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Phase 1 trial of CA-170, a first-in-class, orally available, small molecule immune checkpoint inhibitor (ICI) dually targeting PD-L1 and VISTA, in patients with advanced solid tumors or lymphomas

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

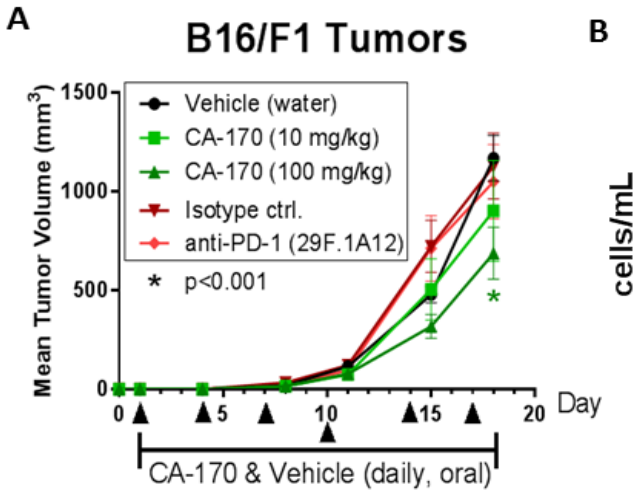
No Relationships to Disclose

CA-170 Compound Overview

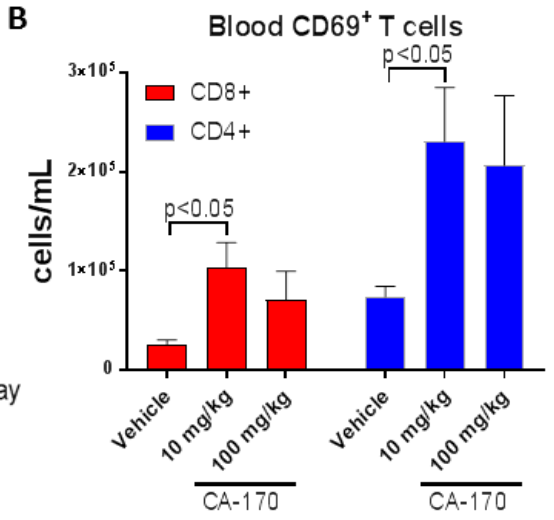
- Rationally designed, Oral small molecule
- Targets 2 separate and non-redundant immune checkpoint pathways:
  - **PD-L1** (Programmed Death Ligand 1)
  - **VISTA** (V-domain Ig-containing Suppressor of T-cell Activation)

Non-Clinical Pharmacology*

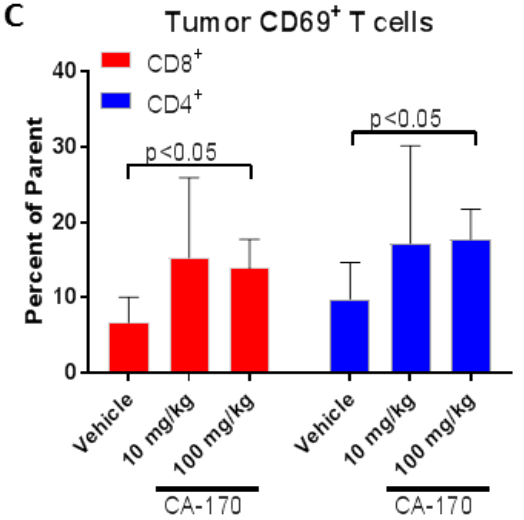
CA-170 Efficacy



Increased peripheral T cell activation



Increased tumor T cell activation

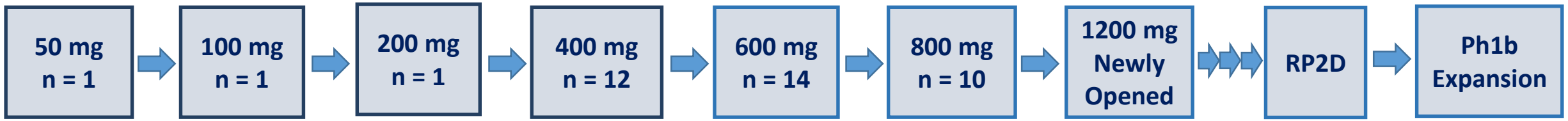


** Ref: Powderly etc, ESMO, 2017*

CA-170 Phase 1 First-in-Human Trial (CA-170-101)

