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First-in-Human Phase 1 Dose Escalation and Expansion of a Novel Combination, Anti–CSF-1 Receptor (cabiralizumab) Plus Anti–PD-1 (nivolumab), in Patients With Advanced Solid Tumors

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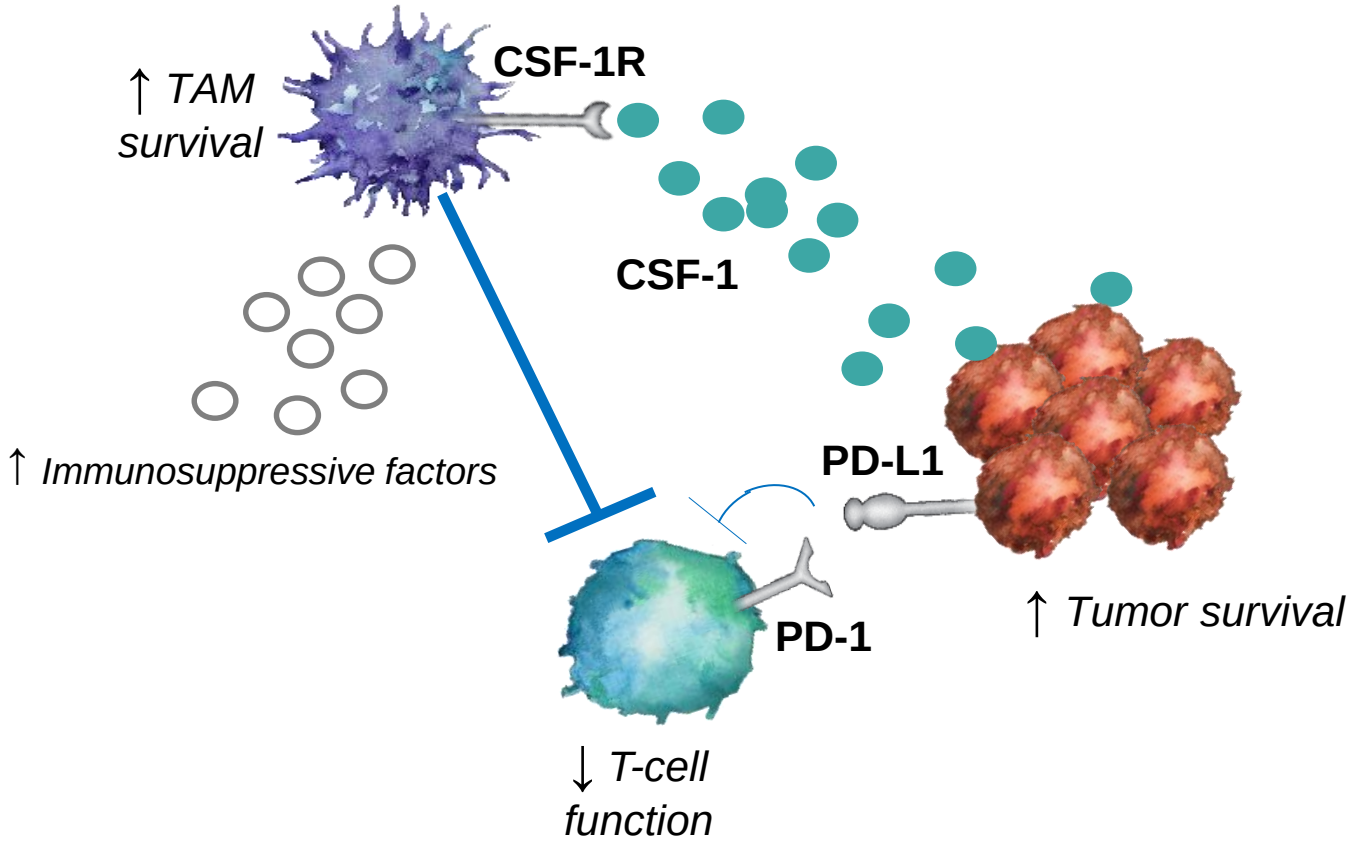
Presenter Disclosures

- Dr Wainberg has no relationships related to this presentation to disclose
  - Outside the scope of this work, he has received consulting fees from FivePrime, Merck, Novartis, and Genentech

There will be discussion about the use of products for non–FDA-approved indications in this presentation

