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Society for Immunotherapy of Cancer

TLR9 Agonists in Combination with Immune Checkpoint Inhibitors in Melanoma

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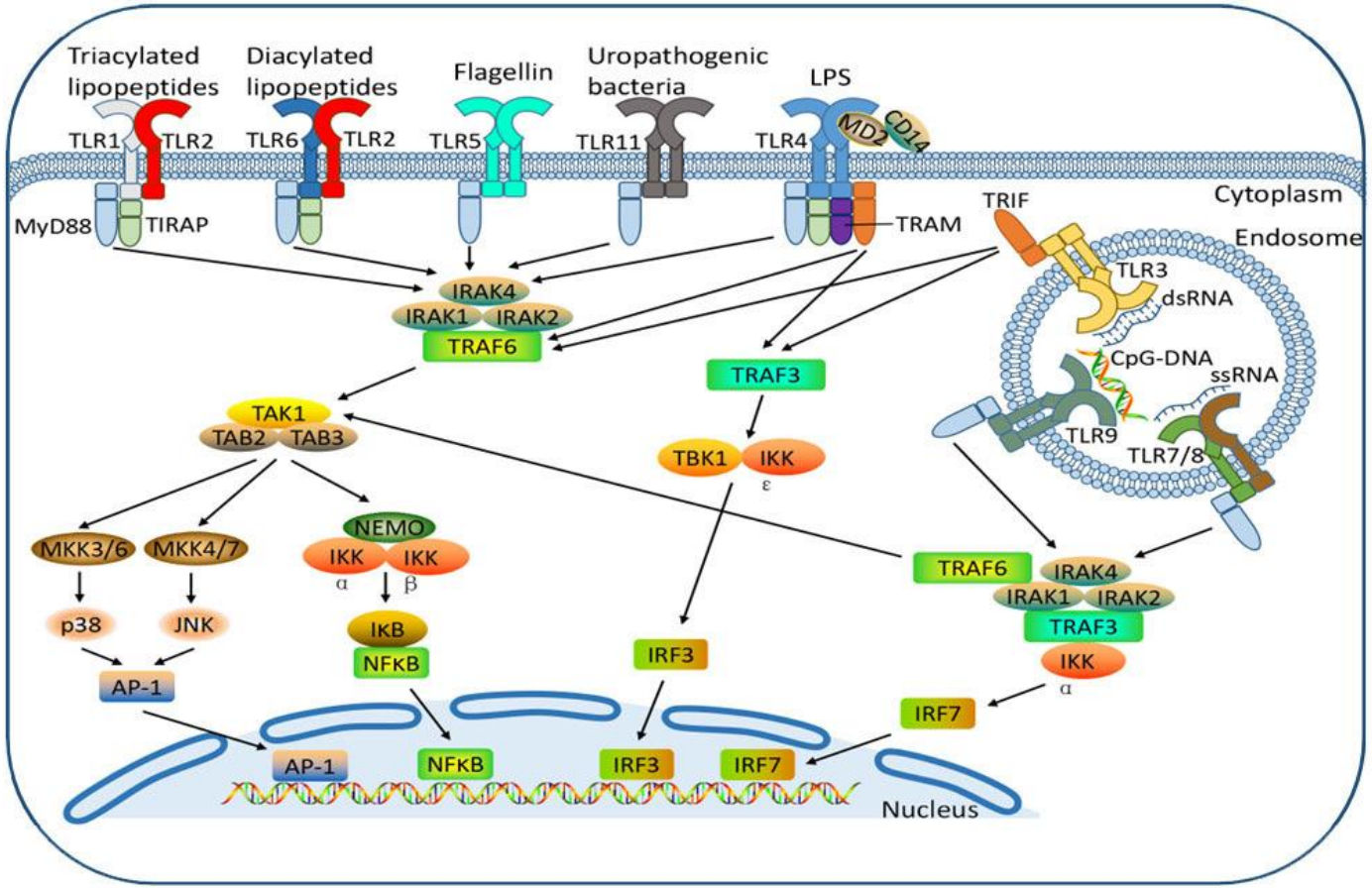
Disclosures

- Consultant Role: Novartis, Sanofi-Genzyme/Regeneron, BioNTech, Array Biopharma, Partner Therapeutics
- Contracted Research: OncoSec, Clinigen, BMS, Merck, Novartis, Genentech

TLR ligands and TLR signaling pathways

- Family of pattern recognition receptors that can induce potent innate and adaptive immune responses
- Cell surface TLRs, including TLR-1, -2, -4, -5, -6, -10, -11
- Intracellular TLRs, including TLR-3, -7, -8, -9
- Recognize their specific PAMPs to activate TLR signaling cascades



Du et al. J Cancer Metastasis Treat 2016;2:463-70

Immune Cells Detect Unmethylated CpG DNA via TLR9 as a "Danger Signal" Inducing Th1 Response

- Krieg et al: an innate immune defense recognizing unmethylated CpG motifs in bacterial or viral DNA
- Akira et al: reported TLR9 in human B cells and in pDCs responsible for sensing CpG motifs in the DNA
- Triggering CpG-TLR9 signaling pathway leads to upregulation of proinflammatory genes such as IL-6, TNF-α and type-I interferons (IFN-α and IFNβ)
- Subsequent efforts resulted in the design of various classes of synthetic oligodeoxynucleotides
- Initial experience with CpG-B oligos (Coley/Pfizer, 1999 to 2011)
  - Excellent safety profile
  - Monotherapy responses with SC injection (melanoma, RCCA, NHL, CTCL)
  - Phase III of CpG-B PF-3512676 combined with paclitaxel/carboplatin in NSCLC failed

Krieg et al, Nature 1995;374:546-549
Akira et al, Nature 2000;408:740-745
Hirsh et al, J Clin Oncol. 2011 Jul 1;29(19):2667-74

CpG ODNs are the strongest CTL-inducing vaccine adjuvants reported in human clinical trials *(Speiser, 2005, Valmori, 2007, Karbach, 2011)*

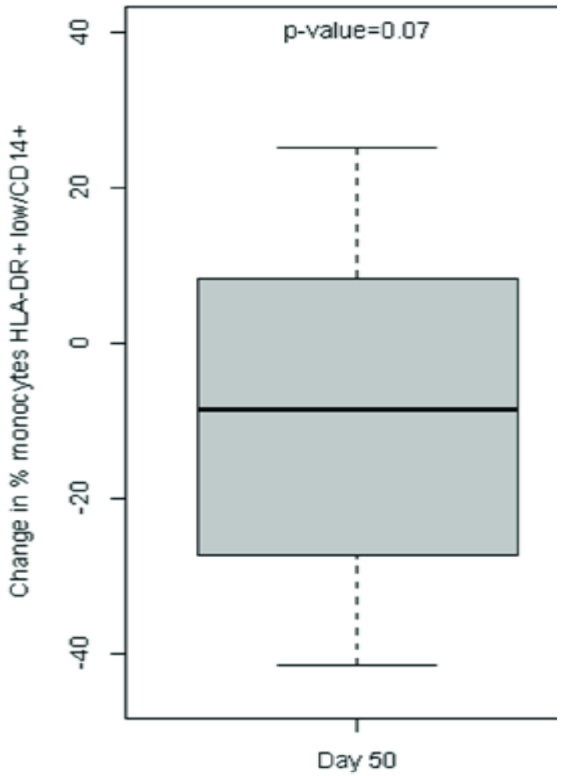
- Tested in human trials as vaccine adjuvants, in cancer immunotherapy; induce potent type I IFN, CTL
  - Heplisav vaccine against HBV: approved in 2017
  - Nuthrax vaccine against anthrax:
    - Acquired for Strategic National Stockpile
    - Submitted to FDA last year for emergency use authorization

Tarhini AA, et al. J Immunother 2012;35:359–366

Safety and Immunogenicity of Vaccination With MART-1 (26–35, 27L), gp100 (209–217, 210M), and Tyrosinase (368–376, 370D) In Adjuvant With PF-3512676 and GM-CSF In Metastatic Melanoma