Ph1a Dose Escalation Stage

Accelerated Titration Followed by 3+3 Design
Selected Dose Levels Back-Filled with Additional Patients



Objectives

- Primary: Recommended Phase 2 Dose (RP2D), Safety
- Secondary: PK, PD, anti-cancer activity

Patient Population

- Patients with advanced solid tumors or lymphoma
- Study sites in South Korea, US, Spain, UK

Treatment

- Oral, once daily, dosing in continuous 21-day cycles

Baseline Patient Characteristics

Characteristics	Overall n = 39
Male, n (%)	21 (54)
Female, n (%)	18 (46)
Age, median (range)	61 (26-86)
ECOG PS 0, n (%)	12 (31)
ECOG PS 1, n (%)	27 (69)
Prior lines median (range)	7 (0-9)

Disease Characteristics

- **Group 1**
  Immune checkpoint inhibitor (ICI) therapy naïve patients with tumor types approved for ICI
- **Group 2**
  ICI naïve patients with tumor types without ICI approval
- **Group 3**
  Patients with prior exposure to at least one line of ICI therapy

Tumor Type, n (%)	Group 1 n = 22	Group 2 n = 12	Group 3 n = 5	Total, n (%) n = 39
NSCLC	8	0	0	8 (20)
Ovarian	0	4	1	5 (13)
Hodgkin Lymphoma	2	0	0	2 (5)
NHL	0	2	0	2 (5)
SCCHN	3	0	0	3 (8)
ccRCC	3	0	0	3 (8)
Colorectal	1[a]	1[b]	1[b]	3 (8)
Melanoma	3	0	0	3 (8)
Esophageal	0	1	1	2 (5)
Breast	0	2	0	2 (5)
Other[c]	2	2	2	6 (15)

a. MSI-H CRC
b. MSS CRC
c. One each of hepatocellular carcinoma, Merkel cell carcinoma (Group 1), lacrimal duct carcinoma, pancreatic cancer (Group 2), leiomyosarcoma and anal cell carcinoma (Group 3)

Clinical Safety

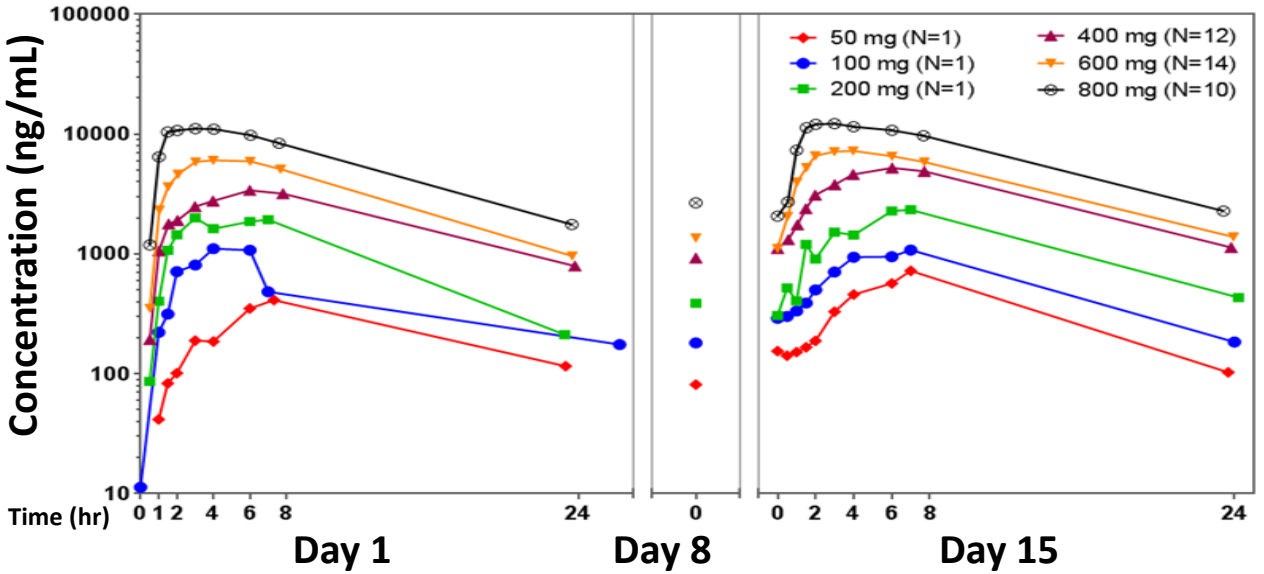
(Data cut-off: 13-Oct-2017)

