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Phase 1 Study Using Mogamulizumab (KW-0761) to Deplete Regulatory T Cells in Combination With Checkpoint Inhibitors Durvalumab (MEDI4736) or Tremelimumab in Patients With Advanced Solid Tumors

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Presenter Disclosure Information

Dmitriy Zamarin, MD, PhD

The following relationships exist related to this presentation:

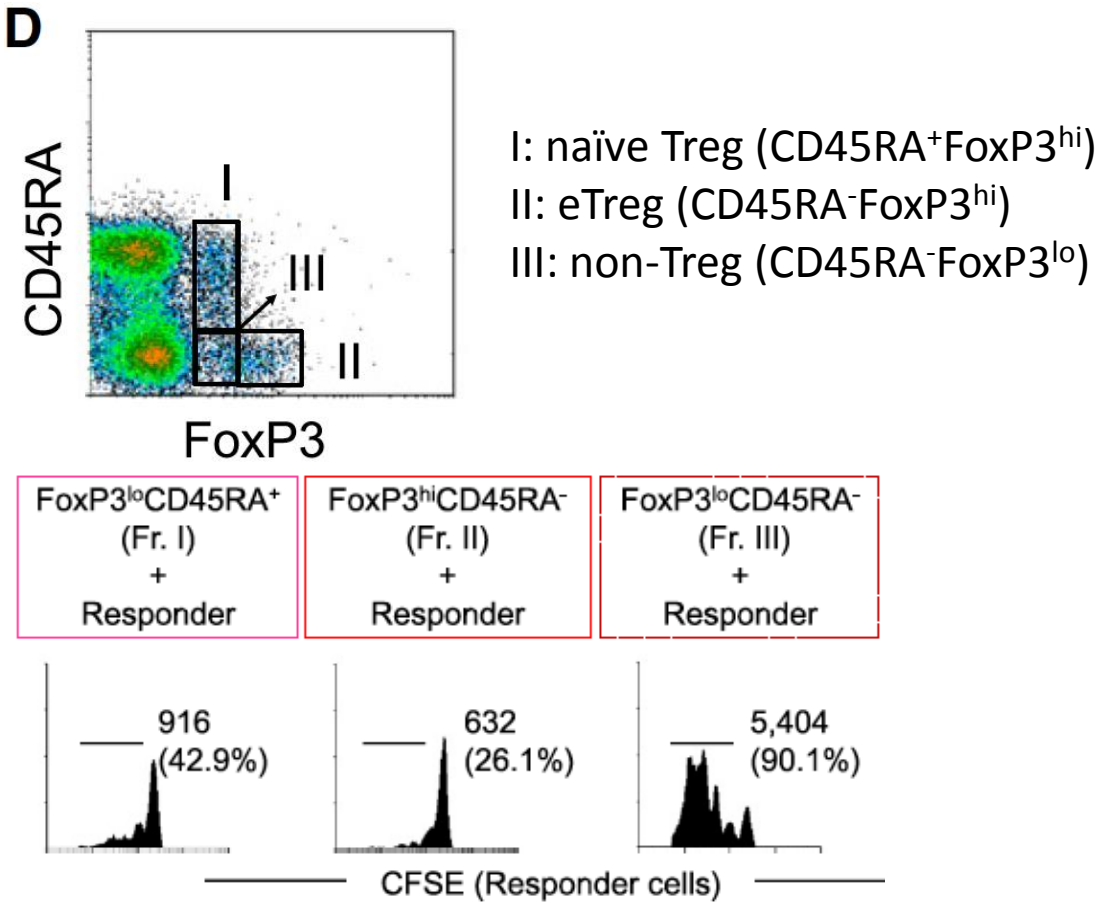
No relationships related to this presentation.

Background

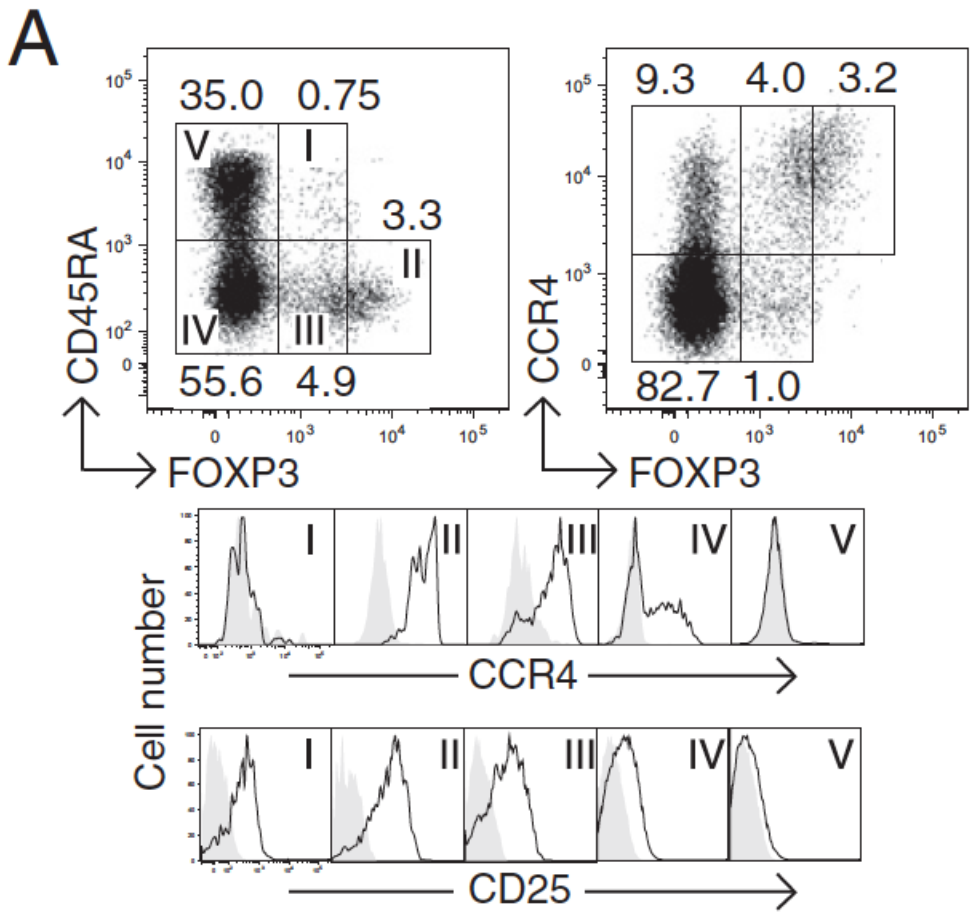
- Antibodies targeting CTLA-4 and PD-1/PD-L1 immune checkpoints have demonstrated clinical benefit in several cancer types, unfortunately response rates have been limited to minority of patients
- Elevated proportions of regulatory T cells (Tregs) among tumor-infiltrating lymphocytes have been seen in various types of cancer such as breast, ovarian, hepatocellular, lung, gastric, and cervical cancers and are an important mechanism of immune suppression in tumors[1]
- CC chemokine receptor type 4 (CCR4) is a lymphocyte receptor expressed on a limited number of cells, including normal human Tregs and on T-cell malignancies[2]
- Mogamulizumab, a first-in-class defucosylated humanized anti-CCR4 monoclonal antibody, is FDA-approved for adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome, which are both subtypes of cutaneous T-cell lymphoma and has been demonstrated to deplete Tregs from peripheral blood in patients with solid tumors[2-5]
- Combining mogamulizumab with approved and investigational immunotherapies that activate anti-tumor immunity may improve clinical outcomes in patients with advanced malignancies

