Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™ Webinar: Clinical Updates from SITC 2020

Tuesday, March 30, 2021

4:00-5:00 p.m. ET

Webinar Agenda

4:00-4:05 p.m. ET Overview: Welcome and Introductions

4:05-4:45 p.m. ET Presentations

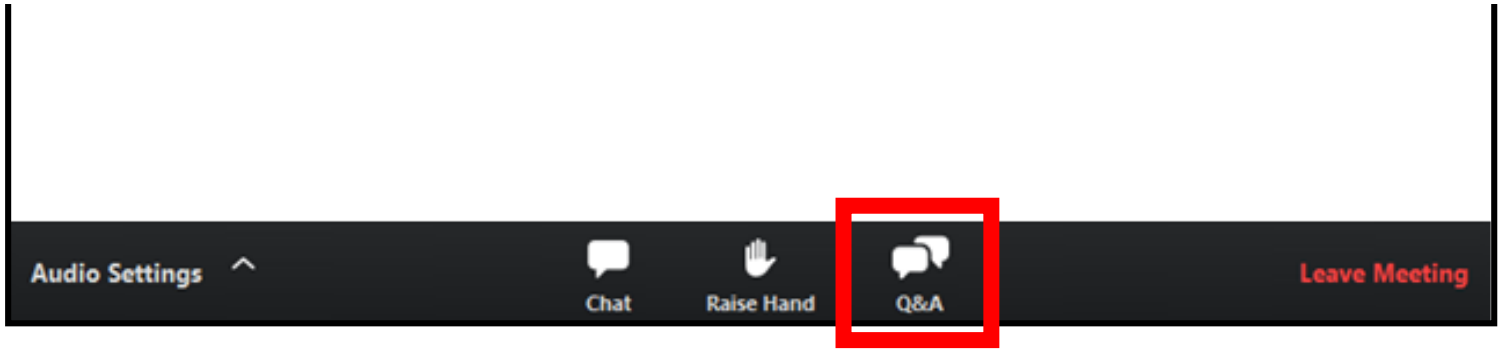
4:45-4:55 p.m. ET Question and Answer Session

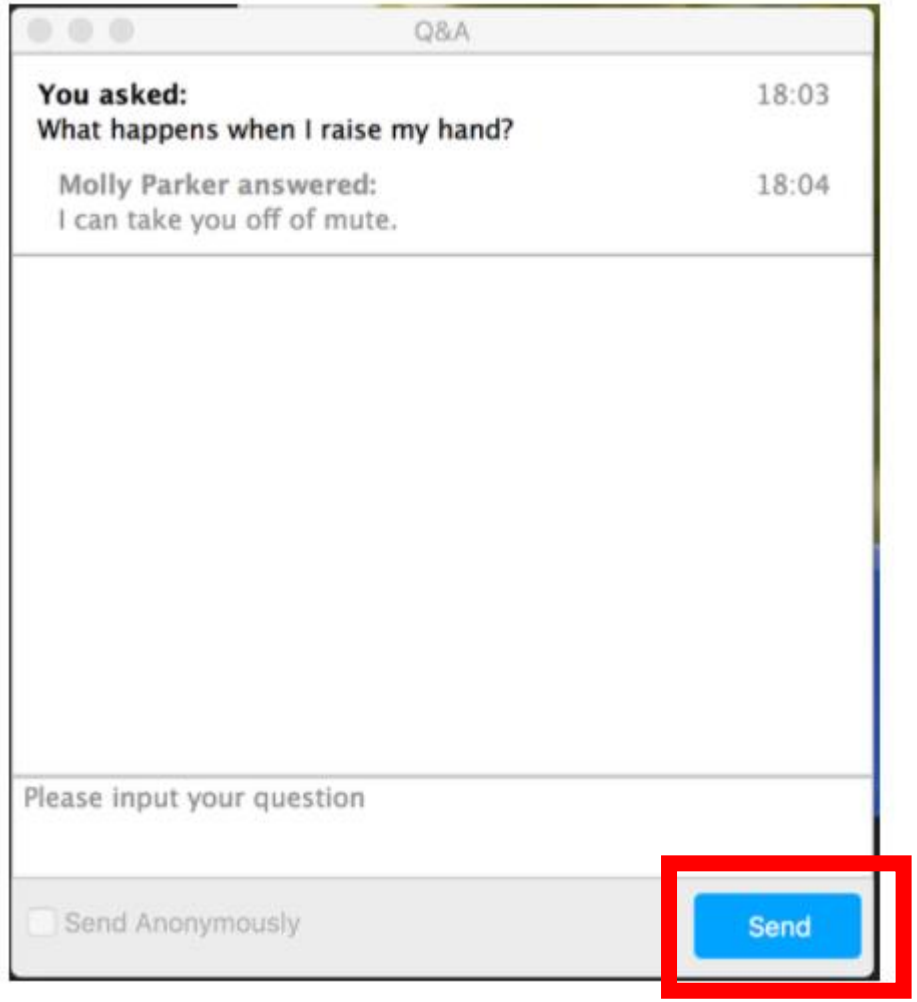
4:55-5:00 p.m. ET Closing Remarks

Society for Immunotherapy of Cancer

How to Submit Questions

- Click the “Q&A” icon located on at the bottom of your Zoom control panel
- Type your question in the Q&A box, then click “Send”
- Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)





Webinar Faculty

Jason Luke, MD – *University of Pittsburgh Medical Center*

Diwakar Davar, MD – *University of Pittsburgh Medical Center*

Karl Lewis, MD – *University of Colorado*

Ignacio Melero, MD, PhD – *Fundación para la Investigación Médica Aplicada*

Hussein Tawbi, MD, PhD – *MD Anderson Cancer Center*

Learning objectives

Upon completion of this webinar, participants will be able to:

- Summarize and integrate the most recent advances in cancer immunotherapy
- Analyze cutting-edge clinical trials to incorporate new research and techniques into clinical application for cancer immunotherapy
- Define the types of resistance to PD-1 pathway inhibitors

Webinar outline

- **Karl Lewis, MD -** Interim analysis of Phase 2 results for cemiplimab in patients with metastatic basal cell carcinoma (mBCC) who progressed on or are intolerant to hedgehog inhibitors (HHIs)
- **Diwakar Davar, MD -** Phase II trial of neoadjuvant nivolumab (nivo) and intra-tumoral (IT) CMP-001 in high-risk resectable melanoma (Neo-C-Nivo): final results
- **Ignacio Melero, MD, PhD -** First-in-human phase I/IIa trial to evaluate the safety and initial clinical activity of DuoBody®-PD-L1×4-1BB (GEN1046) in patients with advanced solid tumors
- **Hussein Tawbi, MD, PhD -** Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce

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Interim Analysis of Phase 2 Results for Cemiplimab in Patients with Metastatic Basal Cell Carcinoma (mBCC) who Progressed on or are Intolerant to Hedgehog Inhibitors (HHIs)

Karl D. Lewis,[1] Ketty Peris,[2] Aleksandar Sekulic,[3] Alexander J. Stratigos,[4] Lara Dunn,[5] Zeynep Eroglu,[6] Anne Lynn S. Chang,[7] Michael R. Migden,[8] Siyu Li,[9] Suk-Young Yoo,[9] Kosalai Mohan,[10] Ebony Coates,[10] Emmanuel Okoye,[10] Jean-François Baurain,[11] Oliver Bechter,[12] Axel Hauschild,[13] Marcus O. Butler,[14] Leonel Hernandez-Aya,[15] Lisa Licitra,[16] Rogerio I. Neves,[17] Emily S. Ruiz,[18] Frank Seebach,[10] David M. Weinreich,[10] George D. Yancopoulos,[10] Israel Lowy,[10] Timothy Bowler,[10] Matthew G. Fury[10]

[1]Division of Medical Oncology, University of Colorado Hospital, Aurora, CO, USA; [2]Institute of Dermatology, Catholic University of the Sacred Heart, Rome, Italy and Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy; [3]Department of Dermatology, Arizona Mayo Clinic, Scottsdale, AZ, USA; [4]Department of Dermatology-Venereology, Andreas Sygros Hospital-National and Kapodistrian University of Athens, Athens, Greece; [5]Department of Medicine, Head and Neck Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA; [7]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [8]Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [10]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [11]University Catholic of Louvain, Brussels, Belgium; [12]Department of General Medical Oncology, University Hospitals, Leuven, Belgium; [13]Department of Dermatology, Schleswig-Holstein University Hospital, Kiel, Germany; [14]Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada; [15]Division of Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA; [16]Medical Oncology Head and Neck Cancer Department, Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [17]Penn State Cancer Institute, Hershey, PA, USA; [18]Department of Dermatology, Dana-Farber Cancer Institute, Boston, MA, USA

Poster number: 428

Presented at Society for Immunotherapy of Cancer (SITC) Virtual Congress; November 9–14, 2020.

Background

- **Basal cell carcinoma (BCC) is the most common type of skin cancer**[1] and ultraviolet exposure is a major risk factor[2]
  - Surgery is a curative option for most patients, but systemic therapy is indicated for a small percentage of patients who develop advanced BCC[3] when curative surgery or radiation may no longer be options
  - Vismodegib is a hedgehog inhibitor (HHI) currently approved for metastatic BCC

- **There are no FDA-approved treatment options for patients who progress on or are intolerant to hedgehog inhibitors**

- **Cemiplimab, a PD-1 inhibitor, is the first systemic therapy to show clinical benefit in patients with laBCC and metastatic BCC (mBCC) after HHI therapy**
  - Data from the pivotal Phase 2 study (NCT03132636) were presented at the ESMO (laBCC cohort primary analysis) and SITC (mBCC cohort pre-specified interim analysis) 2020 congresses

ESMO, European Society for Medical Oncology; SITC, Society for Immunotherapy of Cancer

1. Puig S et al. *Clin Transl Oncol*. 2015;17:497–503; 2. Wu S et al. *Am J Epidemiol*. 2013;178:890–897; 3. Migden MR et al. *Cancer Treat Rev*. 2018;64:1–10.

Study Design, Objectives & Patient Demographics

Group 1
Adult patients with mBCC (nodal and distant)

Group 2
Adult patients with laBCC

Cemiplimab 350 mg IV Q3W for up to 93 weeks

Tumor assessments 1–5 Q9W, 6–9 Q12W

Tumor response assessment by ICR (RECIST 1.1 for visceral lesions or modified WHO criteria for skin lesions)

Number of patients with prior HHI therapy, n (%)	
Vismodegib	28 (100%)
Sonidegib	3 (10.7%)
Vismodegib + sonidegib	3 (10.7%)

Reason for discontinuation of prior HHI, n (%)	
Progression of disease on HHI	21 (75.0%)
Intolerant to prior HHI therapy	10 (35.7%)
Intolerant to vismodegib	11 (39.3%)
Intolerant to sonidegib	2 (7.1%)
No better than stable disease after 9 months on HHI therapy	5 (17.9%)

Primary objectives

- Objective response rate (ORR) by independent central review (ICR)

Secondary objectives

- ORR by investigator review
- Duration of progression free survival (PFS) by ICR and investigator review
- Overall survival (OS)
- Complete response rate by ICR
- Safety and tolerability of cemiplimab

mBCC prespecified interim analysis included patients (n=28) with the opportunity to be followed for approximately 57 weeks to provide an ORR with 95% CI

mBCC, metastatic basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; IV, intravenous; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; WHO, World Health Organization; HHI, hedgehog inhibitor; CI, confidence interval

Tumor response: laBCC cohort primary analysis

Previously presented at the 2020 ESMO Virtual Congress

Primary Analysis Results	laBCC (n=84)
Overall response rate (95% CI)	**31.0% (21.3%-42.0%)***
Complete response	6% (5 patients)
Partial response	25.0% (21 patients)
Stable disease	48.8% (41 patients)
Progressive disease	10.7% (9 patients)
Not evaluable	9.5% (8 patinets)
Disease control rate (95% CI)*	**PD-L1 <1% = 77% (60%-90%)** **PD-L1 ≥1% = 87% (60%-98%)**

Duration of Response (DOR) Results
(per Kaplan-Meier [KM] estimates)

Median DOR per ICR:

