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Preserving CTLA-4 Checkpoint Function for Safer and More effective Immunotherapy

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Deep Dive: Modulation of T regs in Clinical Trials

SITC Webinar, Sept 22nd 2023

Disclosure

- I am a co-founder and full time employee in OncoC4, Inc.
- Gotistobart (ONC-392/BNT316, or HL32/HL12 in pre-clinical experiments) is a next-generation experimental anti-CTLA-4 antibody candidate discovered by OncoC4, and currently jointly developed by BioNTech and OncoC4. Gotistobart is in late-stage clinical development as monotherapy or combination therapy in various cancer indications. The candidate has not been approved for any indication.

CTLA-4 in Cancer Immunotherapy:
Proven Target with Large, Untapped Potential

The first approved immunotherapeutic antibody

- Clinical efficacy in melanoma as monotherapy
- Combination with Nivolumab approved in NSCLC, RCC, HCC, Colon Cancer
- Long lasting remission if patients respond

Limitations: High toxicity limits doses and duration needed for clinical efficacy

- Approved doses significantly lower than what is needed for optimal clinical response:
  4 cycles of anti-CTLA-4 treatment vs two years of anti-PD(L)1 treatments

Important biology of CTLA-4 in regulatory T cells suggests its broad impact on all major cancer types

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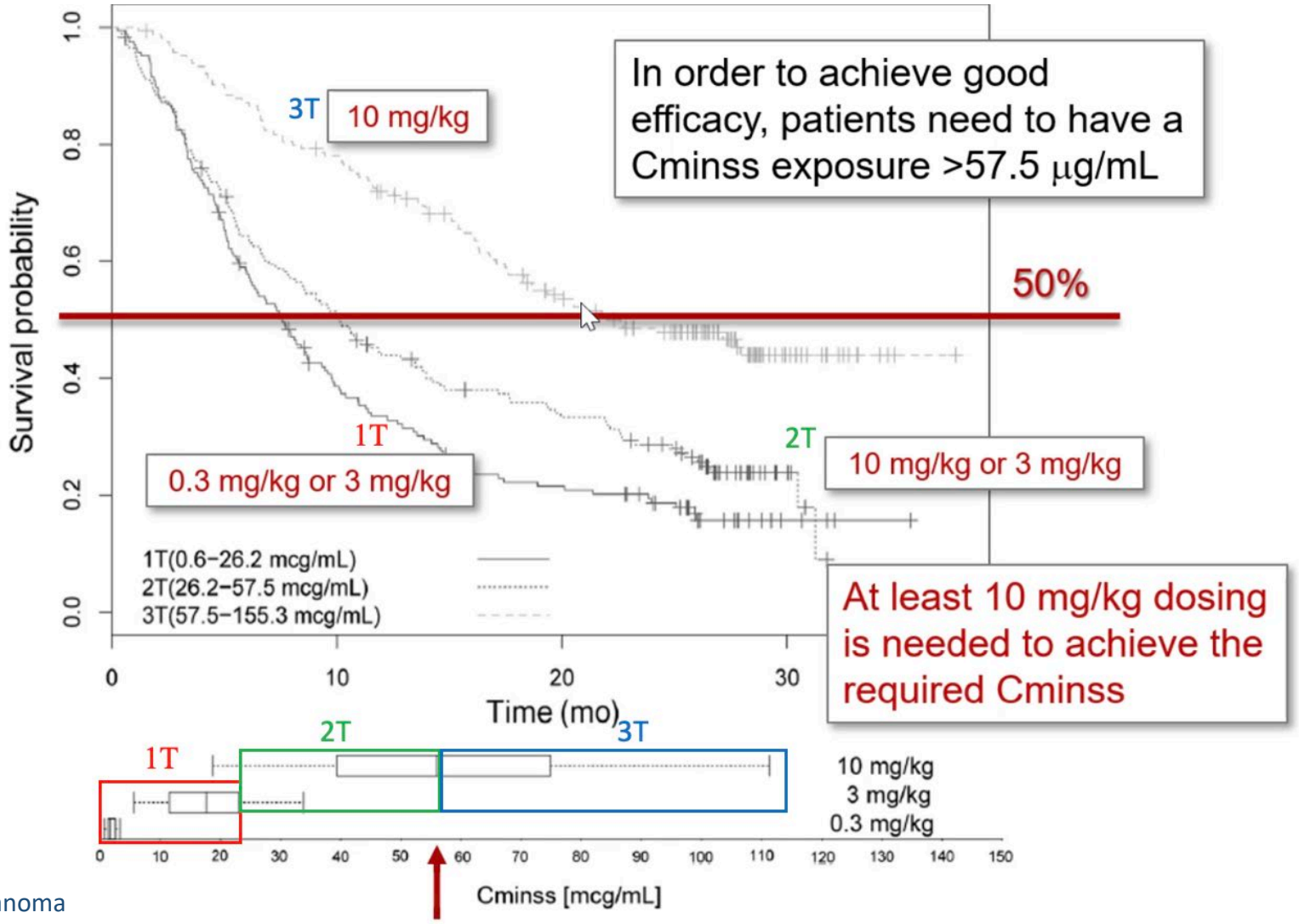
High toxicity limits doses and duration for ipilimumab



Pop-PK analyses on ipilimumab in melanoma
Feng et al, Clin Cancer Res. 2013, 19:3977-86.

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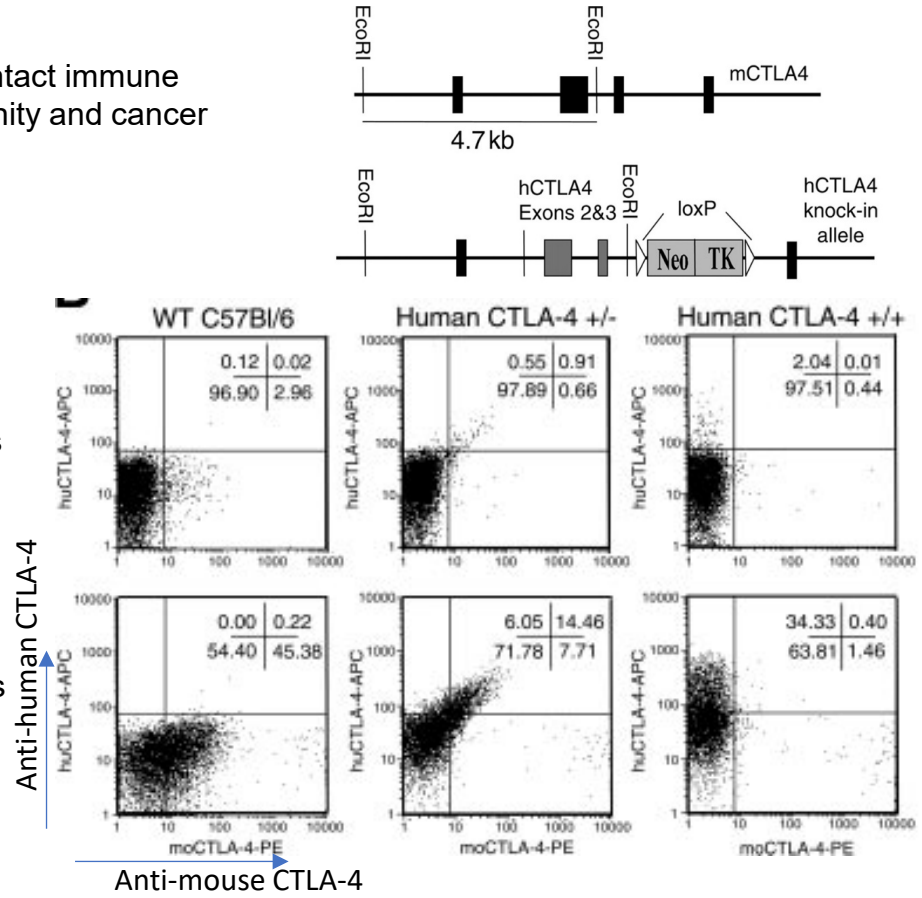
Human CTLA-4 Knock-in Mouse Model and Screening of Safer Anti-human CTLA-4 Antibody

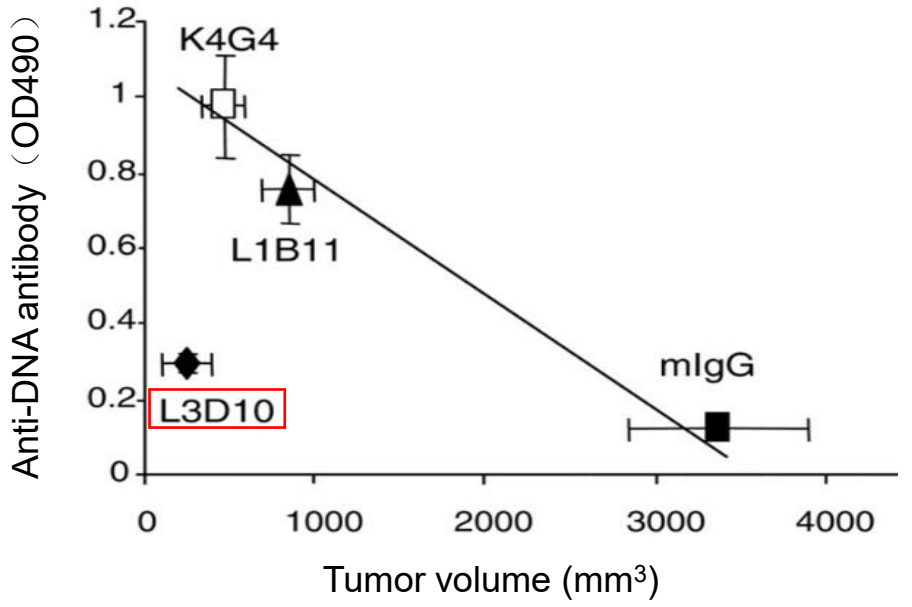
hCTLA-4 KI mice had intact immune system for tumor immunity and cancer immunity.