- MTD and RP2D not established yet
- No DLT or irAEs reported thus far for the dose range of 50 – 800 mg
- TEAEs and TRAEs predominantly Gr 1 or 2 and self-limiting
- No study discontinuation due to a TRAE
- A total of 18 SAEs reported
  - Only 1 SAE possibly related: a confounding case - Gr3 vomiting in a pancreatic cancer patient at 800 mg

Treatment-Emergent AEs (> 10%) n = 39		
AE Term	All Grades **n (%)**	Grade ≥3 **n (%)**
Nausea	9 (23.1)	1 (2.6)
Fatigue	8 (20.5)	0
Constipation	8 (20.5)	1 (2.6)
Anemia	6 (15.4)	1 (2.6)
Vomiting	6 (15.4)	1 (2.6)
Chills	5 (12.8)	0
Pyrexia	5 (12.8)	0
Headache	5 (12.8)	0
Gastritis	5 (12.8)	0
Decreased appetite	5 (12.8)	0
Hypokalemia	4 (10.3)	1 (2.6)
Insomnia	4 (10.3)	0
Cough	4 (10.3)	0
Tumor Pain	4 (10.3)	0

Treatment-Related AEs (> 7%) n = 39		
AE Term	All Grades **n (%)**	Grade ≥3 **n (%)**
Nausea	6 (15.4)	1 (2.6)
Fatigue	5 (12.8)	0
Chills	4 (10.3)	0
Pyrexia	4 (10.3)	0
Hyperhidrosis	3 (7.7)	0
Night Sweats	3 (7.7)	0
Pruritus	3 (7.7)	0
Weight Decreased	3 (7.7)	0
Bone pain	3 (7.7)	0
Headache	3 (7.7)	0

Clinical Pharmacokinetics



- Systemic exposures (Cmax & AUC) generally increased proportionally with increasing doses from 50 to 800 mg
- Inter-patient variability is within the expected range, given the potential impacting variables of oral administration, QD dosing and a highly heterogeneous patient population enrolled thus far

Single Dose PK Parameters		Human						Mouse	
		50 mg (N=1)	100 mg (N=1)	200 mg (N=1)	400 mg (N=12)	600 mg (N=13)*	800 mg (N=10)	10 mg/kg/day	100 mg/kg/day
					Mean ± SD	Mean ± SD	Mean ± SD		
Tmax	hr	7.3	4.0	3.0	5.8 ± 2.4	4.4 ± 2.0	3.3 ±1.7	0.5	0.5
Cmax	ng/ml (uM)	412 (1.14)	1107 (3.07)	1998 (5.55)	3730 ± 946 (10.4 ±2.63)	7422 ± 3201 (20.6 ±8.88)	13125 ± 6992 (36.4 ±19.4)	890 (2.46)	31821 (88.3)
AUCall	hr*ng/ml	5681	11475	27488	50573±13781	87476±39647	152217±85349	3170	136696
T1/2	hr	8.7	9.5	5.3	8.3 ± 2.8	7.3 ± 3.1	7.7 ± 3.0	4.57	3.3

*One pt had no sample collected at 24 hr post-dose, so was included in the conc.-time curve but excluded from the statistical analysis.