Rationale for Cabiralizumab in Combination With Nivolumab

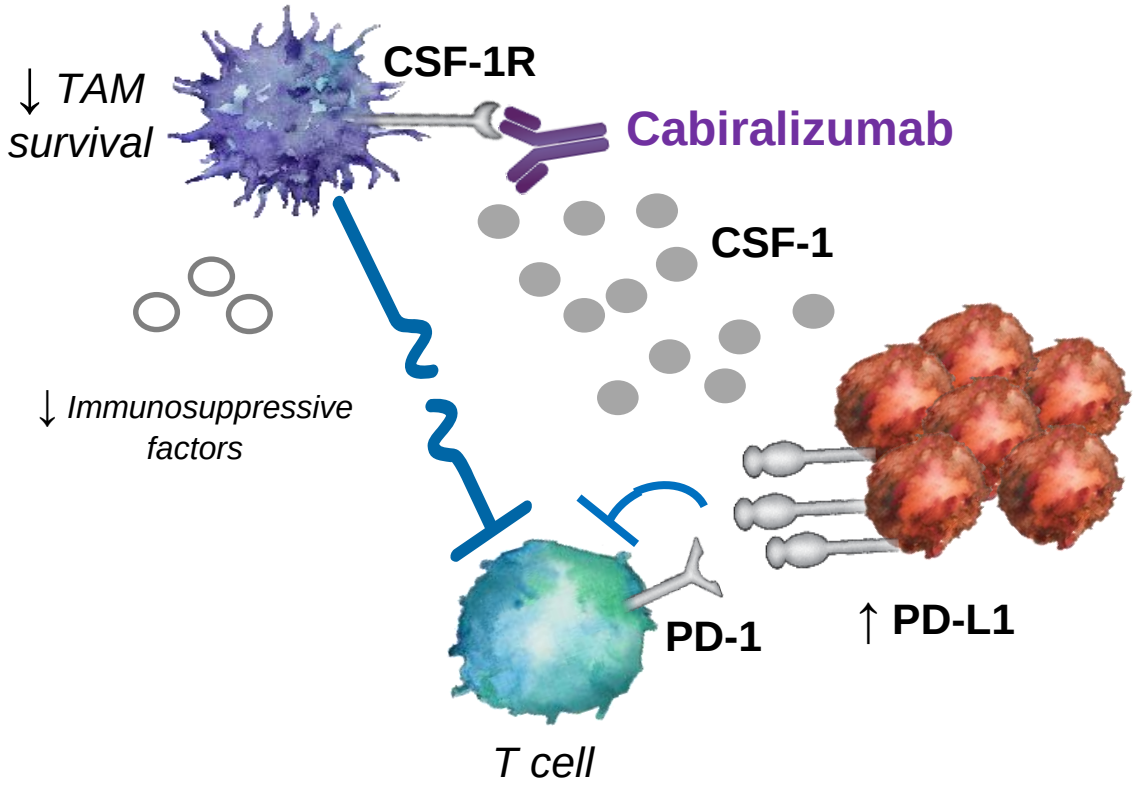


- TAMs inhibit antitumor T-cell activity in the tumor microenvironment[1,2]
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis[3-5]
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]

CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; PD-1 = programmed death-1

1. Ries CH, et al. *Cancer Cell* 2014;25:846–859. 2. Cannarile M, et al. *J ImmunoTher Cancer* 2017;5:53. 3. Hu H, et al. *Tumour Biol* 2016;37:8657–8664. 4. Kurahara H, et al. *J Surg Res* 2011;167:e211–e219. 5. Goswami KK, et al. *Cell Immunol* 2017;316:1–10.

Rationale for Cabiralizumab in Combination With Nivolumab



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- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R[6] and depletes TAMs

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CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; IgG = immunoglobulin G, mAb = monoclonal antibody; PD-1 = programmed death-1

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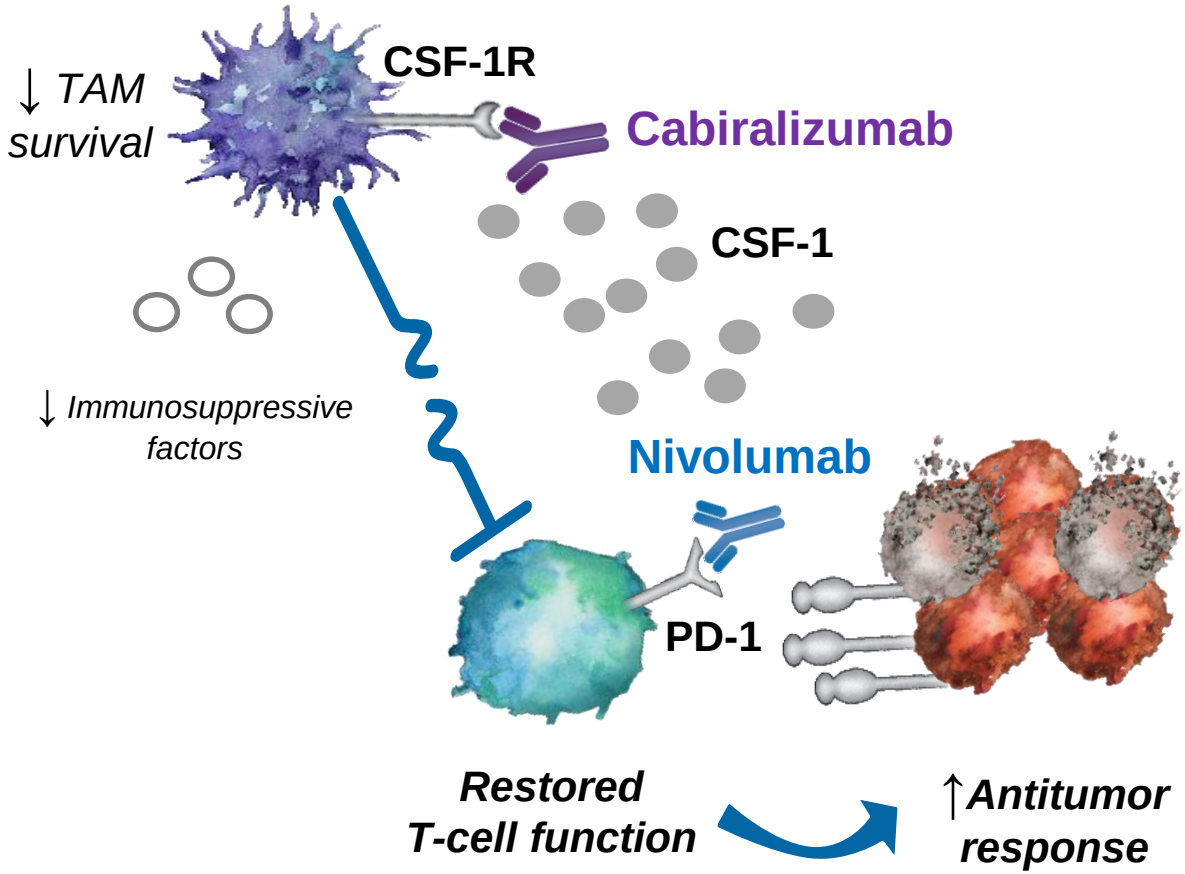
Rationale for Cabiralizumab in Combination With Nivolumab



