Dose escalation of ONC-392, a target preserving anti-CTLA4 mAb, in combination with fixed dose of pembrolizumab in patients with advanced solid tumors and dose expansion in patients with IO-resistant melanoma

Siwen Hu-Lieskovan, MD, PhD[1]*, Kai He, MD, PhD.[2], Mei Tang, MD, PhD[3], Edward Arrowsmith, MD[4], Richy Agajanian, MD[5], Thom George, MD[6], Dan Chen, M.D. PhD.[7], Yang Liu, PhD.[7], and Pan Zheng, MD., PhD.[7], Tianhong Li, MD., PhD.[8*]

Affiliations: [1]Huntsman Cancer Institute, University of Utah, [2]James Comprehensive Cancer Center, The Ohio State University, [3]Sandra & Malcolm Berman Cancer Institute, [4]Tennessee Oncology at Chattanooga, Sarah Cannon Research Institute, [5]Oncology Institute of Hope and Innovation, [6]University of Florida Cancer Center, [7]OncoC4, Inc., [8]UC Davis Comprehensive Cancer Center.

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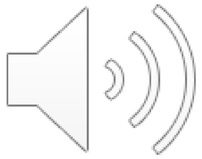
Disclosure



Consultant for: Amgen, Xencor, Genmab, Astellas, Regeneron, Nektar, BMS, Merck

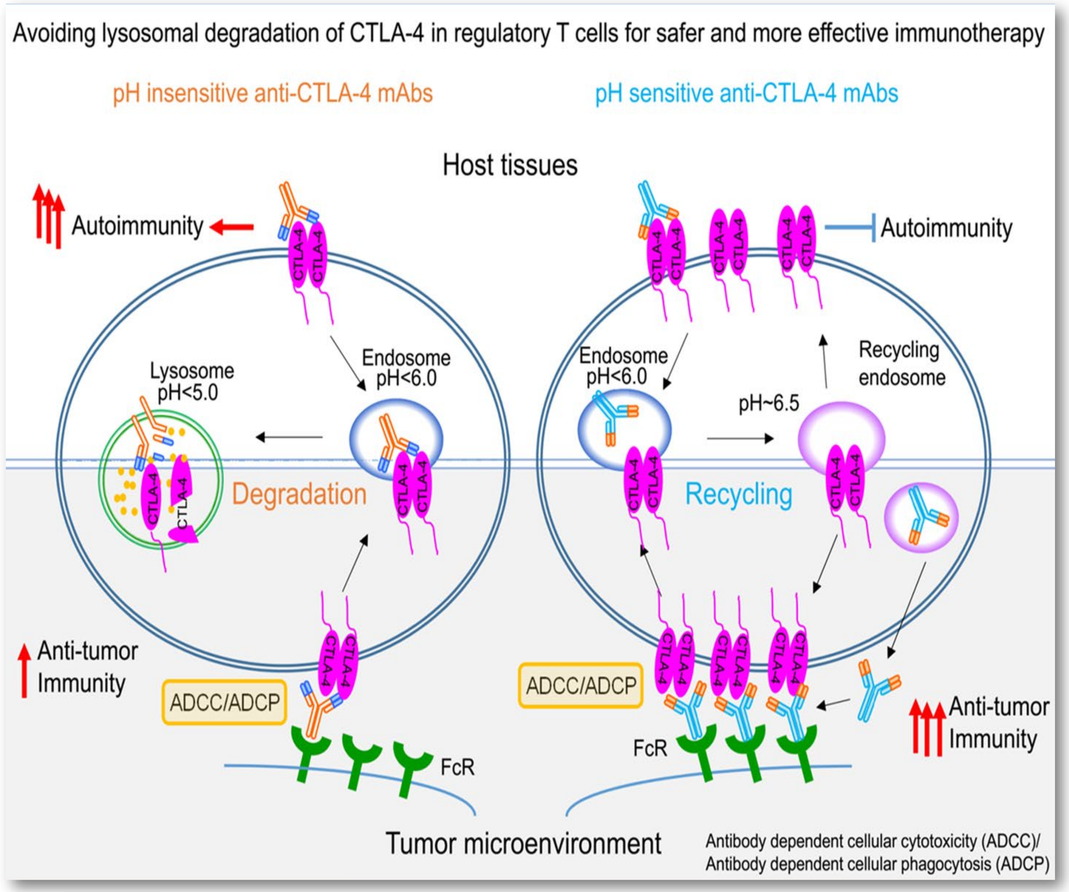
Contracted Research (Active): Xencor, Astellas, Kite Pharma, Vedanta, Merck, Boehringer Ingelheim, Checkmate, Dragonfly, F Star, OncoC4, BioAtla, BMS