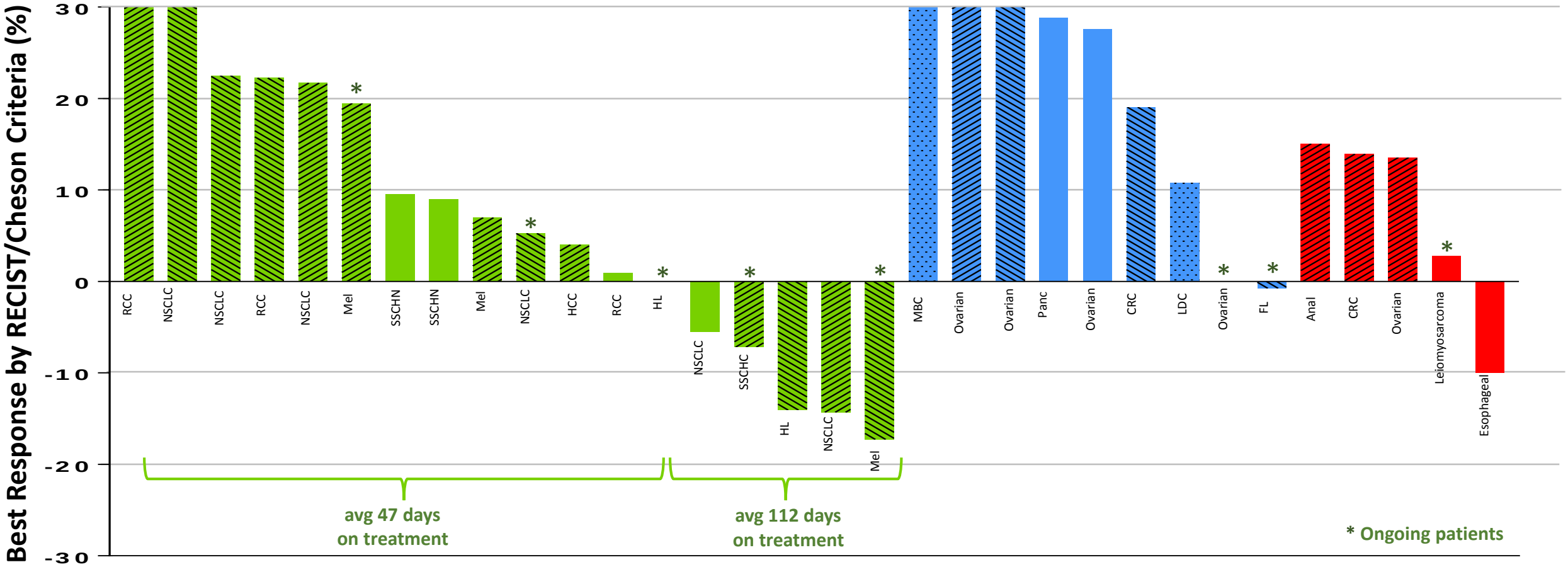
Anti-Tumor Activity Correlated with Tumor Types