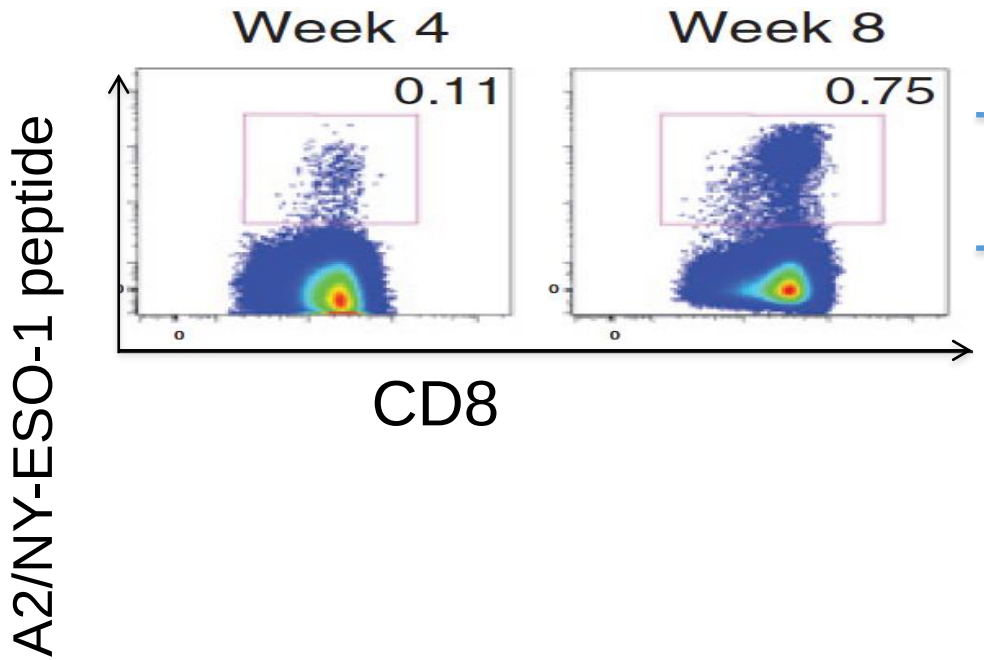
Change in ELIspot CD8+ T cell frequency measured by the ratio of post vs pre treatment value of CD8+ T cells against melanoma specific antigens

	Day 50		Day90	
	Median	p-value	Median	p-value
T2+CD8+Mart 27-35	1.5	0.02	1.4	0.11
T2+CD8+Gp100 209-217	1.3	0.05	1.7	0.06
T2+CD8+Tyr368-376D	1.3	0.03	1.5	0.06



Tarhini AA, et al. J Immunother 2012 May;35:359–366; Tarhini AA, et al. J Immunother 2012 Nov-Dec;35(9):702-10

TLR9 Ligands Induce Anti-tumor CD8$^+$ T Cells



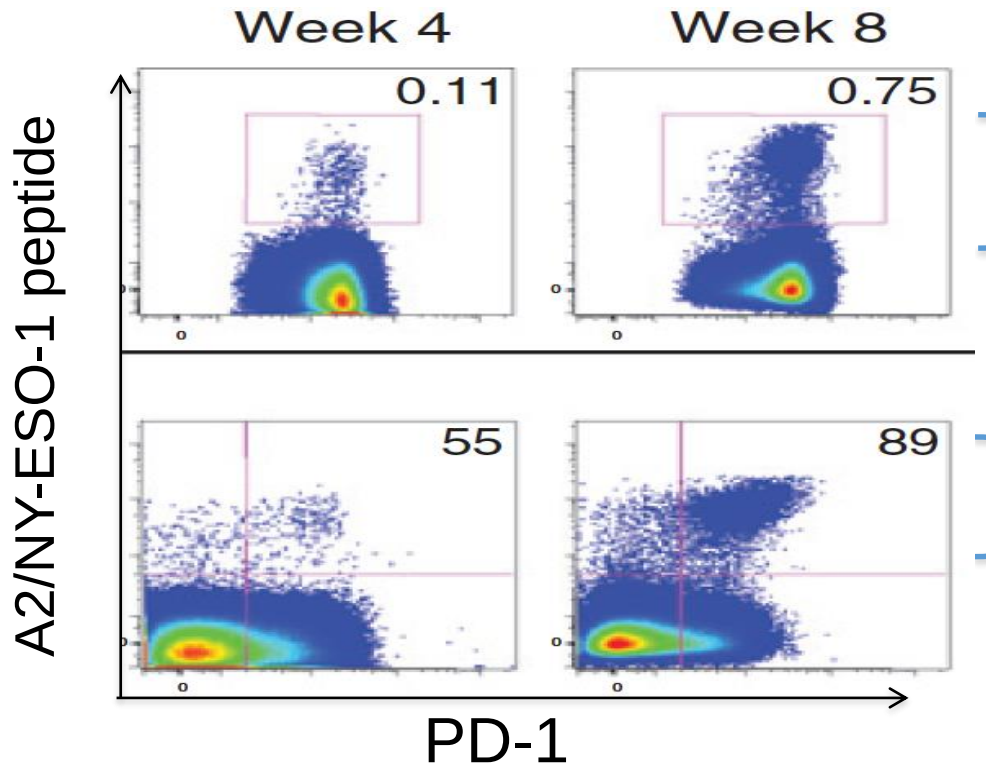
% tumor-specific CD8$^+$ T cells

Rapid expansion of anti-tumor cytolytic T cells

Fourcade et al., Cancer Res, 74:1045, 2014.

TLR9 Ligands Induce Anti-tumor CD8$^+$ T Cells

BUT Also Induce PD-1; "Setting The Immune Brakes"



% tumor-specific CD8$^+$ T cells

Rapid expansion of anti-tumor cytolytic T cells

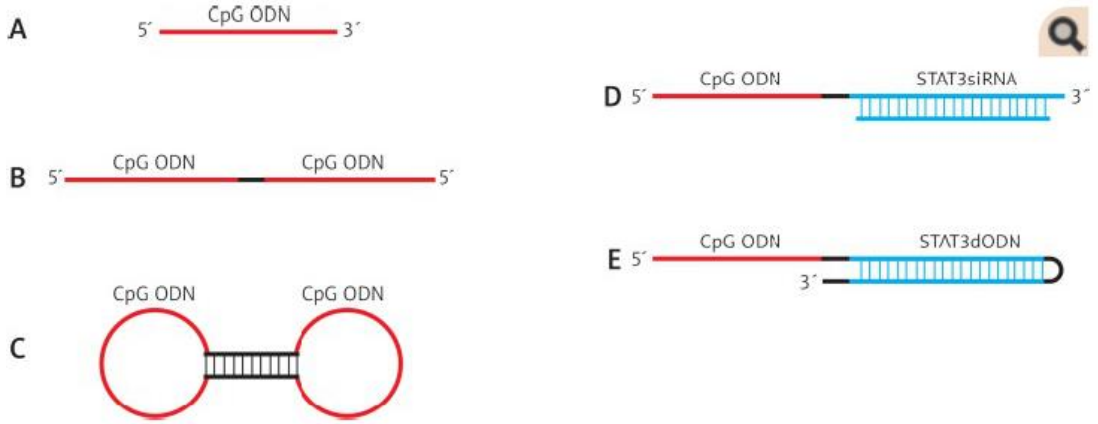
PD-1$^+$ CD8$^+$ T cells

Expression of PD-1: <u>supports synergy for PD-1 blockade combination</u>

Fourcade et al., Cancer Res, 74:1045, 2014.

New combinatorial CpG ODN-based cancer immunotherapies in clinical trials

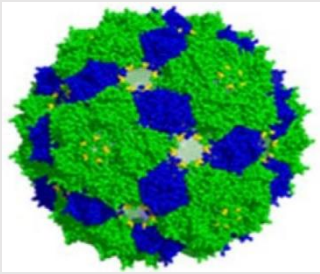
Various classes of CpG ODNs differing in structural characteristics and immunomodulatory activities



Product	Target	Institution	Development phase
IMO-2125 CpG-3'-3' fusion	TLR9/CTLA-4	Idera Pharmaceutical	Phase 1/2 (metastatic melanoma): in combination with ipilimumab
SD-101 CpG-C	TLR9/PD-1	Dynavax	Phase 1/2 (metastatic melanoma): in combination with pembrolizumab
MGN1703 double loop CpG	TLR9/CTLA-4	Mologene AG	Phase 1 (advanced solid tumors): in combination with ipilimumab
CMP-001 CpG-A/VLP	TLR9/PD-1	Checkmate Pharmaceuticals	Phase 1/2 (advanced melanoma): in combination with pembrolizumab
CSI-2 CpG-B conjugate	TLR9/STAT3	City of Hope	Phase 1 planned for 2019 (Non-Hodgkin's B cell lymphoma)

Adamus et al, Contemp Oncol (Pozn). 2018 Mar;22(1A):56-60

CMP-001: CpG-A in a Virus-Like Particle (VLP)



The Qb and G10 components self-assemble into highly-ordered icosahedral VLPs (~30 nm)

CMP-001 has two components:

1. A viral protein (Qb bacteriophage)
2. A CpG-A ODN (G10): TLR9 Agonist

The first dose of CMP-001 induces anti-Qb Ab

On 2nd & subsequent doses, anti-Qb Abs bind to & facilitate VLP uptake into pDC (& other immune cells), inducing type I IFN response