CTLA-4 and PD-1 in Combination Immunotherapy

- **The first FDA-approved combination immunotherapeutic targets**
  - Combination of ipilimumab and nivolumab approved in NSCLC, RCC, HCC, MSI-positive Colon Cancer
- **Toxicity of ipilimumab and nivolumab combination limits dose level and durations**
- **ONC-392, a new anti-CTLA-4 mAb, has shown better therapeutic index**
  - Early clinical data supports safety of prolonged dosing and clinical activity of monotherapy among patients with stage IV solid tumors, including tumor types that are resistant to immunotherapy (See poster # 564 for safety and efficacy in ovarian cancer)
- **Safety and clinical efficacy data of Part B of the PRESERVE-001 clinical study (NCT04140526) and preliminary efficacy data in IO-resistant melanoma are presented in this poster**

Objective: To estimate MTD or RP2D for combination immunotherapy and to test clinical activity of combination therapy

Mechanism of action



Dose escalation

Patients with advanced/metastatic solid tumors with measurable disease as determined by RECIST version 1.1, who may be treatment naïve, or anti-PD-1 treatment naïve or refractory.

Pembrolizumab: 200 mg, Q3W
ONC-392: 3 mg/kg, Q3W

Enroll 6

If 0/6 or 1/6 with DLT → Enroll 6

Pembrolizumab: 200 mg, Q3W
ONC-392: 6 mg/kg, Q3W

If 0/6 or 1/6 with DLT → Enroll 6

Optional: Pembrolizumab: 200 mg, Q3W
ONC-392: 10 mg/kg, Q3W.

If ≥ 2/6 with DLT → Enroll 6

Pembrolizumab: 200 mg, Q3W
ONC-392: 1 mg/kg, Q3W

if ≤ 1/6 with DLT

RP2D-C

Define the RP2D-C

Dose expansion

Advanced/metastatic tumors:
- Arm D: IO naïve NSCLC
- Arm E: IO R/R NSCLC
- Arm F: IO naïve Melanoma
- Arm G: IO R/R Melanoma