1. Shang B, et al. Sci Rep. 2015;5:15179. 2. Ogura M, et al. J Clin Oncol. 2014;32:1157-63. 3. Ishida T, et al. J Clin Oncol. 2012;30:837-42. 4. Poteligeo Product Information. Bedminster, NJ: Kyowa Kirin, Inc.; August 2018. 5. Kurose K, et al. Clin Cancer Res. 2015;21(19): 4327-4336.

CCR4 identifies suppressive effector Tregs (eTregs)



I: naïve Treg (CD45RA^{+}FoxP3^{hi})
II: eTreg (CD45RA^{-}FoxP3^{hi})
III: non-Treg (CD45RA^{-}FoxP3^{lo})



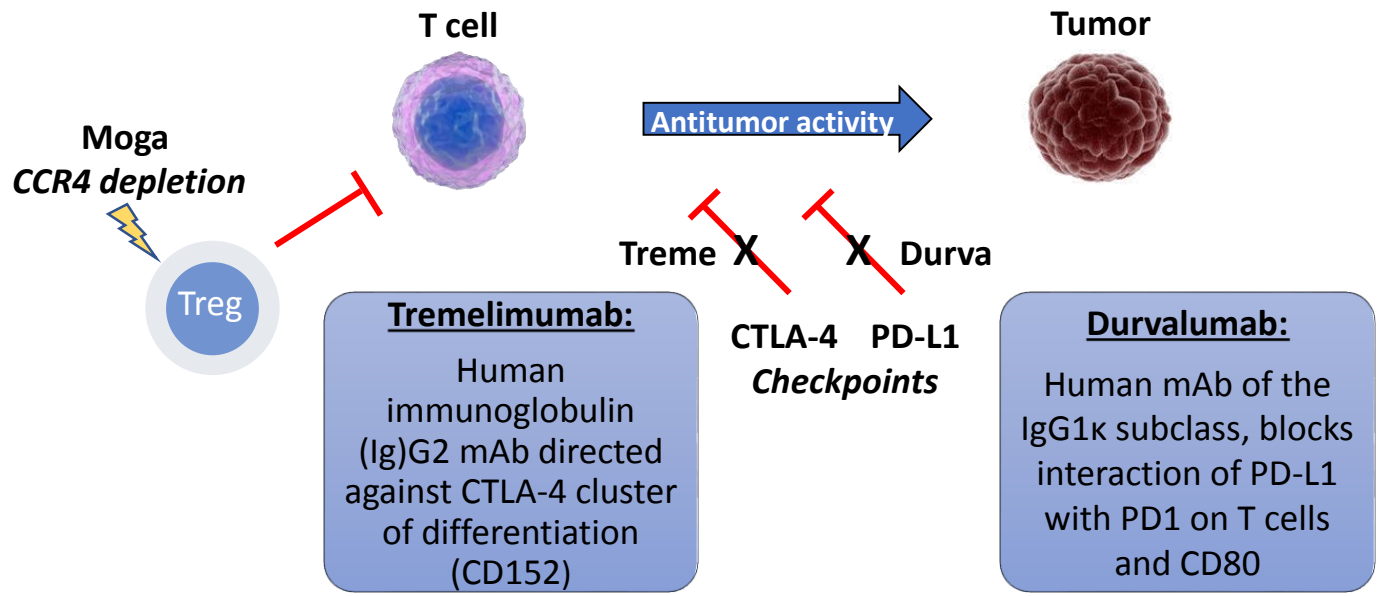
Miyara et al., Immunity 2009: Sugiyama et al., PNAS 2013.

Rationale of Combined Therapy

Combination therapy of mogamulizumab with durvalumab or tremelimumab may produce synergistic effects in the treatment of patients with solid tumors

Mogamulizumab:

Targets CCR4 and effectively removes circulating Tregs as a single agent



Tremelimumab:

Human immunoglobulin (Ig)G2 mAb directed against CTLA-4 cluster of differentiation (CD152)

Durvalumab:

Human mAb of the IgG1κ subclass, blocks interaction of PD-L1 with PD1 on T cells and CD80

1. Creelan BC. Cancer Control. 2014;21:80-9.
2. Sugiyama D, et al. Proc Natl Acad Sci U S A. 2013;110:17945-50.

Study Objectives

- Primary objective: to assess safety and tolerability of combined treatment with mogamulizumab + durvalumab or mogamulizumab + tremelimumab in patients with advanced solid tumors
- Secondary objective: to evaluate antitumor effect of combined treatment with mogamulizumab + durvalumab or mogamulizumab + tremelimumab in patients with advanced solid tumors

Study Design

Two-part, multicenter, Phase 1, open-label, dose-escalation, cohort-expansion study

Part 1: Dose escalation[a] (3+3 design)

Locally advanced or metastatic solid tumors

Treatment A

- 3.0 mg/kg Durva 0.3 mg/kg Moga (Co1A, n=4)
- 3.0 mg/kg Durva 1.0 mg/kg Moga (Co2A, n=3)
- 10.0 mg/kg Durva 1.0 mg/kg Moga (Co3A, n=7)
- 10.0 mg/kg Durva 3.0 mg/kg Moga (Co4A, n=7)

Treatment B

- 3.0 mg/kg Treme 0.3 mg/kg Moga (Co1B, n=3)
- 3.0 mg/kg Treme 1.0 mg/kg Moga (Co2B, n=3)
- 10.0 mg/kg Treme 1.0 mg/kg Moga (Co3B, n=7)
- 10.0 mg/kg Treme 3.0 mg/kg Moga (Co4B, n=6)

Part 2: Cohort Expansion (locally advanced or metastatic non-small cell lung, pancreatic[b], or head and neck cancers)

Treatment A (Co5A)

- 10.0 mg/kg Durva 1.0 mg/kg Moga (n= 12)

Treatment B (Co5B)

- 10.0 mg/kg Treme 1.0 mg/kg Moga (n=13)

Co=cohort; Durva=durvalumab IV every 2 weeks[c]; Moga=mogamulizumab IV every week in 1 cycle, every 2 weeks in >2 cycles[c]; Treme=tremelimumab IV every 4 weeks for first 6 doses, then every 12 weeks[c].