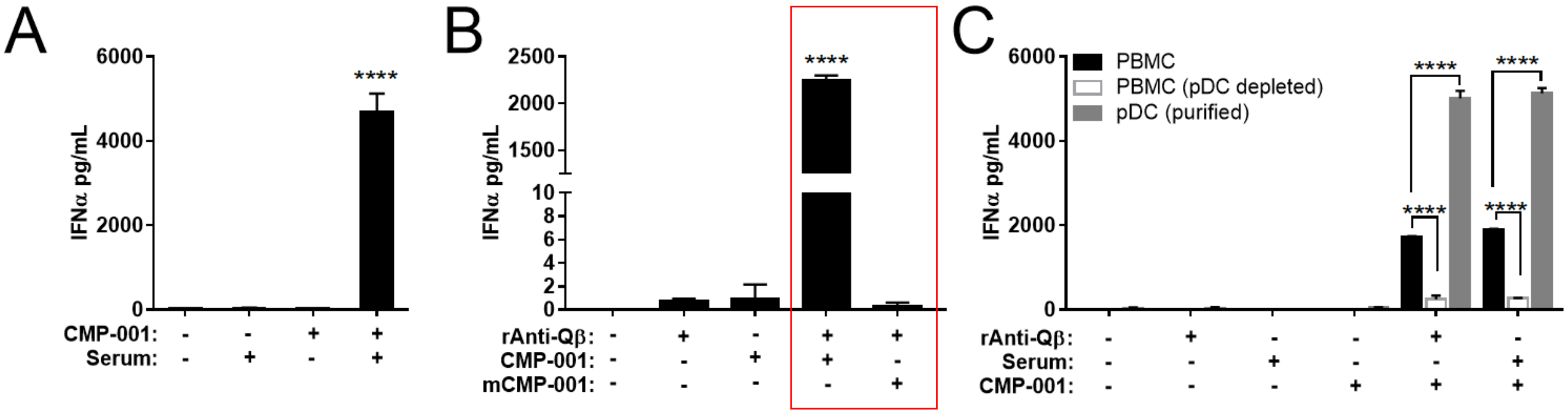
VLP:

1. Protects native DNA G10 from degradation
2. Forms immune complexes in tumor with anti-Qb Ab, activating classical complement pathway, additional immune boost

- G10 is a CpG-A oligodeoxynucleotide, the active ingredient in CMP-001
- **GGGGGGGGGGGACGATCGTCGGGGGGGGGG**
- Synthetic native DNA (phosphodiester)
- Unmethylated CpG mimicking retroviral, viral DNA

Modified from Slide courtesy of Dr. Art Krieg

CMP-001 Induction of Type 1 Interferon is Dependent on Anti-Qβ, Unmethylated CpG DNA and pDCs



IFNα levels from PBMCs cultured with & without CMP-001 and immune serum

IFNα levels from PBMCs cultured with & without CMP-001 or methylated CMP-001 (mCMP-001), and recombinant anti-Qβ

IFNα levels from PBMCs, pDC-depleted PBMCs or purified pDCs cultured with & without CMP-001, recombinant anti-Qβ, & immune serum

Phase 1b Study of Intratumoral CMP-001 + Pembrolizumab in PD-1 Resistant Melanoma

Key Elements of Study Design

- 3+3 Dose Escalation / Expansion
- CMP-001 injected intratumorally / pembrolizumab administered IV
- Two CMP-001 schedules evaluated in escalation:

Weekly x 7 → then Q3 week until discontinuation

Weekly x 2 → then Q3 week until discontinuation

- Q12 week scans. RECIST v1.1 assessment per investigator

CMP-001 Dose Escalation Schema	
1 mg *(1 mg/mL)*	Per label
5 mg *(1 mg/mL or 6 mg/mL)*	Per label
10 mg *(6 mg/mL)*^	Per label

^MTD not reached

Dose Expansion (enrolling)

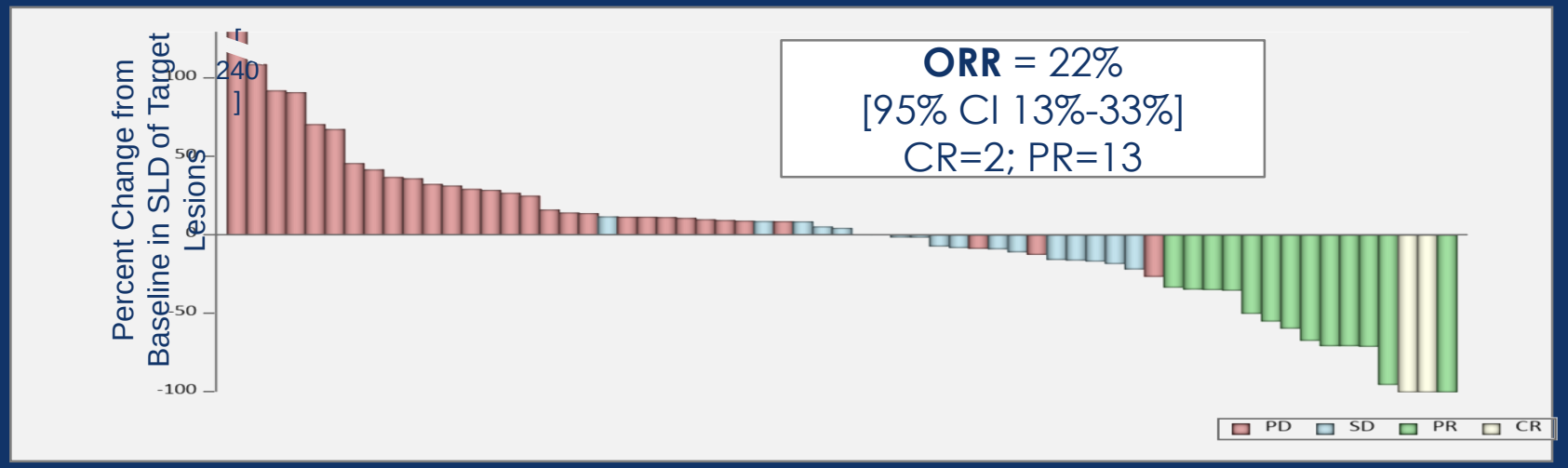
5 mg* *(1 mg/mL) weekly* + pembrolizumab

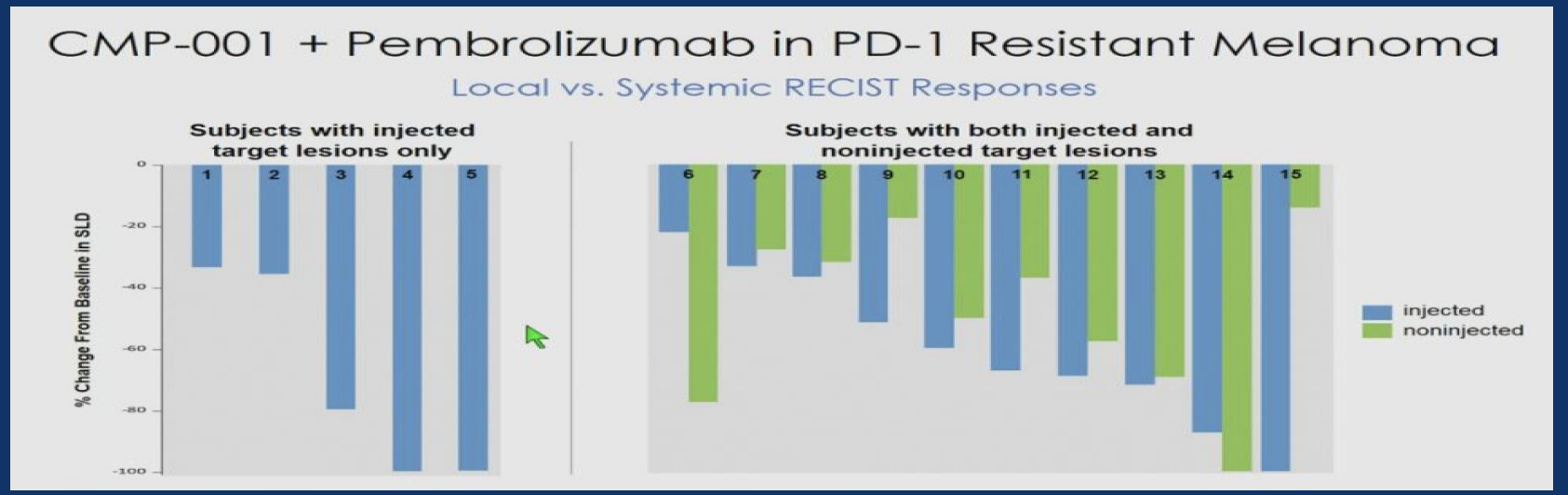
Milhem M et al. AACR 2018

CMP-001 + Pembrolizumab in PD-1 Resistant Melanoma

Best Tumor Response, All Subjects (ITT, RECIST v1.1)

- 69 subjects enrolled
  - ORR 22.5% for q1w (n=40) cohort
  - ORR 7.7% for q3w (n=13) cohort
  - ORR 33.3% for q1w (3 and 5 mg, n=18) cohort
  - Responses seen in non injected lesions
- Increase CD8+ infiltrate & PD-L1 expression





