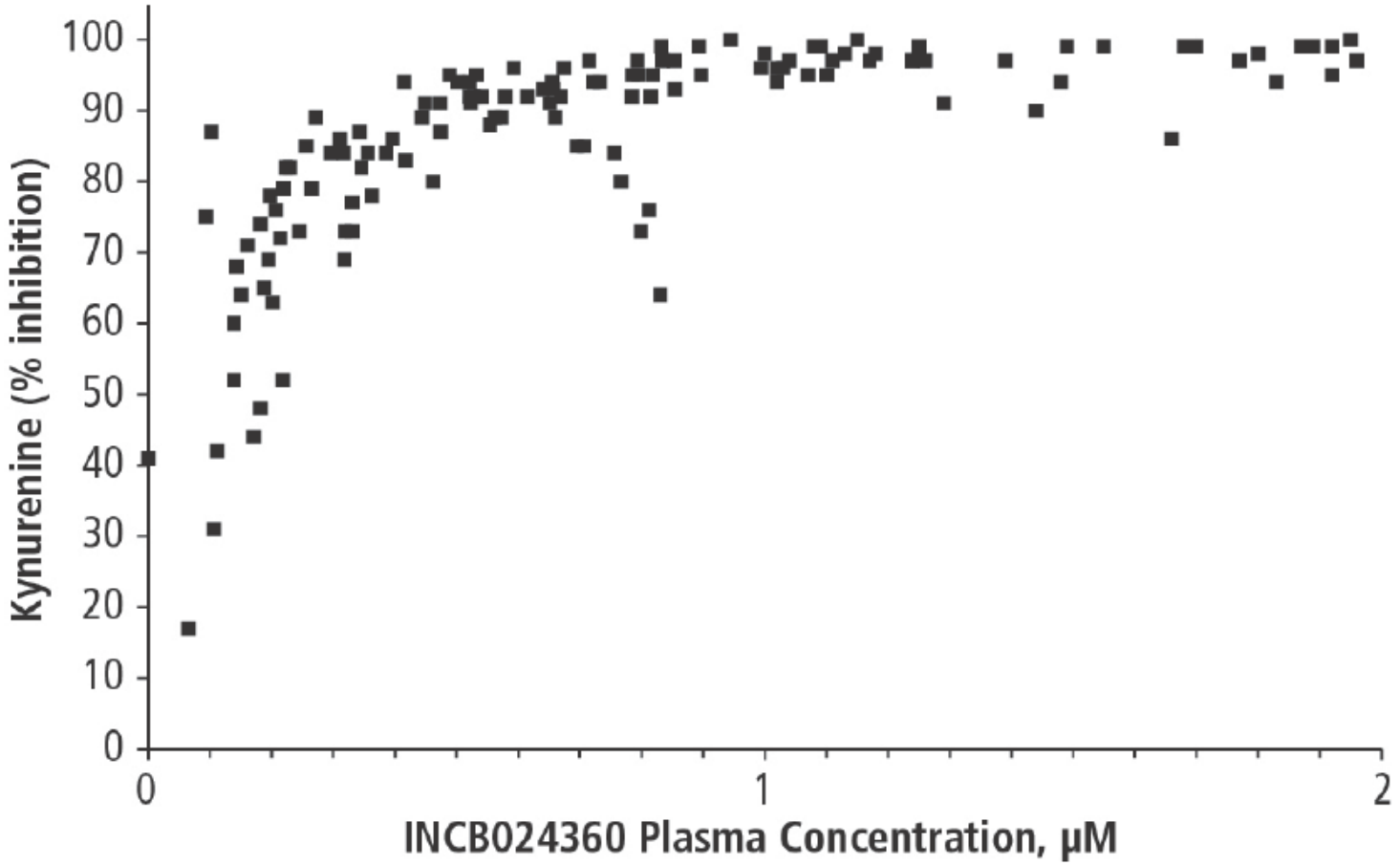


Dashed line represents 112 days (16 weeks) of therapy with INCB024360

Beatty, et al. ASCO. 2013 (abstr 3025).

Pharmacokinetic/Pharmacodynamic Relationship for INCB024360

- Exposures achieved at the doses examined provide plasma concentrations exceeding the projected IC_{90}



Beatty, et al. ASCO. 2013 (abstr 3025).