≤200 400 600 800 mg

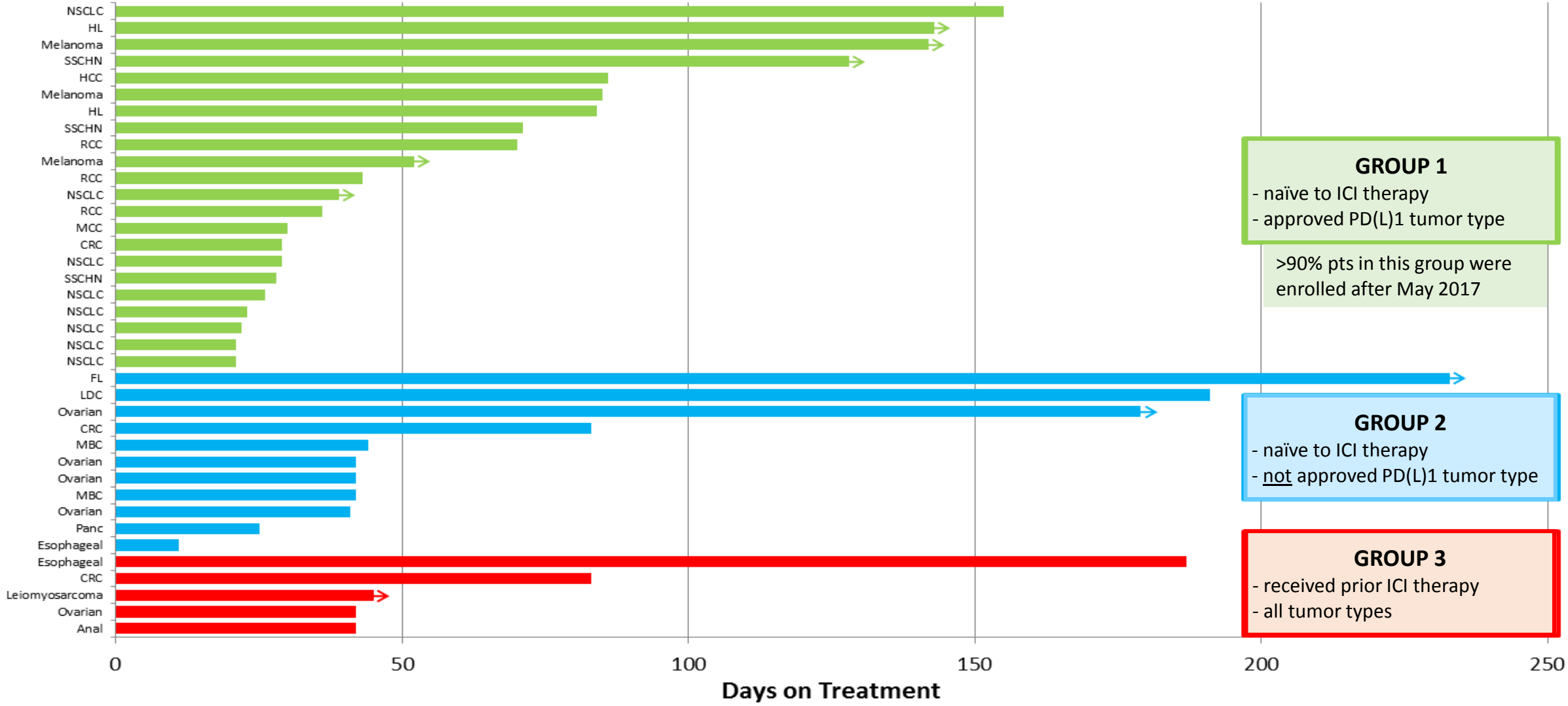
GROUP 1
- naïve to ICI therapy
- approved PD(L)1 tumor type