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  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]
- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R[6] and depletes TAMs
- Preclinical data suggest that CSF-1R inhibition synergizes with PD-1 blockade to enhance antitumor activity[7]

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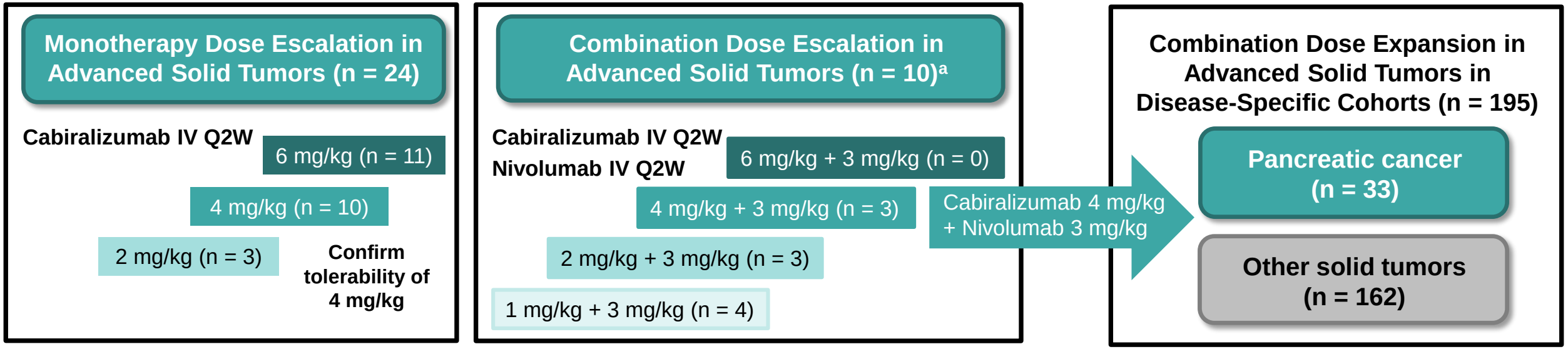
FPA008-003

First-in-Human Phase 1a/1b Dose-Escalation Study of Cabiralizumab ± Nivolumab in Advanced Solid Tumors



August 1, 2017, cutoff

Primary objectives: safety/tolerability, dose-limiting toxicities

Secondary objectives: immunogenicity, PK, pharmacodynamics, preliminary antitumor activity[b]

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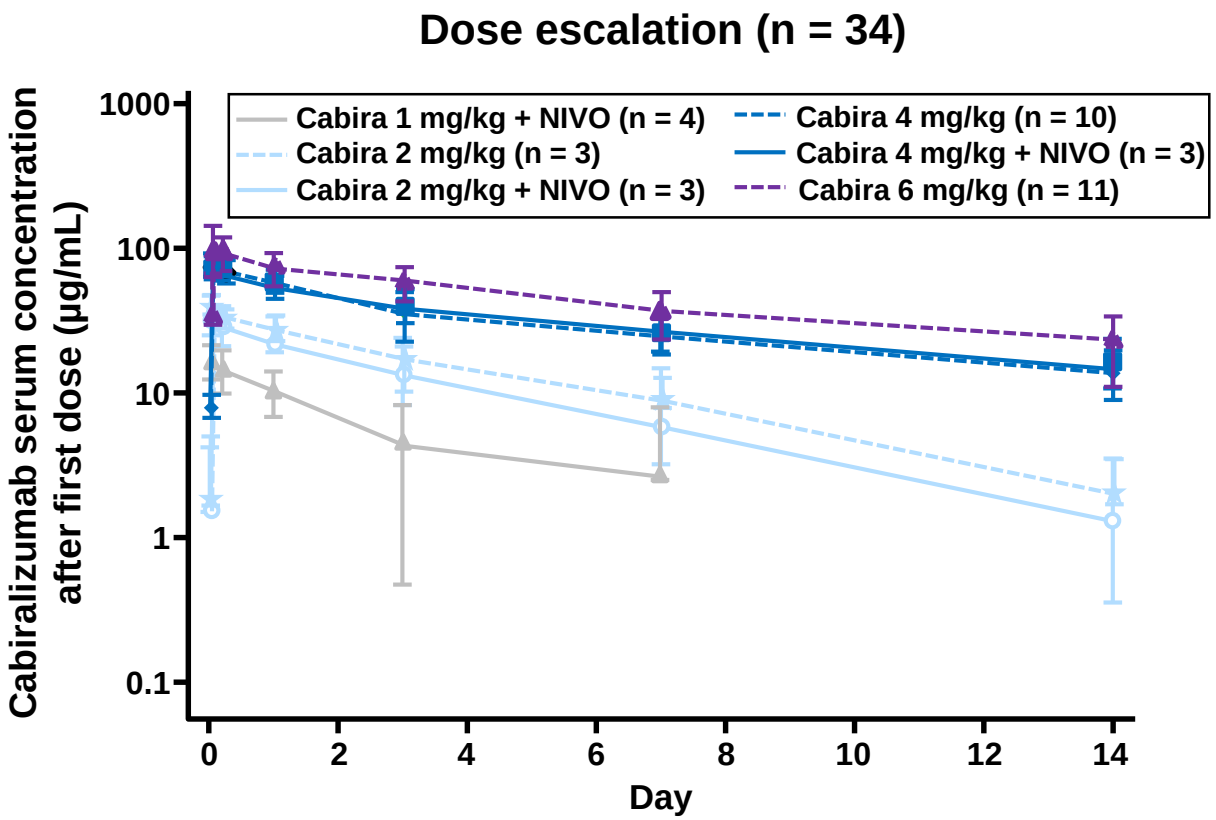
[a]Initiated after corresponding monotherapy doses were deemed tolerable. [b]Primary objective for expansion phase
IV = intravenous; PK = pharmacokinetics; Q2W = every 2 weeks