[a]No dose limiting toxicities observed in dose escalation; maximum tolerated dose not established.

[b]Planned expansion cohorts in tumor types other than pancreatic cancer were not opened.

[c]Treated until progression or unacceptable toxicity.

Summary of Safety and Efficacy Analysis Populations

	Part 1 Dose Escalation All Cancer Types (All Cohorts) (N=40)		Part 2 Cohort Expansion Pancreatic Cancer (Cohort 5) (N=25)		Parts 1 and 2 Subjects with Same Dose Group (Cohort 3/Expansion Cohort 5) All Cancer Types (N=39)	
	Treatment A[a] (Moga+Durva)	Treatment B[b] (Moga+Treme)	Treatment A[c] (Moga+Durva)	Treatment B[d] (Moga+Treme)	Treatment A[e] (Moga+Durva)	Treatment B[f] (Moga+Treme)
Subjects Enrolled, n (%)	21 (100)	19 (100)	12 (100)	13 (100)	19 (100)	20 (100)
Safety Analysis Set, n (%)	21 (100)	19 (100)	12 (100)	12 (92.3)[h]	19 (100)	19 (95.0)[h]
Efficacy Analysis Set, n (%)	21 (100)	18 (94.7)[g]	12 (100)	12 (92.3)[i]	19 (100)	19 (95.0)[i]

[a]Mogamulizumab + Durvalumab, all dose cohorts; [b]Mogamulizumab + Tremelimumab, all dose cohorts; [c]Mogamulizumab 1 mg/kg + Durvalumab 10 mg/kg; [d]Mogamulizumab 1 mg/kg + Tremelimumab 10 mg/kg; [e]Cohort 3A + expansion Cohort 5A (Mogamulizumab 1 mg/kg + Durvalumab 10 mg/kg); [f]Cohort 3B + expansion Cohort 5B (Mogamulizumab 1 mg/kg + Tremelimumab 10 mg/kg); [g]Colorectal tumor subject excluded from efficacy analysis set: did not have postbaseline assessment without clinical PD/death; [h]Pancreatic tumor subject excluded from safety analysis set: did not receive any study drug; [i]Pancreatic tumor subject excluded from efficacy analysis set: did not receive any study drug.

Baseline Patient Characteristics

	Treatment A (Moga + Durva)	Treatment B (Moga + Treme)
Dose Escalation, All Cancer Types (All Cohorts)		
Total	21	19
Gender, male, n (%)	10 (48)	11 (58)
Gender, female, n (%)	11 (52)	8 (42)
Median age, years	63	57
ECOG PS[a] 0, n (%)	7 (33)	9 (47)
ECOG PS[a] 1, n (%)	14 (67)	10 (53)
Dose Expansion, Pancreatic Cancer		
Total	12	12
Gender, male, n (%)	6 (50)	7 (58)
Gender, female, n (%)	6 (50)	5 (42)
Median age, years	68	64.5
ECOG PS[a] 0, n (%)	5 (42)	3 (25)
ECOG PS[a] 1, n (%)	7 (58)	9 (75)

Primary Tumor Type, Dose Escalation (All Cohorts)	Treatment A (Moga + Durva)	Treatment B (Moga + Treme)
Anal	0	1
Breast	1	0
Colorectal	5	5
Head and neck	1	3
NSCLC, non-squamous	1	1
NSCLC, squamous	1	0
Ovarian	2	1
Pancreatic	1	2
Prostate	1	1
Renal cell	1	3
Sarcoma	5	0
Other	2	2

- Treatment A: all subjects had ≥1 prior therapy, and largest proportion (26.3%) had 3 prior therapies
- Treatment B: all subjects had ≥1 prior therapy, and largest proportion (31.6%) had 4 prior therapies

[a]Baseline is defined as the last measurement obtained prior to the first dose of the study drug.
ECOG PS=Eastern Cooperative Oncology Group performance status; NSCLC=non-small cell lung cancer.

Any Drug-Related Treatment-Emergent Adverse Events (TEAEs) Reported by ≥3 Subjects or ≥3 Grade 3 in Any Cycle

Cancer Type and TEAEs	Treatment A (Moga + Durva)		Treatment B (Moga + Treme)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
All Cancer Types, n (%)[a]	N=19	N=19	N=19	N=19
Rash maculo-papular	7 (36.8)	4 (21.1)	5 (26.3)	3 (15.8)
Fatigue	6 (31.6)	1 (5.3)	3 (15.8)	0
Pruritis	5 (26.3)	4 (21.1)	3 (15.8)	2 (10.5)
Infusion-related reactions	4 (21.1)	0	7 (36.8)	0
Diarrhea	4 (21.1)	0	4 (21.1)	0
Hypothyroidism	3 (15.8)	0	0	0
Stomatitis	1 (5.3)	1 (5.3)	4 (21.1)	0
Rash	1 (5.3)	0	3 (15.8)	1 (5.3)
Colitis	1 (5.3)	3 (15.8)	3 (15.8)	2 (10.5)
Decreased lymphocytes	1 (5.3)	0	1 (5.3)	1 (5.3)
Transaminases increased	1 (5.3)	0	1 (5.3)	1 (5.3)
Autoimmune hepatitis	1 (5.3)	0	1 (5.3)	1 (5.3)
Gastritis	1 (5.3)	1 (5.3)	0	0
Blood creatine phosphokinase increased	1 (5.3)	1 (5.3)	0	0
Hyperglycemia	1 (5.3)	1 (5.3)	0	0
Vomiting	0	0	1 (5.3)	1 (5.3)
Abnormal liver function test	0	0	1 (5.3)	1 (5.3)
Hypertension	0	0	1 (5.3)	1 (5.3)

TEAEs ≥Grade 3 and SAEs

	Treatment A (Moga + Durva)	Treatment B (Moga + Treme)
All Cancer Types, n (%)		
Drug-related TEAEs ≥Grade 3	6 (28.6)	9 (47.4)
Drug-related SAEs	4 (19.0)	5 (26.3)
Pancreatic Cancer, n (%)		
Drug-related TEAEs ≥Grade 3	4 (33.3)	4 (33.3)
Drug-related SAEs	3 (25.0)	1 (8.3)

TEAEs=treatment-emergent adverse events; SAEs=serious adverse events.