- **Not reached at time of data cut-off**

Probability of DOR (95% CI):

- **6 months: 90.9% (68.3%-97.6%)**
- **12 months: 85.2% (60.5%-95.0%)**

Safety Results

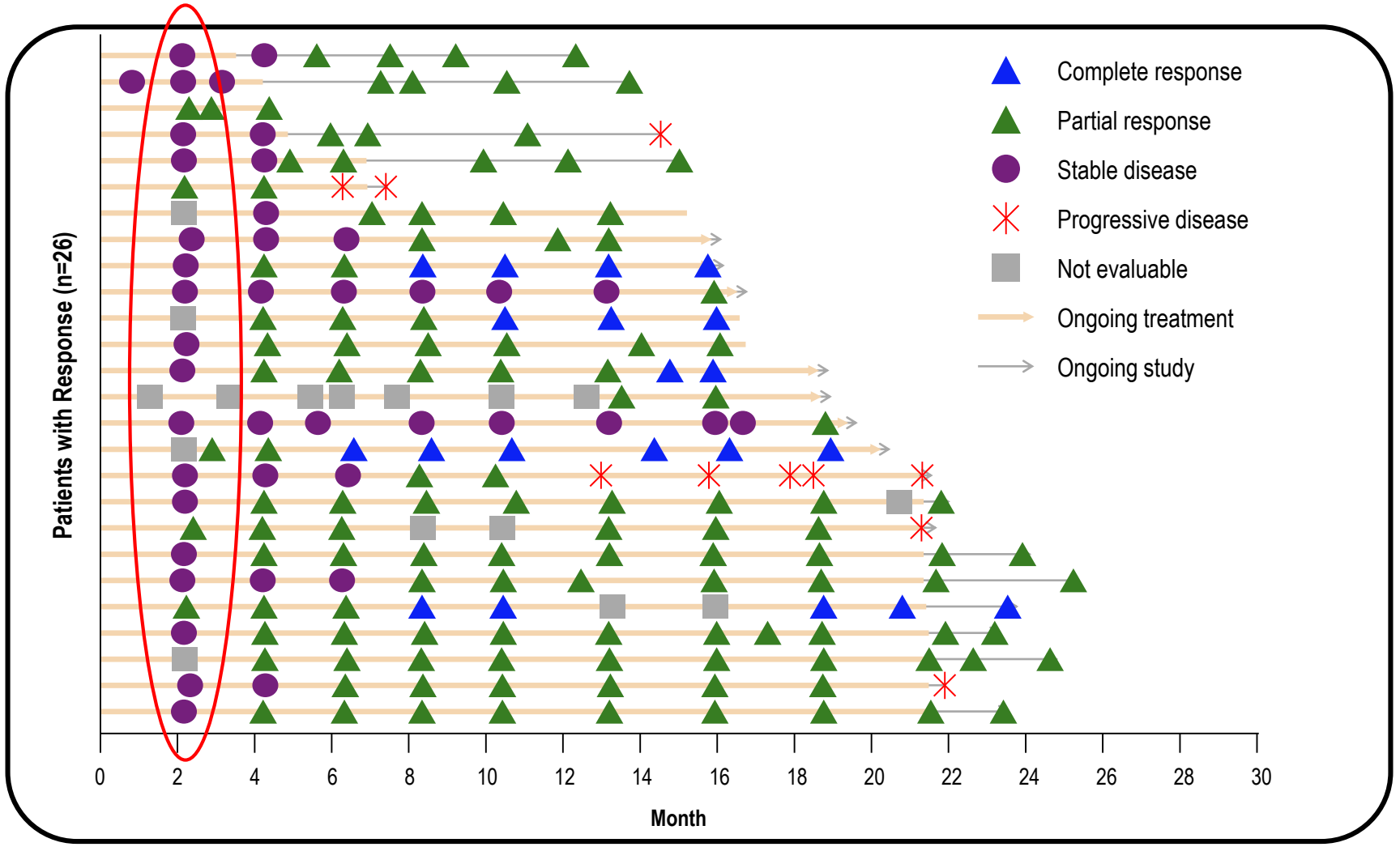
- **Most common treatment-related AEs (TRAEs):** **f**atigue (n=21; 25%), pruritus (n=12; 14%) and asthenia (n=12; 14%)
- **Most common Grade ≥3 TRAEs:** fatigue, colitis, autoimmune colitis and adrenal insufficiency (n=2 each)
- Fourteen patients (17%) discontinued treatment due to treatment-emergent Aes of any grade.

laBCC, locally advanced basal cell carcinoma; PD-1, programmed cell death-1; PD-L1, PD-ligand 1;
*Defined as the proportion of patients with complete response, partial response, stable disease or non-partial response/non-progressive disease at the first evaluable tumor assessment, scheduled to occur at week 9 (defined as 56 days to account for visit windows in the protocol).

Time to and Duration of Response in Patients with laBCC

The median KM estimation of DOR was reached

6m: 91% [95% CI 68-98]
12m: 85% [95% CI 61-95]



Tumor response: mBCC cohort interim analysis

Pre-specified Interim Analysis Results	mBCC (n=28)
Objective response rate (95% CI)	**21.4% (8.3%-41.0%)†**
Complete response	0% (0 patients)
Partial response	21.4% (6 patients)
Stable disease	35.7% (10 patients)
Non-complete response/ non-progressive disease	10.7% (3 patients)
Progressive disease	25.0% (7 patients)
Not evaluable‡	7.1% (2 patients)
Disease control rate (95% CI)§	**67.9% (47.6%–84.1%)**

Duration of Response (DOR) Results# (per Kaplan-Meier [KM] estimates)

Median DOR per ICR:

- **Not reached at time of data cut-off**

Probability of DOR (95% CI):

- **6 months: 100% (68.3%-97.6%)**
- **12 months: 66.7% (19.5%-90.4%)**

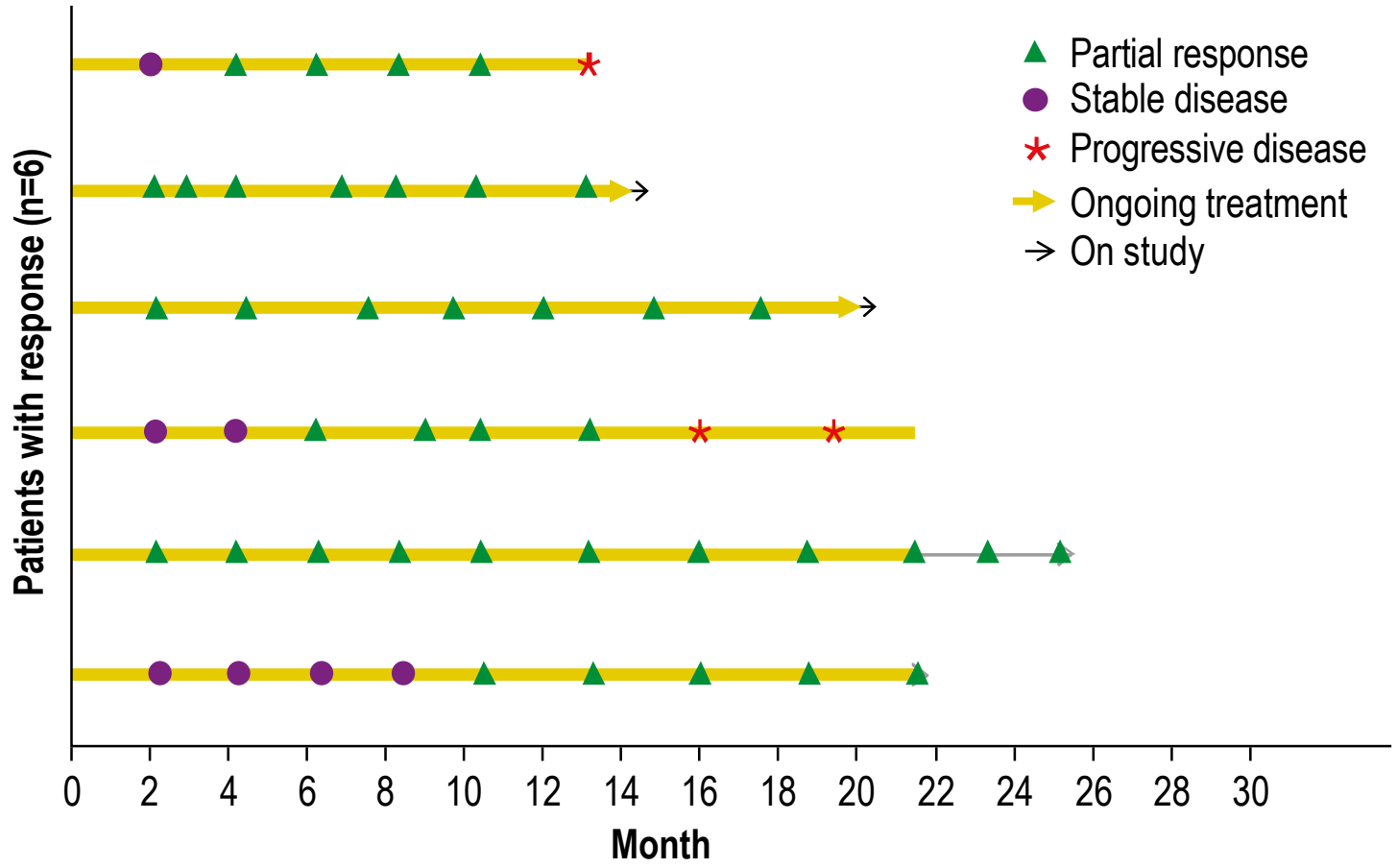
All 6 responses were ongoing at 1 year of treatment, and had observed duration of at least 8 months

Safety Results

- **Most common TRAEs:** Treatment-related adverse events (TRAEs) of any grade occurred in 22 (78.6%) patients
- **Grade ≥3 TRAEs** were observed in five (17.9%) patients
- One death from staphylococcal pneumonia, considered unrelated to study treatment

mBCC, metastatic basal cell carcinoma; ICR, independent central review; CI, confidence interval; TRAE, treatment-related adverse events
†Objective response rate per investigator was 28.6% (95% CI, 13.2–48.7). ‡Of the two patients who were not evaluable, one patient had no post-baseline assessment and one patient had no target or non-target lesions. §Defined as the proportion of patients with complete response, partial response, stable disease or non-partial response/non-progressive disease at the first evaluable tumor assessment, scheduled to occur at week 9 (defined as 56 days to account for visit windows in the protocol). #Data shown are for patients with response.

Time to and Duration of Response in Responding Patients With mBCC per ICR



Lewis KD, et al. Poster presented at: Society for Immunotherapy of Cancer (SITC) Virtual Congress; November 9–14, 2020:Poster 428.