Milhem M et al. AACR 2018

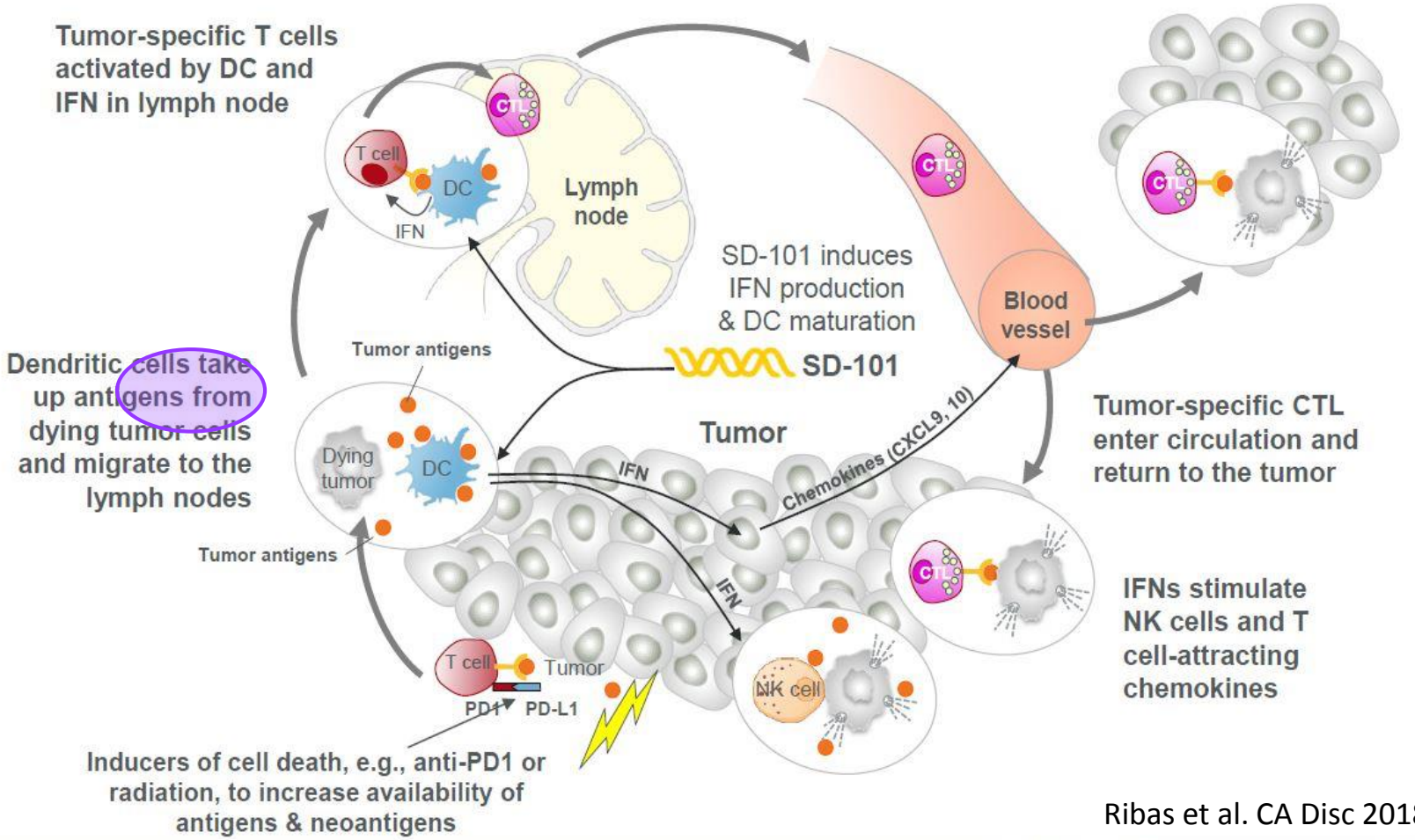
CMP001: Two Abstracts at SITC 2019

- **Abstract #O85; Kirkwood et al**: Durable responses in anti-PD-1 refractory melanoma following intratumoral injection of a Toll-like receptor 9 (TLR9) agonist, CMP-001, in combination with pembrolizumab, CMP-001-001 ongoing Phase 1b evaluating safety and efficacy of CMP-001 in combination with pembrolizumab (Part 1; N = 144) or alone (Part 2; N = 23) in melanoma resistant to prior anti-PD-1
  - ORR in undiluted CMP-001 + Pembro: 24% (18/75; 95% CI, 15% - 35%)
  - ORR with on-site dilution: 12% (7/61; 95% CI, 5% - 22%)
  - ORR CMP-001 alone: 22% (5/23; 95% CI,

- **Abstract #O34; Davar et al**: Phase II Trial of Neoadjuvant Nivolumab (Nivo) and Intra-Tumoral (IT) CMP-001 in High Risk Resectable Melanoma (MEL): Preliminary Results

Localized SD-101 Delivery Optimizes Generation of Tumor-Reactive Cytotoxic T Cells through Dendritic Cell Activation

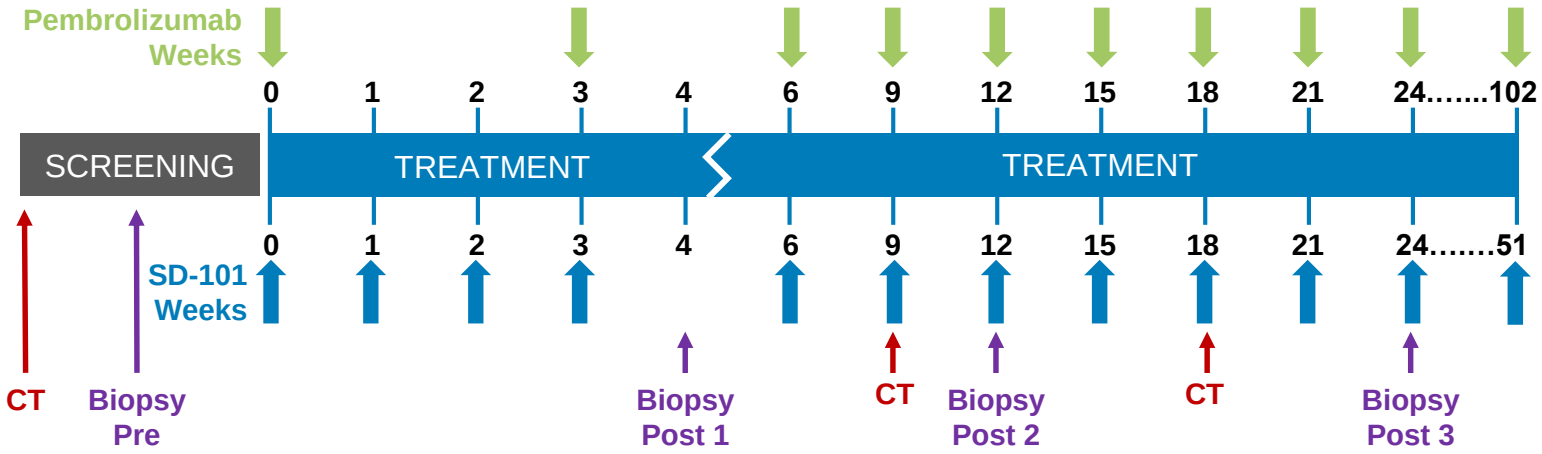
- SD-101 is a synthetic class-C CpG-ODN agonist of TLR9
- Stimulates human pDCs to release IFNα, TNF, IL12 & mature into efficient APCs, enhancing both innate & adaptive immune responses
- Multiple mouse tumor models demonstrated SD-101 IT + PD-1 blockade suppressed tumors at injected & non-injected sites



Ribas et al. CA Disc 2018;
Milhem M et al., ASCO 2019; Abstract 9534

Phase 1b/2, Open Label, Multicenter, Study of the Combination of SD-101 and Pembrolizumab in Patients with Advanced Melanoma Who Are Naïve to Anti-PD-1/L1 Therapy (SYNERGY-001/KEYNOTE-184/NCT02521870)

- Patients with Stage IIIC-IV melanoma with no prior treatment with a PD-1 antagonist
- Pembrolizumab given IV, and SD-101 injected directly into 1 to 4 tumor lesions
- The response to treatment was assessed in both injected and non-injected target lesions
- Two dose levels were evaluated:
  - 2 mg in 1 to 4 lesions
  - 8 mg in 1 lesion