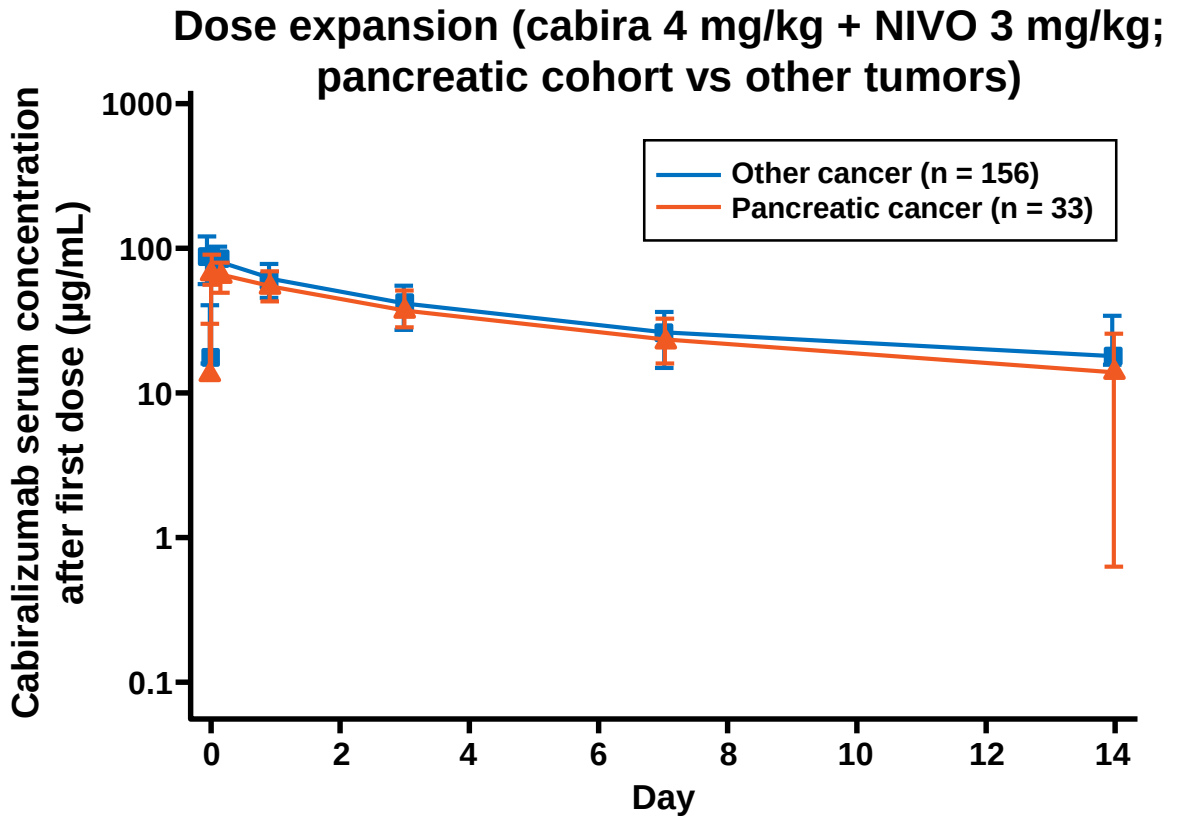
Baseline Demographics and Prior Therapy

	Cabiralizumab monotherapy (n = 24)	Cabiralizumab + nivolumab (n = 205)
Median age (range), years	65.5 (48–88)	64 (25–85)
< 65 years, n (%)	10 (42)	110 (54)
Male, n (%)	13 (54)	100 (49)
ECOG performance status, n (%)		
0	7 (29)	55 (27)
1	17 (71)	145 (71)
2	0	4 (2)
Not reported	0	1 (<1)
No. of prior regimens, n (%)		
0	0	7 (3)
1	5 (21)	47 (23)
2	2 (8)	58 (28)
≥ 3	17 (71)	93 (45)
No. of prior regimens for metastatic disease, n (%)		
0	7 (29)	77 (38)
1	6 (25)	28 (14)
2	3 (13)	44 (21)
≥ 3	8 (33)	56 (27)