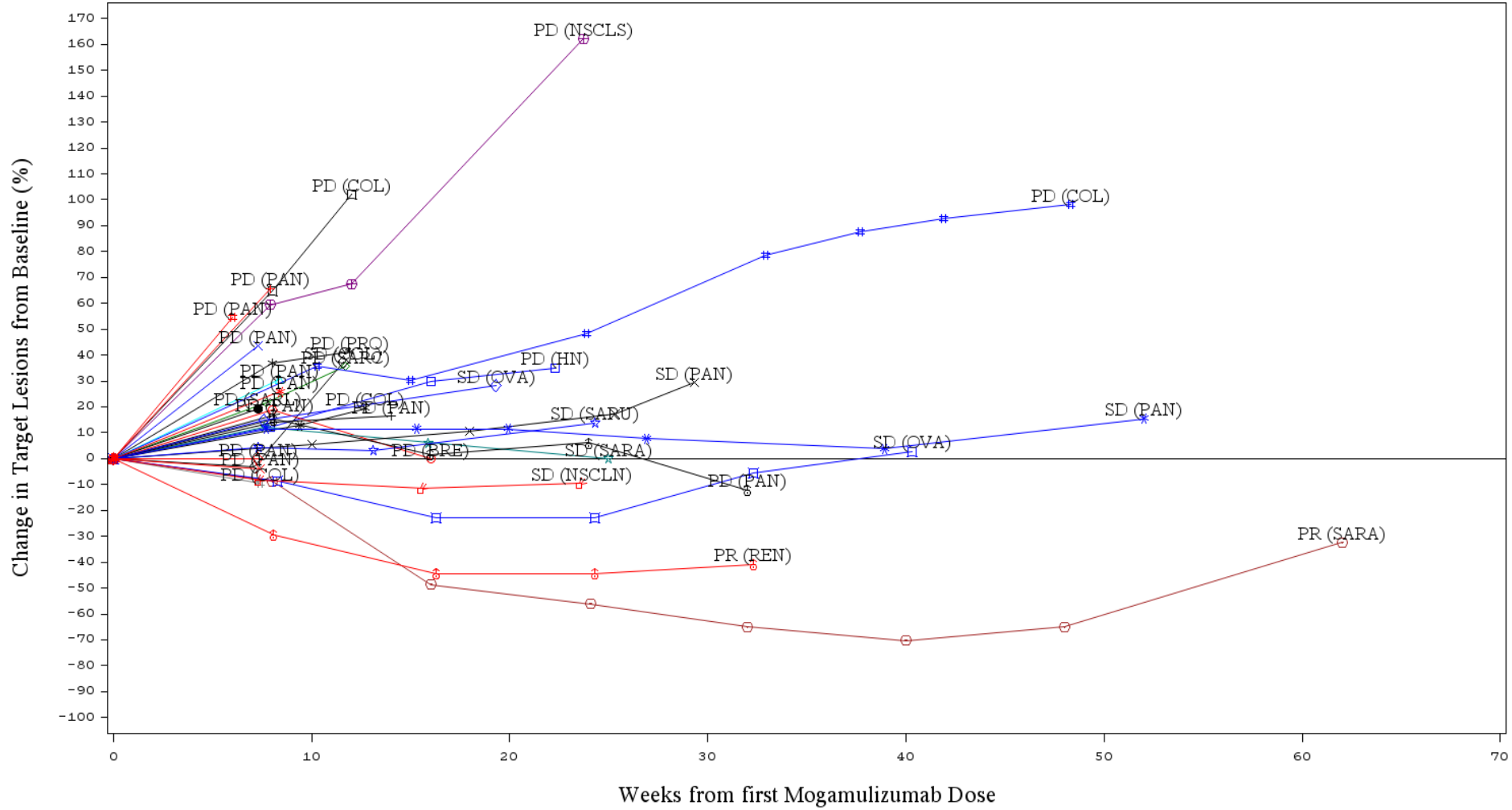
Results: Summary of Overall Response, Efficacy Analysis Set

	Treatment A Moga 1 mg/kg + Durva 10 mg/kg		Treatment B Moga 1 mg/kg + Treme 10 mg/kg	
By RECIST v1.1[a]	All Cancer Types (N=7)	Pancreatic (N=12)	All Cancer Types (N=7)	Pancreatic (N=12)
Number of patients with CR or PR n (%) [95% CI]	1 (5.3) [0.1, 26.0]	0 [0.0, 26.5]	1 (5.3) [0.1, 26.0]	0 [0.0, 26.5]
Complete response (CR)	0	0	0	0
Partial response (PR)	1[b] (5.3)	0	1[c] (5.3)	0
Stable disease (SD)	5 (26.3)	2 (16.7)	7 (36.8)	3 (25.0)
Progressive disease (PD)	12 (63.2)	10 (83.3)	9 (47.4)	7 (58.3)
Inevaluable (NE)	1 (5.3)	0	2 (10.5)	2 (16.7)
Progression-free survival, months Median[d] (95% CI)	1.9 (1.7, 4.4)	1.8 (1.4, 1.9)	1.9 (1.4, 3.7)	1.8 (1.1, 3.7)
Overall survival, months Median (95% CI)	8.9 (4.3, 18.4)	8.5 (1.9, 14.2)	4.4 (2.5, 13.4)	3.8 (1.9, 7.8)

- Due to lack of additional efficacy of Moga+Treme and Moga+Durva compared to historical individual monotherapy, the study was ended early without expansion into other tumor types

