exicure®

Cavrotolimod: Potent TLR9 Agonist for Immuno-Oncology

Agenda

1. Summary & TLR9 Biology
2. Cavrotolimod – Potent TLR9 Agonist
3. Cavrotolimod – Phase 1b/2 Clinical Data
4. Opportunities in Oncology

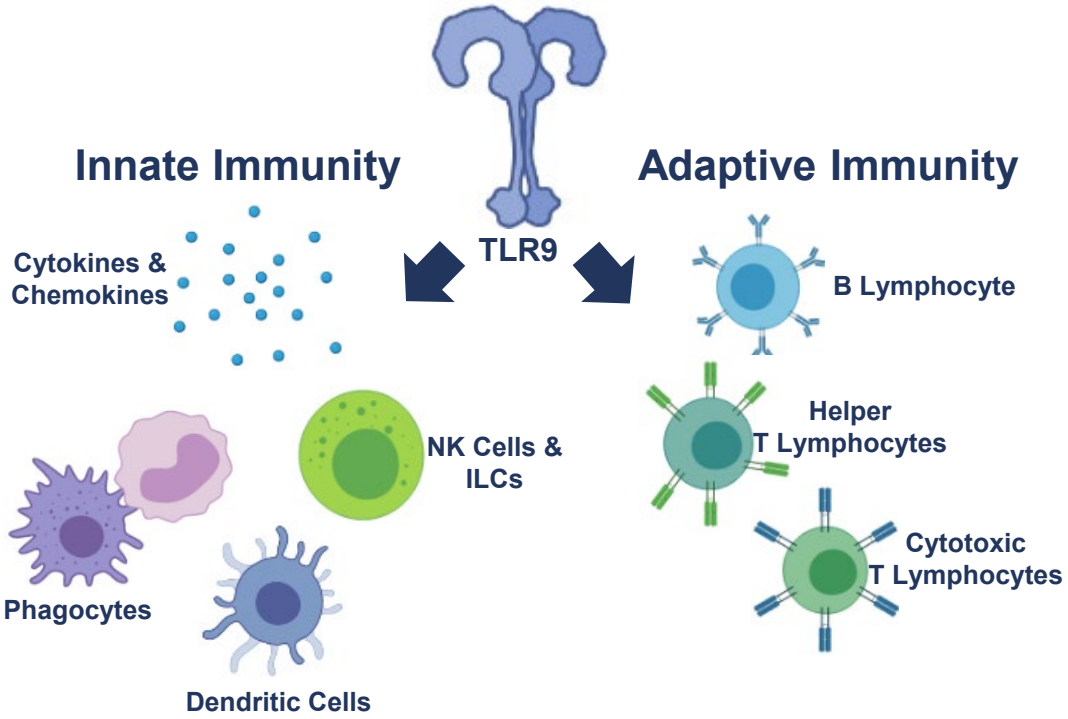
Cavrotolimod: Clinically-Validated TLR9 Agonist for Immuno-Oncology

- TLR9 agonism is a clinically validated mechanism to stimulate the immune system and increase the efficacy of combination therapeutics in IO, immunology and infectious disease settings
- Cavrotolimod: differentiated TLR9 agonist in spherical-nucleic acid (SNA) format
  - SNA format increases cellular uptake of TLR9 agonist vs linear TLR9 agonist oligonucleotides
  - Induces strong Th1 immune response, activating NK and $CD8^+$ T-cells (clinically and preclinically)
- Extensive clinical safety and pharmacodynamic experience via ongoing P1b/2 for solid tumors
  - 50 patients across multiple tumor types (MCC, CSCC, melanoma, etc.) dosed as of August 2021
  - MCC: 21% ORR (interim results, 08/2021) and 13 months median duration of response
- Robust, scalable, and reproducible CMC process and broad IP coverage until 2035[1]
- Given Exicure's increasing focus on neuroscience, we are looking for a partner to maximize cavrotolimod's potential as a potent stimulator of the immune system via Th1 response

1) Not accounting for any potential patent term extension (PTE)
MCC: Merkel Cell Carcinoma; CSCC: Cutaneous Squamous Cell Carcinoma; IO: Immuno-Oncology; NK: Natural Killer Cells; ORR: Overall Response Rate

TLR9 Effectively Activates Innate Immunity, Which Elicits Adaptive Immune Response

TLR9 Activation Effects Both Innate and Adaptive Immunity



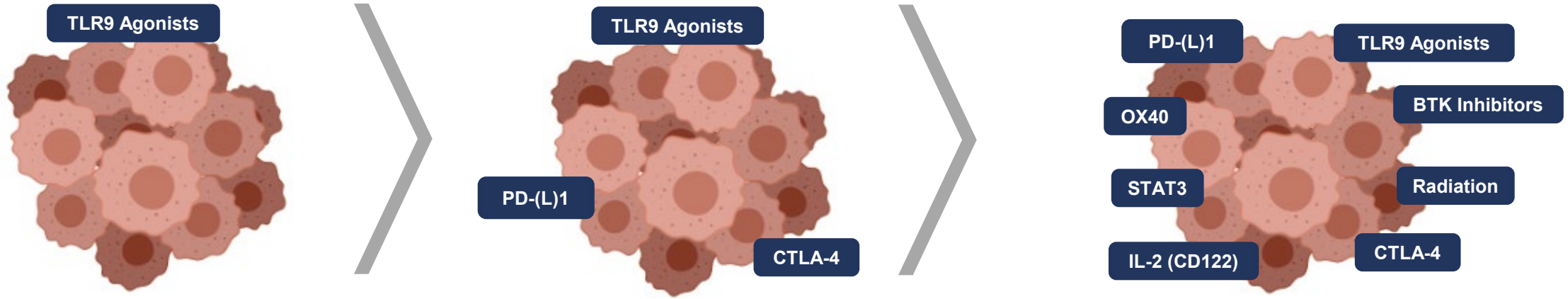
Key Takeaways

- TLR9 bridges two key functions of the immune system – activate innate immune system, which effectively leads to an adaptive immune response
- Expressed predominantly in APCs (B-cells, DCs) and T cells
- The efficacy of TLR9 activation of the immune system has been commercialized with Heplisav for Hep B by Dynavax
- TLR9's ability to prime the immune system a promising approach to address tumors via immunotherapy

APCs: Antigen Presenting Cells, DC: Dendritic Cells; ILC: Innate Lymphoid Cells; NK: Natural Killer

Use of TLR9 Agonists Has Evolved from Monotherapy to Simple Checkpoint Inhibitor Combinations, with Multi-Drug Approaches Next