Milhem M et al., ASCO 2019; Abstract 9534

SYNERGY-001/KEYNOTE-184: Efficacy in Anti-PD-1/L1 Naïve Patients

Best Overall Response Rate (ITT)	2 mg/lesion (N=45)	8 mg/lesion (N = 41)
Objective response rate, n (%) (95% CI)	34 (76) (61, 87)	20 (49) (33, 65)
Complete response	8 (18)	4 (10)
Partial response	26 (58)	16 (39)
Stable disease	2 (4)	7 (17)
Progressive disease	5 (11)	9 (22)
Not evaluable†	4 (9)	5 (12)
Time to response, median (months)	2.2	2.3
Duration of response, median (months) (95%CI)	not reached (NE, NE)	not reached (14.2, NE)

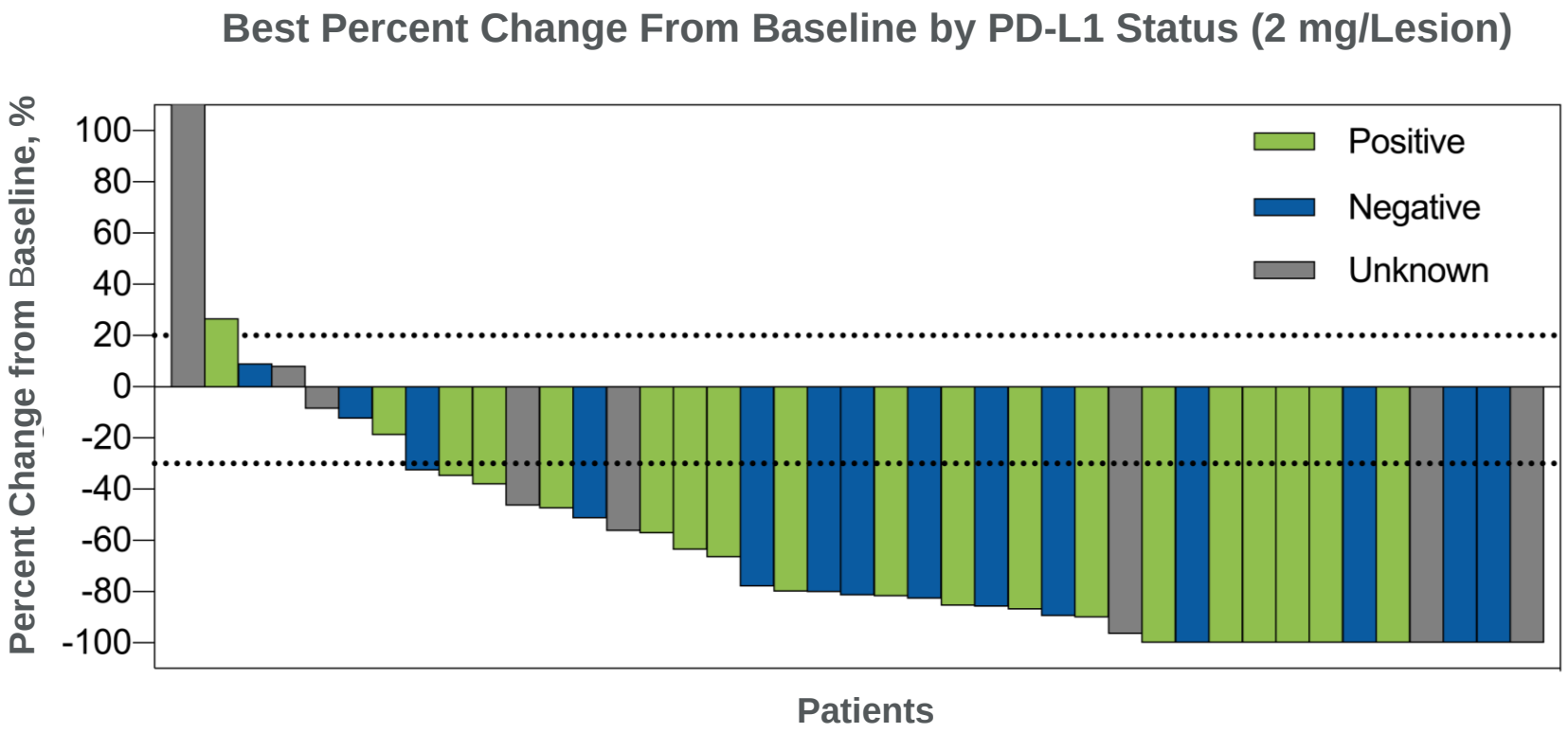
† Patients discontinued prior to first scan: 2 mg—clinical progression (n=3), consent withdrawn (n=1); 8 mg—clinical progression (n=2), irAE/AE (n=2), withdrew consent (n=1). NE, not estimable

Note: The concordance between blinded central assessment and investigator assessment on a subset of the 2 mg group (n=38) was 89%.

- ORR in treatment-naïve patients with BRAF mutant tumors in 2 mg group (n=17) was 65%
- ORR in patients with PD-L1 negative tumors in 2 mg group (n=14) was 79%

Milhem M et al., ASCO 2019; Abstract 9534

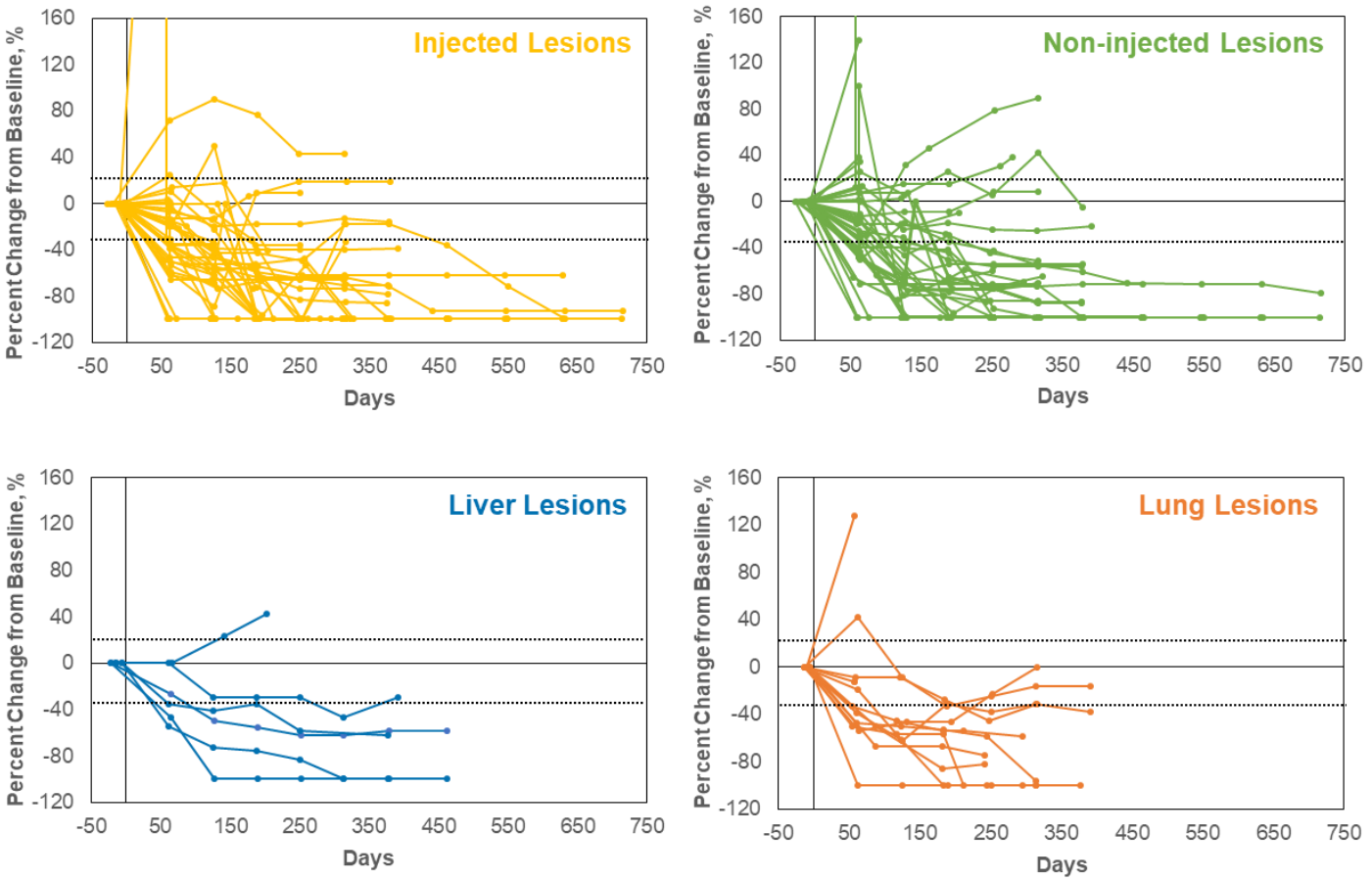
Clinical responses seen in PD-L1 positive and negative baseline tumors