ECOG = Eastern Cooperative Oncology Group

Cabiralizumab Demonstrated Target-Mediated Clearance and Low Immunogenicity



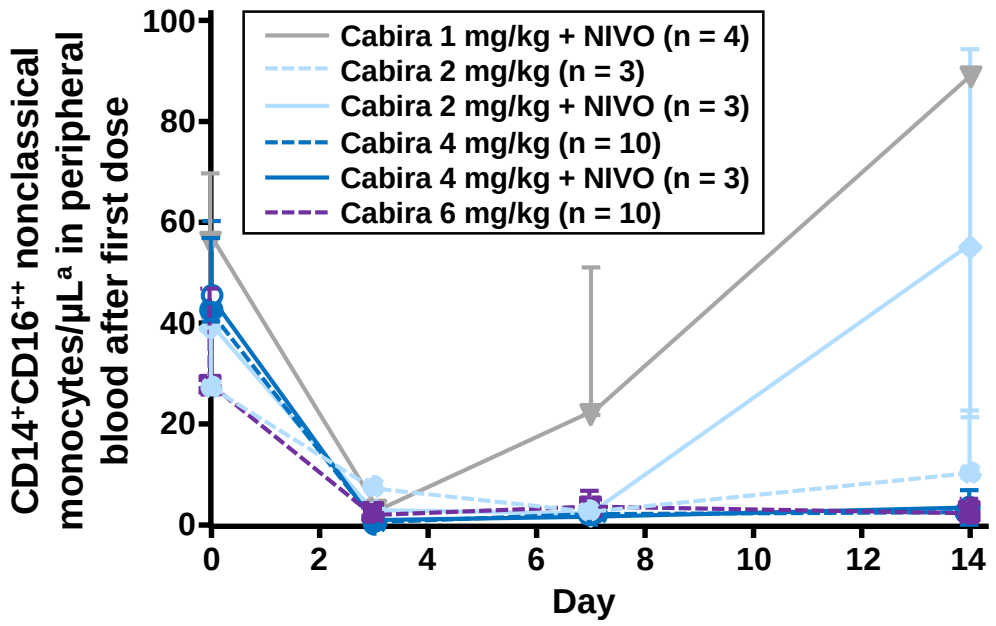


- Cabiralizumab PK is similar when administered as a monotherapy or in combination with nivolumab
- PK of cabiralizumab ≥ 4 mg/kg Q2W approaches the linear dose range, suggesting saturation of target-mediated clearance
- Exposure with the cabiralizumab 4 mg/kg dose in the presence of nivolumab was similar across tumor types
- Cabiralizumab ± nivolumab demonstrated low immunogenicity (data not shown)

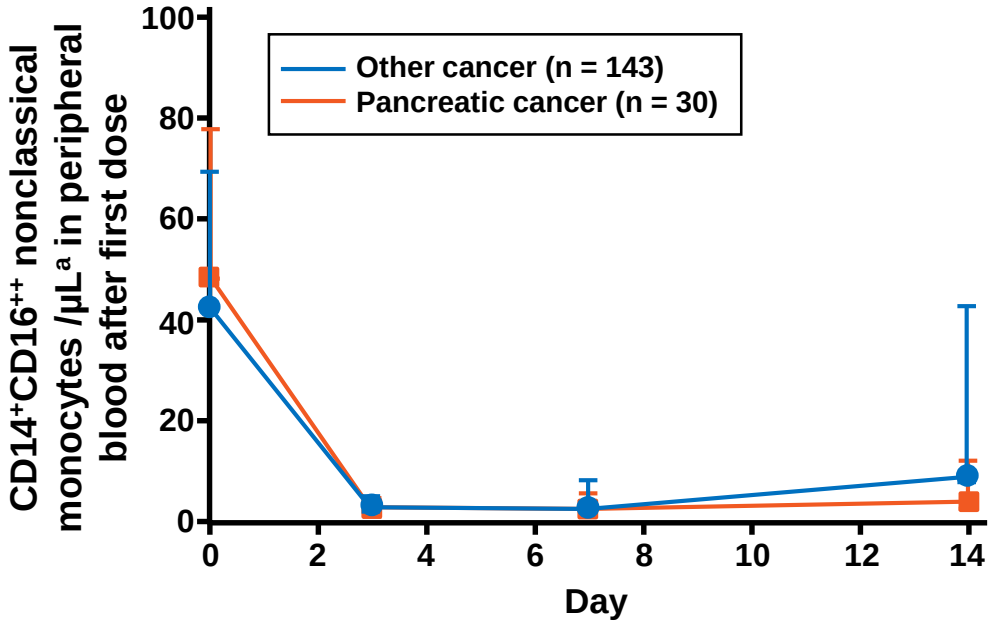
Cabira = cabiralizumab; NIVO = nivolumab