GROUP 2
- naïve to ICI therapy
- not approved PD(L)1 tumor type

GROUP 3
- received prior ICI therapy
- all tumor types



Anti-Tumor Activity (II) Duration of Treatment in Dose Escalation

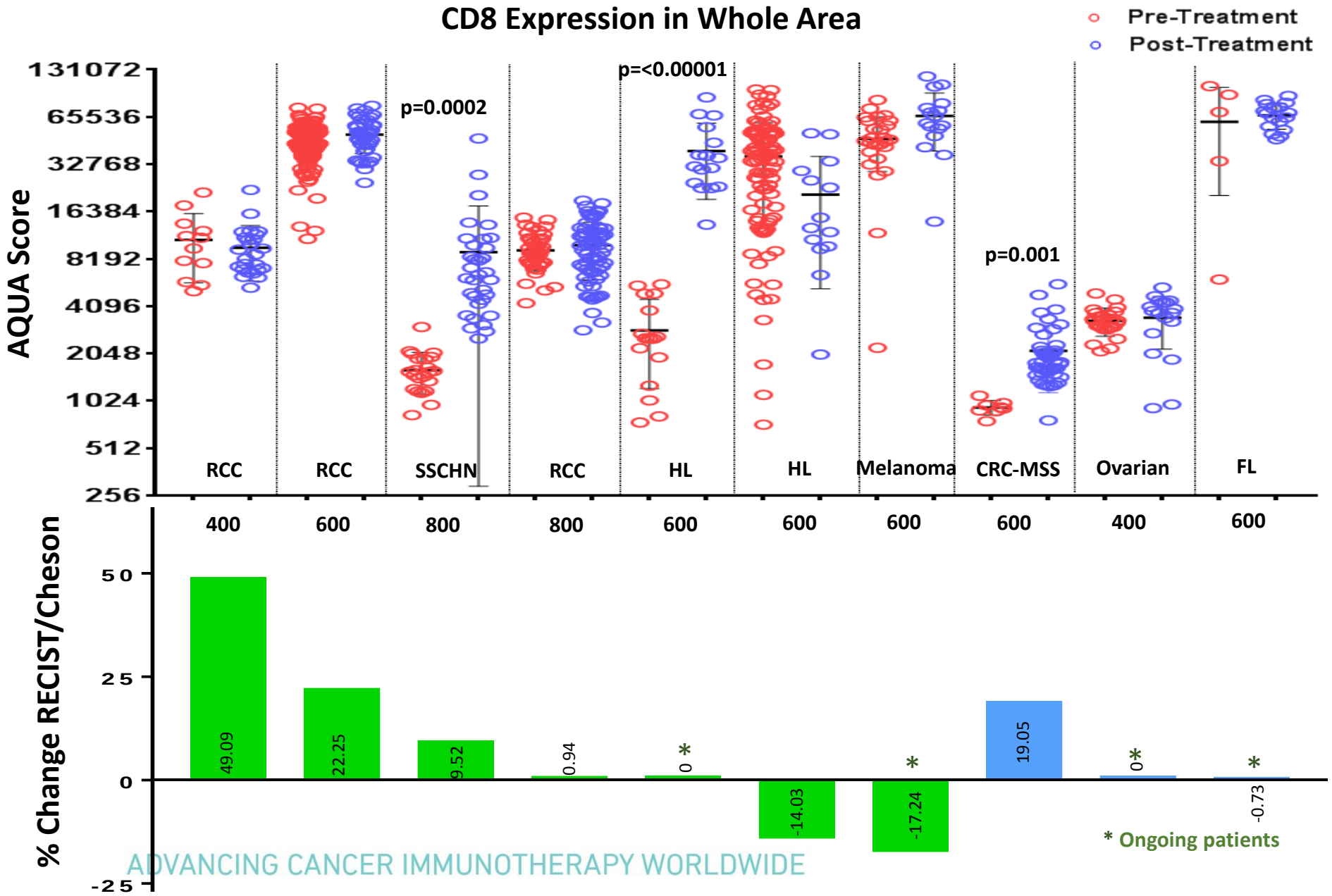


Tumor Pharmacodynamics

Each circle represents the automated quantification (AQUA) score of a single view field of the tumor biopsy for each patient.