Evolution in Utilization of TLR9 Agonists in Oncology



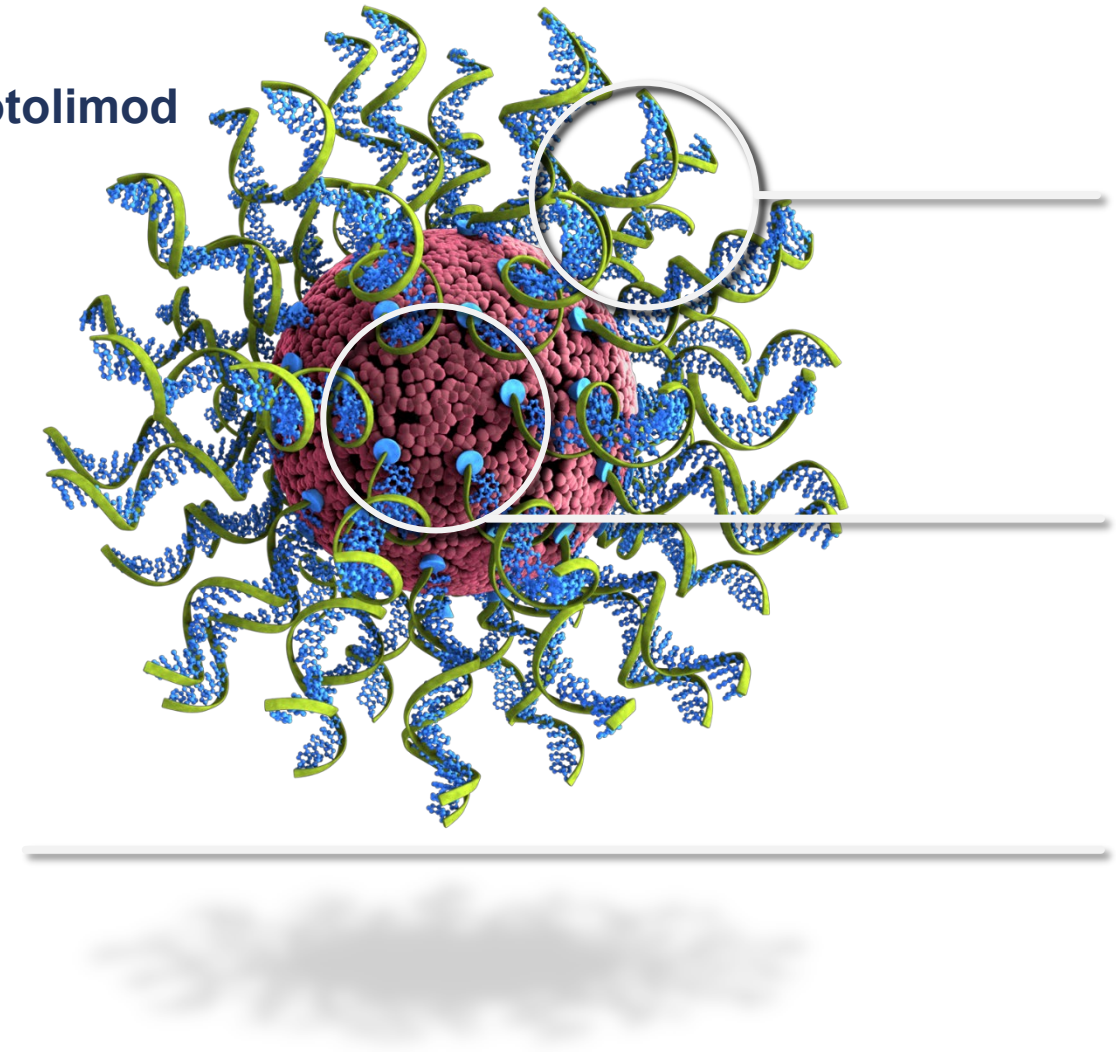
- Early trials of TLR9 agonists as monotherapy were stymied by immune escape of tumors, e.g. expression of checkpoint receptors
- TLR9 agonists can potentiate effect of immune checkpoint inhibitors (ICIs) in a synergistic manner, turning “cold” tumors “hot”, activating anti-tumor T-cells and NKCs that enhance ICI activity
- Combination approach of TLR9 agonist + ICIs (PD-(L)1 and/or CTLA-4) showing encouraging early clinical trial results
- Promising results with TLR9 agonist and ICI in neoadjuvant setting suggest treatment earlier in disease course might increase effectiveness[1]

1) Karapetyan et al. 2020 OncoTargets and Therapy; BTK: Bruton’s Tyrosine Kinase; ICI: Immune Checkpoint Inhibitor; NKCs: Natural Killer Cells

Cavrotolimod

Potent TLR9 Agonist

Cavrotolimod (AST-008) – Exicure's TLR9 Agonist



TLR9 agonist oligonucleotides – potent inducers of immunity

- Cytokines/chemokine signaling (IP-10, IL-12) for immune cell trafficking
- T cell activation
- NK cell activation

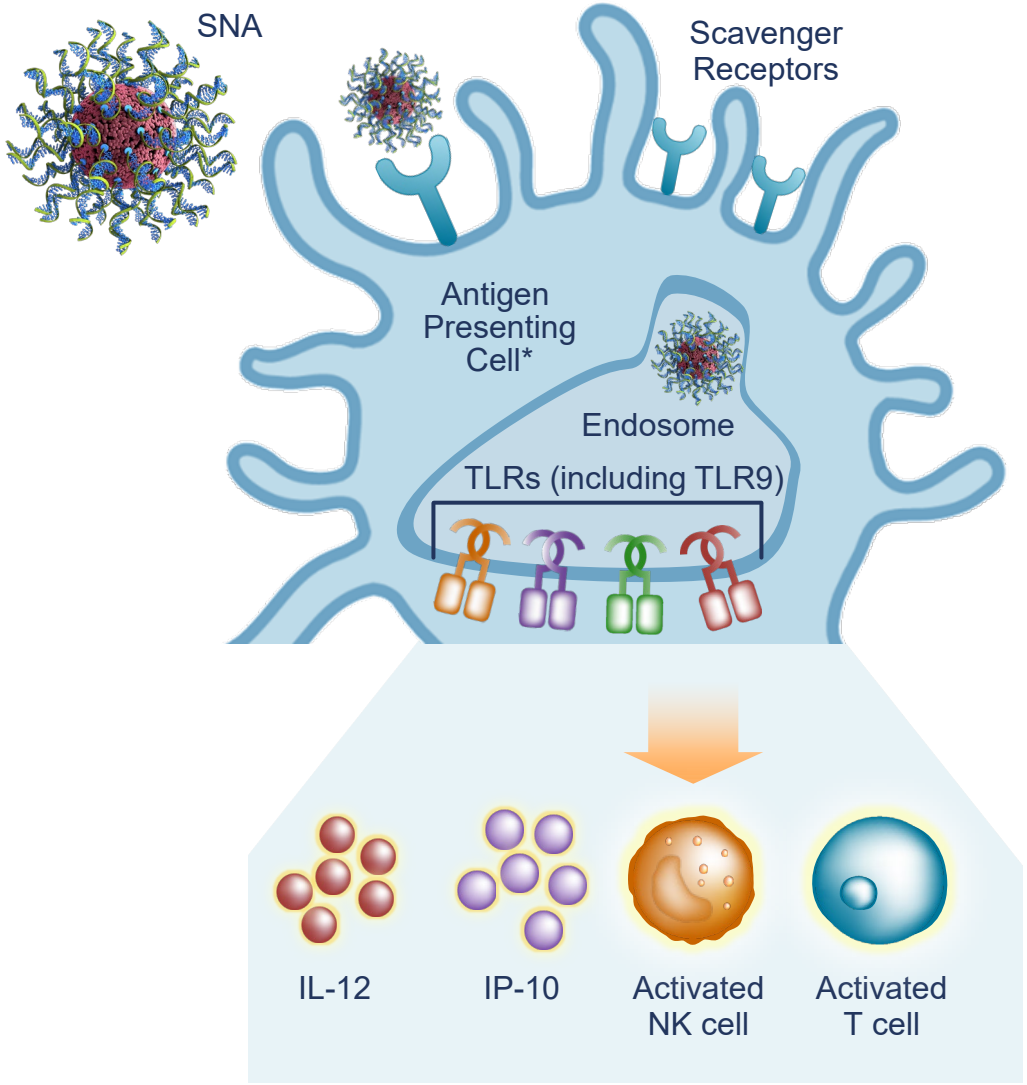
Benign lipid nanoparticle

- Scaffold for SNA structure

Oligonucleotides + nanoparticle = SNA

- Increased cellular and endosomal uptake
  → Endosomes: Location of TLR9 target

SNAs Leverage Endosomal Uptake and Are a Highly Promising Delivery Vehicle Given Endosomal TLR9 Localization