Cabiralizumab ± Nivolumab Depleted Circulating Monocytes in Patients With Advanced Solid Tumors

Dose escalation (n = 33)



Dose expansion (cabira 4 mg/kg + NIVO 3 mg/kg; pancreatic cohort vs other tumors)



- Decreases in levels of circulating nonclassical monocytes are a pharmacodynamic marker of cabiralizumab and have been observed with other CSF-1R–targeting agents[1-3]
- Cabiralizumab 4 mg/kg Q2W was the minimal dose required to consistently deplete circulating nonclassical monocytes throughout the dosing interval; results were similar with cabiralizumab 4 mg/kg + nivolumab
- Decreases in levels of nonclassical monocytes were similar across tumor types

[a]Bars denote 1-sided standard deviation

1. Ries CH, et al. *Cancer Cell* 2014;25:846–859. 2. Gomez-Roca CA, et al. *J Clin Oncol* 2015;33(suppl) [abstract 3005]. 3. Anthony S, et al. *J Clin Oncol* 2011;29(15 suppl) [abstract 3093].

Cabiralizumab ± Nivolumab Demonstrated a Tolerable Safety Profile

- **Safety profile of the combination was generally consistent with that of nivolumab[1,2] and cabiralizumab[3] monotherapy**
- **The most common TRAEs were elevations in creatine kinase and serum liver enzymes (without elevation in bilirubin)**
  - These are believed to be secondary to cabiralizumab's depletion of Kupffer cells (macrophages) and were reported with other CSF-1R–targeting agents[4-6]
  - Isolated enzyme elevations were not associated with other clinical sequelae

	Cabiralizumab monotherapy (n = 24)		Cabiralizumab + nivolumab (n = 205)	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
Any TRAE	15 (63)	13 (54)	184 (90)	100 (49)
AEs leading to discontinuation	3 (13)	2 (8)	15 (7)	10 (5)
Clinical TRAEs (≥ 15% of pts treated with combination)				
Periorbital edema	5 (21)	0	84 (41)	1 (<1)
Fatigue	7 (29)	0	74 (36)	11 (5)
Rash	1 (4)	1 (4)	38 (19)	8 (4)
Pruritus	2 (8)	0	34 (17)	2 (1)
Nausea	3 (13)	0	30 (15)	0
Treatment-related laboratory abnormalities of interest				
Serum enzyme elevations[a]	10 (42)	9 (38)	103 (50)	40 (20)
Pancreatic enzyme elevations[b]	3 (13)	2 (8)	42 (20)	24 (12)
Treatment-related deaths	0		3 (1.5)[c]	

[a]Includes AE terms indicative of elevated CPK, AST, ALT, and LDH. [b]Includes AE terms indicative of elevated amylase and lipase. [c]Includes pneumonitis in a patient with thyroid cancer (cabiralizumab 1 mg/kg + nivolumab 3 mg/kg), and respiratory distress (n = 1, cabiralizumab 4 mg/kg + nivolumab) and acute respiratory distress (n = 1, cabiralizumab 4 mg/kg + nivolumab) in 2 patients with lung cancer.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; TRAE, treatment-related adverse event

1. Brahmer J, et al. *N Engl J Med* 2015;373:123–135. 2. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 3. Sankhala K, et al. *J Clin Oncol* 2017;35(suppl) [abstract 11078].
4. Ries CH, et al. *Cancer Cell* 2014; 25:846–859. 5. Tap WD, et al *N Engl J Med* 2015;373:428–437. 6. Papadopoulos KP, et al *Clin Cancer Res* 2017;23:5703–5710.

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Rationale for Targeting CSF-1R in Pancreatic Cancer

- Pancreatic cancer is associated with high TAM infiltration and poor prognosis[1,2]
- It typically presents as metastatic disease with a 1-year survival rate of 17%-23%[3] and a 5-year survival rate of 1%-3%[4,5]
- Approximately 95%-99% of patients have microsatellite stable (MSS) pancreatic cancer,[6-8] lack response to anti–PD-1/L1 therapy,[5,9] and are in need of new treatment options
- **Combination of cabiralizumab and nivolumab may benefit patients with pancreatic cancer by simultaneous reduction of TAMs and inhibition of PD-1 signaling**

1. Hu H, et al. *Tumour Biol* 2016;37:8657–8664. 2. Kurahara, et al. *J Surg Res* 2011;167:e211–e219. 3. Von Hoff DD, et al. *N Engl J Med* 2013;369:1691-1703. 4. American Cancer Society. Pancreatic cancer. https://www.cancer.org/cancer/pancreatic-cancer.html. Accessed October 20, 2017. 5. Foley K, et al. *Cancer Lett* 2016;381;244–251. 6. Goggins M, et al. *Am J Pathol* 1998;1501–1507. 7. Luttges J, et al. *Mod Pathol* 2003;16:537–542. 8. Laghi L, et al. *PLOS One* 2012;7:e46002. 9. Brahmer JR, et al. *N Engl J Med* 2012;366;2455–2465.