ORR in patients with PD-L1 negative tumors who received 2 mg/lesion 79%

Milhem M et al., ASCO 2019; Abstract 9534

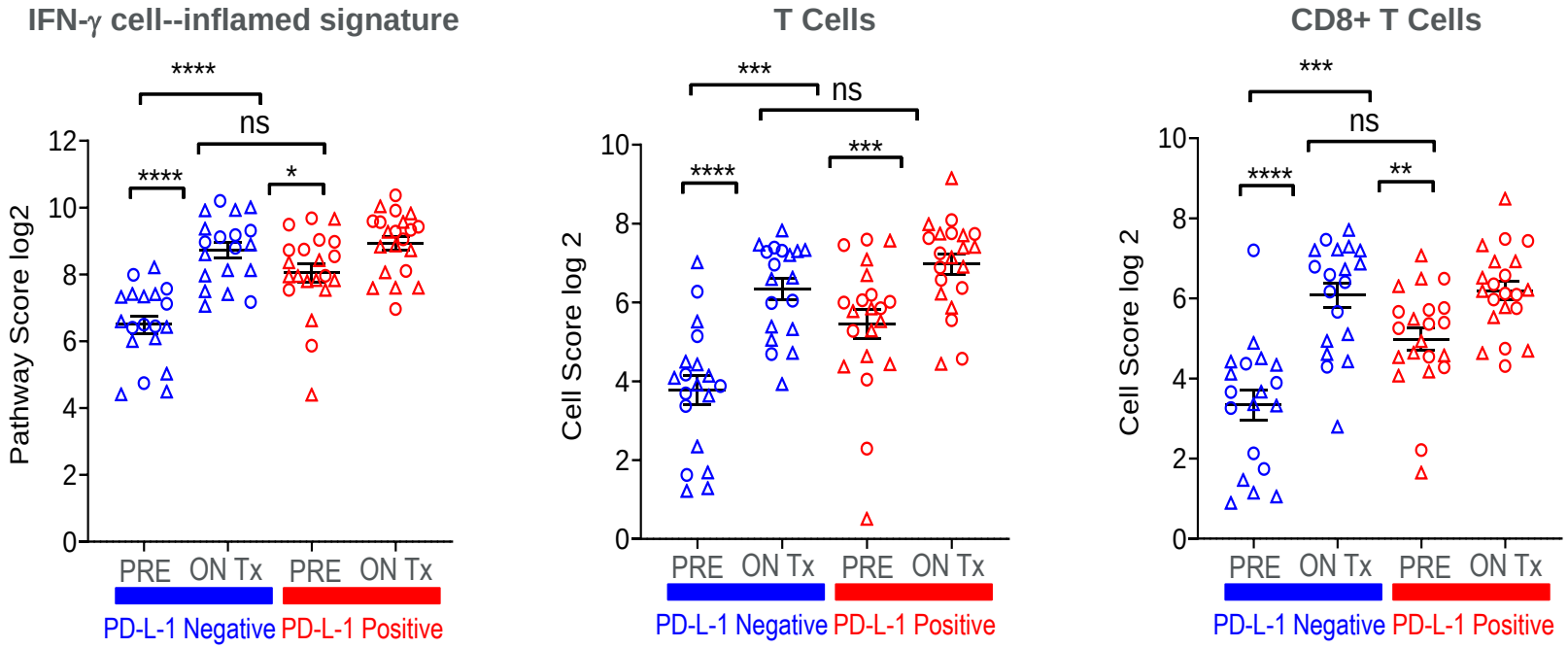
Percent Change from Baseline in Target Lesions (2 mg/lesion)



Milhem M et al., ASCO 2019; Abstract 9534

Combination Treatment of SD-101 + Pembrolizumab Inflames Immunologically "Cold" Tumors

Immunologically cold tumors reach similarly high levels of immune cell activation in response to treatment, as immunologically hot tumors



Patients were biopsied at the start of the trial (PRE) and one week after the fourth dose of SD-101 (ON Tx). **Biopsies were scored for both PD-L1 status by IHC (Clone 22C3)** and assessed for **gene expression using Nanostring**. (2 mg/lesion: triangle; 8 mg/lesion: circle).

Milhem M et al., ASCO 2019; Abstract 9534

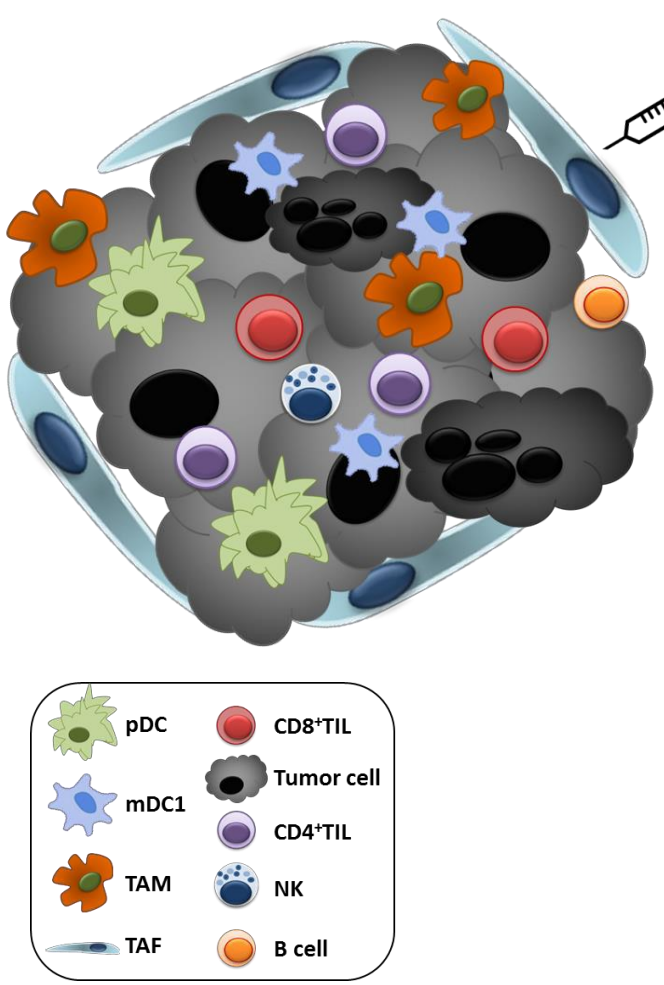
Phase 1b/2, Open Label, Multicenter, Study of the Combination of SD-101 and Pembrolizumab in Patients with Advanced/Metastatic Melanoma Resistant to Anti-PD-1/PD-L1 Therapy (SYNERGY-001/KEYNOTE-184, NCT02521870)

Best Overall Response Rate (ITT)	2 mg/lesion (N=31)	8 mg/lesion (N = 30)
Objective response rate, n (%) (95% CI)	6 (19.4) (7.5, 37.5)	4 (13.3) (3.8, 30.7)
Complete response	0	1 (3)
Partial response	6 (19)	3 (10)
Stable disease	9 (29)	9 (30)
Progressive disease	12 (39)	10 (33)
Not evaluable†	4 (13)	7 (23)
Time to response, median (months)	4.2	3.2
Duration of response, median (months) (Min, Max)	0.03 (not mature) (0.03, 4.1)	6.8 (0.95, 15.8)
Duration of follow up, median (months) (Min, Max)	3.5 (0.6, 7.0)	3.9 (0.6, 21.1)

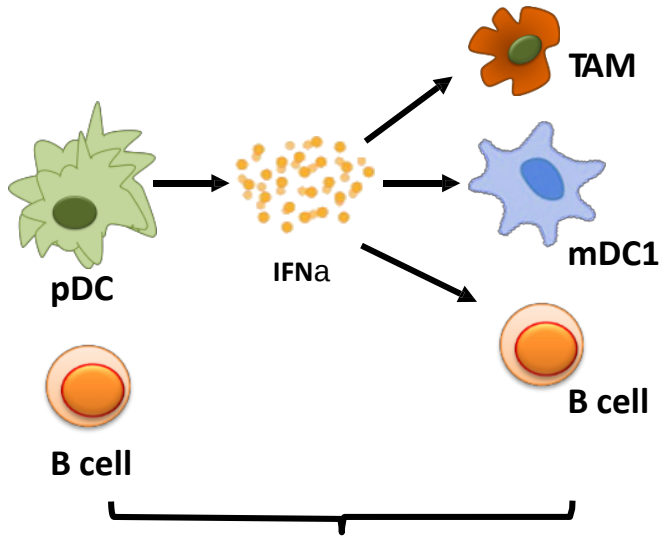
† Patients discontinued prior to first scan: ITT = intention to treat

Amin A et al., ASCO 2019; Abstract 9555

Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125 (tilsotolimod)