Codominant expression of mouse and human CTLA-4 protein by T cells from hCTLA-4 KI heterozygotes. Intracellular staining of mouse or human CTLA-4 protein.

blood
Kenneth D. Lute et al. Blood 2005;106:3127-3133

Autoimmune Disease is Not a Necessary Price For Cancer Immunity



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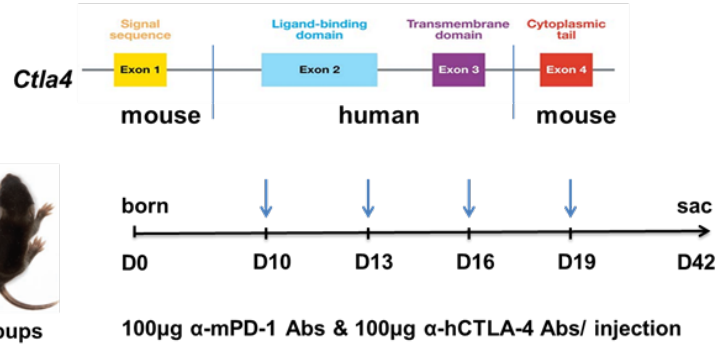
A Novel Model That Faithfully Recapitulates irAE

Human *Ctla4* knock-in mice



Du X et al. Cell Research 2018; 28:433--447

Select AEs/Organ Category	Clinical Observation	Ctla4$^{h/h}$ Pups Model
Gastrointestinal select AEs	Diarrhea, ulceration, inflammation	Inflammation in mucosal layers mild ulceration
Hepatic select AEs	ALT/AST increase inflammation	ALT increase inflammation
Pulmonary select AEs	Pneumonitis (CT)	Severe inflammation
Renal select AEs	Creatinine increase, swelling (CT), inflammation	No function damage, inflammation
Heart select AEs	Myocarditis T cell infiltration	Myocarditis, Organ Morphology T cell infiltration
Hematologic select AEs	Hemolytic Anemia, Pure Red-Cell Aplasia	Anemia, BM failure
Sicca syndrome	Dry mouth symptoms severe salivary hypofunction	Severe inflammation pathologic structural damage in SG
Skin select AEs	Rash, Pruritus...	No rash, hair loss or scratch, slight inflammatory cells infiltration
Endocrine select AEs	Hypothyroidism, Adrenal insufficiency, hypophysitis	ACTH increase, delayed adrenal development
Ovary abnormal	No report	Less mature follicles, hypogonadism

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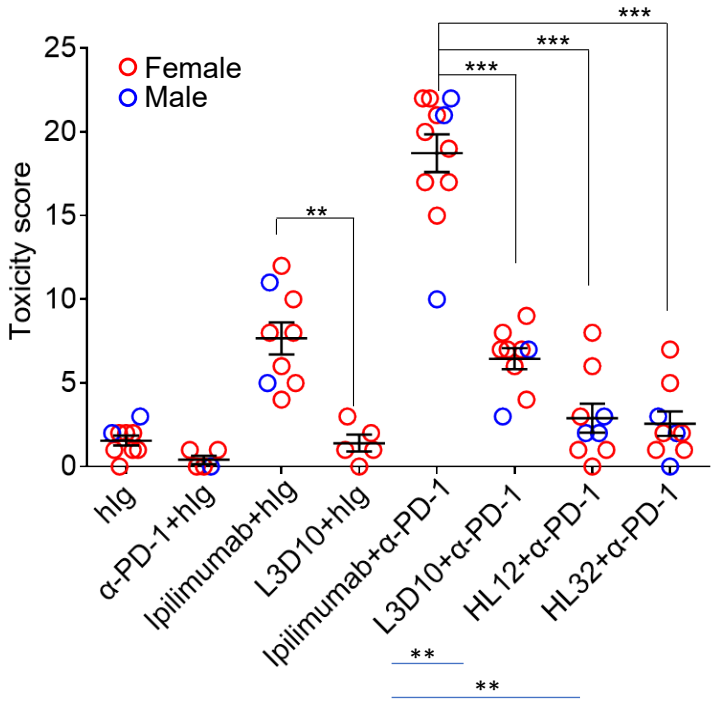
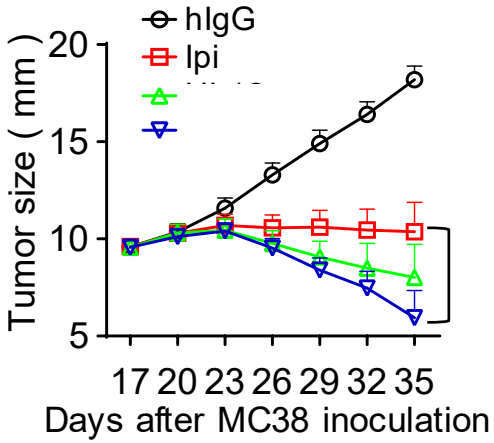
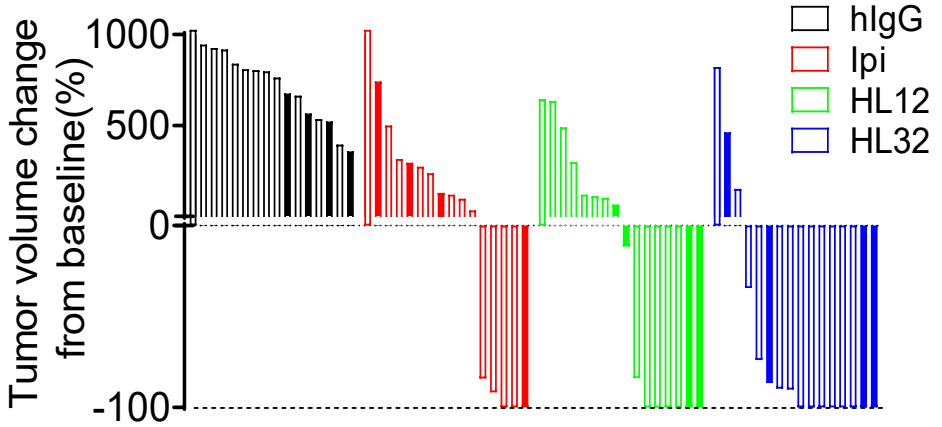
ONC-392: Less irAE and better anti-tumor efficacy







HL12 and HL32 were humanized L3D10 antibody candidates for ONC-392.

Du X et al. Cell Research 2018; 28:433—447

Zhang Y et al. Cell Research 2019; 29:609--627

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ONC-392 vs Other CTLA-4-Targeting Agents: TOX and Efficacy

Antibody	RR* in humanized mice (1.5 mg/kg)	Mouse toxicity at 20 mg/kg	Cynomolgus HNSTD**
Ipilimumab	**31%**	Growth retardation Severe anemia, Multiple organ inflammation Death	**10 mg/kg**
Tremelimumab	**29%**	Growth retardation Severe anemia, Multiple organ inflammation Death	N/A
ONC-392	**82%**	No growth retardation No anemia, Minimal organ inflammation No death	**30 mg/kg**

*Defined as % mice with 50% reduction in tumor volume on Day 18 after antibody treatment

**HNSTD = highest non-severely toxic dose

Zhang Y et al. Cell Research 2019; 29:609--627

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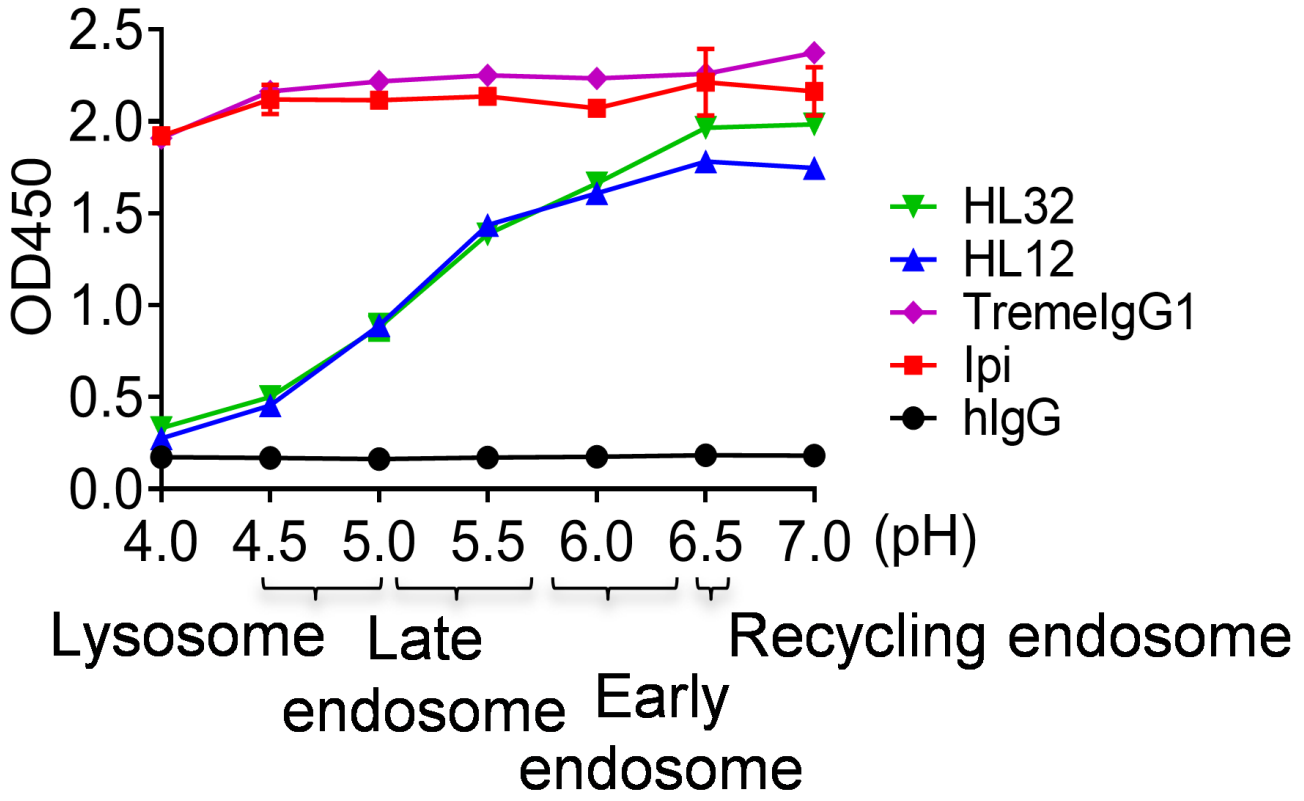
Differential pH sensitivity of anti-CTLA-4 mAbs



HL12 and HL32 were humanized L3D10 antibody candidates for ONC-392.