Pancreatic Cancer Cohort
Baseline Demographics and Safety

- Patient demographics and the safety profile in the pancreatic cohort was similar to those in all patients treated with cabiralizumab + nivolumab

Baseline demographics and prior therapy	Cabiralizumab 4 mg/kg + nivolumab 3 mg/kg
	Pancreatic cancer (n = 33)[a]
Median age (range), years	64 (37–85)
< 65 years, n (%)	17 (52)
Male, n (%)	17 (52)
ECOG performance status, n (%)	
0	13 (39)
1	19 (58)
2	1 (3)
No. of prior regimens, n (%)	
0	1 (3)[b]
1	3 (9)
2	14 (42)
≥ 3	15 (45)
No. of prior regimens for metastatic disease, n (%)	
0	7 (21)
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[a]Of 33 patients, 31 were response evaluable. [b]Patient was ineligible or refused standard therapy.

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No. of prior regimens for metastatic disease, n (%)	
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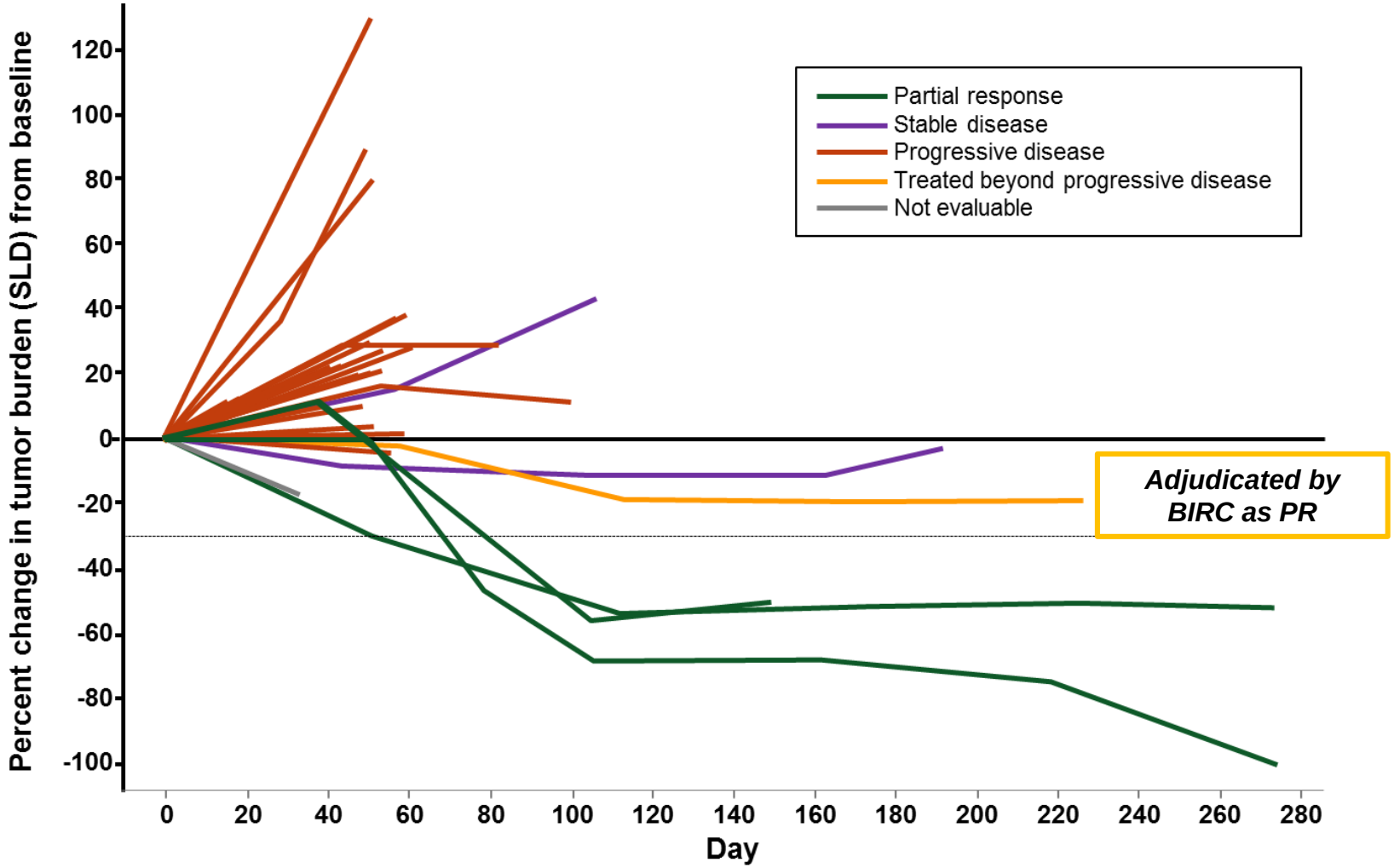
Safety summary	Cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Pancreatic cancer (n = 33)[a]	
	Any grade n (%)	Grade 3/4 n (%)
Any TRAE	31 (94)	20 (61)
AEs leading to discontinuation	3 (9)	3 (9)
Clinical TRAEs in ≥ 15% of patients		
Fatigue	14 (42)	1 (3)
Periorbital edema	10 (30)	0
Rash	7 (21)	0
Vomiting	7 (21)	0
Hyponatremia	6 (18)	3 (9)
Diarrhea	5 (15)	1 (3)
Rash maculopapular	5 (15)	3 (9)
Treatment-related laboratory abnormalities of interest		
Serum enzyme elevations[c]	17 (52)	11 (33)
Pancreatic enzyme elevations[d]	2 (6)	1 (3)
Treatment-related deaths	0	