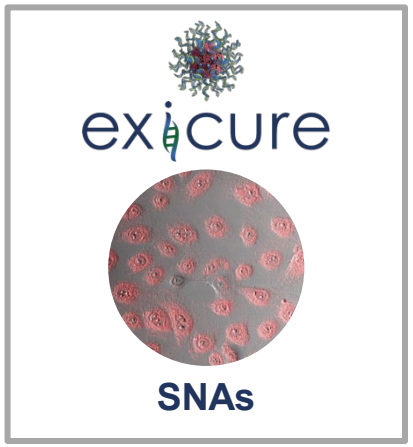


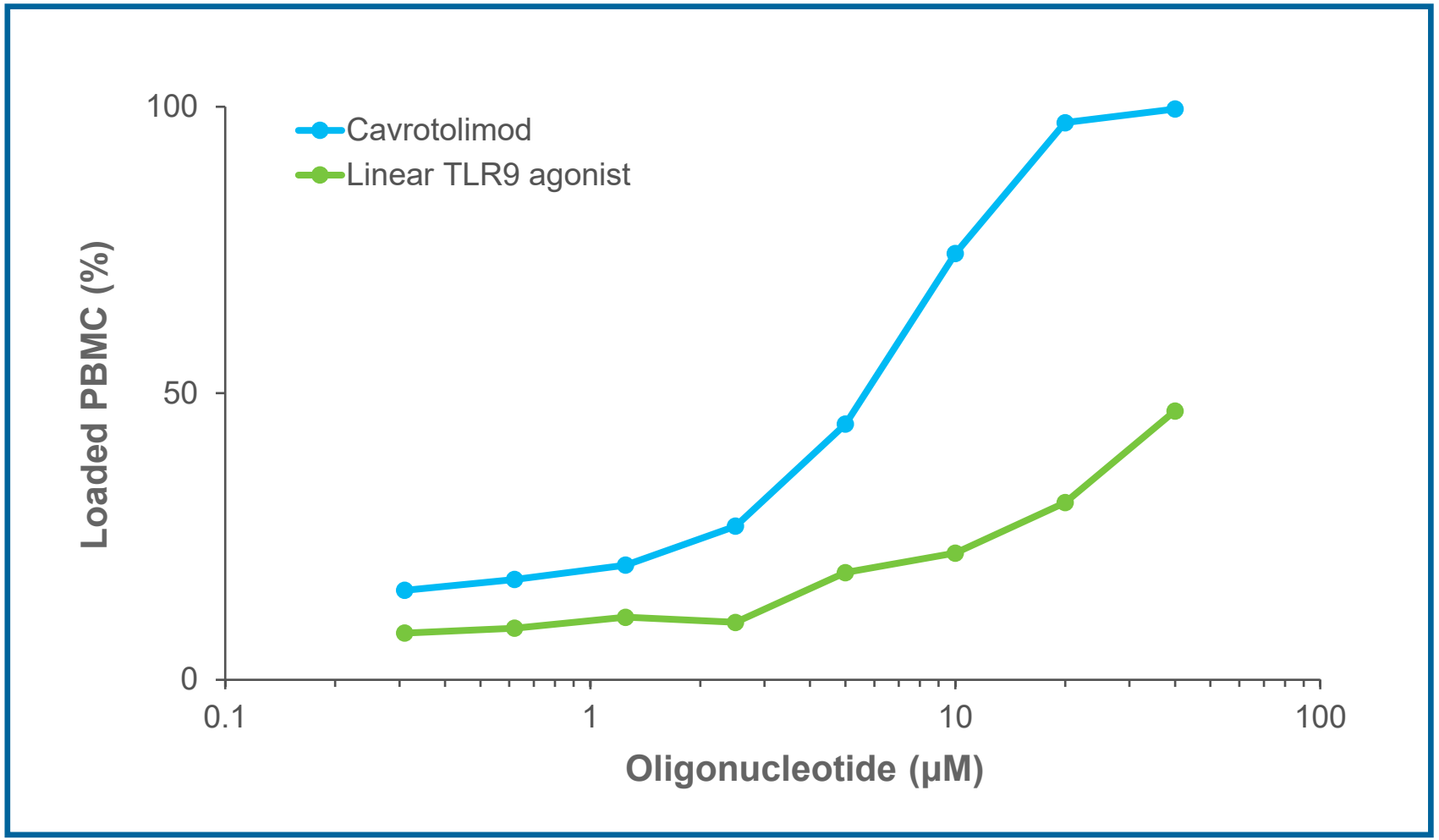
*Exemplary dendritic cell

Key Takeaways

- Toll like receptor 9 (TLR9) agonism can produce the desired pharmacodynamics
- TLR9 is found in the endosome of cells – SNAs are colocalized in the endosome after internalization into cells
- The SNAs are coated externally with oligonucleotides allowing for facile interaction with TLR9
- SNAs have high cellular uptake, driving potency

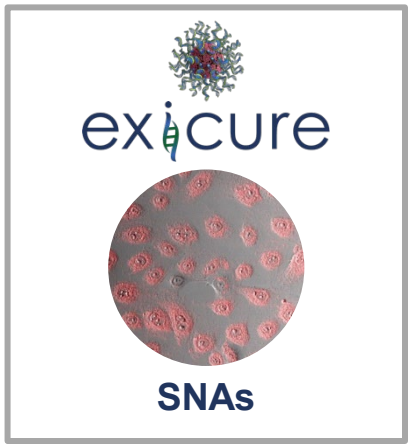
Cavrotolimod Demonstrates Higher Cell Uptake vs Linear Oligos