Abstract 511
Presented at the 18th ECCO - 40th ESMO
European Cancer Congress
Vienna, Austria, September 25–29, 2015

Updated Results From a Phase 1/2 Study of Epacadostat (INCB024360) in Combination With Ipilimumab in Patients With Metastatic Melanoma

Geoffrey T. Gibney,[1*] Omid Hamid,[2] Jose Lutzky,[3] Anthony J. Olszanski,[4] Tara C. Gangadhar,[5] Thomas F. Gajewski,[6] Bartosz Chmielowski,[7] Brent A. Hanks,[8] Peter D. Boasberg,[2] Yufan Zhao,[9] Robert C. Newton,[9] Jill Bowman,[9] Janet Maleski,[9] Lance Leopold,[9] Jeffrey S. Weber[1†]

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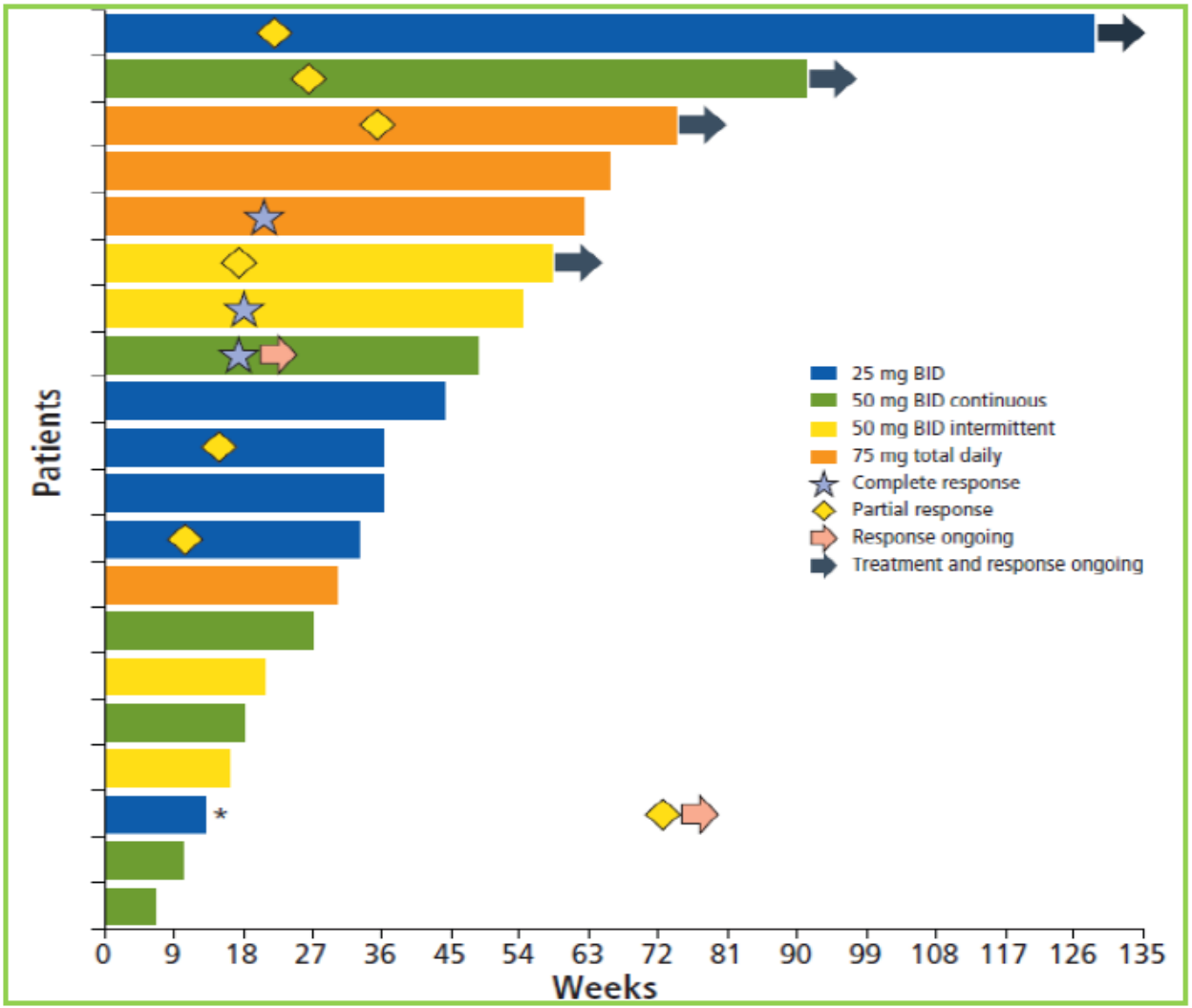
Methods: Study Design and Treatment