Summary and conclusions

- Cemiplimab is the first agent to provide clinically meaningful anti-tumor activity, including durable responses, in patients with mBCC and laBCC after progression or intolerance on HHI therapy

- The safety profile of cemiplimab is generally consistent with previous reports of cemiplimab in other tumor types

- Cemiplimab granted FDA-approval (regular approval for laBCC and accelerated approval for mBCC) in February, 2021

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Phase II trial of neoadjuvant nivolumab (nivo) and intra-tumoral (IT) CMP-001 in high-risk resectable melanoma (Neo-C-Nivo): final results

Diwakar Davar*, Arivarasan Karunamurthy, Douglas Hartman, Richelle DeBlasio, Joe-Marc Chauvin, Quanquan Ding, Ornella Pagliano, Amy Rose, John Kirkwood and Hassane Zarour

**University of Pittsburgh*

Background

- Patients with clinically occult disease with 5-year MSS rates of 76% (N1b), 71% (N2b) and 64% (N3b)[1;] and the standard of care herein is upfront surgery followed by adjuvant therapy either with anti-PD-1 (BRAF mutant or WT) or dabrafenib/trametinib (if BRAF mutant) based pivotal phase III studies.[2-4]

- Neoadjuvant immunotherapy enhances systemic T-cell responses to tumor antigens, resulting in enhanced detection and killing of micrometastatic tumor disseminated beyond resected tumor, hypothesized to etiology of postsurgical relapse.[5]

- Neoadjuvant immunotherapy with anti-PD-1 monotherapy produces pathologic response rates (PRR) of 18-25% of patients;[6-7] while anti-PD-1/anti-CTLA-4 combination results in PRR of 65-78%.[6,8-10]

- TLR9 is an endosomal receptor, expressed by B cells and plasmacytoid DCs (pDCs) in humans that can be activated by unmethylated cytosine guanosine oligodeoxynucleotides (CpG ODN). TLR9 activation induces Type I IFN production via MyD88 and IRAK4 to activate IRF7.[11]

- CMP-001 is a type A CpG that activates pDC and stimulates IFNa production.[12] In studies in PD-1 refractory melanoma, intra-tumoral (IT) CMP-001 produced responses both singly and in combination with pembrolizumab.[13]

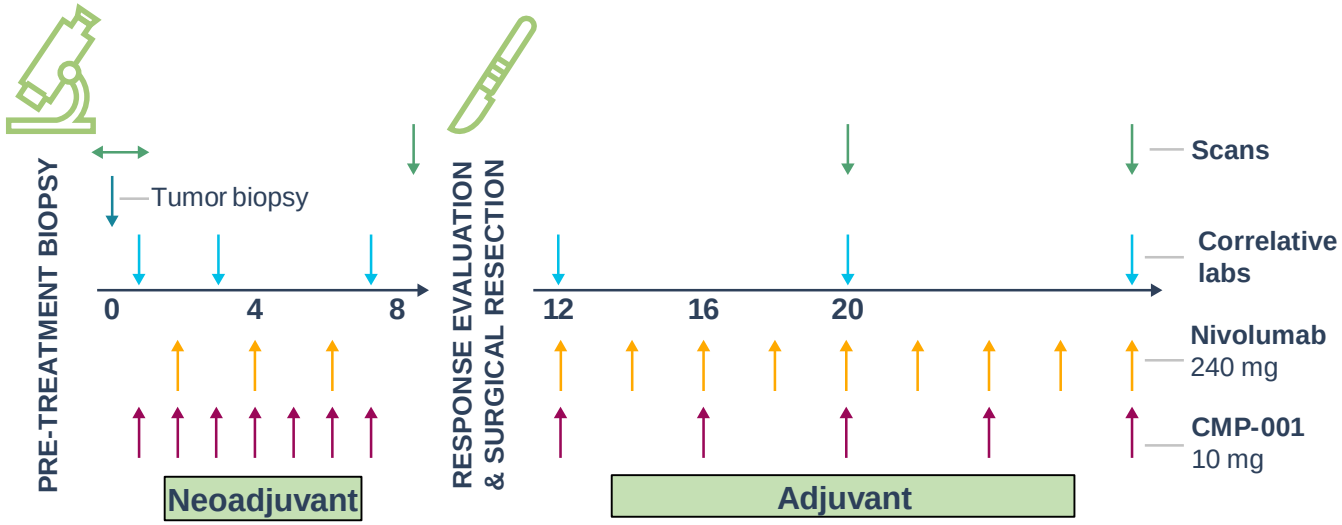
- To evaluate the benefit of neoadjuvant IT CMP-001, we designed a phase II study to evaluate the effects of neoadjuvant IT CMP-001 and nivolumab in high-risk resectable melanoma.

[1]Gershenwald JE, CA Cancer J Clin 2017. [2]Long GV, NEJM 2017. [3]Weber JS, NEJM 2018. [4]Eggermont AMM, NEJM 2019. [5]Liu J, Cancer Discov 2016. [6]Amaria RN, Nat Med 2018. [7]Huang AC, Nat Med 2019. [8]Blank CU, Nat Med 2018. [9]Blank CU, Ann Oncol 2019. [10]Rozeman EA, Lancet Oncol 2019. [11]Krieg AM, Nat Rev Drug Discov 2006. [12]Lemke-Miltner CD, J Immunol 2020. [13]Kirkwood JM, J Immunother Cancer 2019.

Neoadjuvant CMP-001 & Nivolumab: Study Design

Stage III B/C/D melanoma pre-surgery

- No active CNS disease
- Deemed surgically resectable
- Accessible tumor for biopsy
- Accessible tumor for CMP-001 injection
- Planned sample size: 28-32 evaluable patients



Primary endpoint: Major pathologic response (MPR) rate by irPRC[1-3]

Secondary endpoints: Relapse-free survival and overall survival

Pathologic Response[1-3]	%RVT
Complete Response (pCR)	**0%**
Major Response (pMR)	**≤10%**
Partial Response (pPR)	**10%> and ≤50%**
Non-response (pNR)	<50%
RVT, residual viable tumor	

PRR: Complete Response (pCR), Major Response (pMR), Partial Response (pPR)

MPR: Complete Response (pCR), Major Response (pMR)

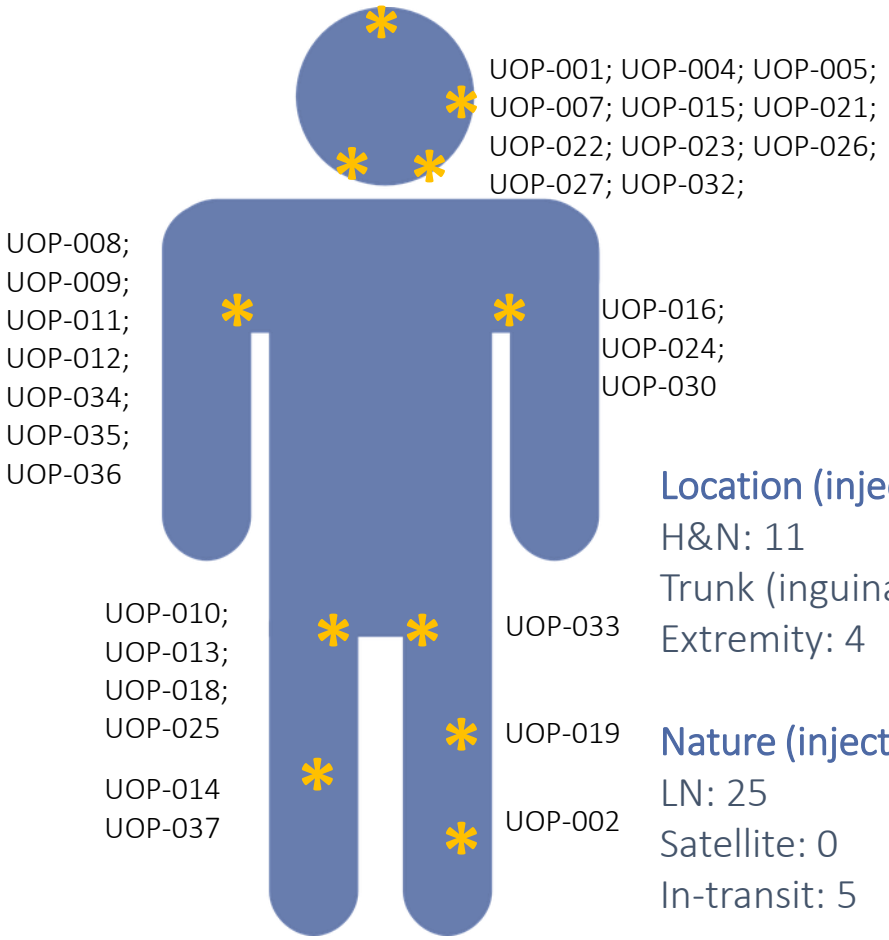
Reference Path Response Rates

Therapy	PRR[1-3]
Pembro x1	19% pCR; 30% PRR[4]
Nivo 3mg/kg x 4 vs. Ipi/Nivo x3	45% pCR[5]
Ipi/Nivo (Ipi→Nivo; Ipi-1/Nivo-3; Ipi-3/Nivo-1)	65-80% PRR[6]
Ipi/Nivo (Ipi-1/Nivo-1)	50% pCR; 71% PRR[7]

[1]Cottrell TR, Ann Oncol 2018; [2]Tetzlaff MT, Ann Oncol 2018; [3]Stein JE, CCR 2020;
[4]Huang AC. Nat Med 2019; [5]Amaria RN, Nat Med 2019; [6]Roseman EA, Lancet Oncol 2019; [7]Blank CU, ASCO 2020

Patient Characteristics

Neoadjuvant CMP-001 & Nivolumab



Location (injected/measurable lesion)

H&N: 11

Trunk (inguinal/axillary): 15

Extremity: 4

Nature (injected/measurable lesion)

LN: 25

Satellite: 0

In-transit: 5

Patient Characteristics	
Enrolled	
• Safety Evaluable	31
• Efficacy Evaluable	30*
Demographics	
• Median age	61 (range 19-93)
• Sex	16M, 14F
Prior Therapy	
• Ipi	1 (5%)
• BRAF/MEK	1 (5%)
AJCC Stage (8th edition)	
• IIIB	17 (57%)
• IIIC	11 (37%)
• IIID	2 (6%)
Mutation Status	
• BRAF	5 (17%)

*At data cut-off: 1 patient with systemic progression prior to surgery evaluable for safety but not response

Safety and Toxicity

Neoadjuvant CMP-001 & Nivolumab

- No DLTs or G4/5 TRAE were observed.
- 8 G3 TRAE in total were observed in 7 patients, only 3 of which required medical intervention. Commonest G3 toxicity was hypertension, requiring intervention in only 1 instance. 1 instance of G3 irAE-colitis was observed
- Majority of TRAE were of G1-2 severity and consistent with the MOA of agents. Incidence of CRS was low, possibly due to prophylaxis used.
- No TRAE resulted in delays in planned surgery.
- 1 patient with G4 skin infection deemed *unrelated to* CMP and nivolumab had a delay in surgery although disease remained resectable at the time of surgery.

Treatment-Related Adverse Events (TRAE) (N=31)

	Grade 1 (n/%)	Grade 2 (n/%)	Grade 3 (n/%)
Constitutional			
- Arthalgia, myalgia	7 (22.6)	6 (19.4)	1 (3.2)
- Fever	14 (45.2)	5 (16.1)	0 (0.0)
- Flu-like symptoms	14 (45.2)	8 (25.8)	0 (0.0)
- Fatigue	14 (45.2)	3 (9.7)	0 (0.0)
- CRS-like reaction* (ECI)	2 (6.5)	3 (9.7)	0 (0.0)
irAE			
- Colitis	0 (0.0)	0 (0.0)	1 (3.2)
Cardiac			
- Hypertension	2 (6.4)	5 (16.1)	3 (9.7)
Electrolyte			
- Hyponatremia	19 (61.3)	0 (0.0)	0 (0.0)
- Hypophosphatemia	12 (38.7)	12 (38.7)	1 (3.2)
Gastrointestinal			
- Nausea/vomiting	4 (12.9)	5 (16.1)	0 (0.0)
Hematologic			
- Anemia	9 (29.0)	1 (3.2)	0 (0.0)
- Thrombocytopenia	10 (32.3)	0 (0.0)	0 (0.0)
Other			
- Injection site reaction	9 (6.5)	4 (12.9)	0 (0.0)
- Injection site infection	3 (9.7)	3 (9.7)	1 (3.2)

Data cutoff: 10/1/2020

Blinded Pathologic Responses

Neoadjuvant CMP-001 & Nivolumab

Pathologic responses[1,2]	% RVT	N	%
Complete response (pCR)	0%	15	50%
Major response (pMR)	1-10%	3	10%
Partial response (pPR)	11-50%	3	10%
Non-response (pNR)	> 50%	9	30%
Total Evaluable		30	