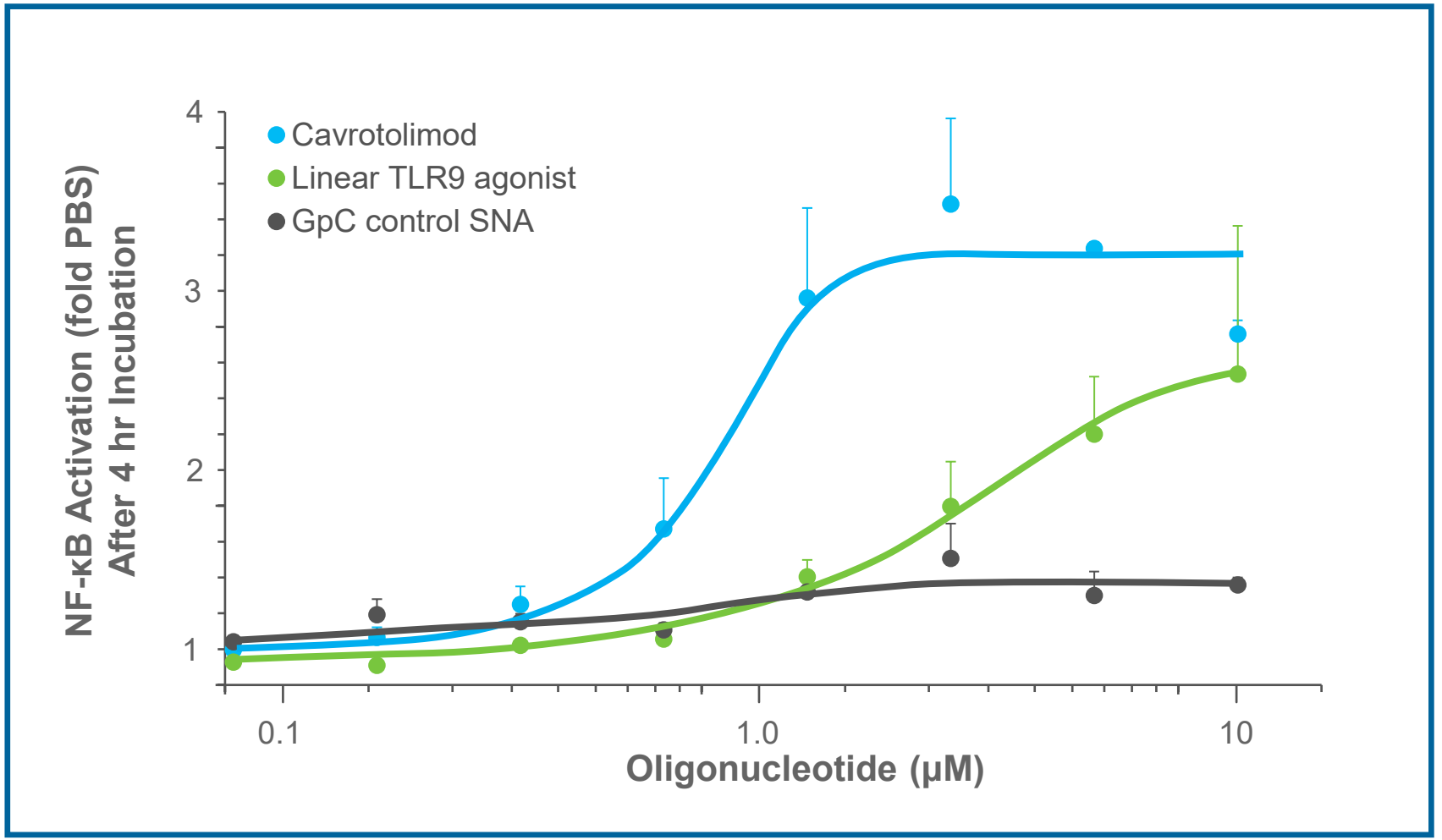




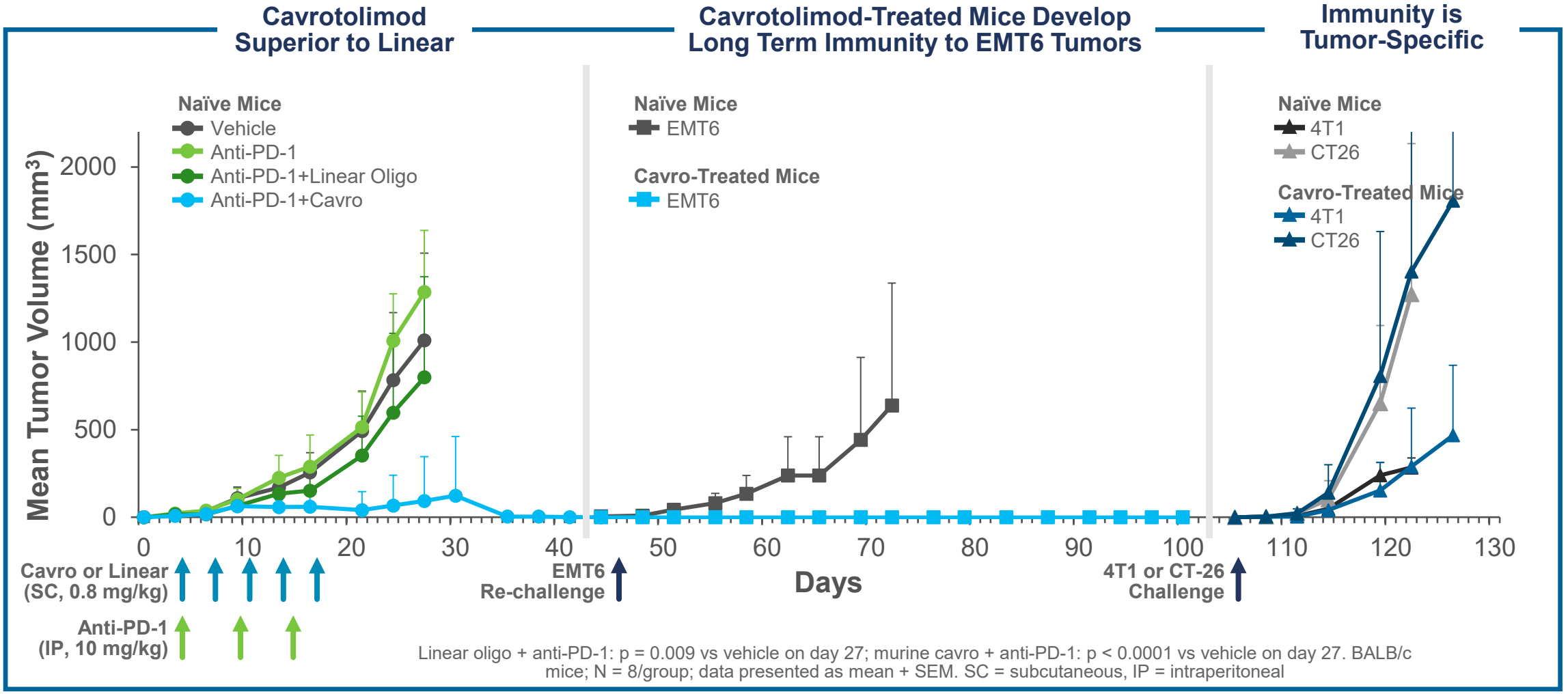
PBMC = peripheral blood mononuclear cells

Cavrotolimod Causes Superior TLR9 Activation vs Linear Oligos





Cavrotolimod Produces a Superior Anti-tumor Response Versus Linear Oligonucleotides and a Tumor-Specific Memory Response In Mice