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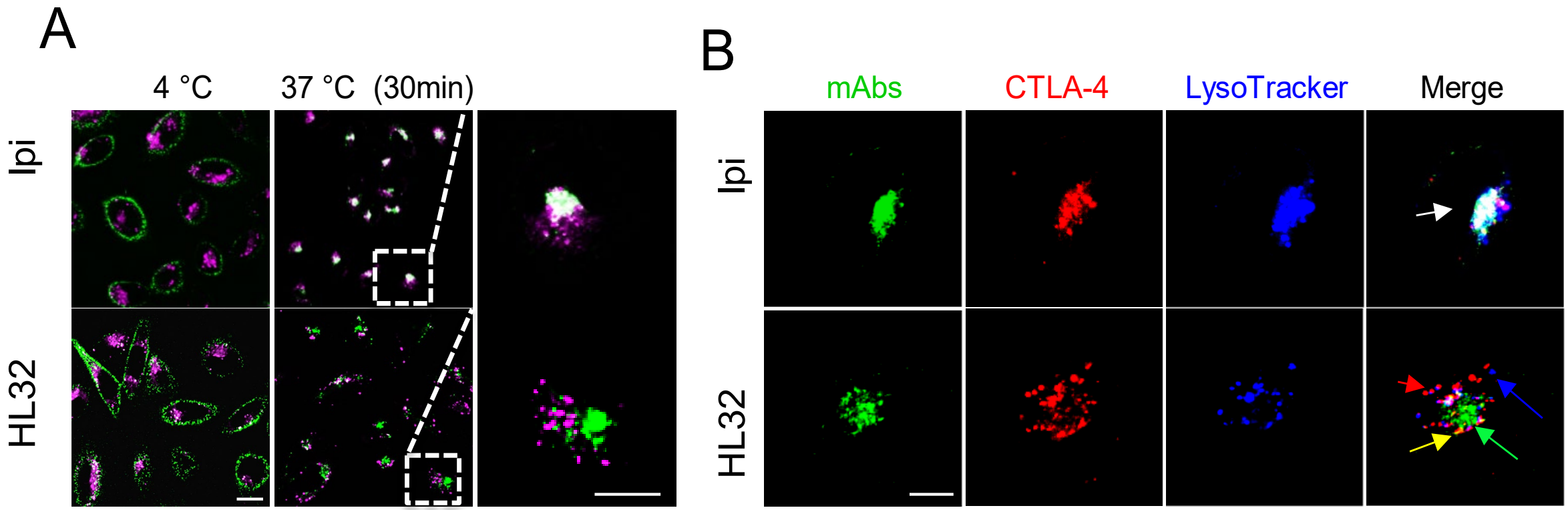
Ipilimumab, But Not ONC-392, Targets CTLA-4 to the Lysosome for Degradation



- Ipilimumab (Ipi) or ONC-392 (HL32) were labeled with AF488 and incubated with CHO stable cell lines expressing hCTLA-4 at 10 mg/ml at 4°C.
- After extra antibodies were washed away, cells were incubated at 37°C for 30 min and further stained with lysotracker.

Zhang Y et al. Cell Research 2019; 29:609--627

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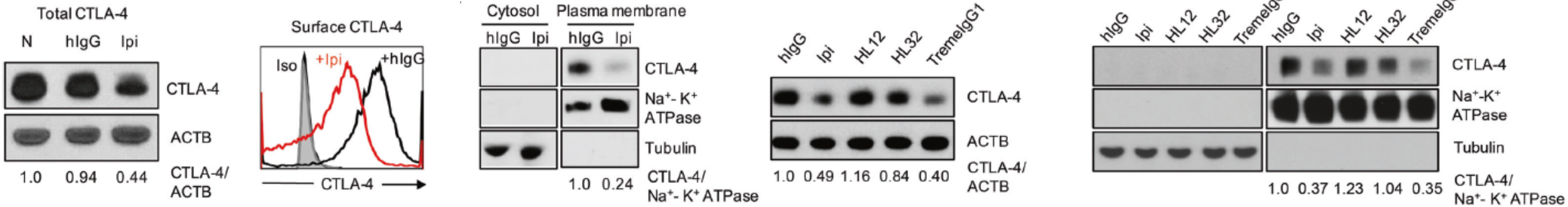
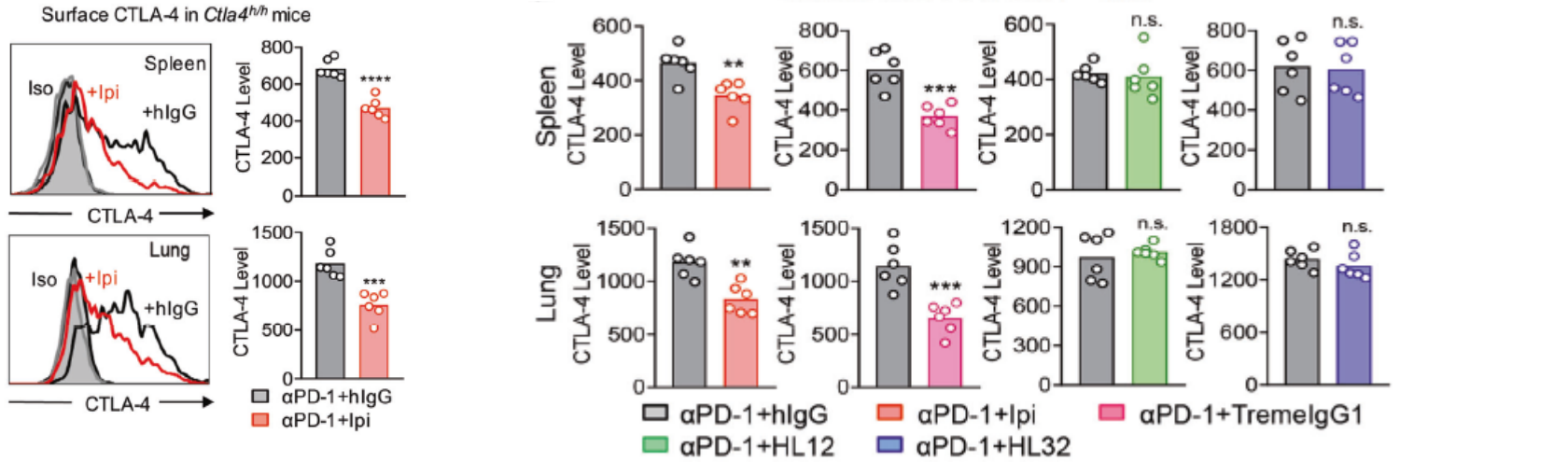
Ipilimumab Reduces Cellular CTLA-4 Expression, but ONC-392 Does Not

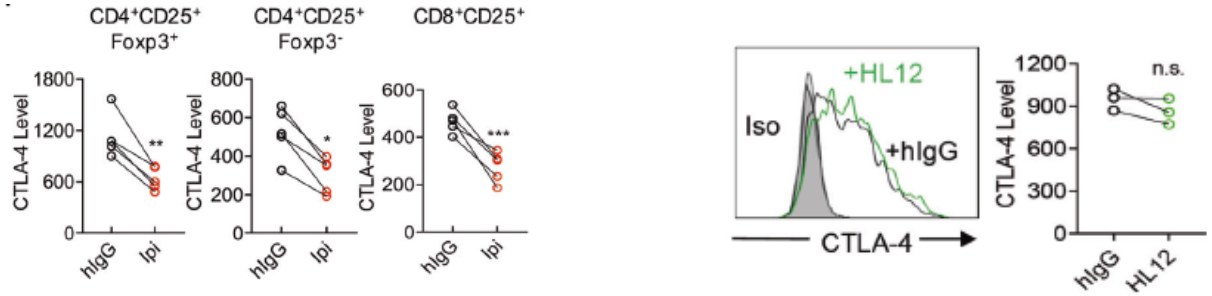
A: In cell culture



B. In mice, treated with aPD-1, then hIgG or Ipi.



C. CD3/CD28 activated PBMC, treated with hIgG or Ipi.



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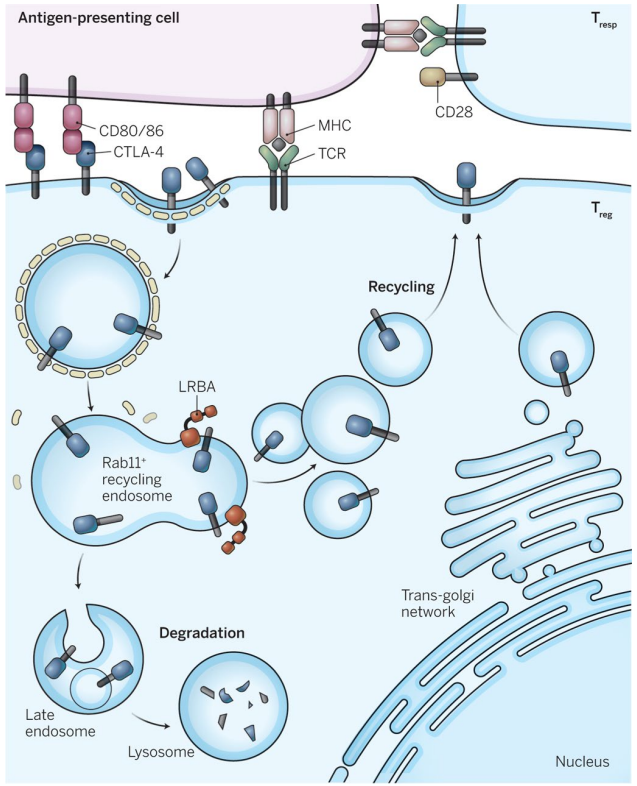
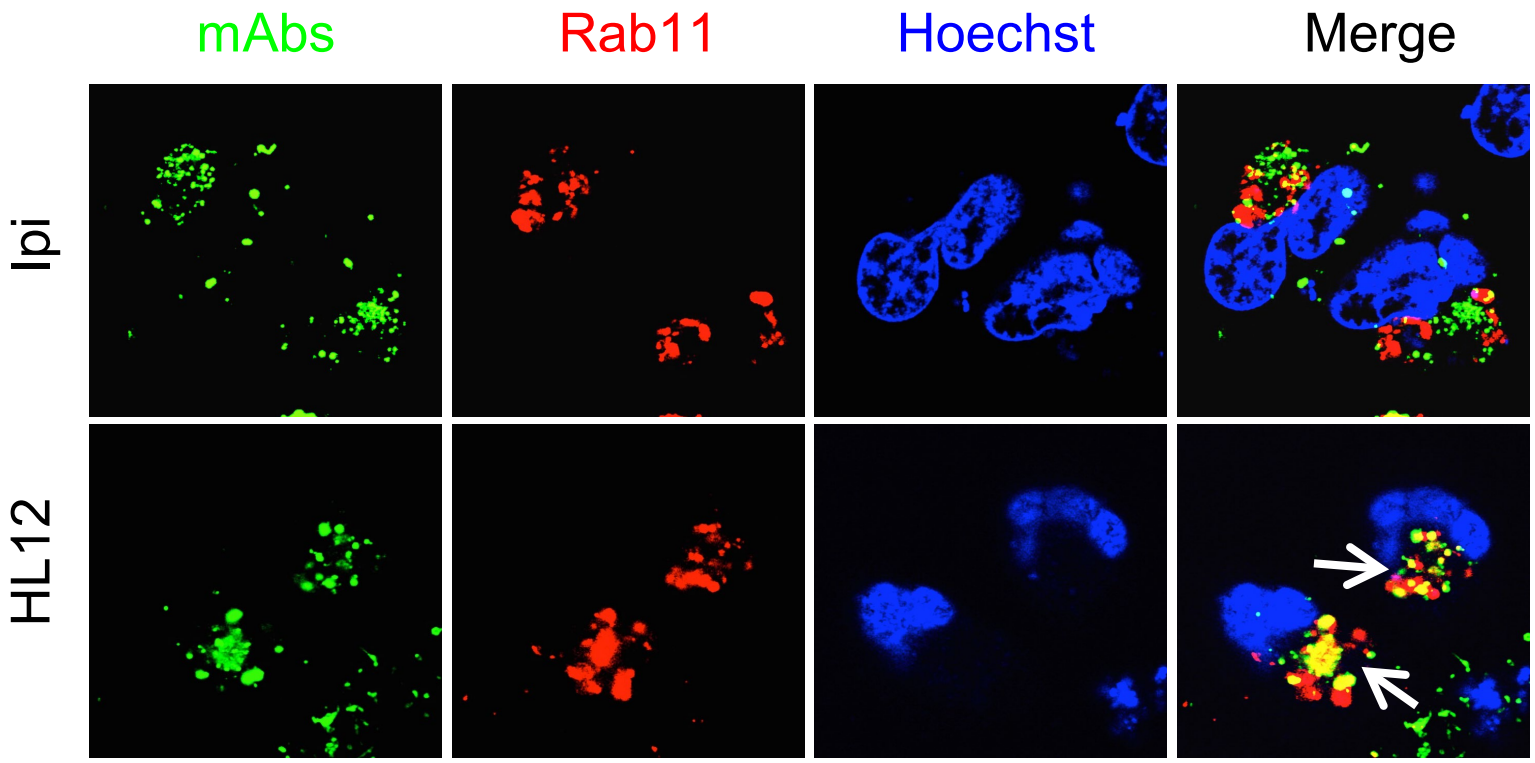
pH Sensitive Antibody (ONC-392/HL12) Enters Recycling Endosomes