- In the initial phase 1 dose-escalation portion, 5 out of 7 patients receiving epacadostat 300 mg BID in combination with 4 doses of ipilimumab (3 mg/kg q3 weeks) developed clinically significant ALT elevations; therefore, the study was amended to evaluate lower epacadostat doses
- Subsequent cohorts received 25 mg BID, 50 mg BID continuous, 50 mg BID intermittent (2 weeks on, 1 week off), and 75 mg (50 mg AM/25 mg PM) with 4 doses of ipilimumab 3 mg/kg q3 weeks
  - Doses of ≥100 mg BID were not reexplored
  - Patients were observed for ≥8 weeks for dose-limiting toxicities (DLTs) before enrollment of the next cohort
  - The dose was escalated if <2 of the 6 evaluable patients or ≤3 of 12 patients experienced a DLT
  - After the 4 cycles with ipilimumab, patients continued on epacadostat monotherapy until experiencing an AE, progressive disease, or death

Gibney et al., ECCO ESMO. 2015 (abstr 511).

Figure 2. Duration of Treatment in Immunotherapy-Naive Patients With Stable Disease or Better by irRC



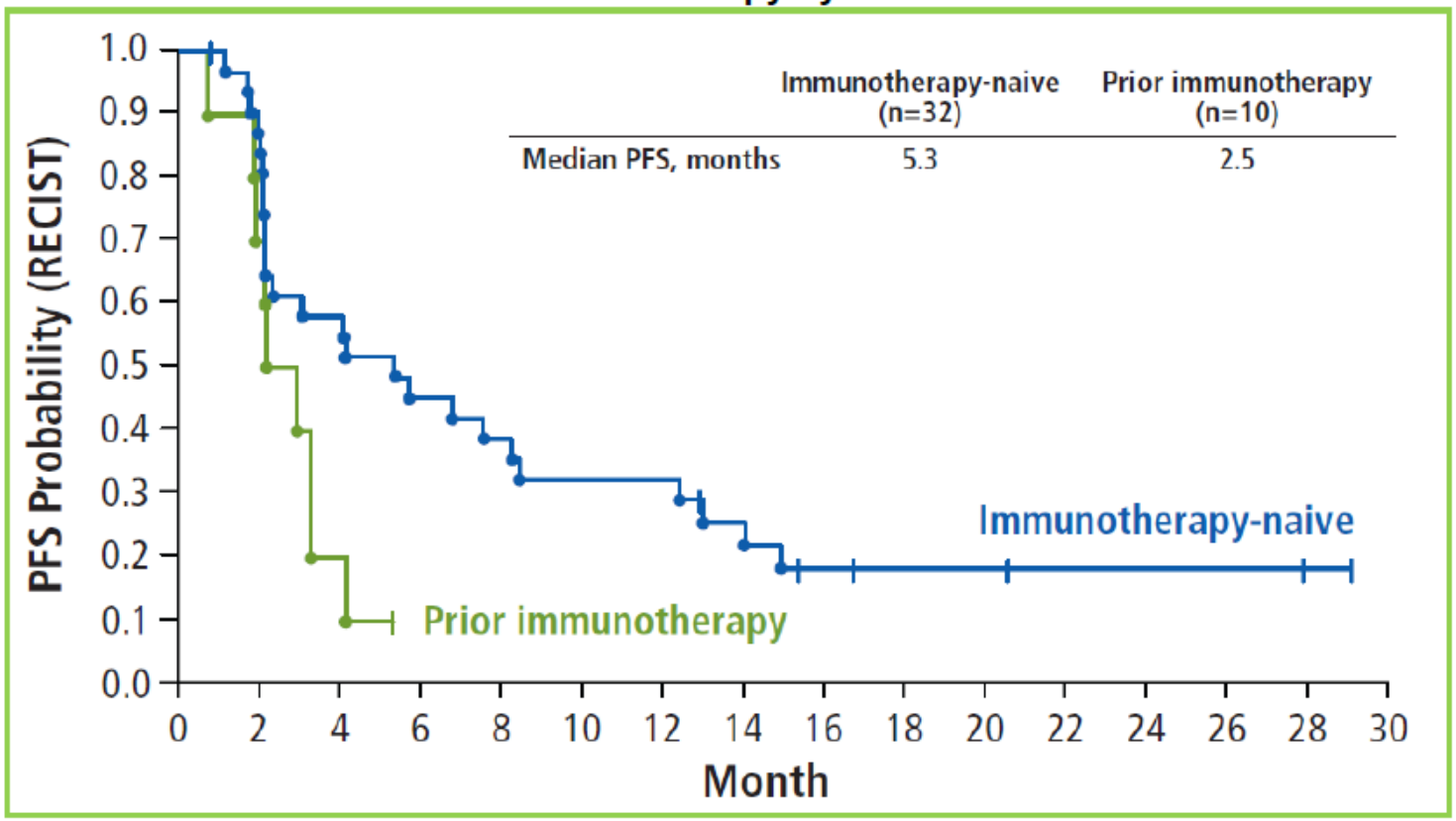
BID, twice daily; irRC, immune-related response criteria.
*Patient discontinued from study for an adverse event and did not receive subsequent therapy. The patient later achieved a partial response.