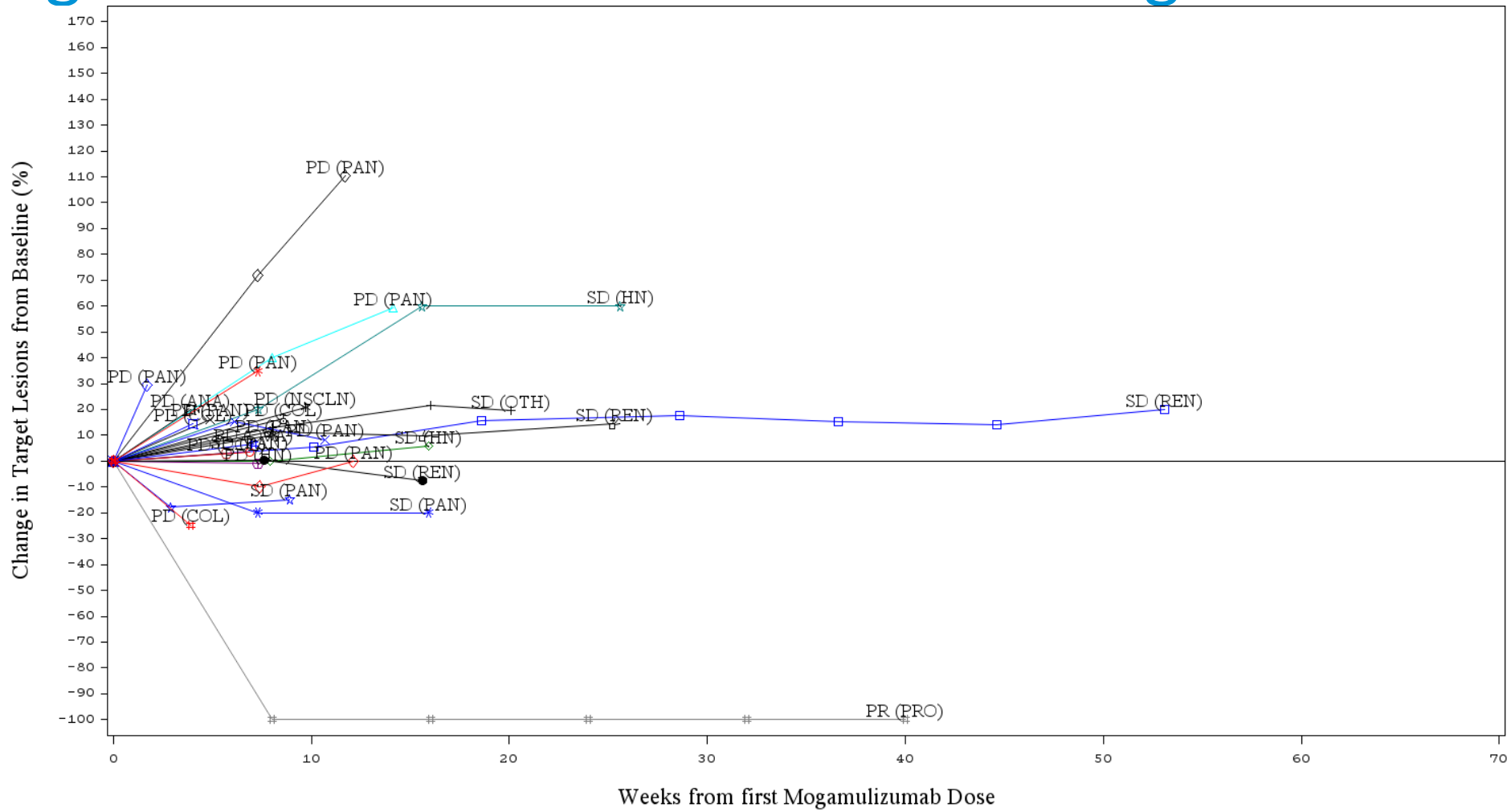
[a]Overall response results did not differ significantly when using irRECIST criteria; [b]Median duration of response was 10.6 months and the median time to response was 3.68 months; [c]Median duration of response was 3.7 months and the median time to response was 1.84; [d]The median time, along with its two-sided 95% CI, was estimated using the Kaplan-Meier method.

Change in Tumor Burden Over Time: Moga+Durva



Tumor types (in parentheses): ANA=anal; BRE=breast; COL=colorectal; HN=head and neck; NSCLN=non-small cell lung - non-squamous; NSCLS=non-small cell lung – squamous; OTH=other; OVA=ovarian; PAN=pancreatic; PRO=prostate; REN=renal cell; SARA=sarcoma: alveolar soft part; SARC=sarcoma: chondrosarcoma; SARL=sarcoma: leiomyosarcoma; SARU=sarcoma: uterine carcinosarcoma.