Sansom DM. Science 2015; 349:377-8.



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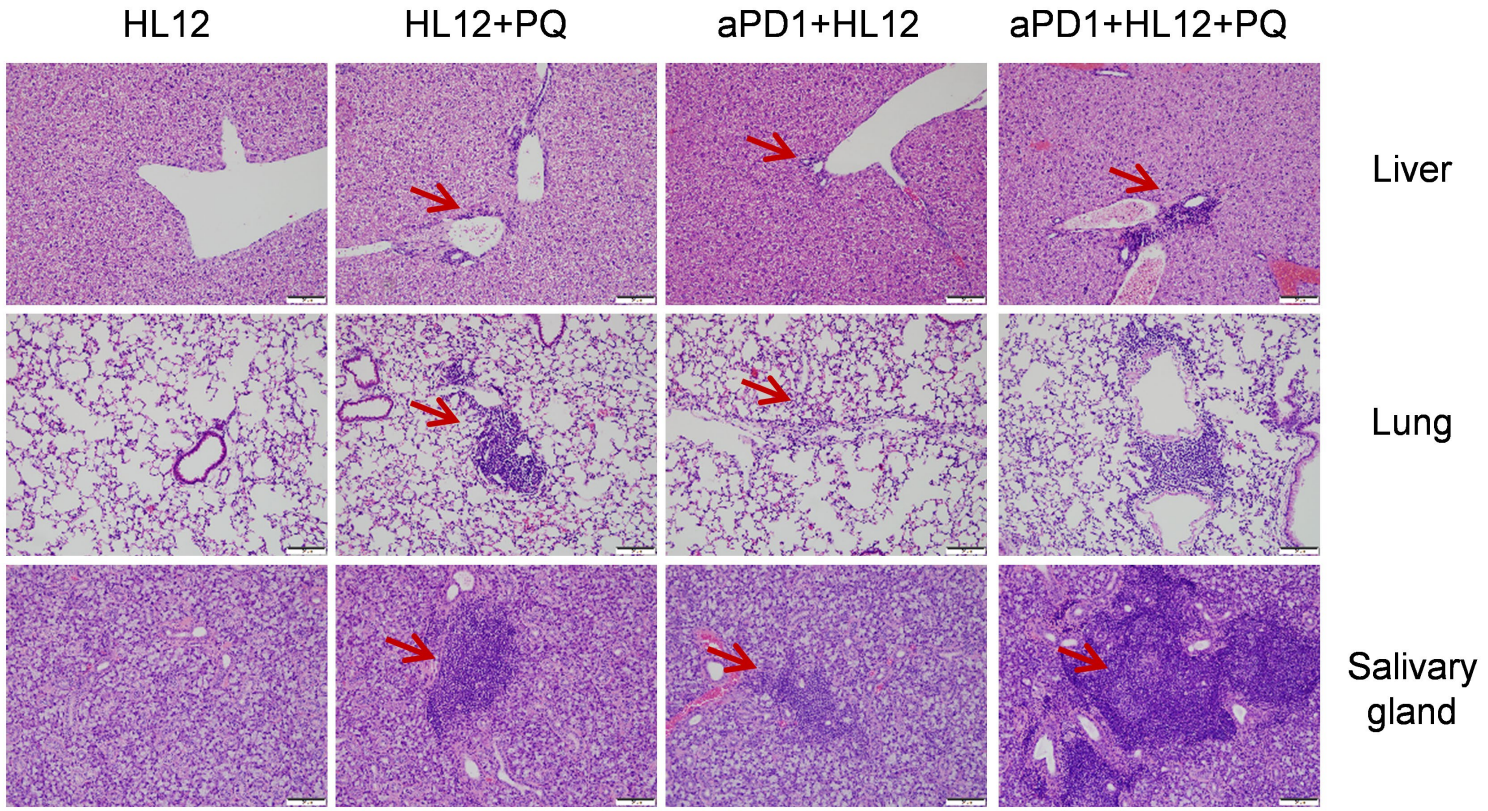
Pharmacological inhibition of recycling increases toxicity of pH-sensitive antibodies

PQ (Primaquine, endocytosis inhibitor) increased toxicity of HL12, either as monotherapy or as combination therapy in conjunction with anti-PD-1



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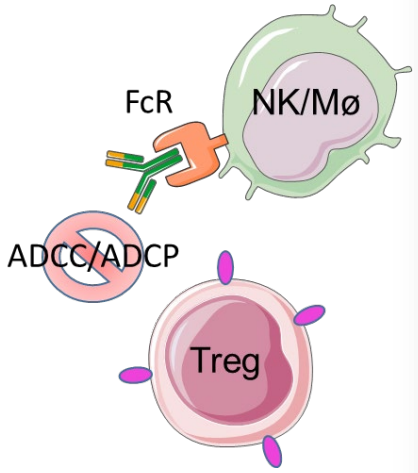
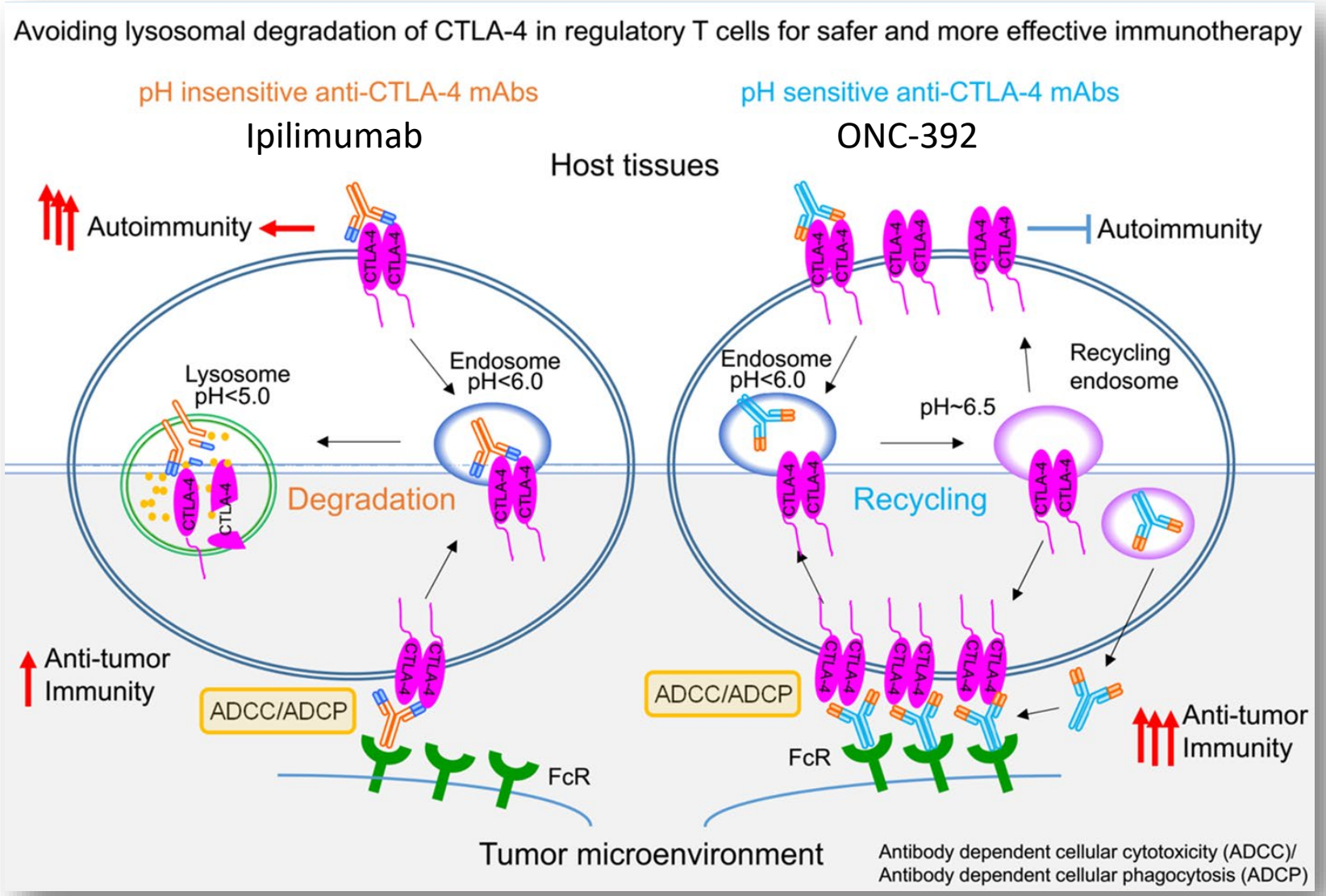
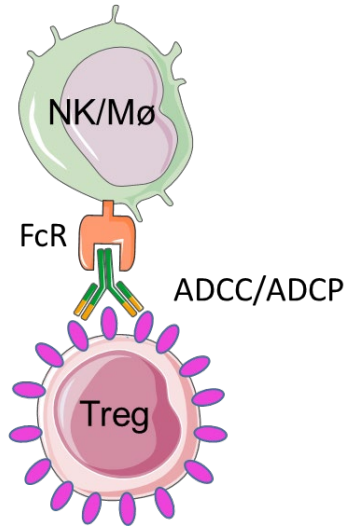
CTLA-4 Checkpoint Preservation in Cancer Immunotherapy

Insufficient target for ADCC/ADCP





Effective ADCC/ADCP



Liu Y, Zheng P. *Trends Pharmacol Sci*. 2020;41(1):4-12.