Gibney et al., ECCO ESMO. 2015 (abstr 511).

Results: Efficacy (cont)

- By RECIST, median PFS was 5.3 months in immunotherapy-naive patients and 2.5 months in patients who had received prior immunotherapy

Figure 3B. Kaplan-Meier Estimated Progression-Free Survival in Immunotherapy-Naive Patients vs Patients With Prior Immunotherapy by RECIST



RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival.

Gibney et al., ECCO ESMO. 2015 (abstr 511).

Results: IDO1 Inhibition

- Pharmacodynamic analysis demonstrated dose-dependent inhibition of IDO1 at all doses
- The degree of inhibition achieved at all doses was similar to those sufficient in preclinical models to achieve therapeutic effect

Table 6. Whole Blood Analysis of IDO1 Inhibition

	Mean ± SD (Range)		
Dose Group	**Maximal Inhibition, %**	**Average Inhibition (0-6 h), %**	**Trough Inhibition, %**
25 mg BID (n=4)	60±15 (40–77)	70±9 (31–79)	48±29 (8–76)
50 mg BID continuous (n=14)	87±12 (58–100)	70±20 (29–99)	46±38 (0–98)
50 mg BID intermittent (n=1)	86	59	14
75 mg total daily dose (n=5)	71±36 (7–90)	46±24 (7–69)	6±10 (0–22)

BID, twice daily; IDO1, indoleamine 2,3-dioxygenase 1; SD, standard deviation.

Gibney et al., ECCO ESMO. 2015 (abstr 511).

A Phase 1/2 Study of Epacadostat in Combination with Pembrolizumab in Patients with Selected Advanced Cancers (NCT02178722)