Change in Tumor Burden Over Time: Moga+Treme



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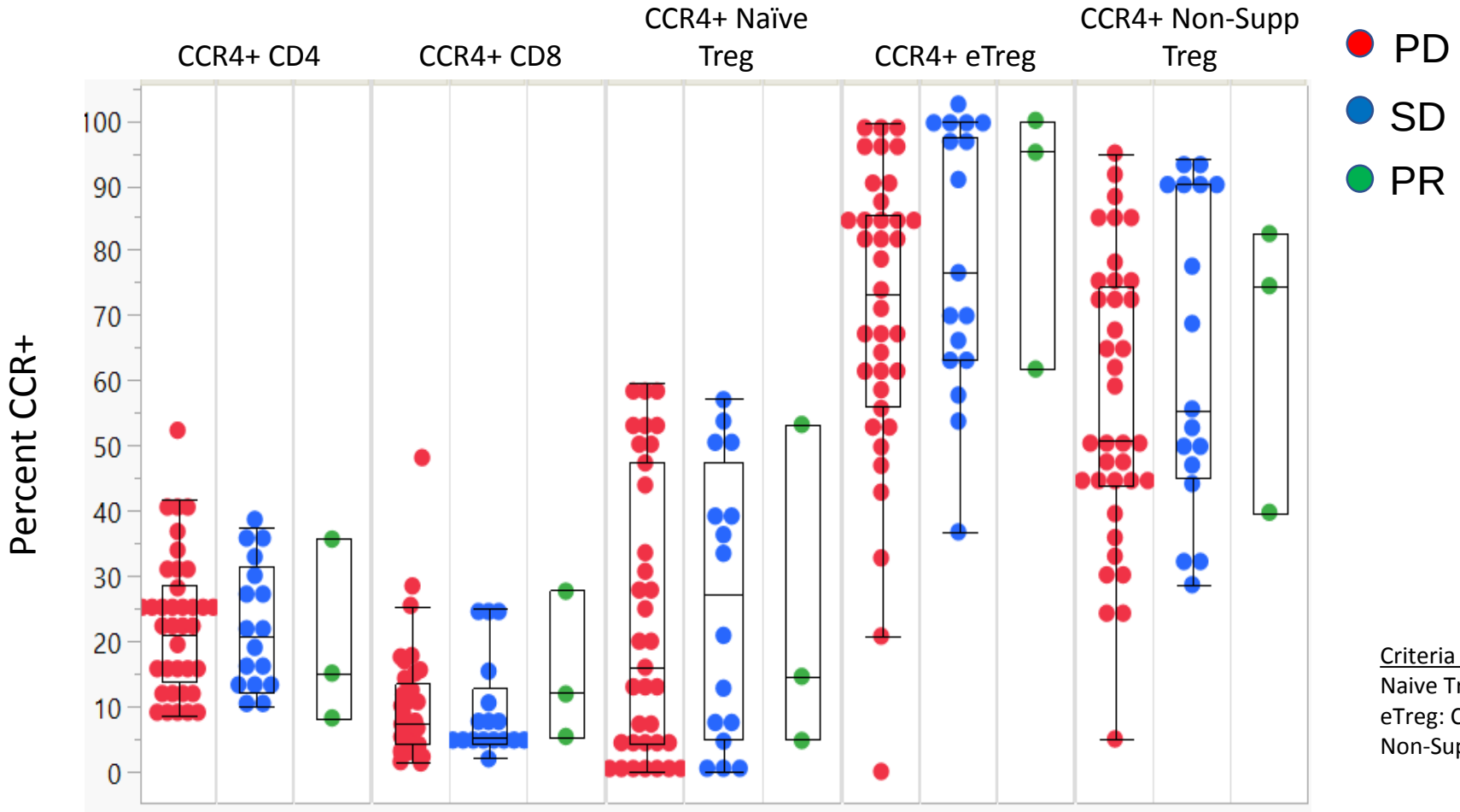
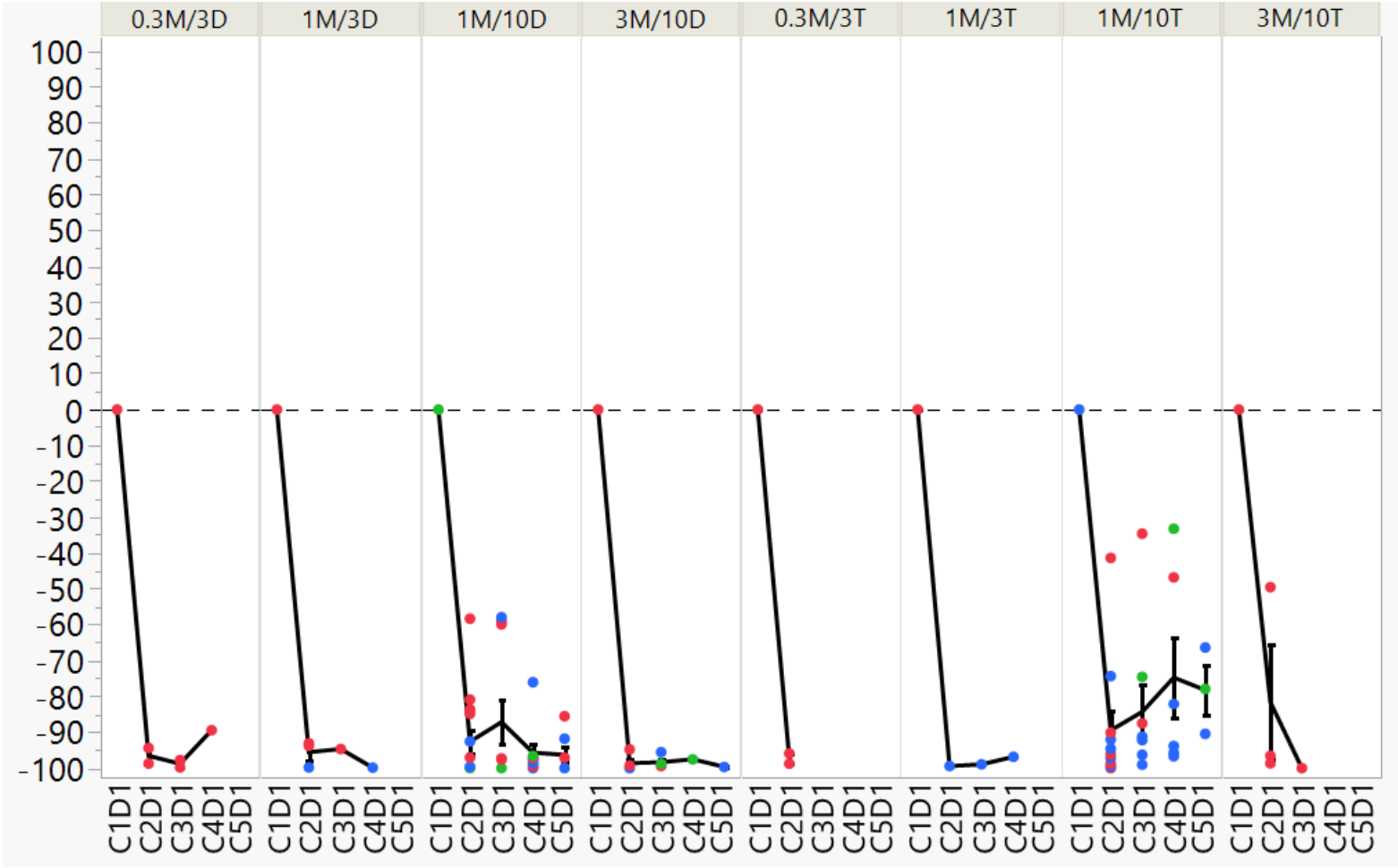
No Apparent Relationship of Clinical Response With Baseline Expression of CCR4 on T Cell Subsets



Criteria for Naïve and Non-Supp Tregs
Naive Treg: CD4+CD45RA+FoxP3lo
eTreg: CD4+CD45RA-FoxP3hi
Non-Supp Treg: CD4+CD45RA-FoxP3lo

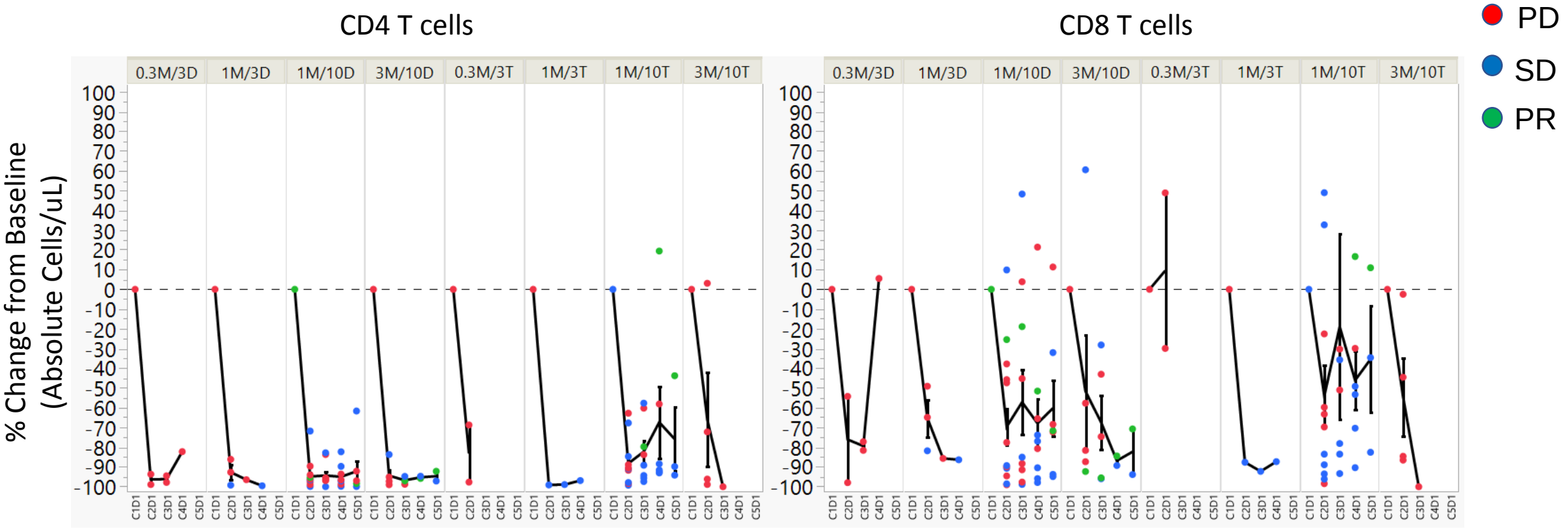
Moga With Durva or Treme Reduces Peripheral Blood CCR4+ Effector Tregs (eTregs) Cells