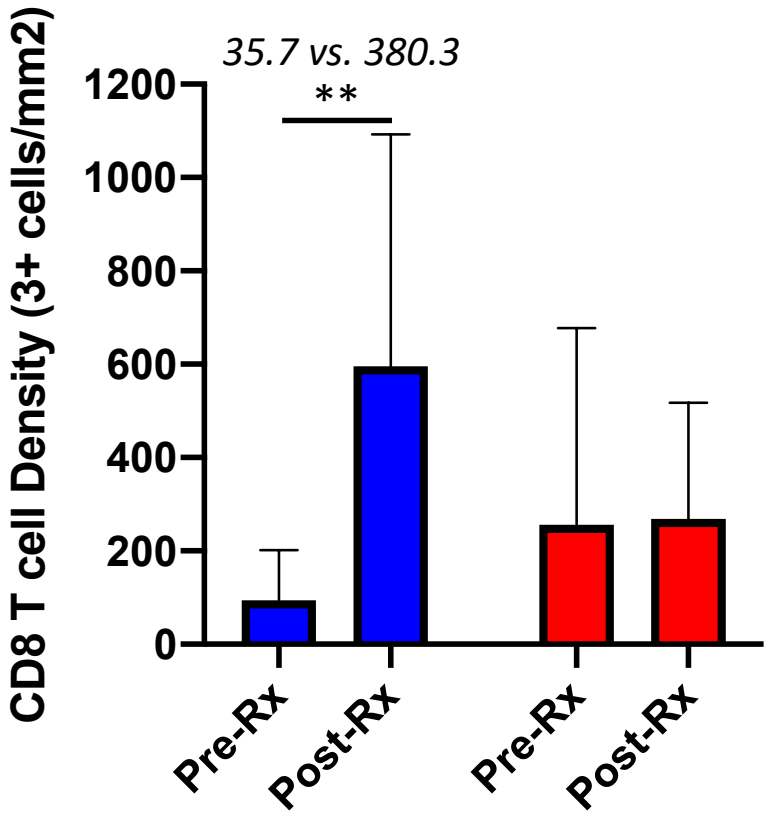
Pathological Response = 70%

Major Pathological Response = 60%

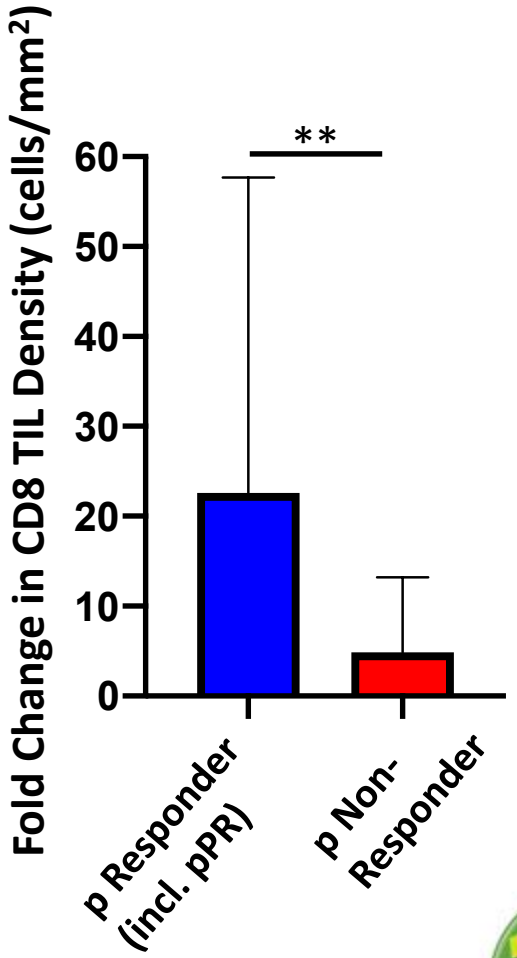
- %RVT calculated using %tumor viable
- Pathologist blinded to clinical and radiographic outcome
- N=30 evaluable

Changes in CD8 TIL Density (cells/mm2)

Neoadjuvant CMP-001 & Nivolumab



Pathologic responders had median greater fold change in CD8 T cells (10.3 vs. 0.8; N = 26 incl 17 R and 9 NR with paired samples)

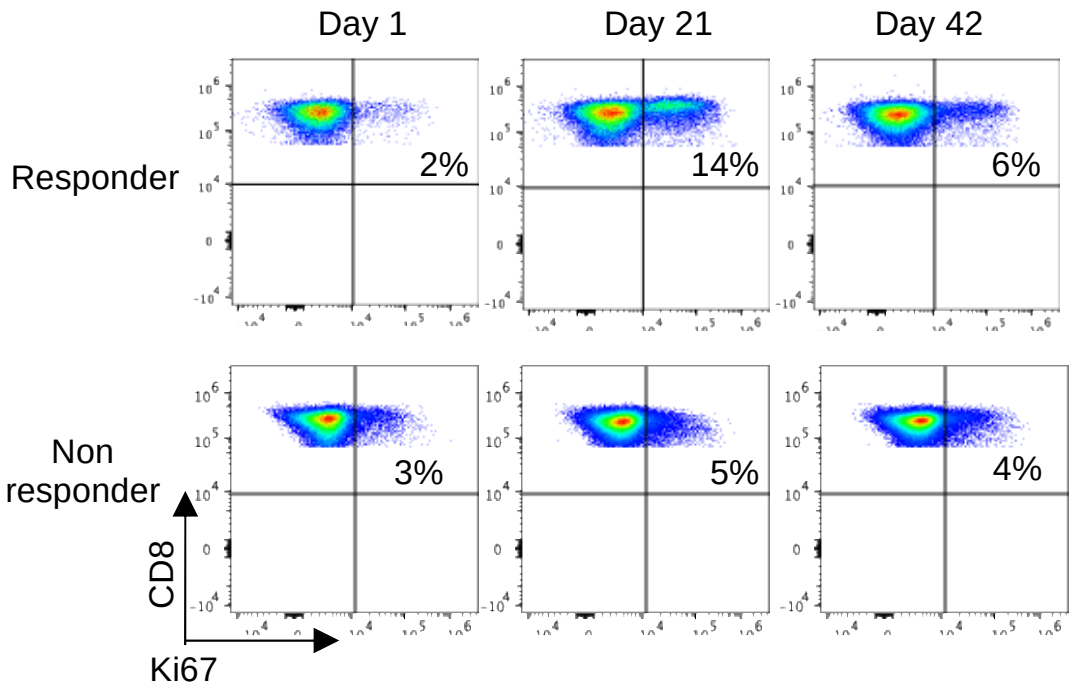


Peripheral Immune Kinetics

Neoadjuvant CMP-001 & Nivolumab

Responders had evidence of activated CD8⁺ T cells peripherally.

Tim-3 upregulation was noted on CD8⁺ T cells in non-responders.



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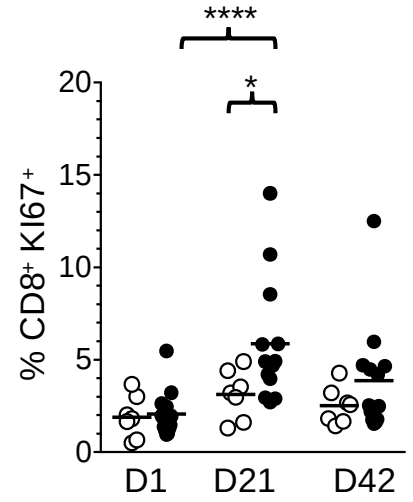
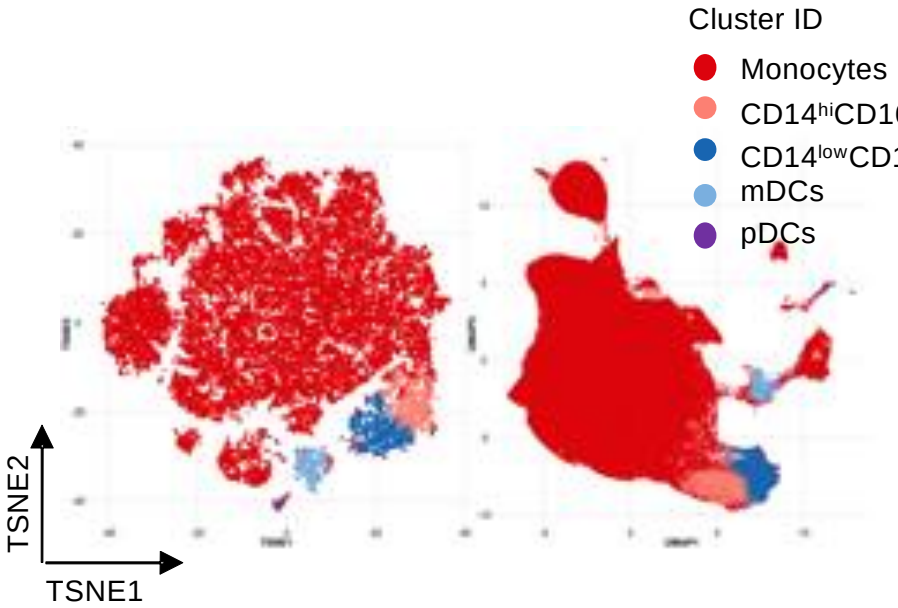
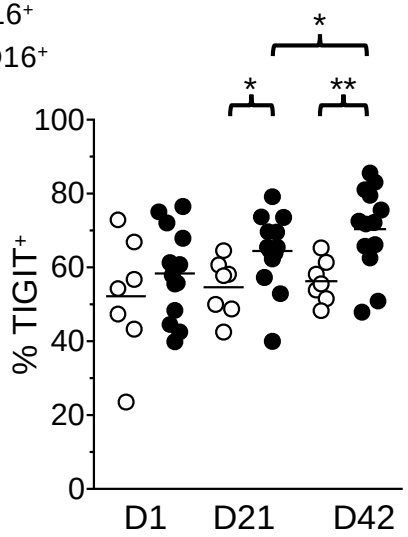
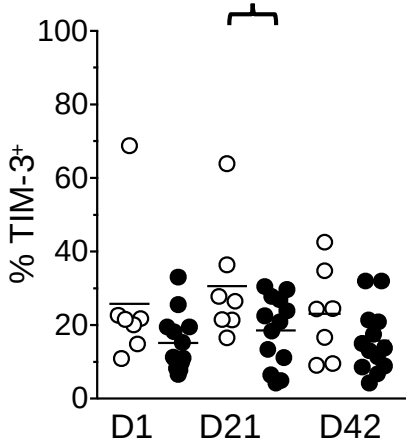
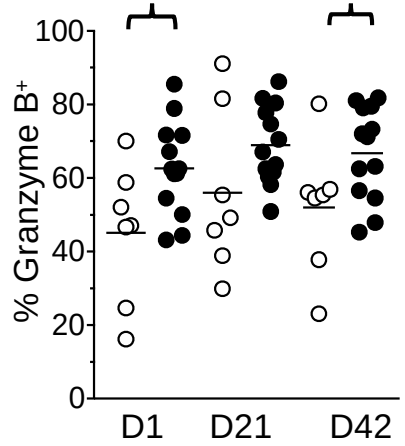