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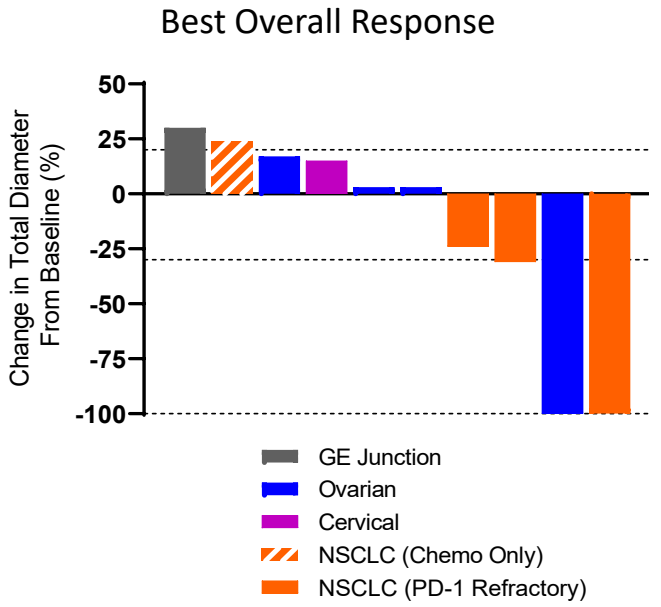
ONC-392 First-in-Human Trial (NCT04140526)

- Part A: ONC-392 Monotherapy Dose Finding (SITC 2021, LBA #949)
- Part B: ONC-392 + Pembrolizumab Combo Therapy Dose Finding (SITC 2022, Oral and Poster #594)
- Part C: Expansion Cohorts
  - ONC-392 Monotherapy: 12 Arms with different cancer indications. 10 mg/kg cohorts (7) and 6 mg/kg cohorts (5).
  - ONC-392 + Pembrolizumab Combo Therapy: 5 Arms in melanoma and NSCLC. 3 mg/kg or 6 mg/kg with Pembrolizumab 200 mg, Q3W.
- Part D: Phase 2 ONC-392 Monotherapy for a rare cancer

Part A: ONC-392 Monotherapy Dose Finding (SITC 2021, LBA #949)

Weeks	3	6	9	12			24				36		
#1: Ovarian cancer	0.1	0.3	1.0 SD	3.0	3.0	3.0 SD	3.0	3.0	3.0 SD	3.0	3.0	PD	
#2: Cervical cancer	0.3	1.0	3.0 SD	3.0	3.0	PD							
#3: Gastroesophageal cancer	3.0	3.0	3.0 PD	3.0	PD								
#4: NSCLC	3.0	3.0	3.0 SD	3.0	3.0	3.0 PD#	3.0	Surg#	3.0 SD	3.0	PD		
#5: NSCLC	10.0	10.0	10.0 PD	10.0	PD								
#6: NSCLC	10.0	10.0	10.0 SD	10.0 CR	CR*								
#7: Ovarian cancer	10.0	10.0	10.0 SD	10.0		SD							
#8: Ovarian cancer	10.0	10.0	10.0 SD	PD									
#9: NSCLC	10.0	10.0	10.0 SD	10.0	SD								
#10: Ovarian cancer	10.0	10.0	10.0 PR	CR*									

*Unconfirmed as of 10/25/21.
#Surgical tissue IHC demonstrated heavy CD4+ and CD8+ T cell infiltration into tumor (biomarker top image).



Safety Summary

ONC-392 monotherapy was well tolerated.

Two patients dosing at 3 mg/kg for 8 or 9 cycles.

No DLT or Grade 3/4 AEs during the DLT observation period at any dose.

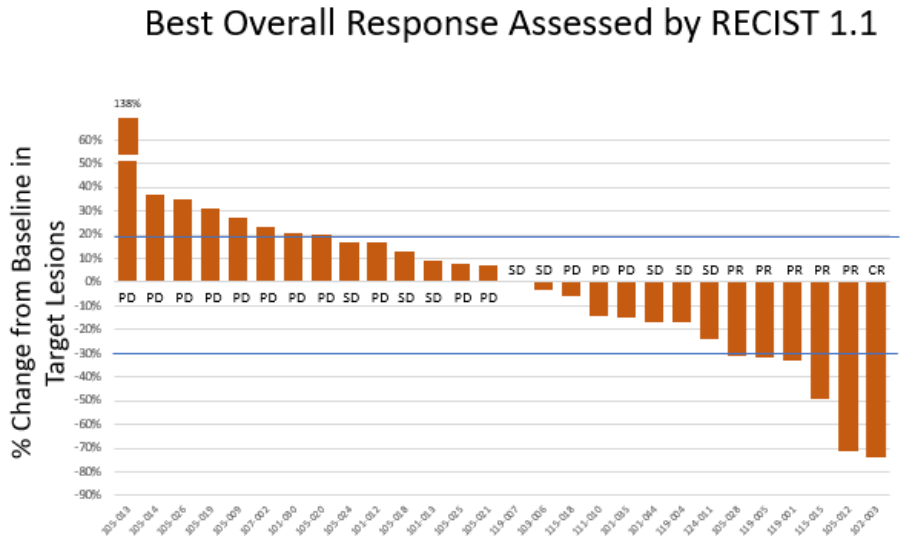
MTD has not been reached; RP2D for monotherapy: 10 mg/kg Q3W.

Grade 3 immunotherapy-related AEs occurred in 3 patients after 3 or 4 cycles treatment at 10 mg/kg dose – colitis/diarrhea (2) and pancreatitis (1); 2 of these 3 patients had unconfirmed CR, one had SD with 24% reduction in tumor burden.

Other TEAEs were grade 1/2. Those occurred in ≥2 patients included infusion-related reactions, pruritus, fatigue, and TSH increase.

PRESERVE-001 Part C Arm L: ONC-392 Monotherapy in Pre-treated Ovarian Cancer (NCT04140526) (SITC 2022, Poster #564, Cutoff Date 10/15/2022)

Categories	Data
Subject enrolled	32
Race (white/Ascian/Black)	27/3/2
Ethnicity (Hispanic or Latino)	5 (16%)
Median age (range)	67.5 (40-82)
Cancer type	
High grade serous OC	30
Carcinosarcoma	1
Peritoneal Adenocarcinoma	1
ECOG score	
ECOG = 0	13 (41%)
ECOG = 1	19 (59%)
Tumor Burden at Baseline Median (Q1, Q3), mm	87.5 (39, 126)
Have Metastatic Lesions	29 (91%)
ONC-392 related AE (TRAE): all grades	81% (26/32)
TRAE: Grade 3	31% (10/32) Diarrhea or colitis (6) Myocarditis (1), Hepatitis (1) Fatigue (1), AKI (1).
TRAE: Grade 4	3% (1/32) shock
TRAE: Grade 5	0



Initiated Phase 2 study with ONC-392 and Pembrolizumab (NCT05446298)