PD
SD
PR

0.3M/3D	0.3 mg/kg Mogamulizumab & 3 mg/kg Durvalumab
1M/3D	1 mg/kg Mogamulizumab & 3 mg/kg Durvalumab
1M/10D	1 mg/kg Mogamulizumab & 10 mg/kg Durvalumab
3M/10D	3 mg/kg Mogamulizumab & 10 mg/kg Durvalumab
0.3M/3T	0.3 mg/kg Mogamulizumab & 3 mg/kg Tremelimumab
1M/3T	1 mg/kg Mogamulizumab & 3 mg/kg Tremelimumab
1M/10T	1 mg/kg Mogamulizumab & 10 mg/kg Tremelimumab
3M/10T	3 mg/kg Mogamulizumab & 10 mg/kg Tremelimumab

Moga With Durva or Treme Reduces Peripheral Blood CCR4+ CD4 and CD8 T Cells



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3M/10D	3 mg/kg Mogamulizumab & 10 mg/kg Durvalumab
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1M/10T	1 mg/kg Mogamulizumab & 10 mg/kg Tremelimumab
3M/10T	3 mg/kg Mogamulizumab & 10 mg/kg Tremelimumab

Lessons and Take Home Messages

- Combining Moga with either Durva or Treme in solid tumors was tolerable with observed AEs being manageable and generally mild to moderate
  - No differences in the safety profiles of Moga, Durva, or Treme combinations compared with historic monotherapy with the individual agents
- Moga showed pharmacologic activity by reducing the number of peripheral blood CCR4+ eTregs, with either Durva or Treme
  - Other CCR4+ cell types were also depleted
- There was no enhancement of efficacy beyond what was anticipated from the individual monotherapy with Durva or Treme, and no patients with pancreatic cancer responded

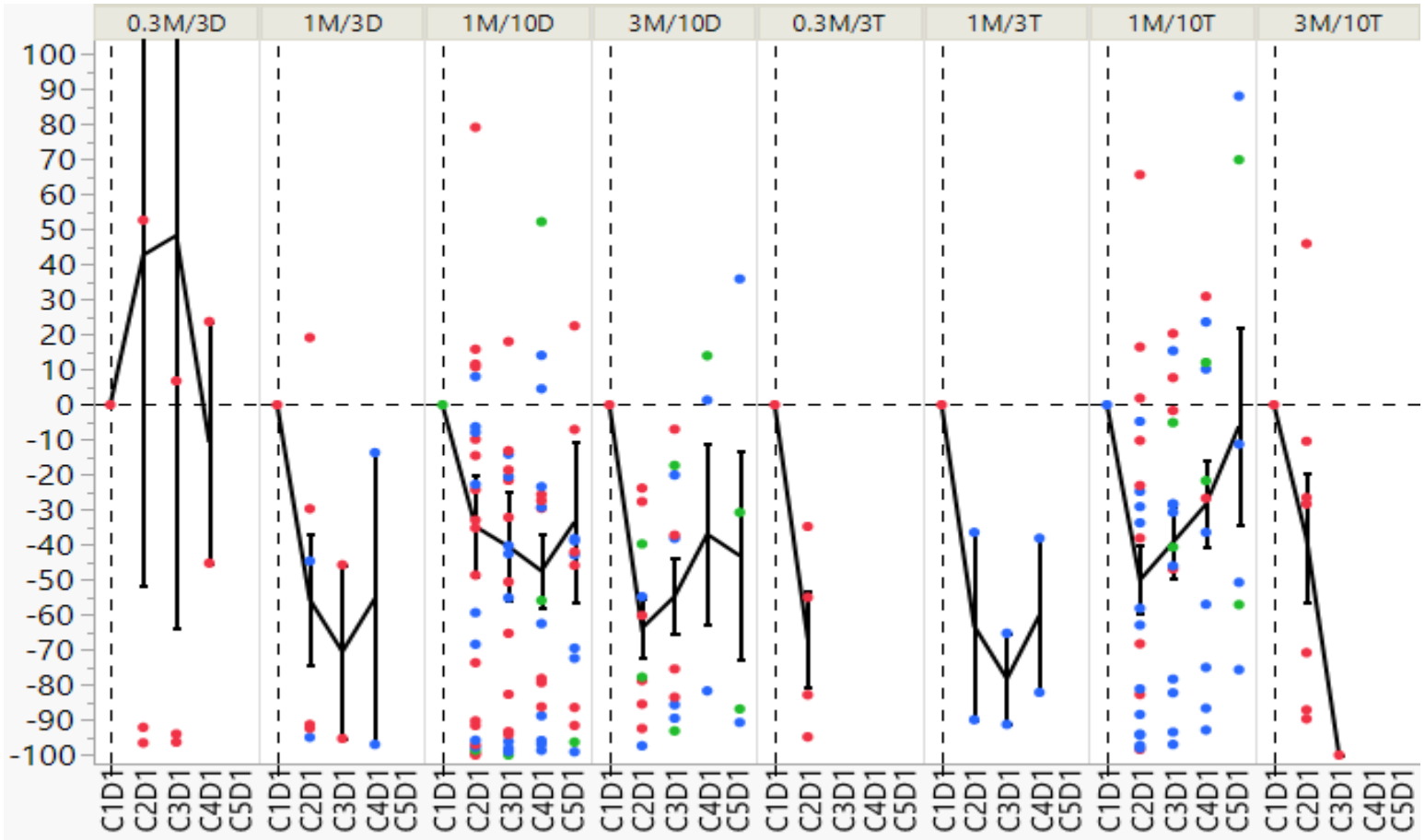
Thank You

We would like to extend a special thank you to the clinical trial investigators, members of the Kyowa Kirin translational science team, and the patients and their families.