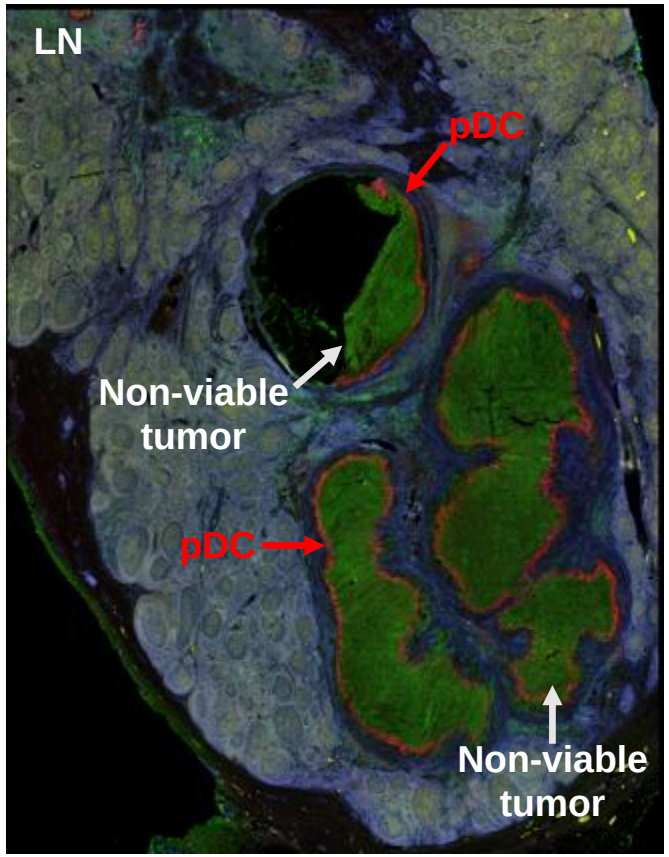
● R (incl pPR)
○ NR

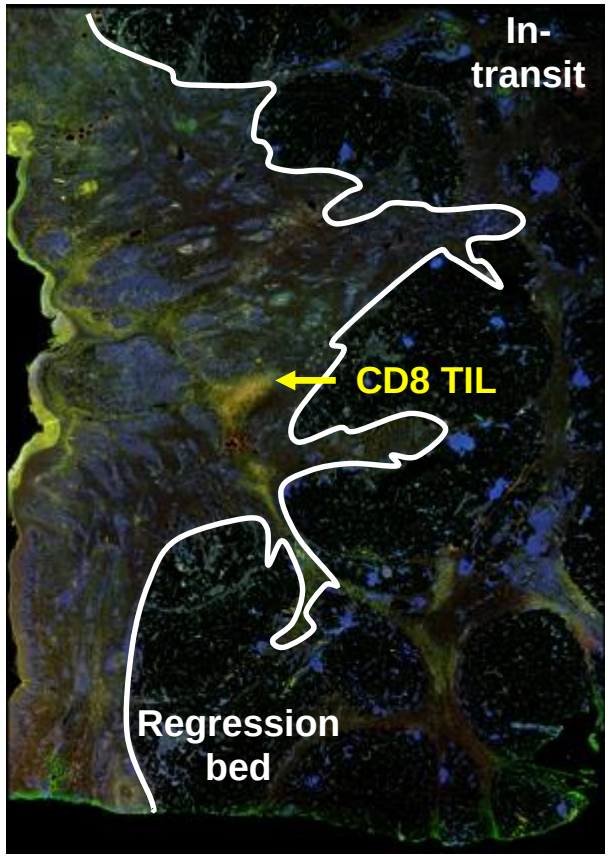
Digital Spatial Profiling (DSP, GeoMx) Revealed Distinct Patterns of Pathologic Response

Neoadjuvant CMP-001 & Nivolumab

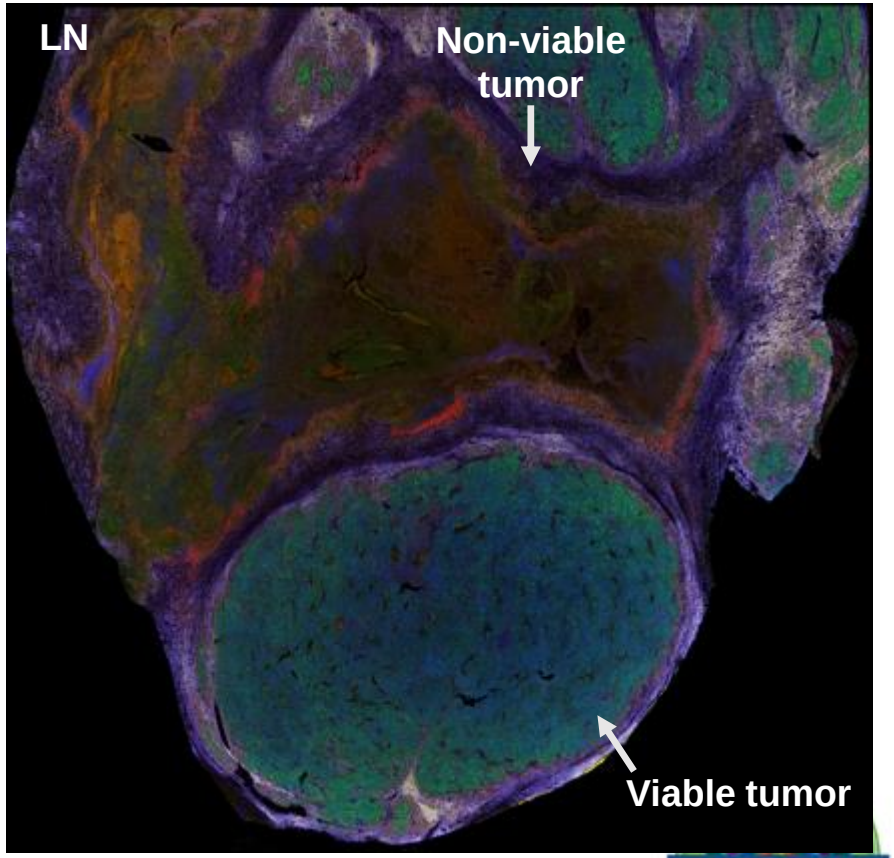
CD303
CD45
S100B
DNA

Major Pathologic Response





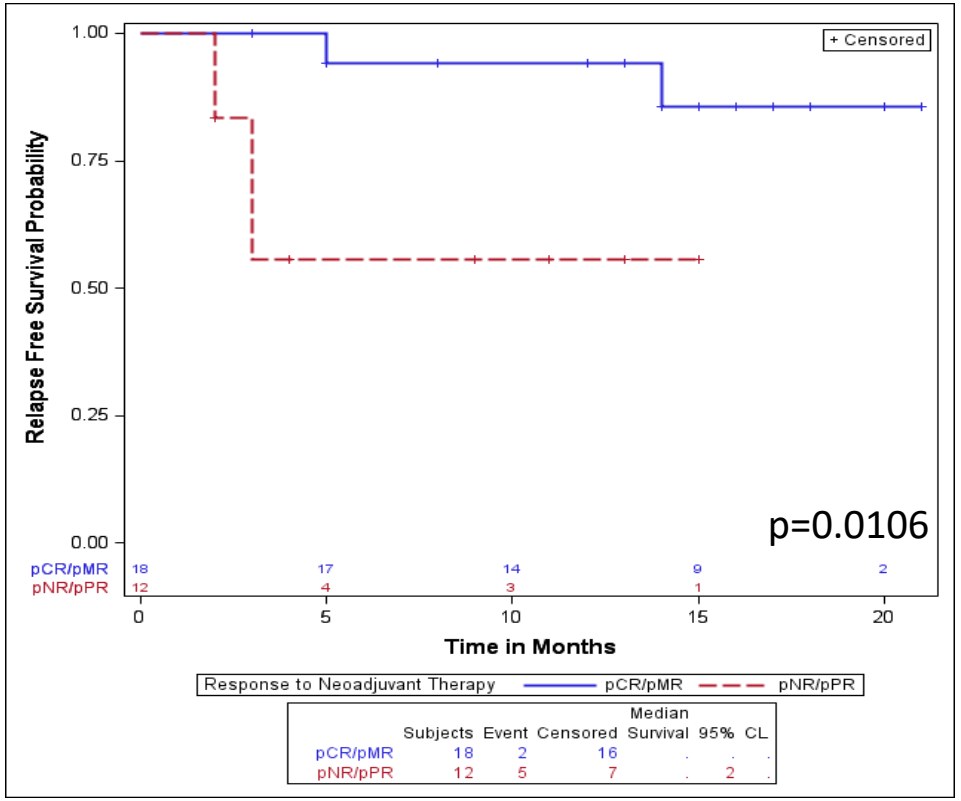
Pathologic Non-Response



Pathological Response is Associated with Durable RFS

Neoadjuvant CMP-001 & Nivolumab

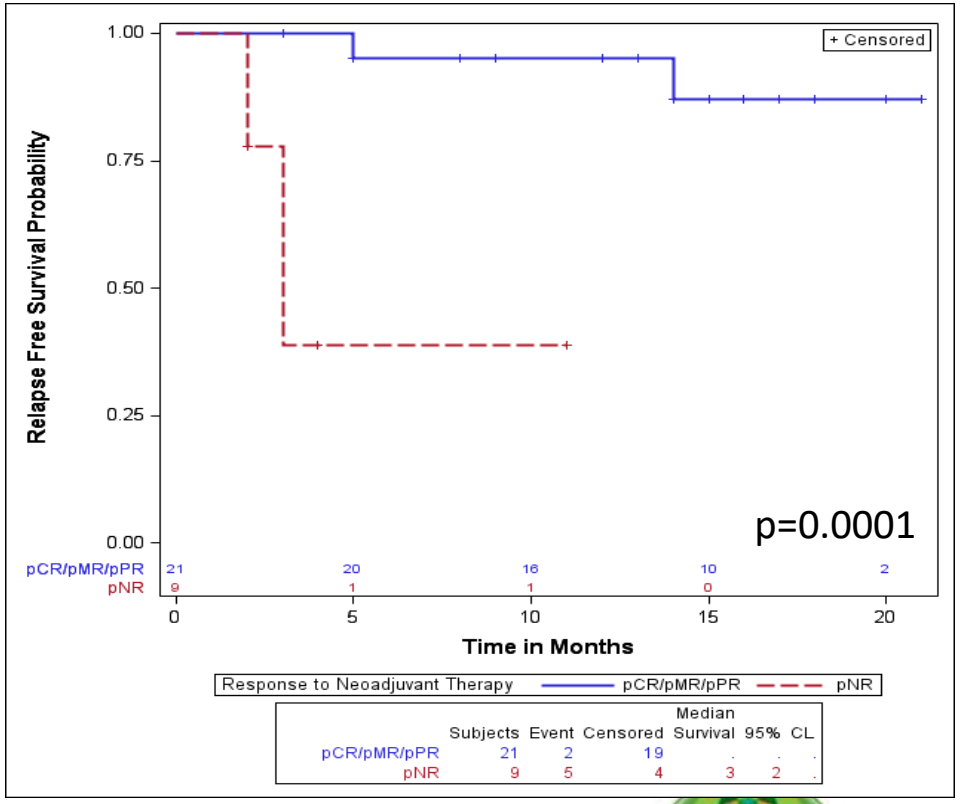
RFS in major pathologic responders



Median RFS: not reached in R (17, ∞) vs. not reached (5, ∞)

Landmark 1-year RFS:
89% (pCR + pMR)
90% (pCR/pMR + pPR)

RFS in all pathologic responders



Median RFS: not reached in R (not available) vs. 5 (4, ∞)

Conclusions

Neoadjuvant CMP-001 & Nivolumab

1. Neoadjuvant CMP and nivolumab was well-tolerated with a low incidence of Grade 3 TRAE. No Grade 4/5 TRAEs were reported.

2. Neoadjuvant CMP and nivolumab produced a high rate of pathologic response: 60% major pathologic response (%RVT ≤ 10%), and up to 70% if pPR (%RVT <10% to ≤50%) included.

3. Neoadjuvant CMP and nivolumab produced compelling evidence of immune activation peripherally and intra-tumorally; with clear evidence of pDC presence within TME in responders.