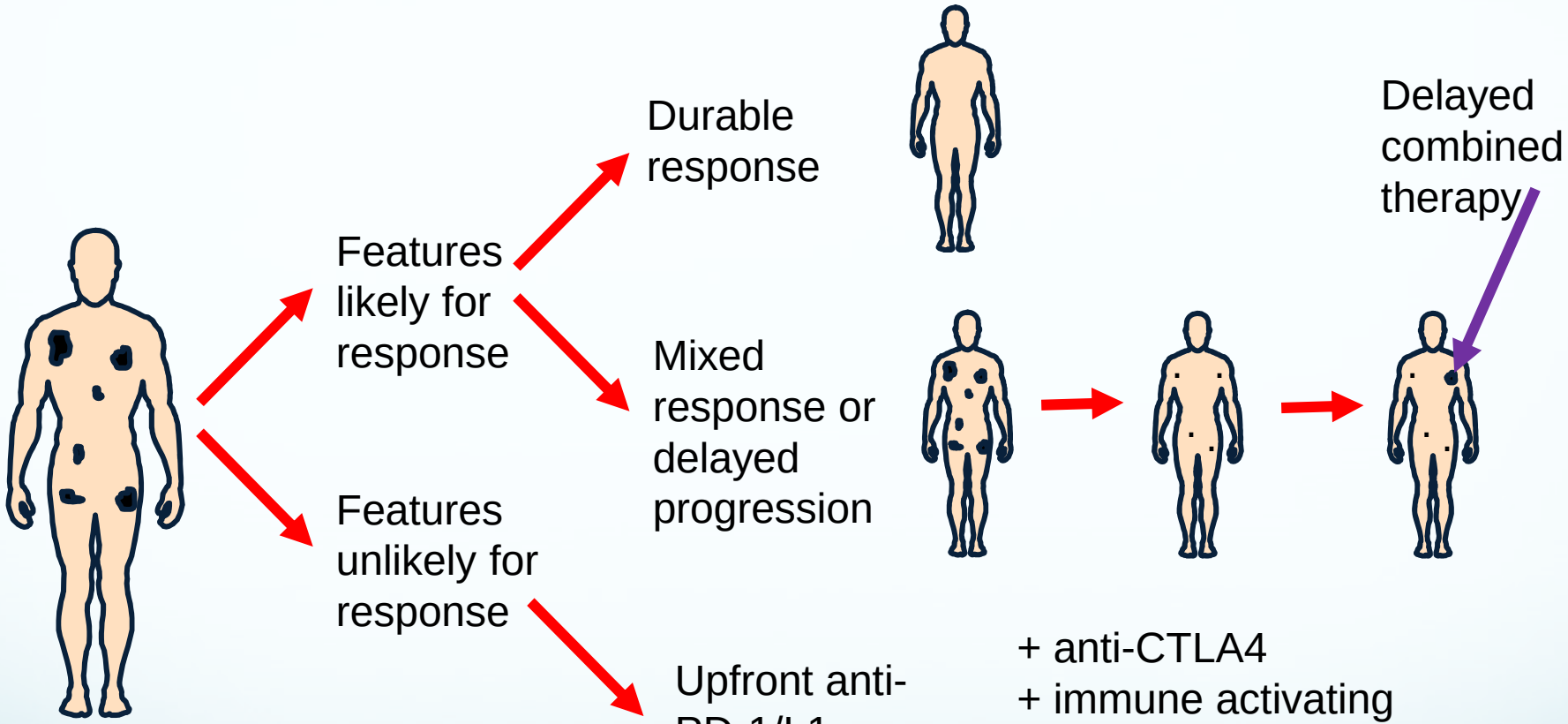
Evaluable patients*, n (%)	Melanoma (n=7)	RCC (n=5)	TCC (n=2)	NSCLC (n=2)	EA (n=2)	SCCHN (n=1)
ORR (CR+PR)	**4 (57)**	**2 (40)**	**1 (50)**	**1 (50)**	**1 (50)**	**1 (100)**
CR	2 (29)	0	0	0	0	0
PR	2 (29)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
SD	2 (29)	2 (40)	0	1 (50)	0	0
DCR (CR+PR+SD)	**6 (86)**	**4 (80)**	**1 (50)**	**2 (100)**	**1 (50)**	**1 (100)**
PD	1 (14)	0	1 (50)	0	0	0
Not assessable	0	1 (20)	0	0	1 (50)	0

*Patients with ≥ 1 post-baseline response assessment or discontinued from study or died before response could be assessed.

- DLT (grade 3 rash) in 1/8 patients with epacadostat 50mg BID/pembrolizumab 2 mg/kg;
- No DLTs were observed with epacadostat 100mg BID/pembrolizumab 2mg/kg.
- The most common (≥20%) all grade AEs were fatigue, diarrhea, rash, arthralgia, and nausea; the majority of these were grade 1 or 2.
- Grade ≥3 immune-related AEs were mucosal inflammation and rash (n=1 [4%] each).

SITC 30th Anniversary Annual Meeting, Abstract #142

Management of cancer in the anti-PD-1/L1 era



Courtesy of Dr. Ribas