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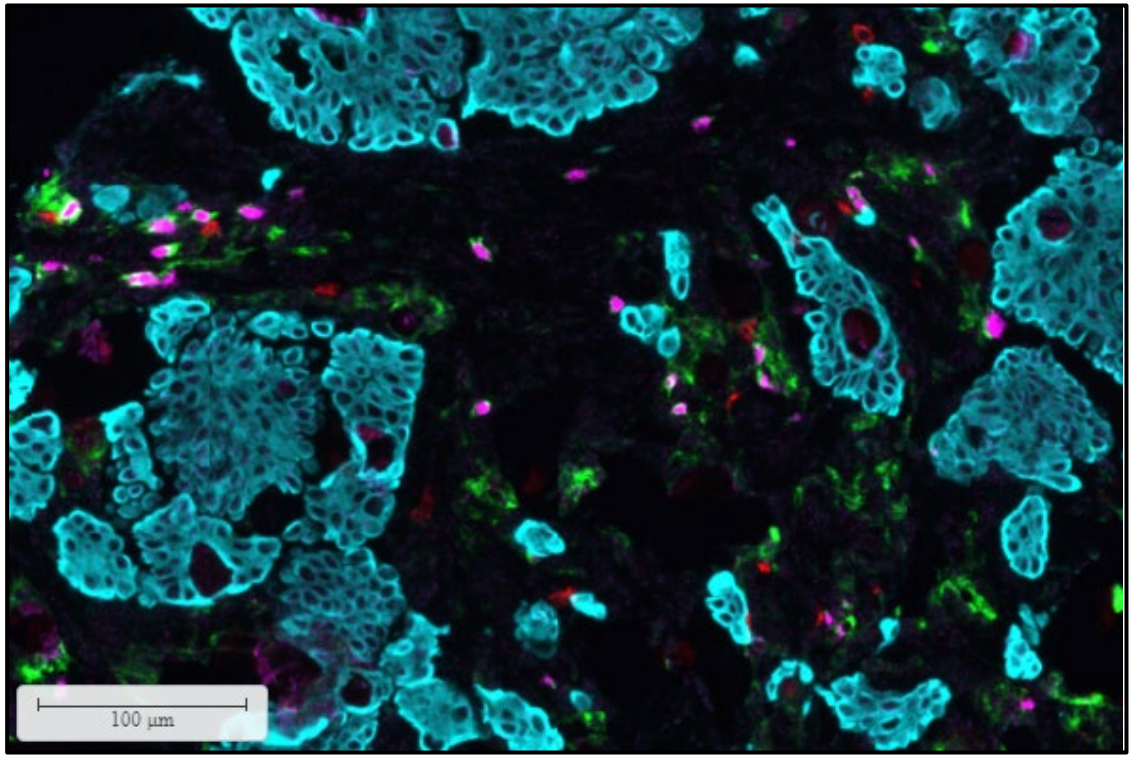
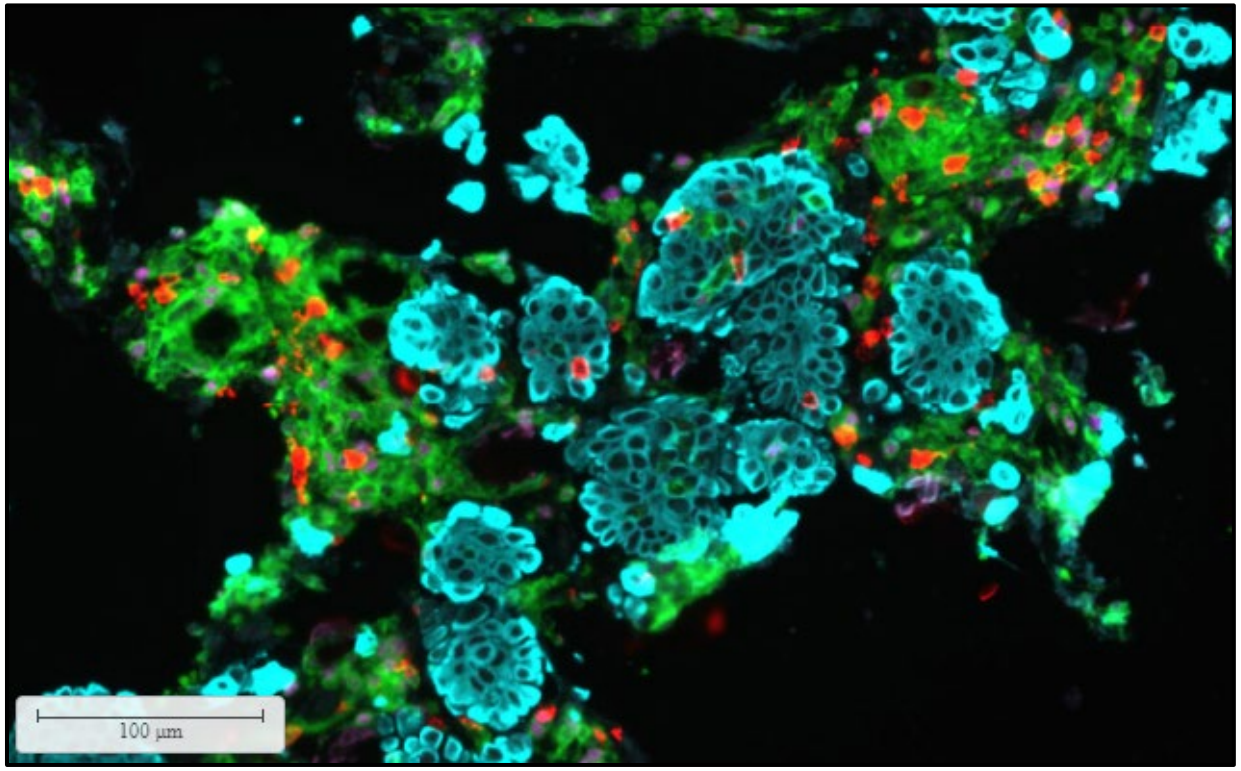
Tumor Biopsy Supports MOA of Increased Lymphocyte Infiltration

Ovarian Cancer, Pre-treatment biopsy.



Ovarian Cancer, 4 cycles of 10 mg/kg ONC-392.



Pink: Foxp3, Red: CD8, Green: CD4, Cyan: CK

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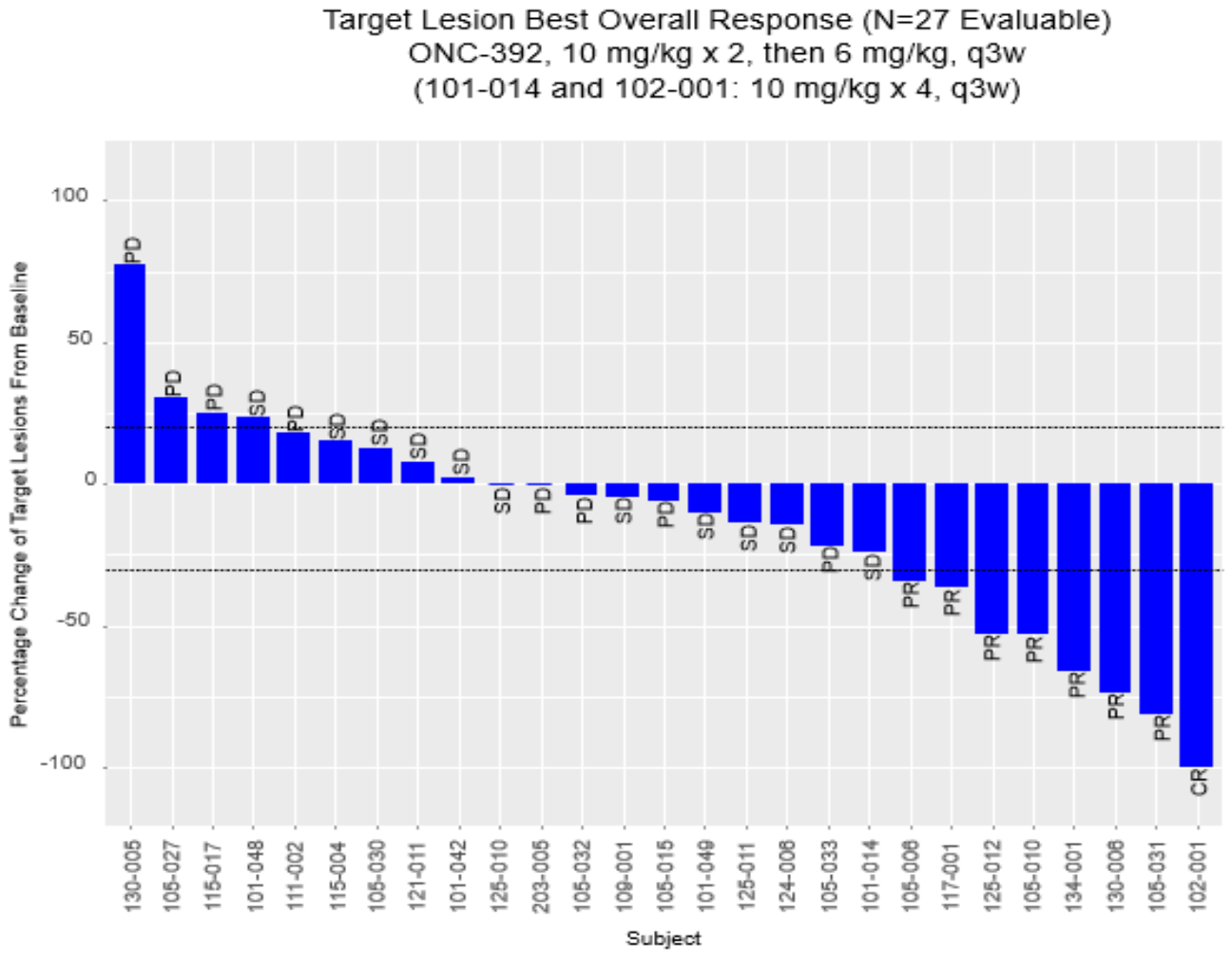
PRESERVE-001 Part A and Part C Arm I: ONC-392 Monotherapy in PD-1 R/R NSCLC (NCT04140526) (ASCO 2023, Abstract #9024, Cutoff Date 04/30/2023)

Categories	Demographics and basic characteristics
Subject enrolled	35
Median age (range) [Q1, Q3]	66 (43 - 89) [60, 75]
Gender	15F (43%), 20M (57%)
Race (white/Black)	33/2
Ethnicity (Hispanic or Latino)	2
Cohorts	
Part A: NSCLC, PD-1 R/R, 10 mg/kg, q3w	2
Arm I: NSCLC, PD-1 R/R 10 mg/kg x 2, then 6 mg/kg, q3w	33
Non-squamous cell carcinoma	20 (57%)
Squamous cell carcinoma	15 (43%)
ECOG score	
ECOG = 0	9 (26%)
ECOG = 1	26 (74%)
Have Metastatic Lesions	35 (100%)
Safety Data (cutoff date: 03/10/2023)	
ONC-392 related AEs (TRAEs): All grades	26 (74%)
TRAEs: Grade 3-4	15 (43%)
irAEs: All grades	19 (54%)
irAEs: Grade 3-4	12 (34%)



Evaluable patients are defined as patients who had at least one tumor assessment at Week 8.

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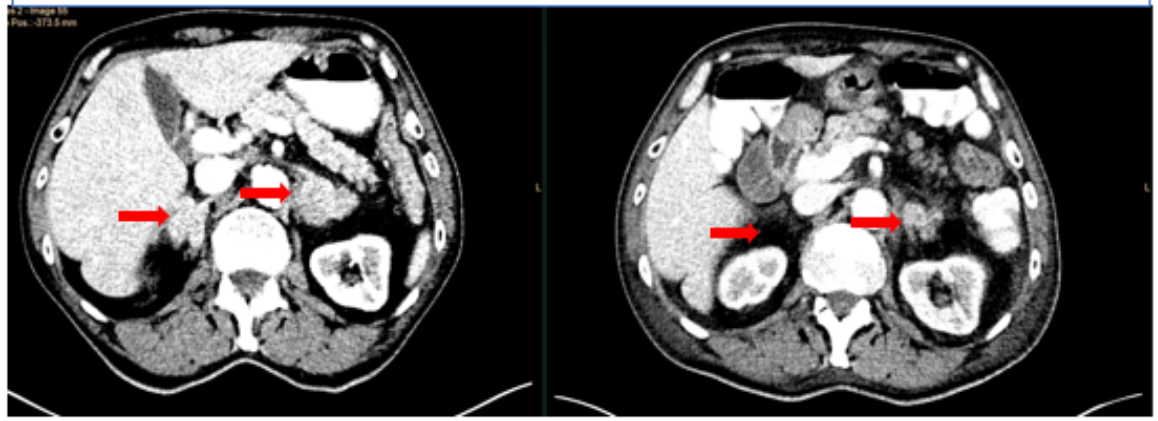
Response to ONC-392 Treatment: Representative Cases

Case 1

- 75-year-old male was diagnosed with stage IV lung adenosquamous carcinoma in Jan 2019. Tumor PD-L1 25%. TMB 8. No actionable mutations. MMS.
- Since Feb 2019, received 1st line treatment with carboplatin, paclitaxel, and pembrolizumab, followed by pembrolizumab maintenance.
- SBRT for oligo-progression in LUL In Jan 2022
- Systemic cancer progressed with metastases in adrenal glands and brain in May 2022. s/p SRS to brain lesion Jun 2022.
- Started Onc-392 monotherapy 07/13/2022.