4. Pathologic response was associated with durable RFS.

Webinar outline

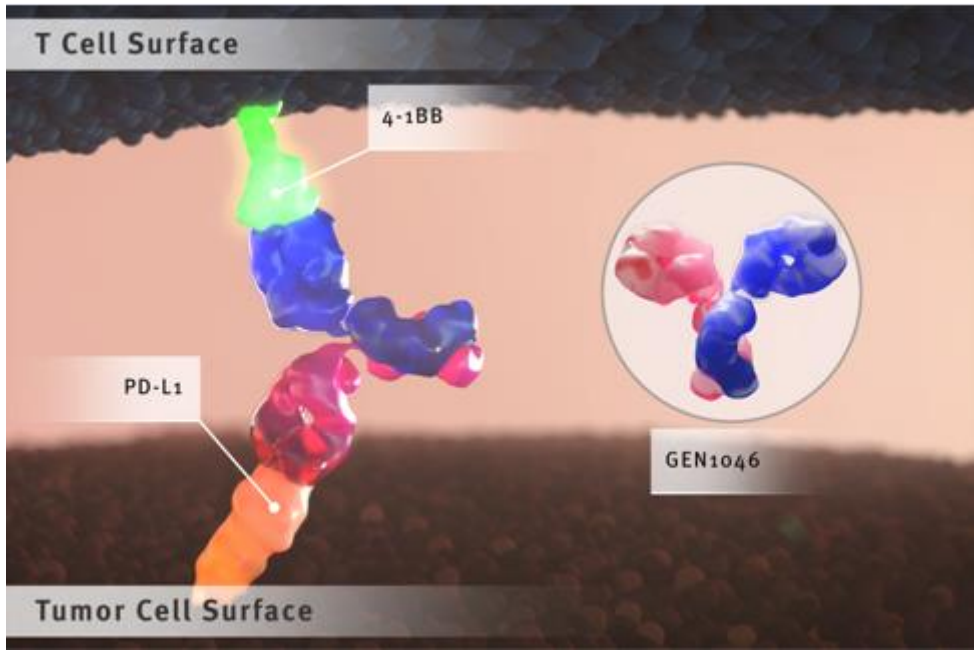
- **Karl Lewis, MD -** Interim analysis of Phase 2 results for cemiplimab in patients with metastatic basal cell carcinoma (mBCC) who progressed on or are intolerant to hedgehog inhibitors (HHIs)
- **Diwakar Davar, MD -** Phase II trial of neoadjuvant nivolumab (nivo) and intra-tumoral (IT) CMP-001 in high-risk resectable melanoma (Neo-C-Nivo): final results
- **Ignacio Melero, MD, PhD -** First-in-human phase I/IIa trial to evaluate the safety and initial clinical activity of DuoBody®-PD-L1×4-1BB (GEN1046) in patients with advanced solid tumors
- **Hussein Tawbi, MD, PhD -** Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce

First-in-human phase I/IIa trial to evaluate the safety and initial clinical activity of DuoBody®-PD-L1×4-1BB (GEN1046) in patients with advanced solid tumors

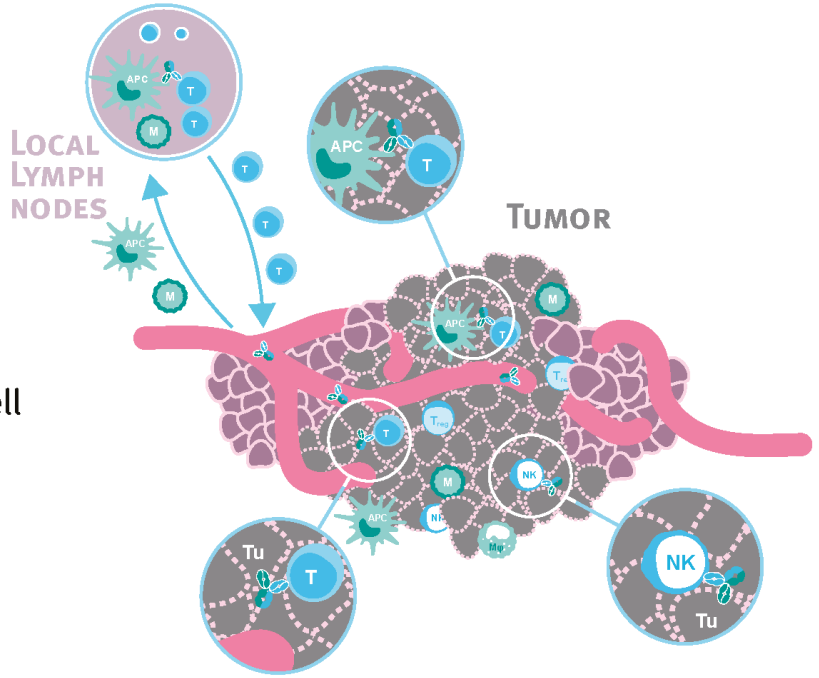
Elena Garralda, Ravit Geva, Eytan Ben-Ami, Corinne Maurice-Dror, Emiliano Calvo, Patricia LoRusso, Özlem Türeci, Michelle Niewood, Uğur Şahin, Maria Jure-Kunkel, Ulf Forssmann, Tahamtan Ahmadi and Ignacio Melero*

**Clinica Universidad de Navarra*

Background: GEN1046 (DuoBody®-PD-L1×4-1BB)



PD-L1×4-1BB bsAbs
Tumor cell
Antigen presenting cell
T cell
Myeloid cell
Natural killer cell
Macrophage



GEN1046 is a first-in-class, next generation immunotherapy designed to simultaneously block the PD-L1 axis while activating T cells through conditional 4-1BB co-stimulation

PD-L1, programmed death ligand 1.

GEN1046 I/IIa Trial Design (NCT03917381)

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Primary objectives:

- Characterization of GEN1046 safety and tolerability profile
- Determination of maximum tolerated dose (MTD)

Other objectives:

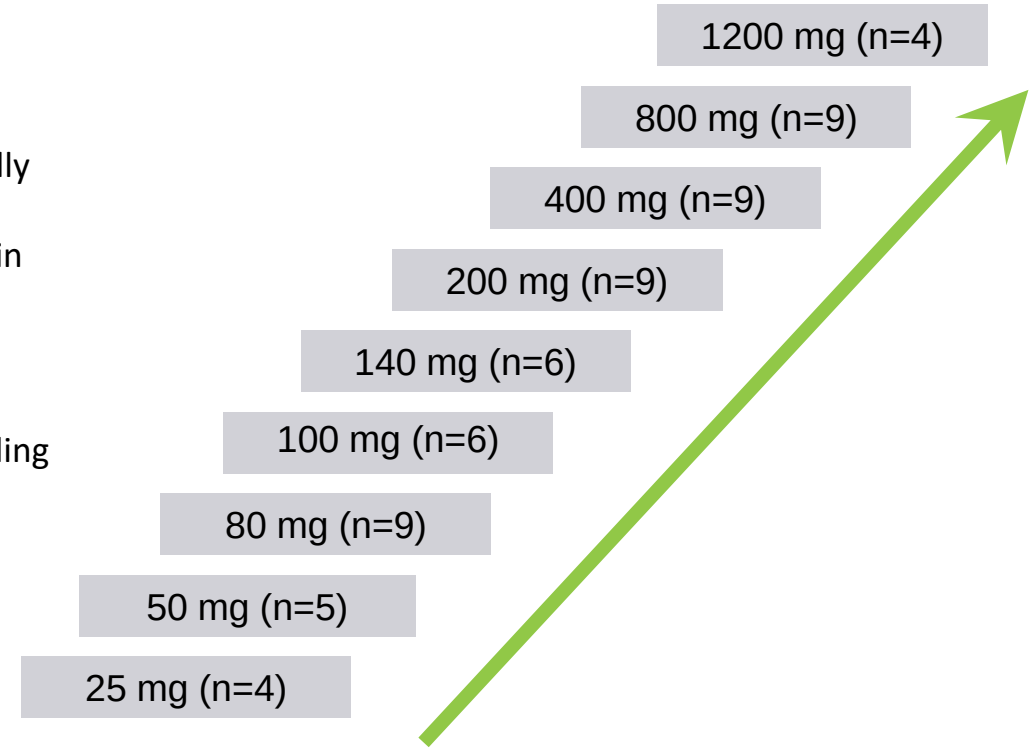
- Establishment of PK/PD profiles
- Anti-tumor activity

Monotherapy Dose Escalation

GEN1046 intravenous flat dosing every 3 weeks until disease progression or unacceptable toxicity

Inclusion criteria:

- ≥18 years of age
- Histologically or cytologically confirmed metastatic or unresectable solid tumors in patients who are not candidates for standard therapy
- Measurable disease according to RECIST 1.1
- ECOG PS 0–1
- Adequate renal, liver, and hematologic function



ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, pharmacodynamics; PD-L1, programmed death ligand 1; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Patient Demographic and Disease Characteristics

Dose Escalation Cohort	All Patients (N=61)
Median age, years (range)	59 (23–79)
Age group, n (%)	
<65 years	44 (72.1)
≥65 years	17 (27.9)
Female, n (%)	28 (45.9)
Cancer type,[a] n (%)	
Colorectal	12 (19.7)
Ovarian	9 (14.8)
Pancreatic	6 (9.8)
NSCLC	6 (9.8)
Other	28 (45.9)
ECOG performance status, n (%)	
0	32 (52.5)
1	29 (47.5)
Median number of prior regimens (range)	3 (1–11)
Prior treatment with PD-(L)1 inhibitor, n (%)	23 (37.7)

Data cut-off: August 31, 2020.
[a]Cancer types occurring in <5 patients were categorized as "Other".
ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death (ligand) 1.

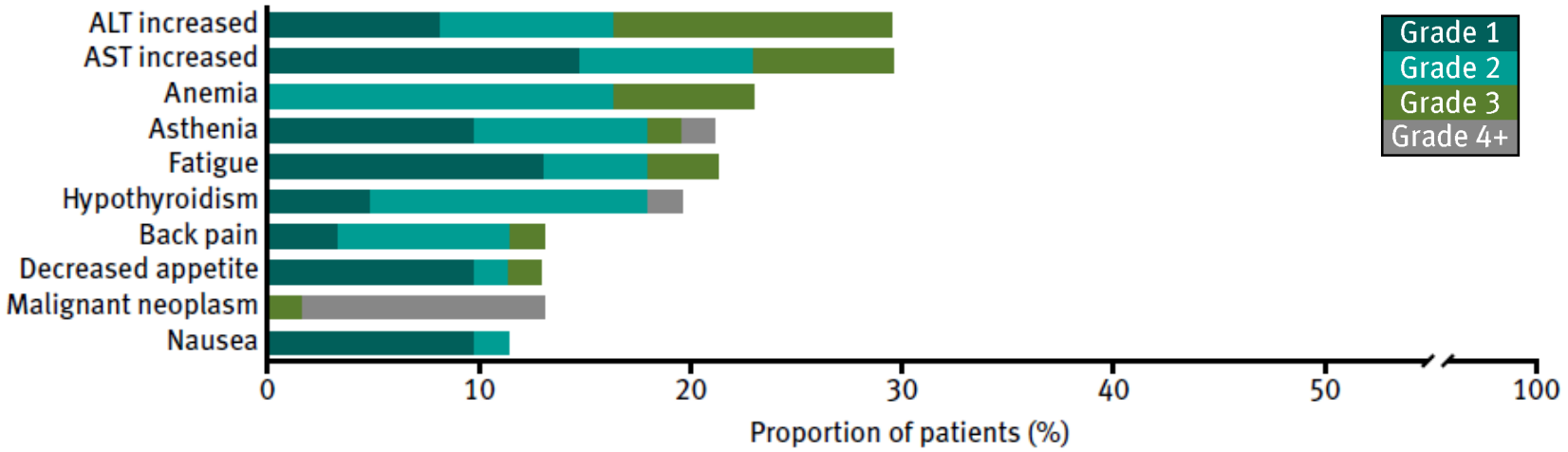
Patient Disposition and Treatment Exposure

Dose Escalation Cohort	All Patients (N=61)
Median duration of follow-up, months (range)	6.0 (0.3–14.7)
Treatment ongoing, n (%)	10 (16.4)
Treatment discontinued, n (%)	51 (83.6)
Progressive disease	44 (72.1)
AE	6 (9.8)
Death	1 (1.6)[a]
Median number of GEN1046 dose infusions (range)	4 (1–18)
Median duration of exposure, months (range)	3 (0.7–13.9)

Data cut-off: August 31, 2020.
[a]Related to disease progression.
AE, adverse event.