ONC-392 RP2D-C, IV, Q3W
Pembrolizumab, 200 mg, IV, Q3W

Treat until: RECIST v1.1 defined progression*
or
unacceptable toxicity

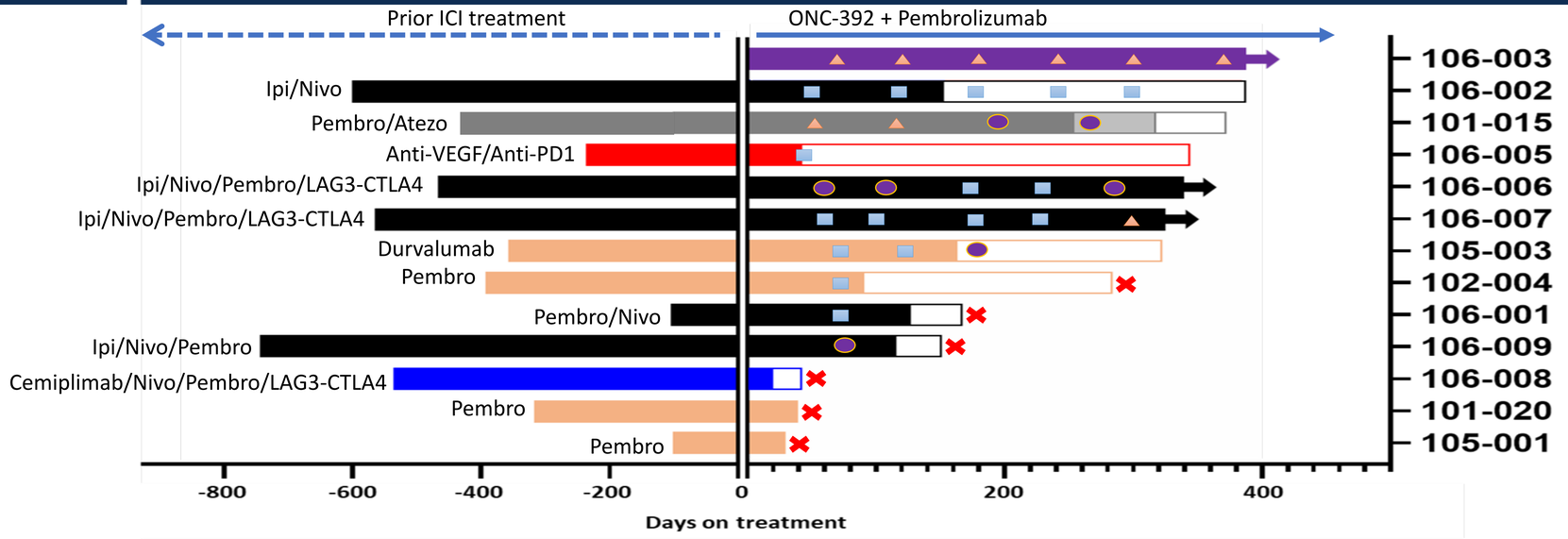
*Treatment beyond progression may occur under protocol-defined condition.

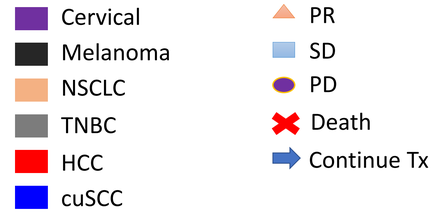
Dose escalation: Demographics and Safety Data Summary

	ONC-392 + Pembrolizumab	
	3mg/kg +	6mg/Kg +
N	7	6
Gender (F/M)	3F, 4M	3F, 3M
White/others	7 White	6 White
Median age (range)	62 (48-83)	66 (59-72)
ECOG score:		
0	2	4
1	5	2
Prior lines of systemic treatment, Median (range)		
Lines	4 (1-6)	3 (1- 14)
Prior PD-1/L1	6	6
Prior CTLA-4	2	3

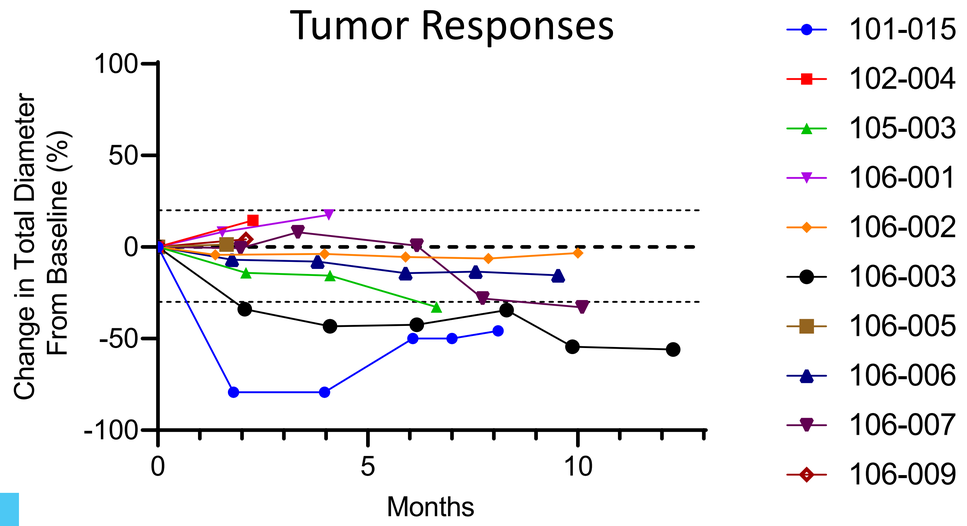
	ONC-392 + Pembrolizumab		Total
	3mg/kg +	6mg/Kg +	
N	7	6	13
Tx cycles, mean (range)	5.7 (1-13) (ongoing)	4.5 (1-9) (ongoing)	1-13 (ongoing)
Tx duration in Months, mean (range)	5.2 (1-10) (ongoing)	4.1 (1-7) (ongoing)	1-13 (ongoing)
Any TEAE	7 (100%)	6 (100%)	13 (100%)
Gr ≥ 3	5 (71%)	3 (50%)	8 (61%)
Leading to study drug d/c	2 (29%)	0	2 (15%)
Any TRAE	6 (86%)	5 (83%)	11 (85%)
Gr = 3	3 (43%)	2 (33%)	5 (38%)
Leading to study drug d/c	1(14%)	0	1 (8%)
Gr = 3 irAE	2 (29%)	1 (17%)	3 (23%)
DLT	0	0	0