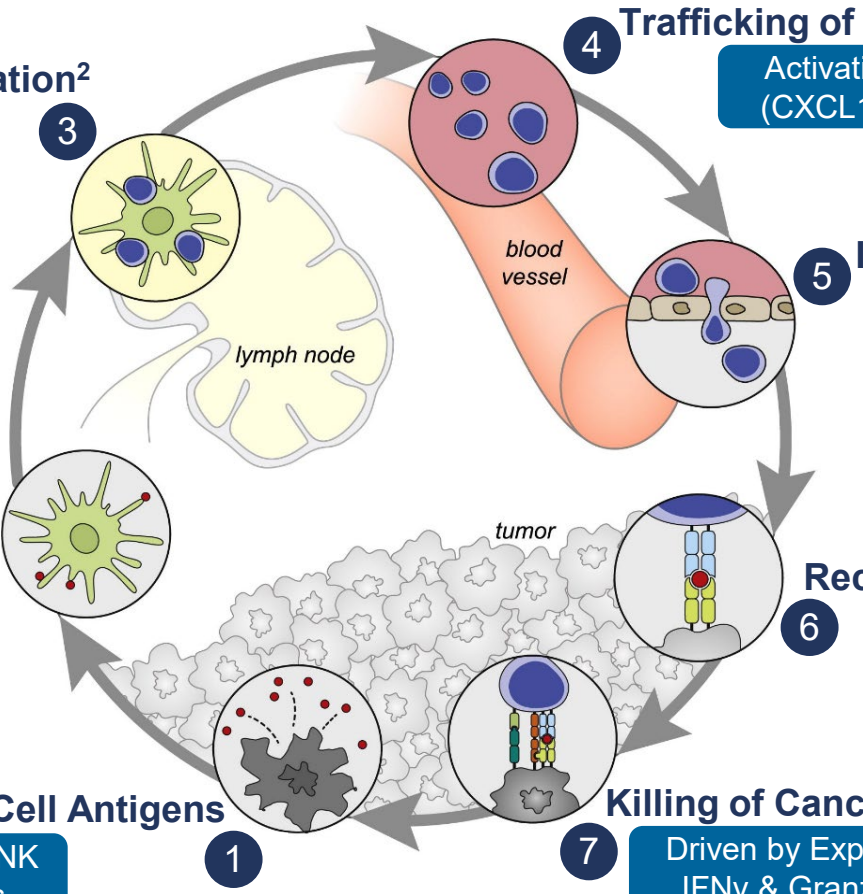


Linear oligo + anti-PD-1: p = 0.009 vs vehicle on day 27; murine cavro + anti-PD-1: p < 0.0001 vs vehicle on day 27. BALB/c mice; N = 8/group; data presented as mean + SEM. SC = subcutaneous, IP = intraperitoneal

Tumor shrinkage observed in multiple tumor types and different routes of administration (IV, S/C, IT)

In Patients, Cavrotolimod Demonstrates Activation of Key Factors in the Cancer Immunity Cycle[1] to Produce Anti-tumor Response

Effect of Cavrotolimod



Cavrotolimod shows activation of key factors in all steps critical for immune response to tumors

1) Immunity, Volume 39, Issue 1, 25Jul2013, Pages 1-10.; 2) Steps in the immunity cycle where immune checkpoint inhibitors prevent tumor escape.

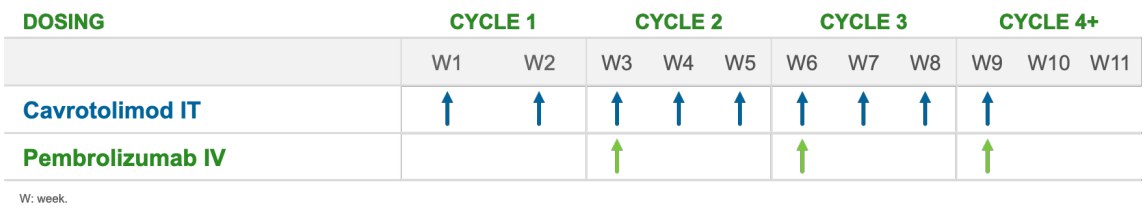
Cavrotolimod

Phase 1b/2 Clinical Data

Cavrotolimod - Extensively Profiled via Phase 1b/2 in Solid Tumors

Phase 1b/2 Study Design

Phase 1b Dose-Escalation Stage → **Phase 2 Dose-Expansion Stage**



W: week.

MCC[1] (up to 29 patients)

CSCC[1] (up to 29 patients)

Melanoma (exploratory, up to 10 patients)

SC Dosing (exploratory, up to 10 patients)

- MAD cohorts of 2, 4, 8, 16 and 32 mg dosed intratumorally (IT) in combination with pembrolizumab
- Basket design included patients with locally advanced or metastatic MCC, CSCC, melanoma, HNSCC, leiomyosarcoma
- Prior history of anti-PD-(L)1 therapy in 95%, and failure of prior anti-PD-(L)1 therapy in 85%
- Intensive local and systemic pharmacodynamic assessments

- 32 mg dosed intratumorally (IT) in combination with pembrolizumab (MCC, melanoma) or cemiplimab (CSCC)
- Dose-expansion cohorts of patients with locally advanced or metastatic MCC or CSCC
- Exploratory cohorts of patients with melanoma or solid tumors without superficial lesions (subcutaneous dosing)
- All patients with recent progression on anti-PD-(L)1 therapy

1) Simon's 2-Stage Design; identical dosing schedule and key assessments to Phase 1b; CSCC: Cutaneous Squamous Cell Carcinoma; MCC: Merkel Cell Carcinoma; HNSCC: Head and Neck Squamous Cell Carcinoma

Phase 1b/2 Summary of Cavrotolimod Clinical Findings

Clinically Meaningful Overall Response Rate

Confirmed ORR 21% in all evaluable MCC patients in Phase 1b/2 (3 out of 14; 1 CR and 1 PR in P1b and 1 CR in P2)

2 PRs achieved in Phase 1b melanoma cohort (out of 16 evaluable melanoma patients in Phase 1b/2)

Phase 2 CSCC and exploratory cohorts continuing enrollment and data accrual

Durable Responses

In Phase 1b/2, all 5 responders show durable responses of ≥6 months

Median duration of response in Phase 1b/2 13 months and longest response 20 months and ongoing

Observed Systemic (Abscopal) Effects

Regression of noninjected regional and distant lesions in all 3 MCC responders in Phase 1b/2

Efficacy in Refractory Population

92% progressive disease on prior anti-PD-1 and 67% with two or more lines prior systemic therapy

Safety & Adverse Events (AE)

>90% of treatment-related AEs were Grade 1/2 with most common TRAEs: flu-like symptoms, injection site reactions

Two patients experienced treatment-related serious AEs: hypotension, flu-like symptoms and infusion-related reaction