Adverse Events

TEAEs occurring in ≥10% of patients



TRAEs occurring in ≥10% of patients

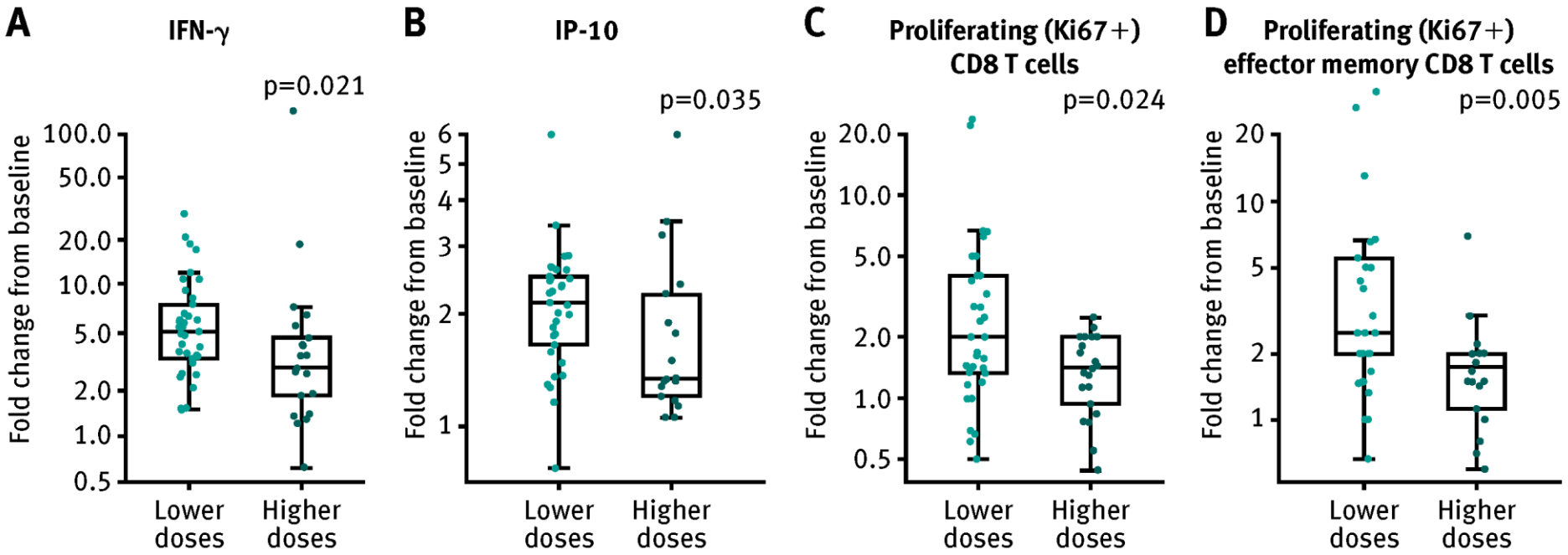
Dose Escalation Cohort	All Patients (N=61)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Any TRAE	43 (70.5)	15 (24.6)	3 (4.9)
TRAEs in ≥10% of patients			
Transaminase elevation	16 (26.2)	6 (9.8)	0
Hypothyroidism	11 (18.0)	0	1 (1.6)
Fatigue	8 (13.1)	1 (1.6)	0

Data cut-off: August 31, 2020. Transaminase elevations include the following preferred terms: AST increased, ALT increased, transaminase increased.
Adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- The most common treatment-related adverse events were transaminase elevations, hypothyroidism, and fatigue
- Treatment-related transaminase elevations occurred in 26.2% of patients; 9.8% of patients had grade 3 transaminase elevations
- No patient had Grade 4 transaminase elevations, or treatment-related bilirubin increases

Pharmacodynamics

Modulation of peripheral pharmacodynamic markers



Increased levels of IFN-γ and IP-10
Increased frequency of proliferating (Ki67+) total CD8 and effector memory CD8 T cells

Data extraction: June 26, 2020.
Maximal fold-change from baseline measured during cycle 1. Lower doses correspond to dose levels ≤200 mg and higher doses correspond to dose levels ≥400 mg.
Wilcoxon-Mann-Whitney test.
IFN, interferon; IP-10, interferon-gamma–inducible protein 10.

Anti-tumor Activity – Dose Escalation

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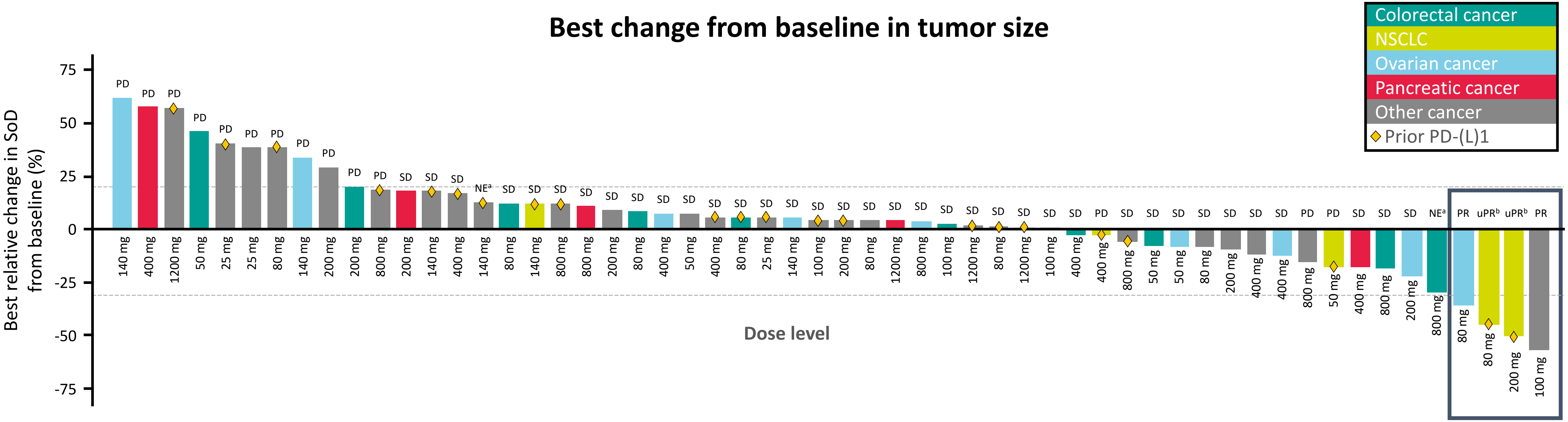


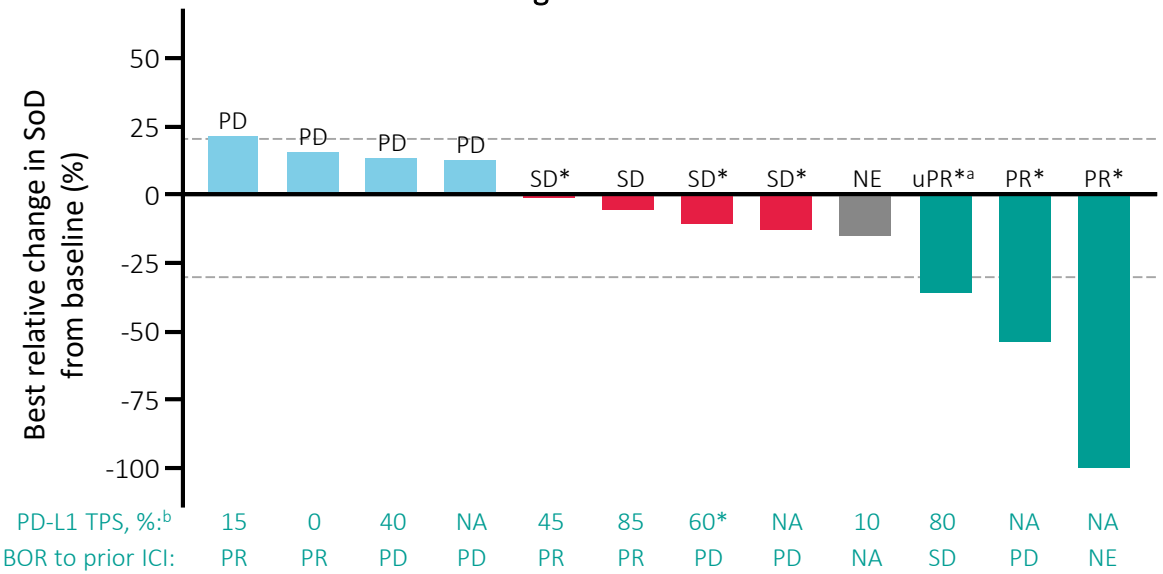
Disease control achieved in 65.6% of patients; four patients with PR

Data cut-off: September 29, 2020. Postbaseline scans were not conducted for 5 patients.
[a]Minimum duration of response (5 weeks) per RECIST v1.1 not reached.
[b]PR was not confirmed on a subsequent scan.
NE, non-evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SoD, sum of diameters; uPR, unconfirmed partial response.

Anti-tumor Activity – ICI-R/R NSCLC Expansion

Society for Immunotherapy of Cancer

A



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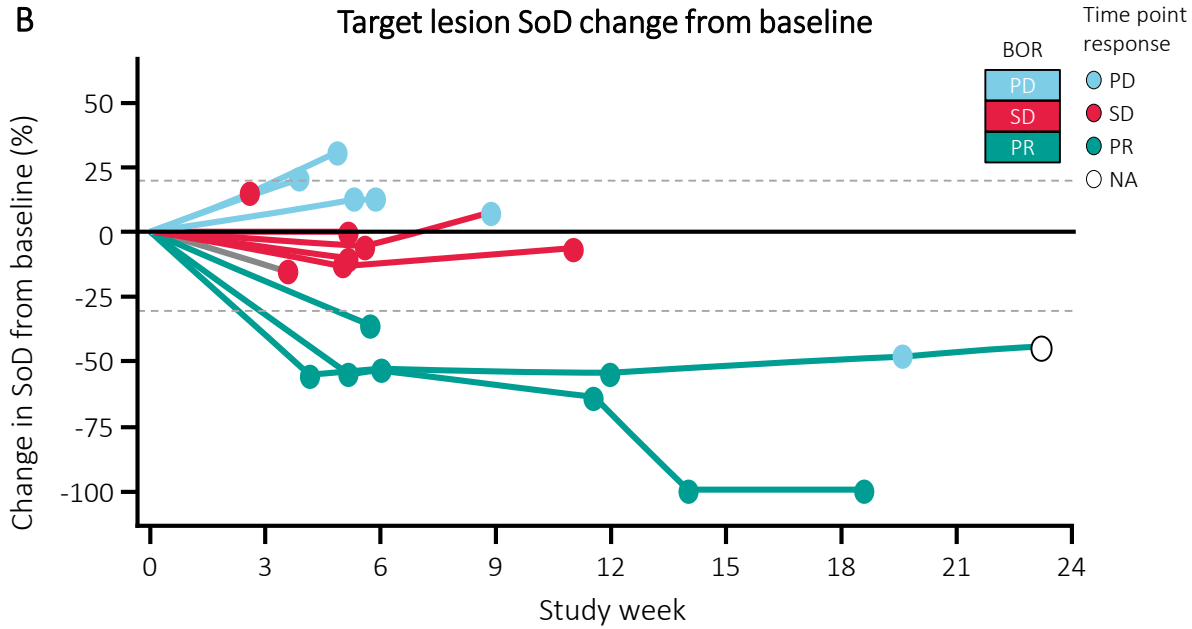

12 patients with ICI–pre-treated NSCLC, including two PR; one uPR; four SD

Data cut-off: October 12, 2020.
*Denotes patients with ongoing treatment at the time of cut-off.
[a]PR was not confirmed by a subsequent scan.
[b]PD-L1 expression was assessed in tumor biopsies obtained prior to initiation of GEN1046 treatment.
Includes all patients who had at least one postbaseline tumor assessment (schedule is every 6 weeks), and thus could be assessed for clinical benefit.
Of the remaining 12 patients not shown, 3 patients had clinical progression prior to first response assessment, and 9 patients are still receiving treatment and have not had a first response assessment.

Summary and Conclusions

- GEN1046 is a first-in-class, next-generation, PD-L1x4-1BB bispecific antibody with an acceptable safety profile and encouraging early clinical activity, potentially addressing key limitations of the existing 4-1BB agonists
- Modulation of pharmacodynamic endpoints was observed across a broad range of dose levels demonstrating biological activity
- GEN1046 was generally well tolerated - most AEs were mild to moderate in severity
  - No Grade 4 transaminase elevations; Grade 3 treatment-related transaminase elevations resolved with corticosteroids
  - No treatment-related bilirubin increases
  - Six patients had DLTs (resolved without sequelae); MTD was not reached
- Clinical benefit observed across different GEN1046 dose levels in dose escalation cohort, including patients resistant to prior immunotherapy and those with tumors typically less sensitive to immune checkpoint inhibitors
  - Disease control was achieved in 65.6% of patients, including partial responses in triple negative breast cancer (n=1), ovarian cancer (n=1), and ICI pre-treated NSCLC (n=2)
  - Encouraging preliminary responses have been observed in the expansion cohort currently enrolling patients with NSCLC who have received prior checkpoint immunotherapy, NCT03917381

AE, adverse event; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.