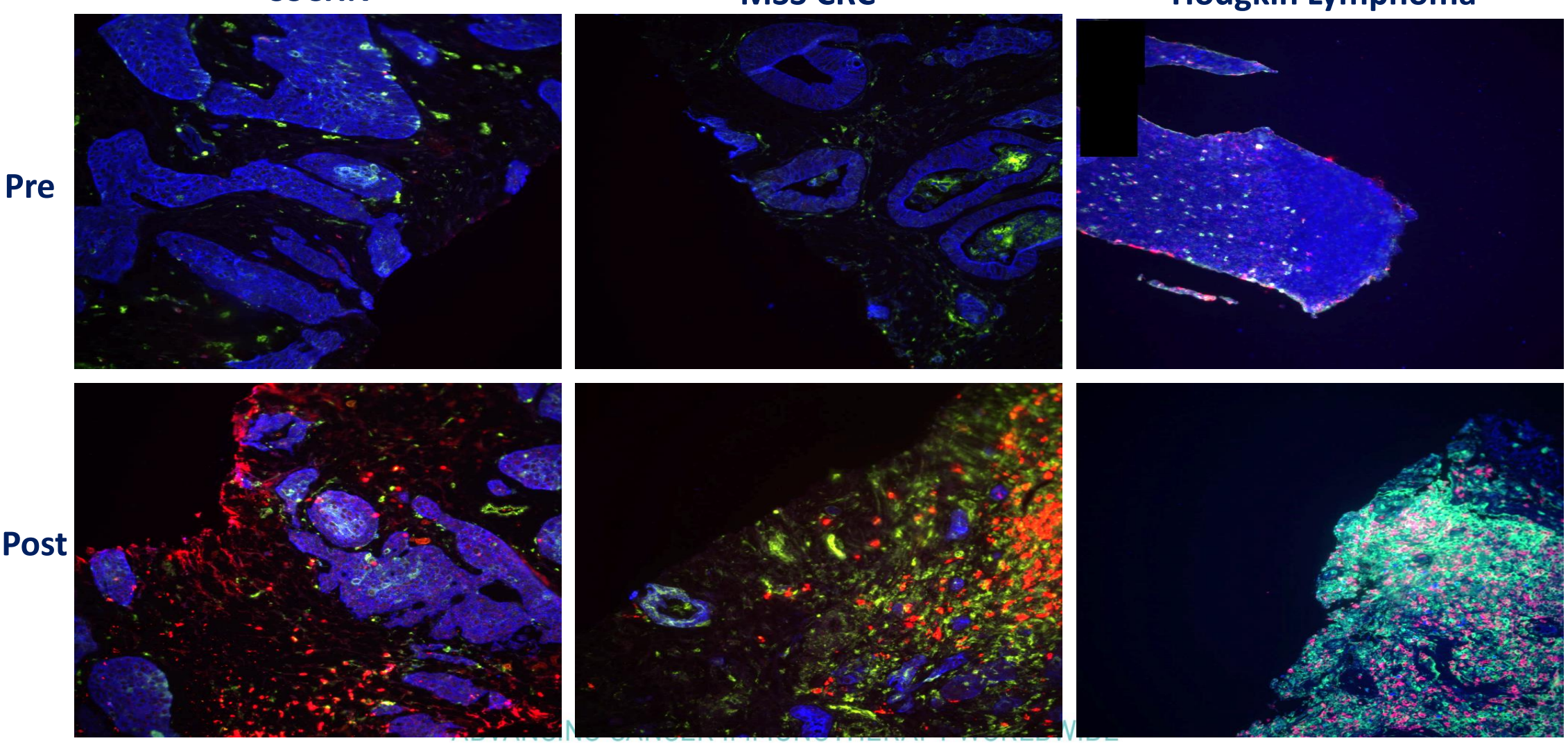
GROUP 1
- naïve to ICI therapy
- approved PD(L)1 tumor type

GROUP 2
- naïve to ICI therapy
- not approved PD(L)1 tumor type



Tumor Pharmacodynamics (II)

Red=CD8; Green=VISTA
Yellow=CD8+VISTA
Blue=cytokeratin



Conclusion and Future Directions

- The emerging clinical data suggest that CA-170 has an acceptable safety profile with approximately dose proportional PK profile and preliminary evidence of immune modulation in tumor.
- MTD and RP2D have not yet been established.
- Data from a small number of patients shows preliminary signs of anti-tumor activity, including tumor regressions less than 30% per RECIST and prolonged stable disease.
- These clinical data warrant the continued clinical development of CA-170. Dose escalation is ongoing. Expansion cohorts in selected indications are planned.