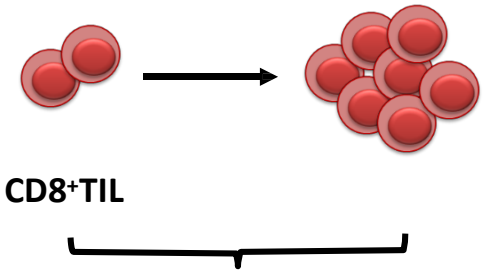


1. TLR9 induction of IFNa and APC maturation



Activation of APCs to improve T-cell priming

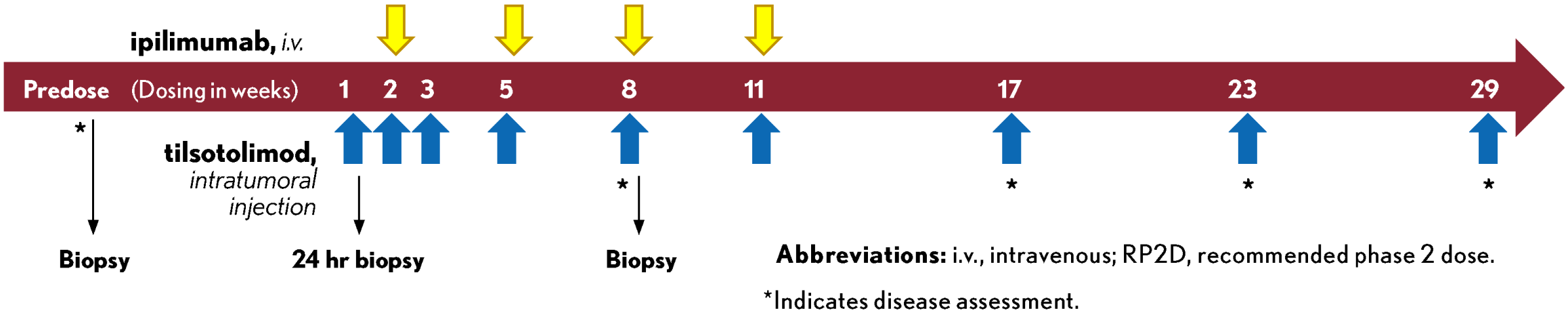
2. TIL Activation and Proliferation



Improved antigen presentation results in TIL activation and proliferation

Haymaker C, et al. SITC 2017
Yu et al., Antimicrob Agents Chemother, 2008; Rodriguez-Torres, AASLD abstract 2010

ILLUMINATE-204 Study Design: Tilsotolimod + Ipilimumab in second line (Patients Progressing on Anti-PD-1 Therapy)



Diab A, et al. ASCO 2018

ILLUMINATE-204: Best Overall Response

Best overall tumor response	Response rate (RECIST v1.1), N=26
Complete response (CR)	2 of 21 (9.5%)*
Partial response (PR)	6 of 21 (28.6%)
Stable disease (SD)	7 of 21 (33.3%)
Progressive disease (PD)	6 of 21 (28.6%)
Not yet assessed	5
Overall response rate (CR, uCR, or PR)	8 of 21 (38.1%)
Disease control rate (CR, PR, or SD)	15 of 21 (71.4%)

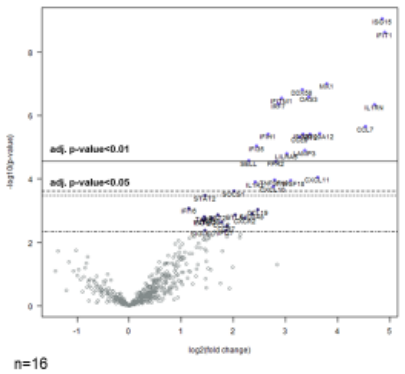
As of 9 May 2018.

*One CR unconfirmed.

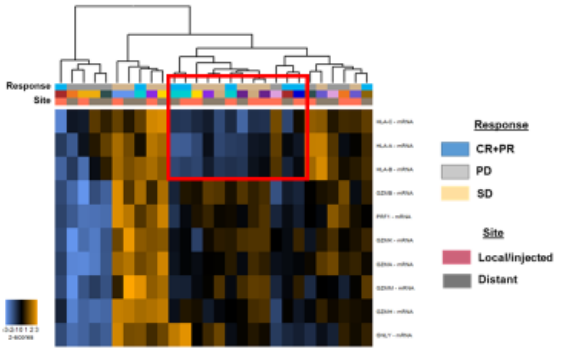
Diab A, et al. ASCO 2018

Induction of IFNα-response gene signature after i.t. IMO-2125

Induction of type 1 IFN response gene signature at 24 h post TLR9 agonist (IMO-2125)

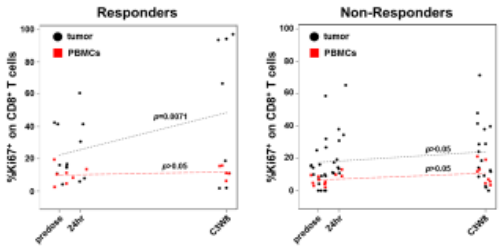


Responses seen in HLA-ABC neg/low tumors at baseline (red box)

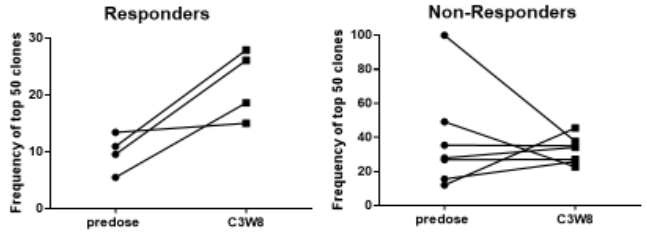


Selective increase in CD8⁺ T-cell proliferation in the tumors of responding patients

CD8+ T cell proliferation is specific to the tumor of responding patients

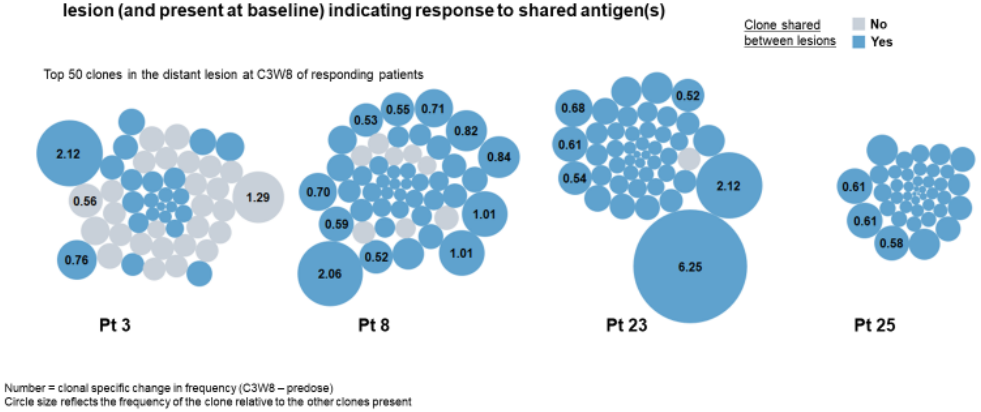


Expansion of top 50 clones in DISTANT tumor lesions of responding patients



Expanding clones in the distant lesion are shared with the injected lesion

Expanding clones in the distant lesion are shared with the local/injected lesion (and present at baseline) indicating response to shared antigen(s)



Number = clonal specific change in frequency (C3W8 – predose)
Circle size reflects the frequency of the clone relative to the other clones present

Haymaker C, et al. SITC 2017; Diab A, et al. ESMO 2018

ILLUMINATE-204 Results to Date Imply Potential for Clinically Meaningful Benefit

illuminate
Tilsotolimod Clinical Trials

Best Overall Response	tilsotolimod + ipilimumab (N=49)[1]	ipilimumab monotherapy post PD-1 (N=321)[2] *(pooled post-hoc analysis of six studies)*
Overall Response Rate (CR or PR)	**24% (12)**	4-16%
Disease Control Rate (CR, PR, or SD)	**71% (35)**	17-45%

- 11 of 12 responses confirmed per RECIST v1.1
  - 3 Confirmed Complete Responses (CR)
- 5 of 10 RECIST v1.1 responses evaluable for durability (>6 mos.) to date
- Median OS (overall survival) not yet reached (min/max: 1.6 – 35 mos.)
- Safety profile observed consistent with previously reported results

[1] 49 of 53 subjects had at least 1 post-baseline disease assessment at time of October 2019 data update
[2] References available on Slide 7