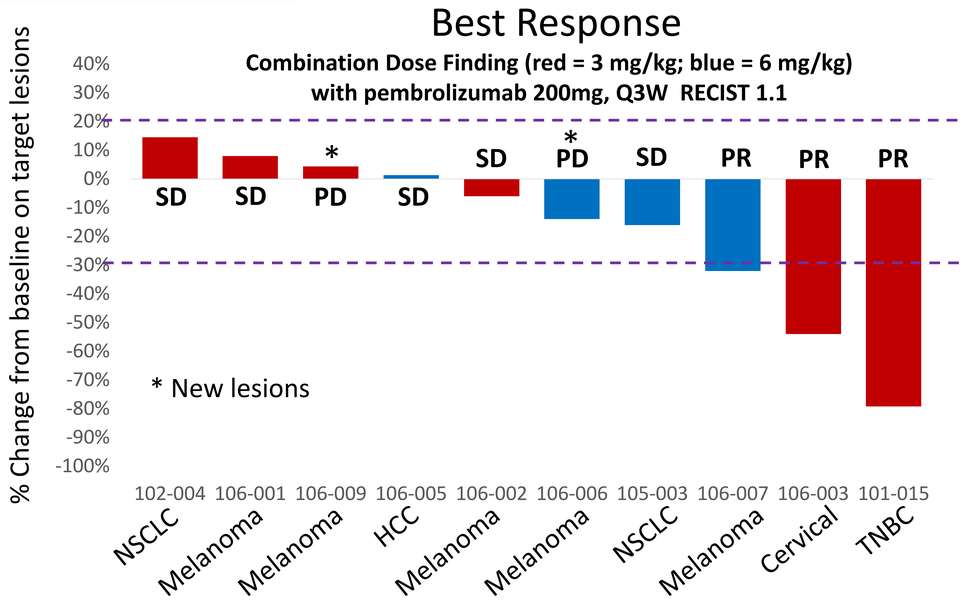
Clinical activity in dose-escalation cohort





Solid bar indicates on ONC-392/pembro combination treatment time; empty bar indicates off-treatment time; shaded bar indicates time on ONC-392 monotherapy; Arrow at the end of bar indicates that patient is still active on treatment.