Any Drug-Related Treatment-Emergent Adverse Events (TEAEs) Reported by ≥3 Subjects or ≥3 Grade 3 in Any Cycle

Cancer Type and TEAEs	Treatment A (Moga + Durva)		Treatment B (Moga + Treme)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Pancreatic Cancer, n (%)	N=12	N=12	N=12	N=12
Rash maculo-papular	5 (41.7)	3 (25.0)	3 (25.0)	1 (8.3)
Fatigue	5 (41.7)	1 (8.3)	1 (8.3)	0
Infusion-related reactions	4 (33.3)	0	6 (50.0)	1 (8.3)
Pruritis	3 (25.0)	0	2 (16.7)	1 (8.3)
Colitis	1 (8.3)	1 (8.3)	2 (16.7)	1 (8.3)
Decreased lymphocytes	1 (8.3)	0	1 (8.3)	1 (8.3)
Blood creatine phosphokinase increased	1 (8.3)	1 (8.3)	0	0
Hyperglycemia	1 (8.3)	1 (8.3)	0	0
Vomiting	0	0	1 (8.3)	1 (8.3)
Hypertension	0	0	1 (8.3)	1 (8.3)

Mogamulizumab With Durva or Treme Reduces Peripheral Blood Total Effector Tregs (eTregs) Cells



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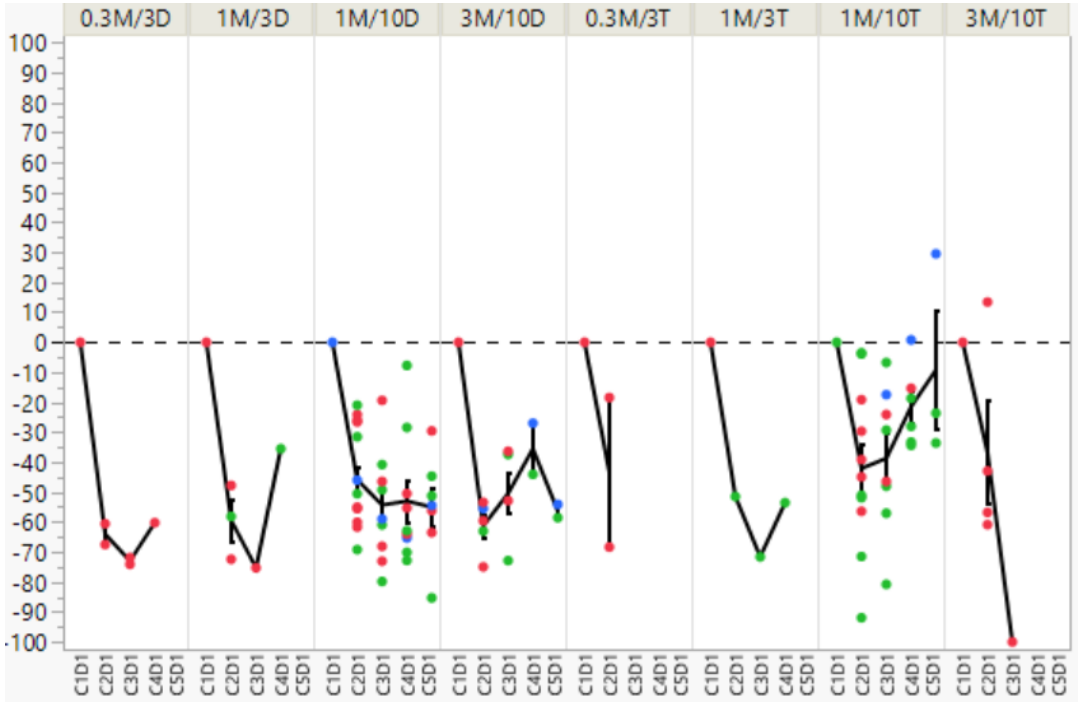
Mogamulizumab With Durva or Treme Reduces Peripheral Blood Total CD4 and CD8 T Cells

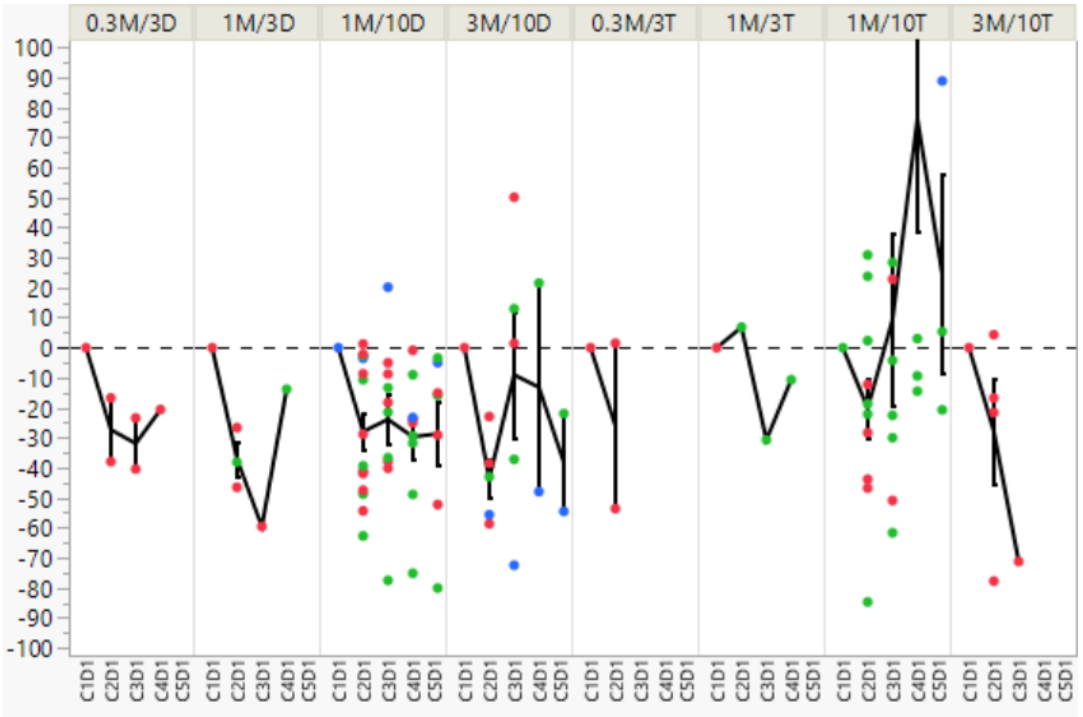
CD4 T cells

CD8 T cells

PD
SD
PR

% Change From Baseline (Absolute Cells/uL)





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