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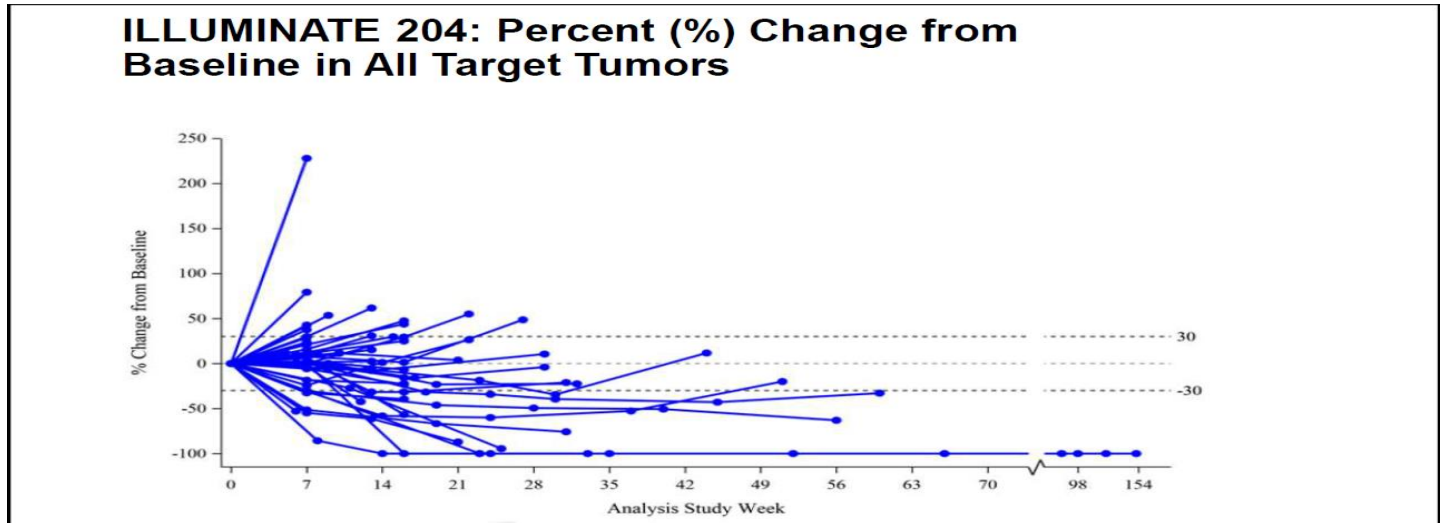
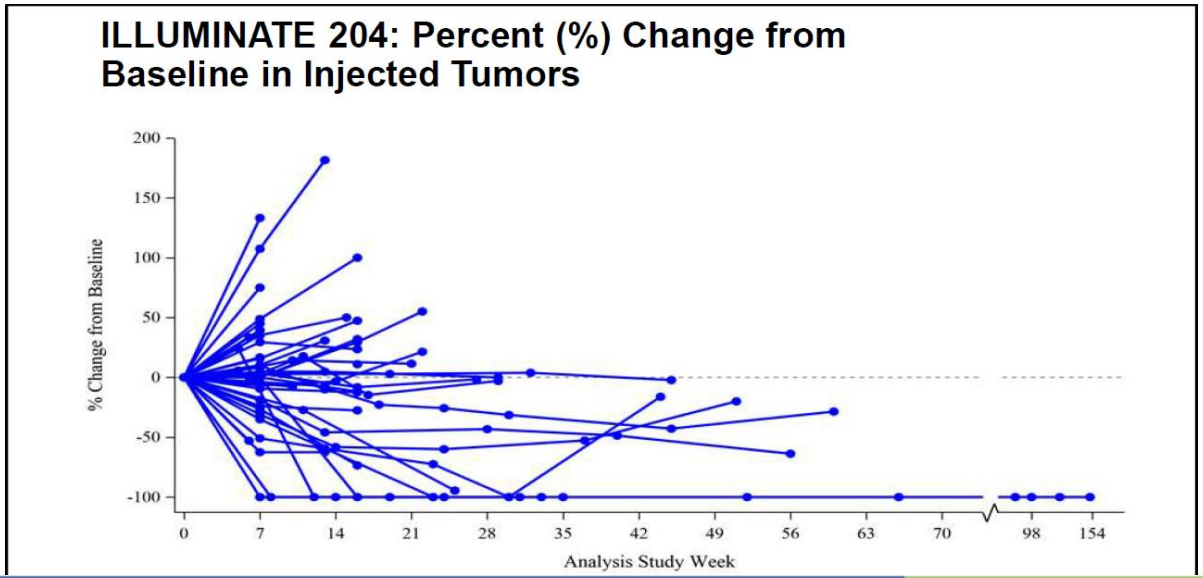
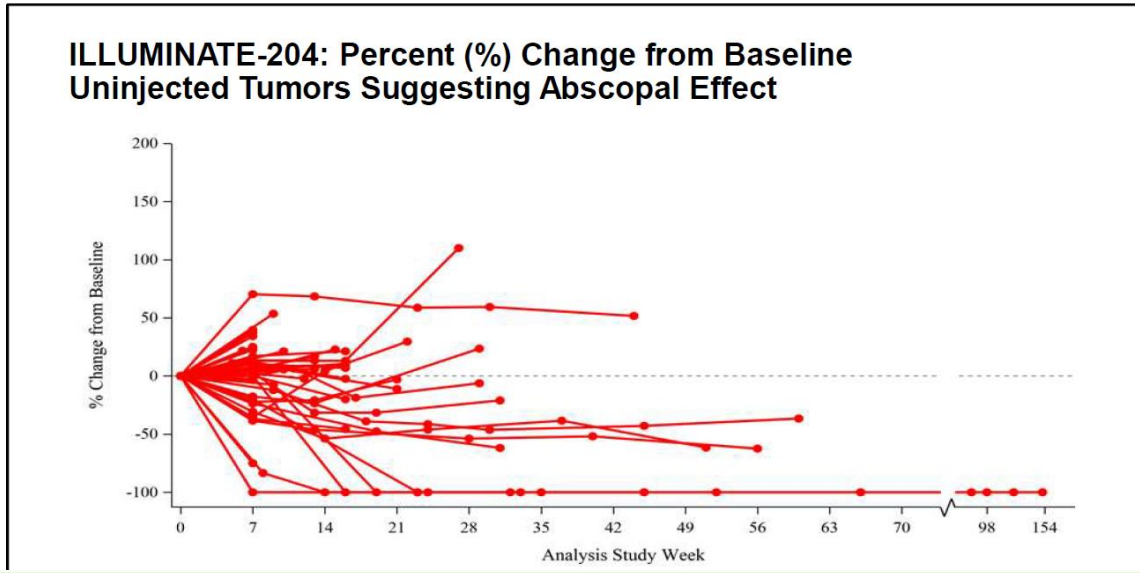
ILLUMINATE 204: Percent (%) Change from Baseline







ILLUMINATE-301 – Trial Design
PD-1 Refractory Metastatic Melanoma

illuminate
Tilsotolimod Clinical Trials

Patient Stratification
– Duration of prior anti-PD-1 therapy (<12 or ≥12 weeks)
– Metastasis stage (M1c or other)
– BRAF mutation status and prior targeted therapy
BRAF wild type, mutation positive with, or without prior targeted

Key Inclusion Criteria:
- Age ≥18 years
- Stage III or Stage IV melanoma
- ≥ 1 measurable lesion accessible for injection
- ECOG PS ≤1
- Adequate organ function

Key Exclusion Criteria:
- Prior TLR agonists
- Prior ipilimumab
- CNS disease

Randomization
1:1
N≈454

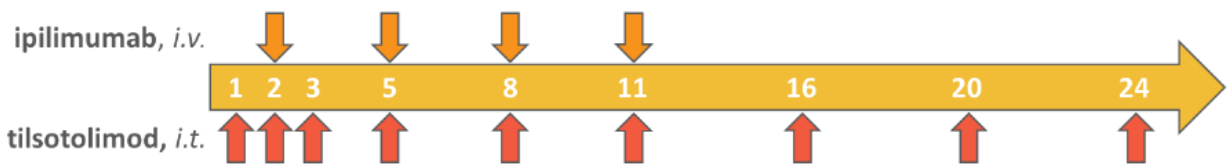
Arm A
- Ipilimumab 3 mg/kg (4 doses: weeks 1, 4, 7, and 10)
- Treatment Duration: 10 weeks

No crossover

Arm B
- Ipilimumab 3 mg/kg (4 doses: weeks 2, 5, 8, and 11) +
- Intratumoral tilsotolimod 8 mg (9 doses: weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24)
- Treatment Duration: 24 weeks

Endpoints
Primary endpoint family
– ORR by independent review per RECIST v1.1
– OS

Key secondary endpoints
– Durable response rate
– Time to response
– Progression-free survival
– Patient-reported outcomes
– Safety



i.v., intravenous; i.t., intratumoral; ORR, overall response rate; OS, overall survival,

idera

CONCLUSIONS

- CpG ODNs are potent vaccine adjuvants; induce strong pDC-driven type I IFN, CTL responses
- TLR9 agonists are potent innate immune activators with type I IFN induction that could enhance TME immunogenicity
- Strong rationale to combine with immune checkpoint inhibitors
- Various classes of synthetic CpG ODNs in development
- In melanoma, combinations with anti-CTLA4 (tilsotolimod) and anti-PD1 (CMP-001 and SD-101) show promising clinical activity, currently in phase II/III

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