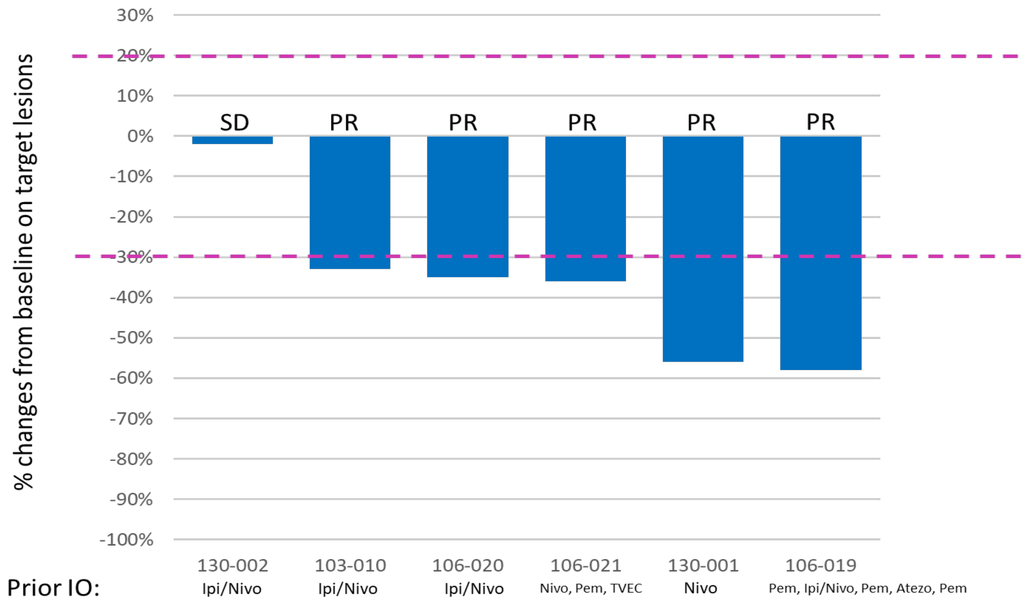
Preliminary clinical activity of in IO-resistant melanoma patients

IO R/R Melanoma

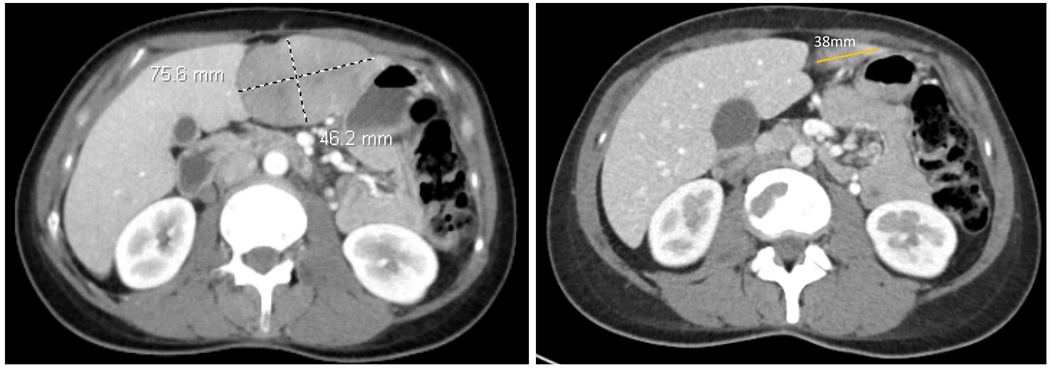
ONC-392 6 mg/kg, IV, Q3W
Pembrolizumab, 200 mg, IV, Q3W

Treat until: RECIST v1.1 defined progression*
or
unacceptable toxicity

*Treatment beyond progression may occur under protocol-defined condition.



Subject 106-020, Large liver lesion



Day -5
7.6cm

Day 52
3.8cm

Summary And Conclusions

Safety Summary (07/15/2022 Datacut)

- ONC-392 was well tolerated when used in combination with fixed dose (200 mg/dose) with Pembrolizumab.
  - Longest dosing at 3 mg/kg up to 18 cycles and continuing.
  - No DLT or Grade 3/4 AEs during the DLT observation period at any dose.
  - MTD has not been reached; RP2D for combination therapy: 6 mg/kg.
- Grade 3 TRAEs were observed in 5 pts (38.5%) (3/7 in cohort 1 and 2/6 in cohort 2). No Gr 4 or 5 TRAE was observed. Three patients (23%) had Gr 3 irAEs of immune colitis.
  - 2 infusion reactions
  - 3 immune-mediated colitis.