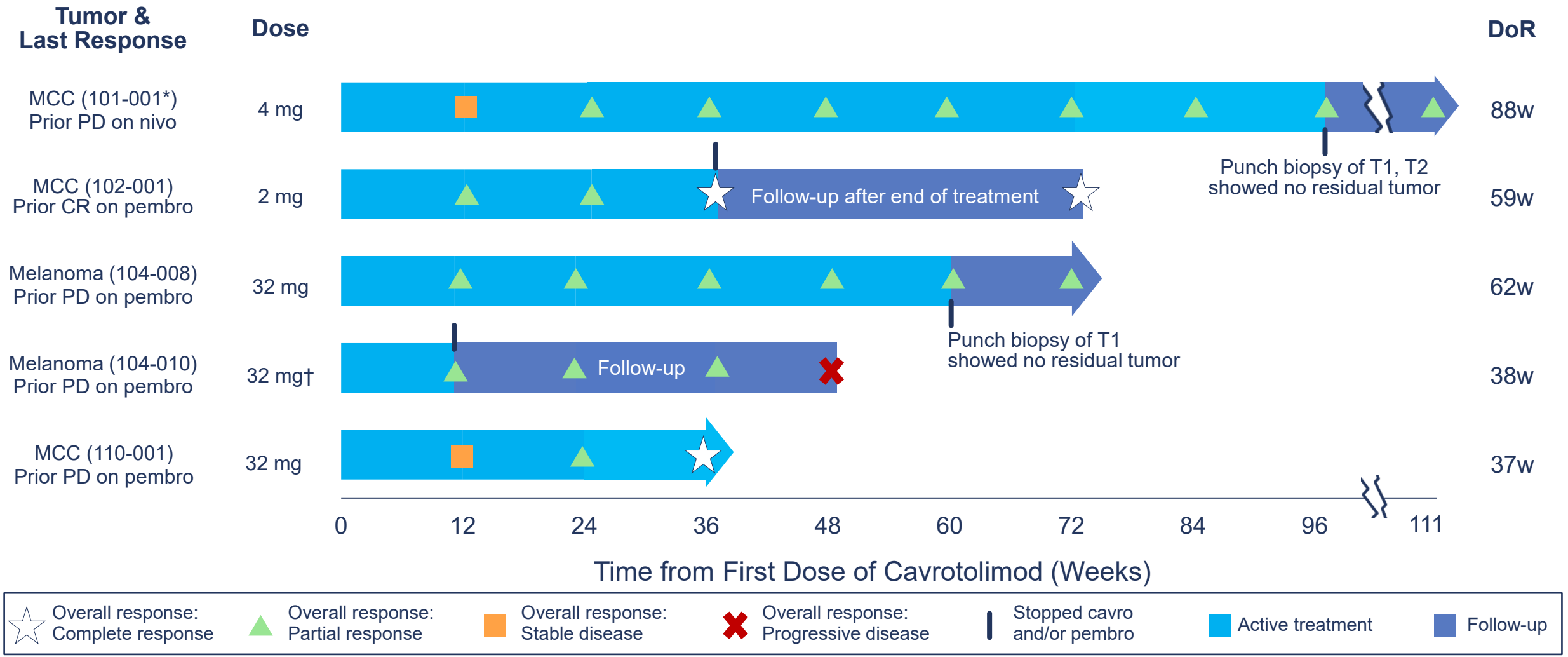
Phase 1b/2 Interim Results as of Data Cut-off Date of July 23, 2021

Vast Majority of Phase 1b/2 Patients Previously Progressing on PD-1

Baseline Characteristics (N=50†)		Phase 1b/2 N (%)
Cancer type	Melanoma	24 (48%)
	Merkel cell carcinoma	17 (34%)
	Cutaneous squamous cell carcinoma	5 (10%)
	Head & neck squamous cell carcinoma	2 (4%)
	Sarcoma*	2 (4%)
Cancer stage	Metastatic disease	48 (96%)
Prior anti-PD-(L)1	History of anti-PD-(L)1 use	49 (98%)
	Best prior response: progressive disease†	27 (55%)
	Last prior response: progressive disease	47 (94%)
	Time since last dose ≤20 weeks	45 (90%)
Prior lines of systemic therapy† (N = 49)	1	16 (33%)
	2	12 (25%)
	3+	21 (43%)

*1 diagnosis of sarcoma, lung, 1 leiomyosarcoma (LMS)
† N= 49 used to evaluate lines of prior therapy and related entries due to missing information for one patient

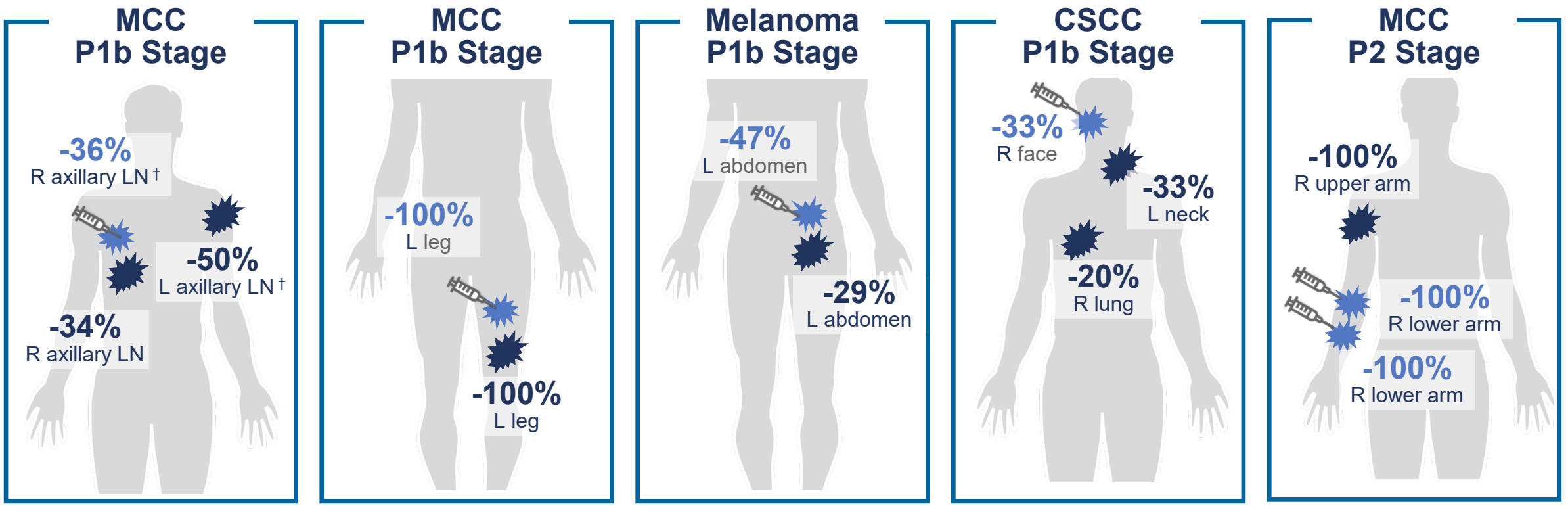
Phase 1b/2 Responders: 2 CR, 3 PRs and Median DoR of 13 Months



*Patient completed maximum protocol-specified DoR for cavrotolimod
†Patient received SC doses after complete resolution of superficial lesions DoR: duration of response SLD: maximum decrease in sum of target lesion diameters. Data cut off 7 Sep 2021

Phase 1b/2: Regression of Noninjected Regional & Distant Lesions

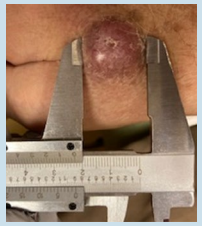
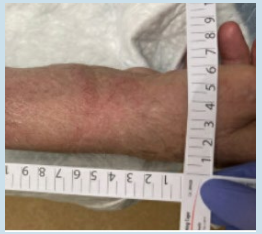
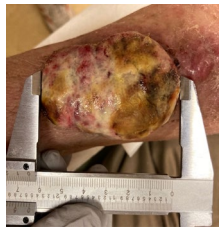
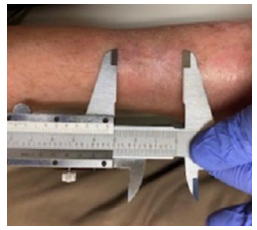
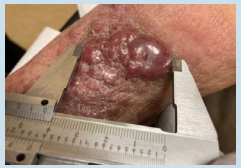
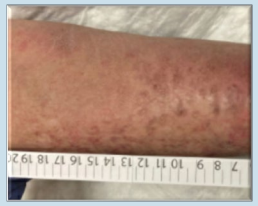
Best Overall Response* per RECIST v1.1 in Evaluable Patients as of July 23, 2021



* Includes non-responders with significant abscopal effect
† Biopsy showed no residual tumor
** Patients had progressed on anti-PD-1 therapy prior to study enrollment
‡ Patient previously treated with anti-PD-1 therapy with CR. Patient had progressed off of anti-PD-1 therapy prior to study enrollment.