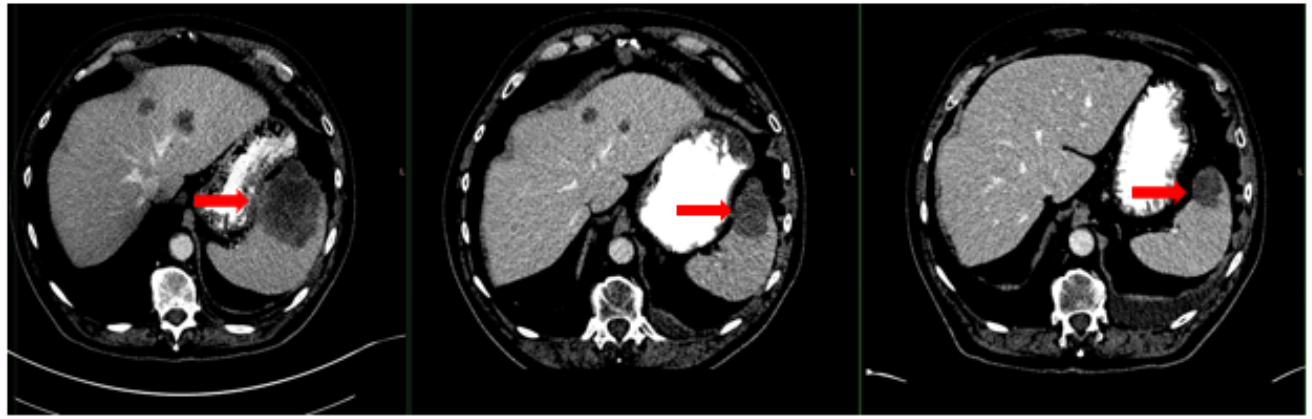


Jun. 2022, baseline

Sep. 2022, Right adrenal lesion resolved

Case 2

- 64-year-old male, with 100 pack years smoking history (quit 15 years ago) was diagnosed with squamous cell carcinoma of lung in Aug 2021. Tumor PD-L1 <1%. TMB 4. No actionable mutations. Microsatellite status is stable.
- Initially treated at outside hospital with chemo-RT (weekly paclitaxel and carboplatin), completed in Nov 2021. PET/CT on 12/10/21 showed disease progression with metastases in spleen and liver.
- Started with carboplatin, paclitaxel, Ipilimumab and nivolumab; however, cancer continued to progress after 2 cycles of treatment.
- Onc-392 monotherapy started 03/07/2022. Patient is active in treatment and in cycle 19 as of May 2023.

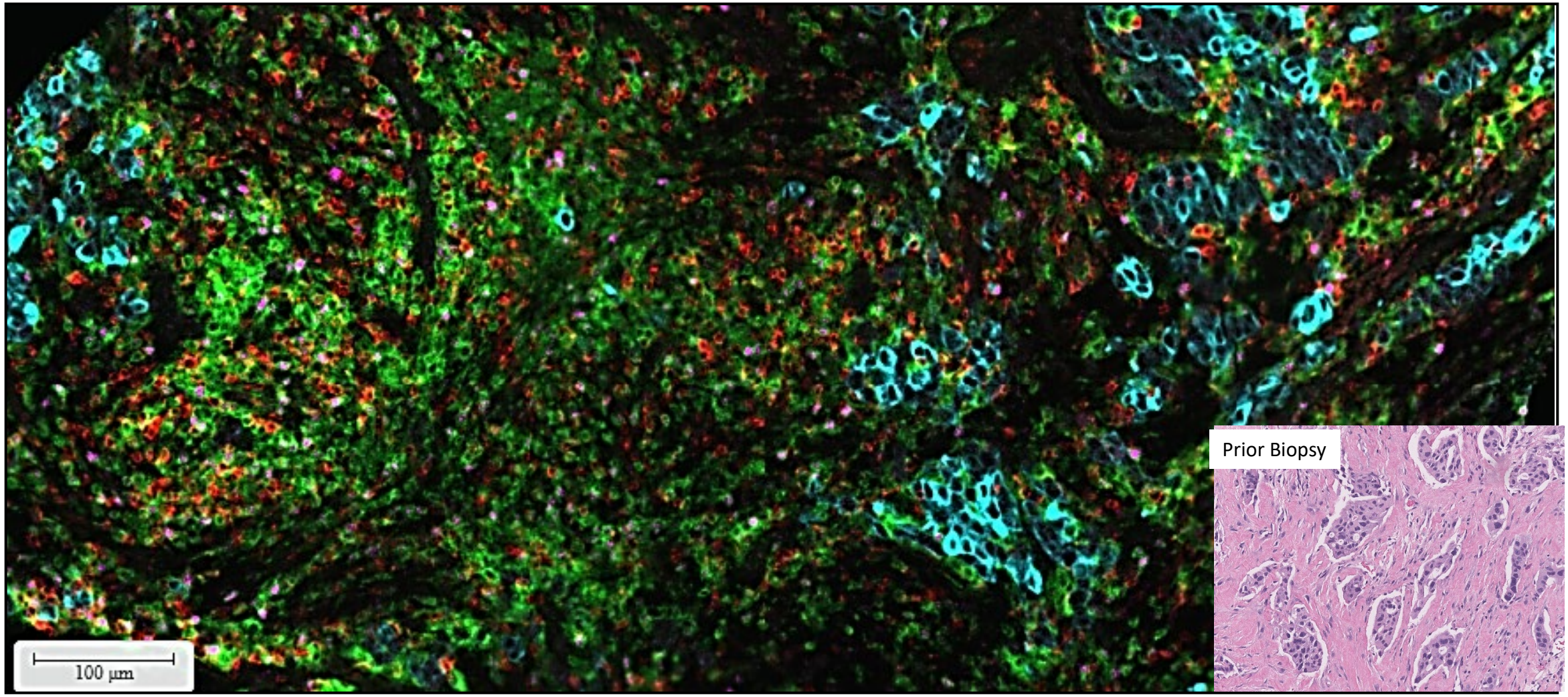


Feb. 2022, baseline

Jul. 2022

Oct. 2022

Tumor Biopsy Supports MOA of Treg Depletion

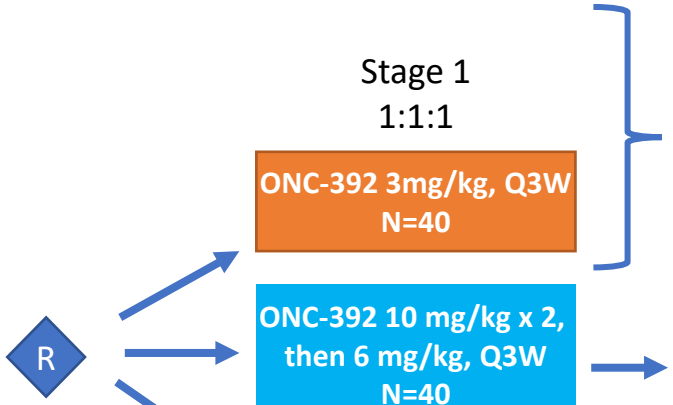


#4 post cycle 7, 3 mg/kg. Pink: Foxp3, Red: CD8, Green: CD4, Cyan: CK

ONC-392 Phase 3 Study Design: PRESERVE-003 (NCT05671510)

Seamless two stage, randomized, active controlled, multicenter Phase 3 trial

- Adult patients with NSCLC.
- Had systemic platinum-based chemotherapy, either before or in combination with Anti-PD-1/PD-L1 antibodies with at least 12 weeks or 4 cycles of regular doses of anti-PD-1/PD-L1 antibody treatment.
- Disease Progressed on Anti-PD-1/PD-L1 treatment.
- Have RECIST 1.1 measurable lesions.
- ECOG 0/1.
- Adequate organ functions.



Stage 1
1:1:1

ONC-392 3mg/kg, Q3W
N=40

ONC-392 10 mg/kg x 2, then 6 mg/kg, Q3W
N=40

Docetaxel
75 mg/m^2, Q3W
N=40

Stage 2
1:1

ONC-392
Selected dose, Q3W
N=240

Docetaxel
75 mg/m^2, Q3W
N=240

17 cycles or until toxicity, withdraw consent or no clinical benefit.
Post-PD treatment is allowed for ONC-392 arm. Treatment cross over is not allowed.

Interim analysis to decide Treatment Selection after 120 patients enrolled with minimal follow up of 70 days. DMC will review the data and make treatment dose selection based on prespecified rules.

Primary endpoints: OS
Other endpoints: PFS, ORR, DoR, DCR, BOR.