Clinical Activity

- Beneficial clinical activity(responder or SD) in 8/13 patient in the dose escalations
  - 2 PR and 3 SD among 6 evaluable patients at 3 mg/kg ONC-392 plus pembrolizumab, and 1PR and 2 SD among 4 evaluable patients at 6 mg/kg ONC-392 plus pembrolizumab
- Robust clinical activities observed in IO-resistant melanoma patients in preliminary analysis of available data in the dose expansion studies
  - 5 PR and 1SD among 6 evaluable IO-resistant patients who has progressed on multiple lines of mono- and / or combination immunotherapies including ipilimumab plus nivolumab

Conclusions

- When used in combination with fixed dose of pembrolizumab, ONC-392 was generally safe and well-tolerated, treatment-related AEs can be managed. At the 6 mg/kg dose, MTD was not reached.
- Severe irAE rate in the dose escalation cohorts (23%) is considered lower than what was reported for similar combination therapies.
- Early readout of expansion cohort show strong clinical activities in patients with IO-resistant melanoma.

Acknowledgments

Patients and their Families

Co-investigators and their team members

Tianhong Li, MD., PhD, UC Davis Comprehensive Cancer Center
Kai He, MD, PhD, James Comprehensive Cancer Center, The Ohio State University
Mei Tang, MD, PhD, Sandra & Malcolm Berman Cancer Institute
Edward Arrowsmith, MD, Sarah Cannon Research Institute
Richy Agajanian, MD, Oncology Institute of Hope and Innovation
Thom George, MD, University of Florida Cancer Center

OncoC4 Team

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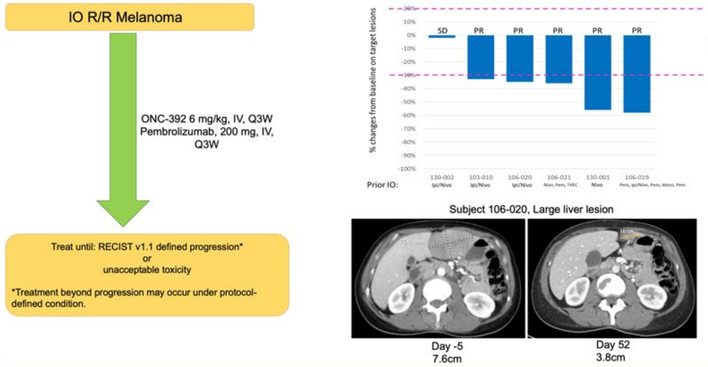

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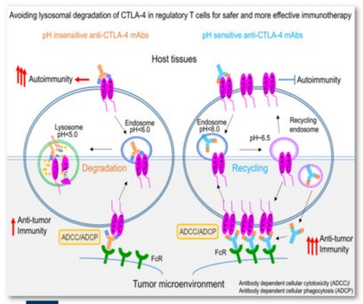

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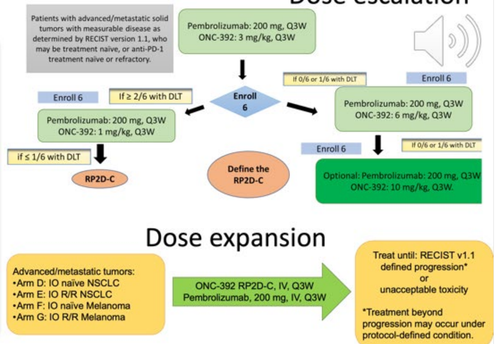
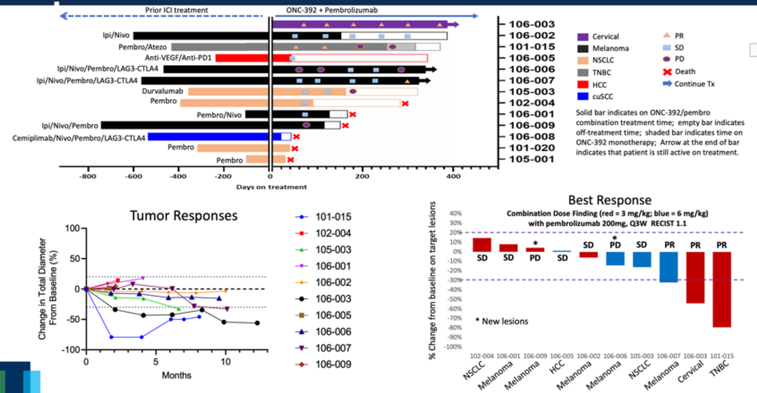


Dose expansion

Clinical activity in dose-escalation cohort



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Poster #594