Webinar outline

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Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce

Hussein Tawbi

MD Anderson Cancer Center

Society for Immunotherapy of Cancer

SITC Immunotherapy Resistance Committee Update

Ryan Sullivan, MD
Massachusetts General Hospital

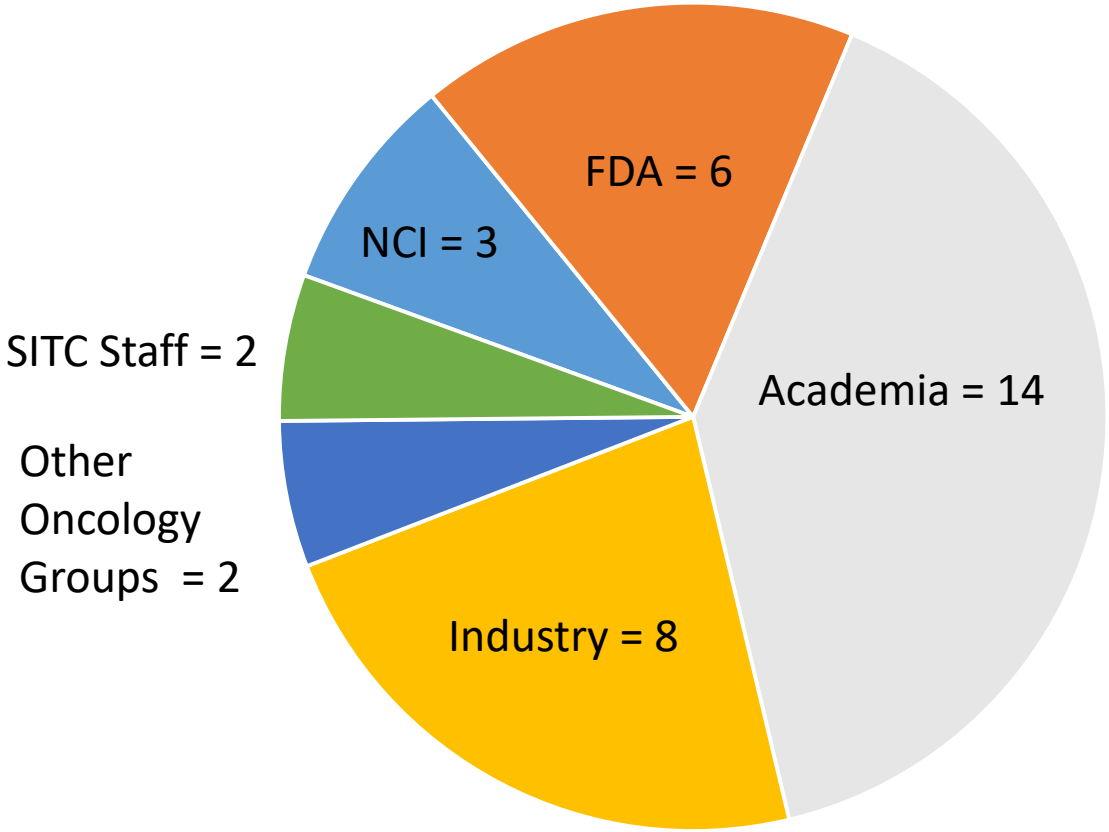
Hussein Tawbi, MD, PhD
MD Anderson Cancer Center

Harriet Kluger, MD
Yale School of Medicine

Problem Statement

- The majority of patients treated with immune checkpoint inhibitors (ICI) experience *de novo* progression or acquired resistance
- Clinical trials of novel therapies and combinations are currently being designed to address the clinical challenge of treating ICI-resistant patients
- Uniform definitions of PD-(L)1 inhibitor resistance are needed to standardize enrollment of patients in order to better enable effective comparisons among regimens and treatment approaches
- There is a current lack of comprehensive clinical trial data sets available to effectively assess clinical PD-(L)1 resistance

Immunotherapy Resistance Workshop Attendees



Total Workshop Attendees: 36

April 1, 2019

Industry Representatives

AstraZeneca
Bristol-Myers Squibb
CytomX Therapeutics
Genentech
Merck

Other Oncology Groups

Cancer Research Institute
Parker Institute for Cancer Immunotherapy

Workshop Outputs

Primary Resistance – Consensus Definitions

Resistance Phenotype	Drug Exposure Requirement	Best response	Confirmatory Scan for PD Requirement	Confirmatory Scan Time Frame
Primary Resistance	≥ 6 Weeks	PD; SD for < 6 months*	Yes**	At least 4 weeks after initial disease progression***

***Indolent tumor types might require modification of the timeframe**

****Other than when tumor growth is very rapid and patients are deteriorating clinically**

*****Per RECIST**

Kluger H., Tawbi, H,…., Sullivan R. J Immunother Cancer. 2020 Mar;8(1)

Workshop Outputs

Secondary Resistance – Consensus Definitions

Resistance Phenotype	Drug Exposure Requirement	Best response	Confirmatory Scan for PD Requirement	Confirmatory Scan Time Frame
Secondary Resistance	≥ 6 Months	CR, PR, or SD for > 6 months*	Yes**	At least 4 weeks after disease progression***

***Indolent tumor types might require modification of the timeframe**

****Other than when tumor growth is very rapid and patients are deteriorating clinically**

*****Per RECIST**

Kluger H., Tawbi, H,…., Sullivan R. J Immunother Cancer. 2020 Mar;8(1)

Workshop Outputs

Adjuvant and Neoadjuvant Setting

Adjuvant Therapy	Drug Exposure Duration Prior to PD	Confirmatory Biopsy Requirement*
Primary Resistance	< 12 weeks	Yes
Secondary Resistance	≥ 12 Weeks	Yes

***In this setting, a confirmatory biopsy would supplant a confirmatory scan**

Neoadjuvant Therapy		
Major Pathological Response	Yes	No
Resistance Definition Recommendation	Follow Secondary Resistance Definitions	Follow Primary Resistance Definitions

Kluger H., Tawbi, H,…., Sullivan R. J Immunother Cancer. 2020 Mar;8(1)

Workshop Outputs

Treatment Discontinuation Setting

Stopped Therapy (CR/PR/end of study)	Drug Exposure Duration Prior to PD	Confirmatory Biopsy Requirement*
Primary Resistance	NA	NA
Secondary Resistance	≥ 12 Weeks	Yes

***In this setting, a confirmatory biopsy would supplant a confirmatory scan**

Stopped Therapy for toxicity		
Major Pathological Response	Yes	No
Resistance Definition Recommendation	Follow Secondary Resistance Definitions	Follow Primary Resistance Definitions

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Future Action Items to Refine Immunotherapy Resistance Definition (as Identified by the SITC Resistance Committee)

1) Identify rate of pseudoprogression with described definitions using large clinical trial databases

2) Collect and analyze data concerning patients with primary/secondary resistant tumors retreated with PD-(L)1 inhibitors

3) Define resistance for individual drugs and combination therapies (Workshop on combinations currently planned in May 2021)

4) Define resistance for distinct tumor types

SITC 2020 summary and trends

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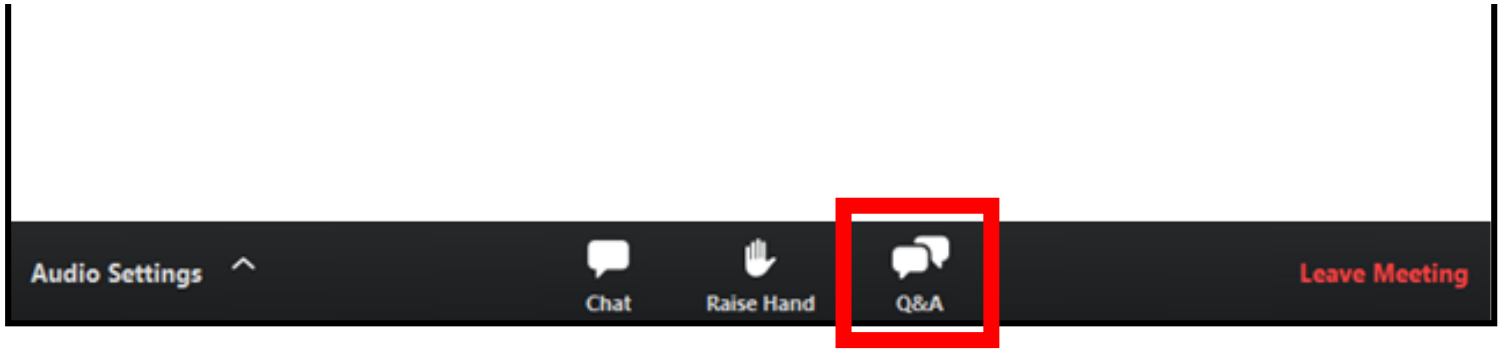
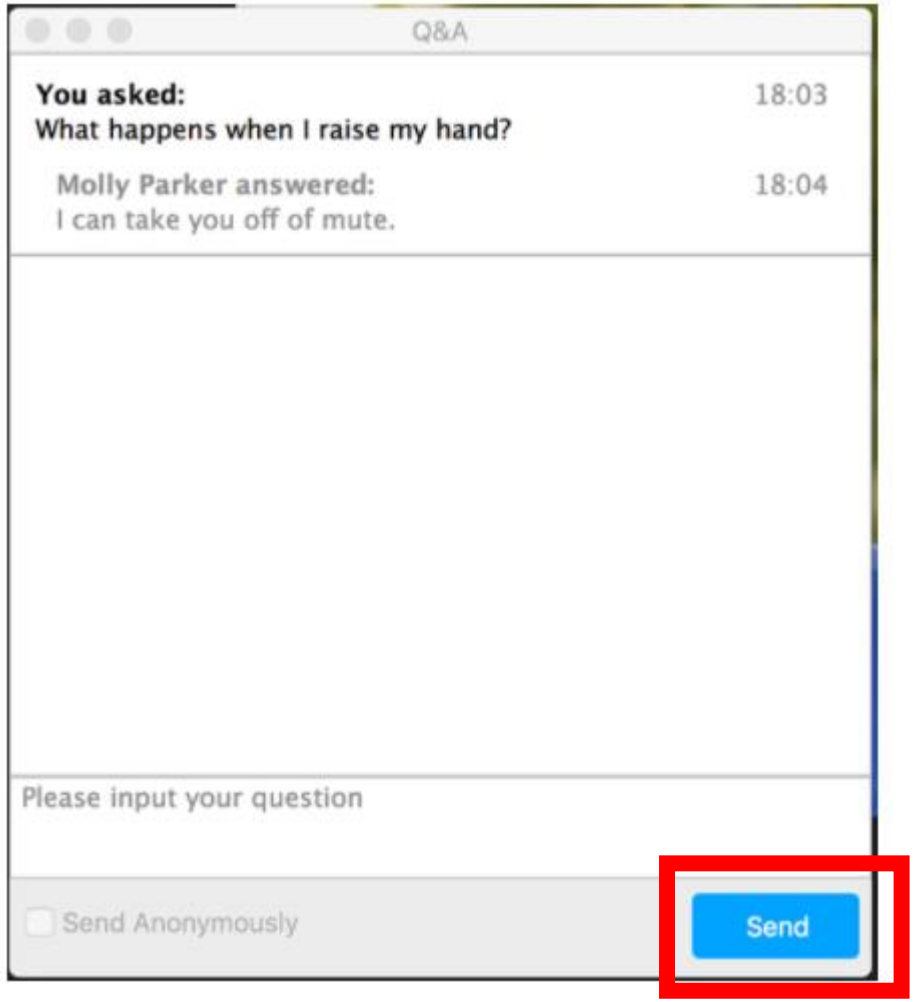
How to Submit Questions

- Click the “Q&A” icon located on at the bottom of your Zoom control panel
- Type your question in the Q&A box, then click “Send”
- Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)





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