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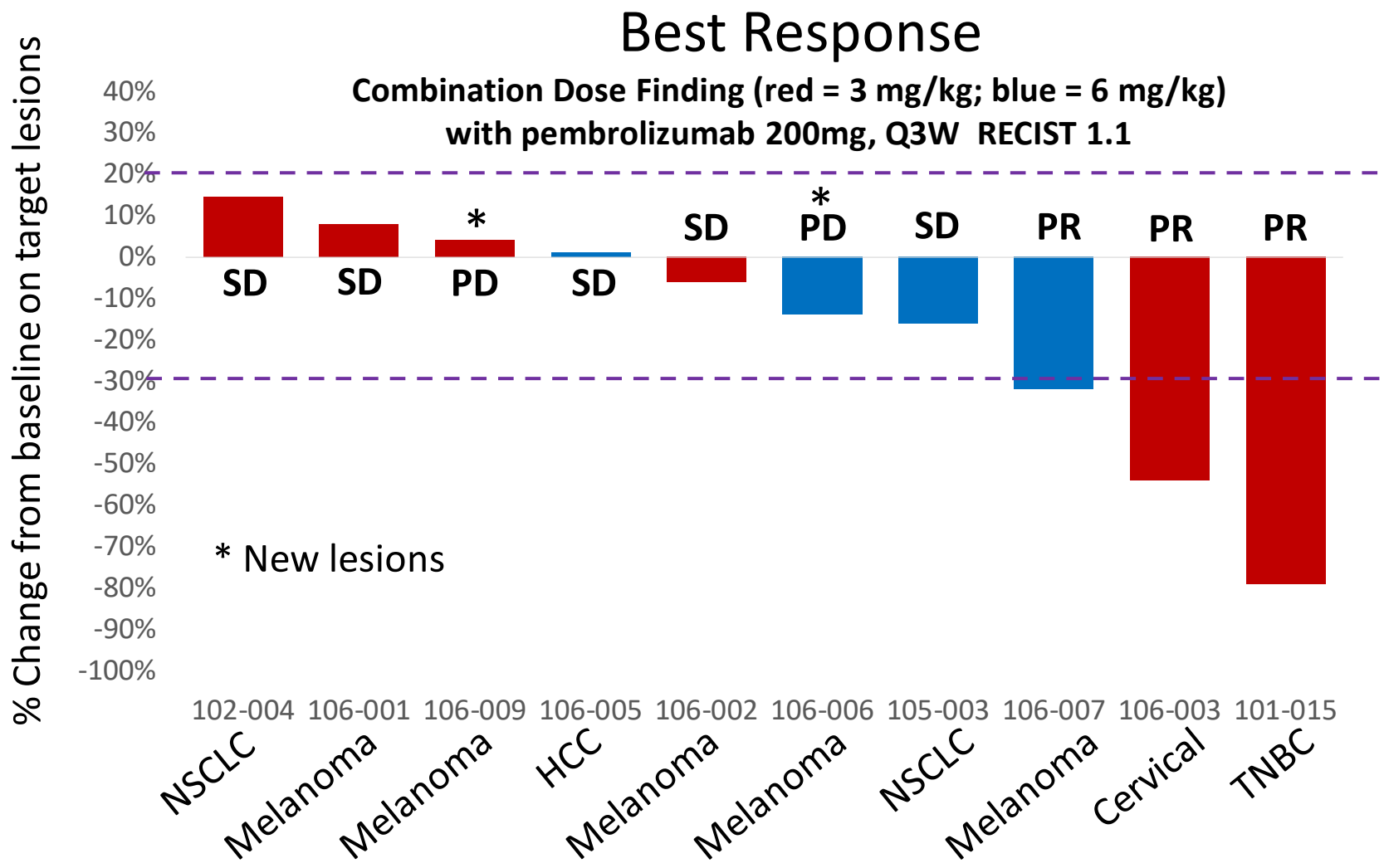
PRESERVE-001 Part B: ONC-392 + Pembrolizumab Combo Therapy Clinical Activities (NCT04140526, SITC 2022, Poster #594)



Reported at SITC 2022

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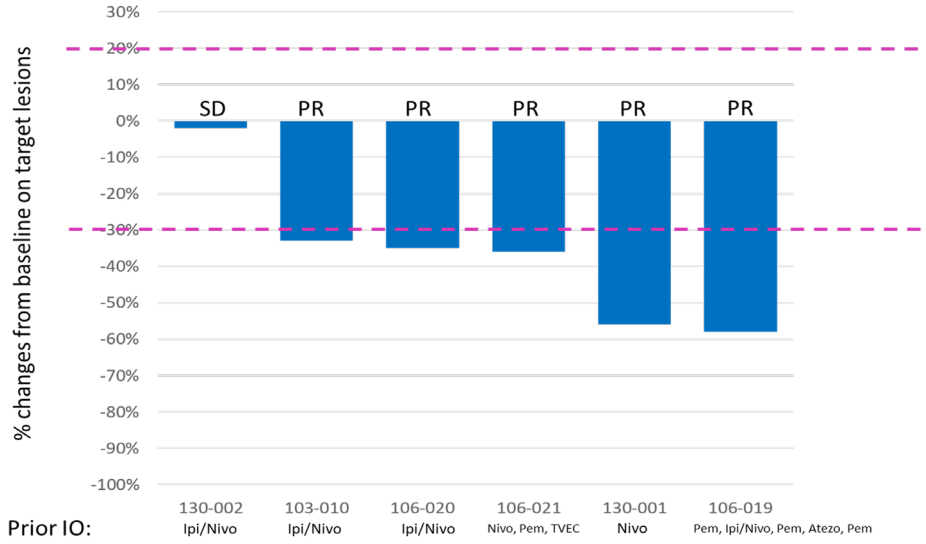
PRESERVE-001 Part C Arm G: ONC-392 + Pembrolizumab Combo Therapy in Melanoma (NCT04140526, SITC 2022, Poster #594)

IO R/R Melanoma

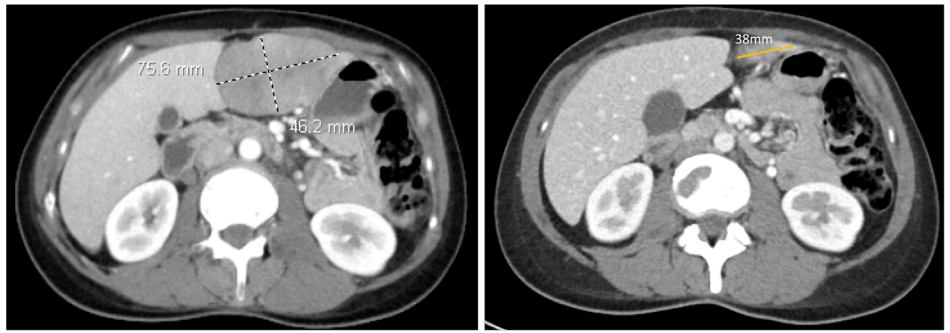
ONC-392 6 mg/kg
IV, Q3W
+
Pembrolizumab, 200 mg
IV, Q3W

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

Reported at SITC 2022

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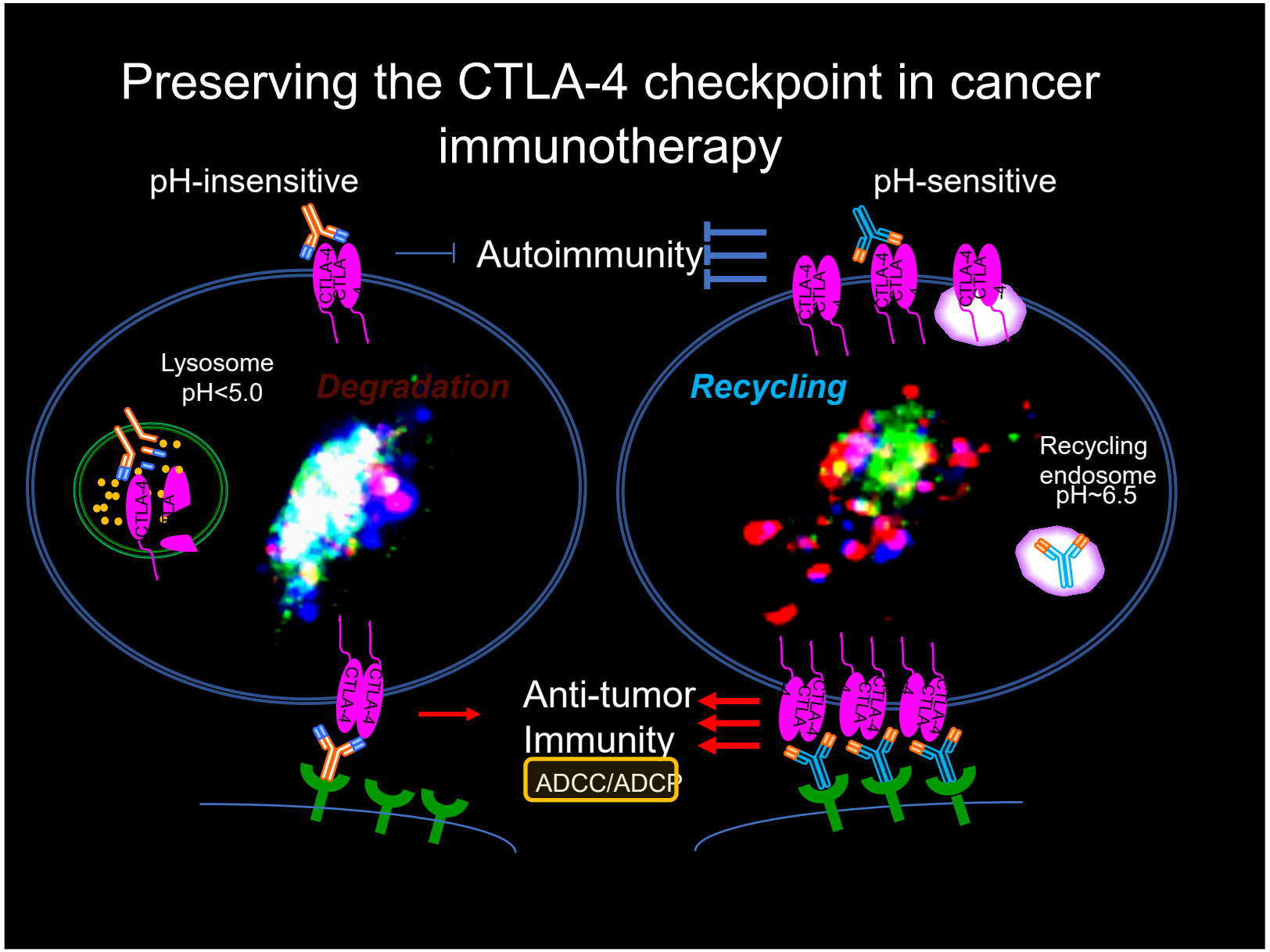

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ONC-392/BNT316 are currently jointly developed by BioNTech and OncoC4

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Clinical Sites for PRESERVE-001 Study

US Sites				Australia Sites	
101	UC Davis (CA)	121	Ocala Oncology (VA)	202	Southern Oncology Clinical Res Unit (SA, Australia)
102	GBMC (MD)	122	U of Colorado (CO)	203	Cancer Research SA (SA, Australia)
103	U of Florida (FL)	123	U of Connecticut (CT)	204	Newcastle (NSW, Australia)
104	MSKCC (NY)	124	Norton Cancer Institute (KY)		
105	Ohio State U (OH)	125, 126, 129, 130	Sarah Cannon Research Institute (4 sites)		China Sites for ONC-392 dose escalation
106	U of Utah, Huntsman CC (UT)	127	City of Hope CC (CA)		The Number 301 Hospital in Beijing
107	Atlantic Health (NJ)	128	Emory University (GA)		The Renmin Hospital affiliated with Wuhan Univ Med Sch
109	Center for Cancer and Blood Disorders (MD)	131	University of Michigan (MI)		
110	Houston Methodist CC (TX)	132	Memorial Cancer Institute (FL)		
111	Innovative Clinical Research Institute (CA)	133	AdventHealth (FL)		
114	U of Cincinnati (OH)	134	Georgetown U CC (DC)		
115	Oncology Consultants (TX)	135	Prisma Health (SC)		
117	Pennsylvania Cancer Specialist (PA)	136	Dana-Farber Cancer Institute (MA)		
118	Mass General Hospital (MA)	137	Highlands Oncology Group (AR)		
119	Nuvance Health (CT)	138	Seattle Cancer Alliance, U Wash (WA)		
120	Next Oncology/Virgina (VA)				

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