Phase 2 MCC Patient with Overall Complete Response by RECIST v1.1

92-year-old Male Patient w/ Documented Progression on Pembrolizumab Monotherapy

	Baseline		Week 36	
Overall Response (RECIST v1.1)	-		Complete Response	
#1 – Injected Target Lesion Right wrist		20 mm		0 mm
#2 – Injected Target Lesion Right lower arm		53 mm		0 mm
#3 – Noninjected Lesion Right upper arm		25 mm		0 mm
Sum of 3 Lesion Diameters		**98 mm**		**0 mm**

Phase 1b/2: Decreased Total Target Tumor Diameter in 44% of Patients[1]

Target Tumor Response: Sum of Injected and Noninjected Lesions

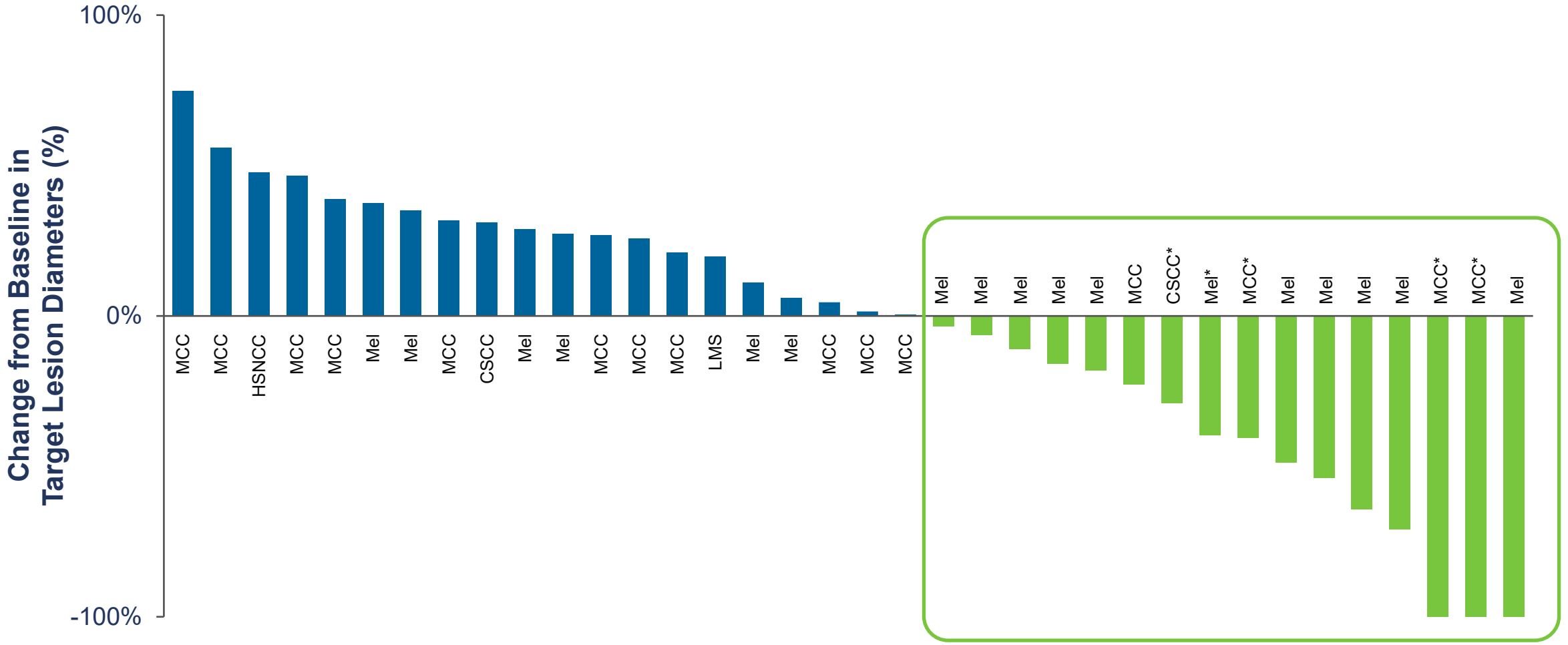


Figure excludes patients who did not have post-treatment CT scan assessment
1) In evaluable patients *Patients shown on abscopal effect slide

Phase 1b/2: Cavrotolimod Generally Safe and Well Tolerated

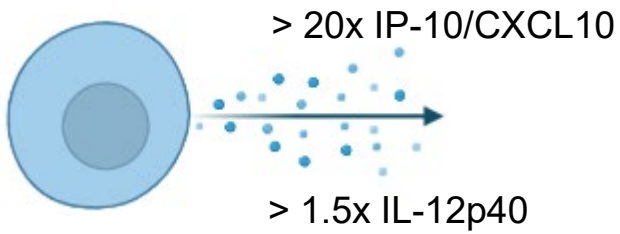
Injection Site Reactions and Flu-like Symptoms as Expected from Local and Systemic Immune Activation

- Majority (>90%) of treatment-related adverse events (AEs) were Grade (G) 1 or 2
- Most commonly reported treatment-related AEs observed:
  - Injection site reactions (25/50, 50%)
  - Flu-like symptoms (41/50, 82%)
  - Post injection reactions primarily manifest as flushing (8/50, 16%)
- No apparent exacerbation of anti-PD-1 toxicity
- Treatment-related serious adverse events observed in 2 subjects (2/50, 4%)
  - No SAE occurred in >1 subject
  - Hypotension and flu-like symptoms were observed in 1 subject, and injection site reaction in 1 subject
- G3 or 4 treatment-related AEs in 10 subjects (10/50, 20%)
  - G3/4 AEs observed in >1 subject: flu like symptoms (4/50, 8%) and injection site reaction/pain (5/50, 6%)

Phase 1b/2 Interim Results as of Data Cut-off Date of July 23, 2021

Comprehensive Pharmacodynamic Profile[1] Consistent with Antitumor Immune Activation

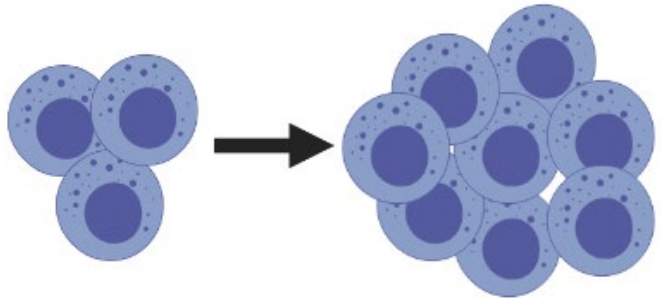
Increase in Cytokines and Chemokines



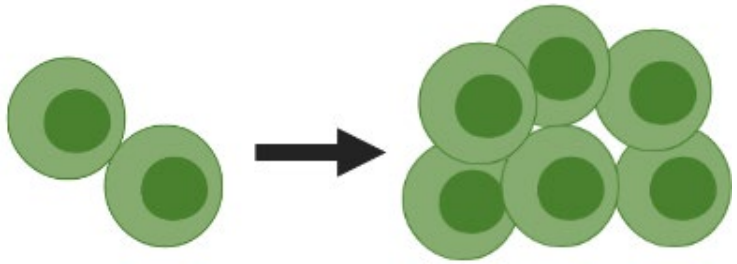
cavrotolimod 16-32 mg monotherapy vs baseline. N = 8

In patients administered cavro robust activation in a panel of chemokines and cytokines observed, including key factors in the cancer immunity cycle

Increase in Activated Circulating Immune Effector Cells



56% Increase in Active NK cells (35% to 91%)



41% Increase in Activated Cytotoxic T cells (21% to 62%)

cavrotolimod 16-32 mg monotherapy. N = 8

Induced Tumor Infiltration and Killing by Cytotoxic Immune Cells

2x more cytotoxic and CD8 T cells

3x more granzyme B transcript expression

3x less TGF-β2 transcript expression

cavrotolimod 2-32 mg monotherapy vs baseline. N = 9

- Cavro monotherapy effects in injected tumors
- Enhanced immune effects observed with PD-1 in injected and non-injected tumors

1) Data cutoff: Phase 1b patients (N=20) where all patients were sampled with data from patients with evaluable data.

Cavrotolimod: Potent Immune Stimulator for IO Combination Therapy

- Extensive clinical experience: Safety & PK/PD experience in >50 patients, including sub-cutaneous dosing
- Induces strong Th1 immune response in patients, activating NK cells and $CD8^+$ cytotoxic T-cells
- Cavrotolimod's SNA architecture drives increased cellular uptake of TLR9 agonist
- Robust, scalable, and reproducible CMC process
- Broad IP coverage until 2035[1]
- Opportunity to be readily combined with multiple IO agents to potentiate therapeutic response via innate immune system
  - Substantial GMP-quality API on hand, readily convertible to drug product
  - SC dosing experience enables clinical settings without superficial tumors; IV dosing for liver indications possible
  - Strong scientific rationale for potential therapeutic IO combination regimens

1) Not accounting for any potential patent term extension (PTE)

Cavrotolimod

Opportunities in Oncology

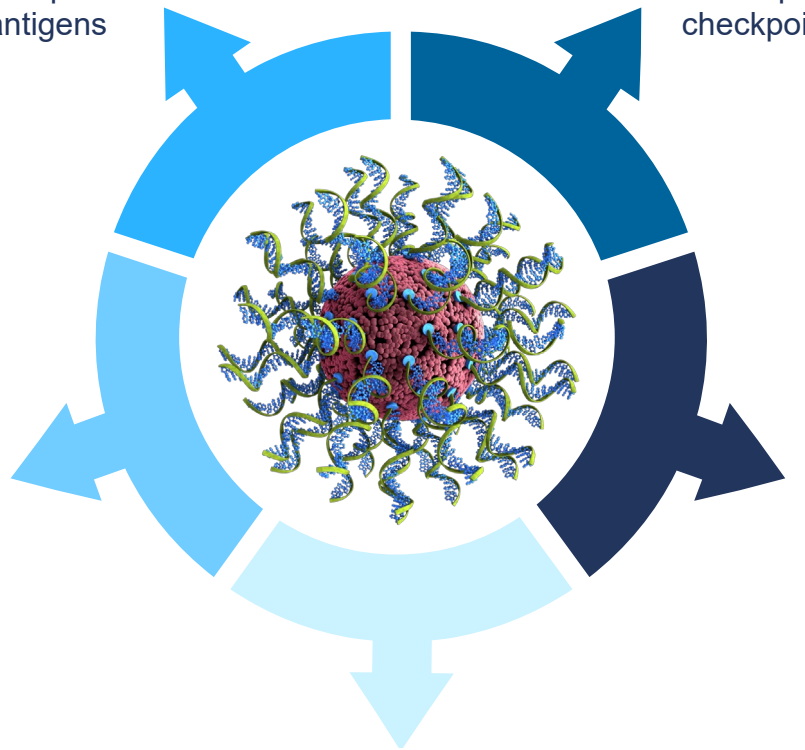
With Robust Elicitation of Immune Response in Patients Administered Cavrotolimod Multiple Opportunities Exist in Oncology

Turn Cold Tumors Hot

Intratumoral TLR9 agonist stimulates Th1 immune response against tumor-specific antigens

Novel IO Combinations

Evaluate rational TLR9-containing dual/triple regimens beyond checkpoint-inhibitor combinations



Liver-Targeting with IV

SNAs preferentially distribute to the liver following IV dosing, making them ideal for liver applications

SC Dosing

Address non-superficial tumor indications by systemic administration (evaluated in healthy volunteers and exploratory cohort in cavro Phase 1b/2)

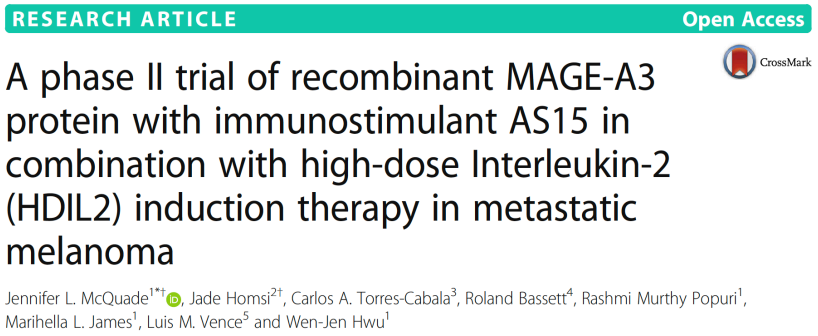
CAR T Enhancement

TLR9 downstream effector MyD88 being assessed for enhancing CAR T function

IO: Immuno-Oncology; IV: Intravenous; SC: Sub-cutaneous

TLR9 Agonism Has Demonstrated Benefit as an Adjuvant for Infectious Diseases and Cancer Vaccines

TLR9 Cancer Vaccine Adjuvant for Melanoma



RESEARCH ARTICLE Open Access

A phase II trial of recombinant MAGE-A3 protein with immunostimulant AS15 in combination with high-dose Interleukin-2 (HDIL2) induction therapy in metastatic melanoma

Jennifer L. McQuade[1*†], Jade Homsi[2†], Carlos A. Torres-Cabala[3], Roland Bassett[4], Rashmi Murthy Popuri[1], Marihella L. James[1], Luis M. Vence[5] and Wen-Jen Hwu[1]

- MAGE-A3 protein + IL-2 + AS15 adjuvant consisting of CpG 7909 (TLR9 agonist) and a saponin
- 25% ORR (4/16), incl. 3 complete responses
- Use of AS15 adjuvant was safe and well tolerated
- Stable disease in 6/16 (38%) patients for a disease control rate of 63%

TLR9 Vaccine Adjuvant for Hepatitis B

- HBsAg combined with TLR9 adjuvant (CpG 1018)
- Approved by FDA (2017) and EMA (2021)
- CpG 1018 being actively evaluated for other infectious disease vaccines

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