[a]Of 33 patients, 31 were response evaluable. [b]Patient was ineligible or refused standard therapy. [c]Includes AE terms indicative of elevated CPK, AST, ALT, and LDH. [d]Includes AE terms indicative of elevated amylase and lipase

Deep and Durable Responses Observed in Patients With Pancreatic Cancer

Best change in tumor burden over time in efficacy-evaluable patients treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg (n = 31)[a]



- In this heavily pretreated population, durable clinical benefit was observed in **5 patients (16%)**

  Confirmed ORR = 10%
  (Updated confirmed ORR = 13%)

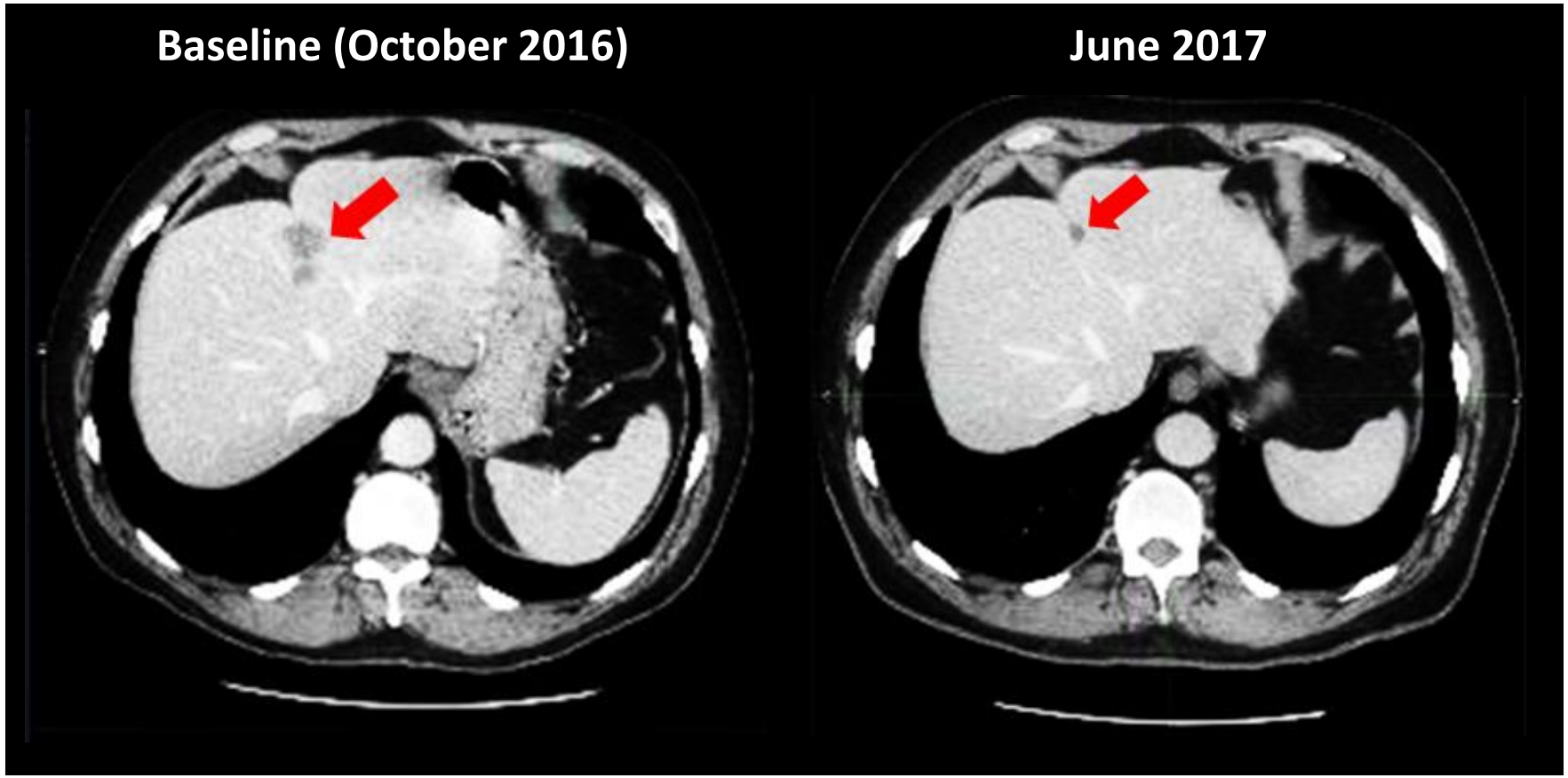
  Duration of treatment for responders = 275+, 168+, 258, and 247+ days

- All 4 confirmed responses were observed in patients with MSS disease, who historically have not shown benefit with anti–PD-1/L1 therapy[1,2]

- Responses were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline

[a]Plot shows 31 efficacy-evaluable patients; 2 patients discontinued treatment early due to AEs before disease evaluation. BIRC = blinded independent review committee; ORR = objective response rate; PR = partial response; SLD = sum of longest diameters 1. Overman M et al. *Ann Oncol*. 2016;27:149-206 [abstract 479P]. 2. Le DT, et al. *N Engl J Med* 2015;372;2509–2520.

Durable Response in the Liver of a Heavily Pretreated Patient With MSS Pancreatic Cancer

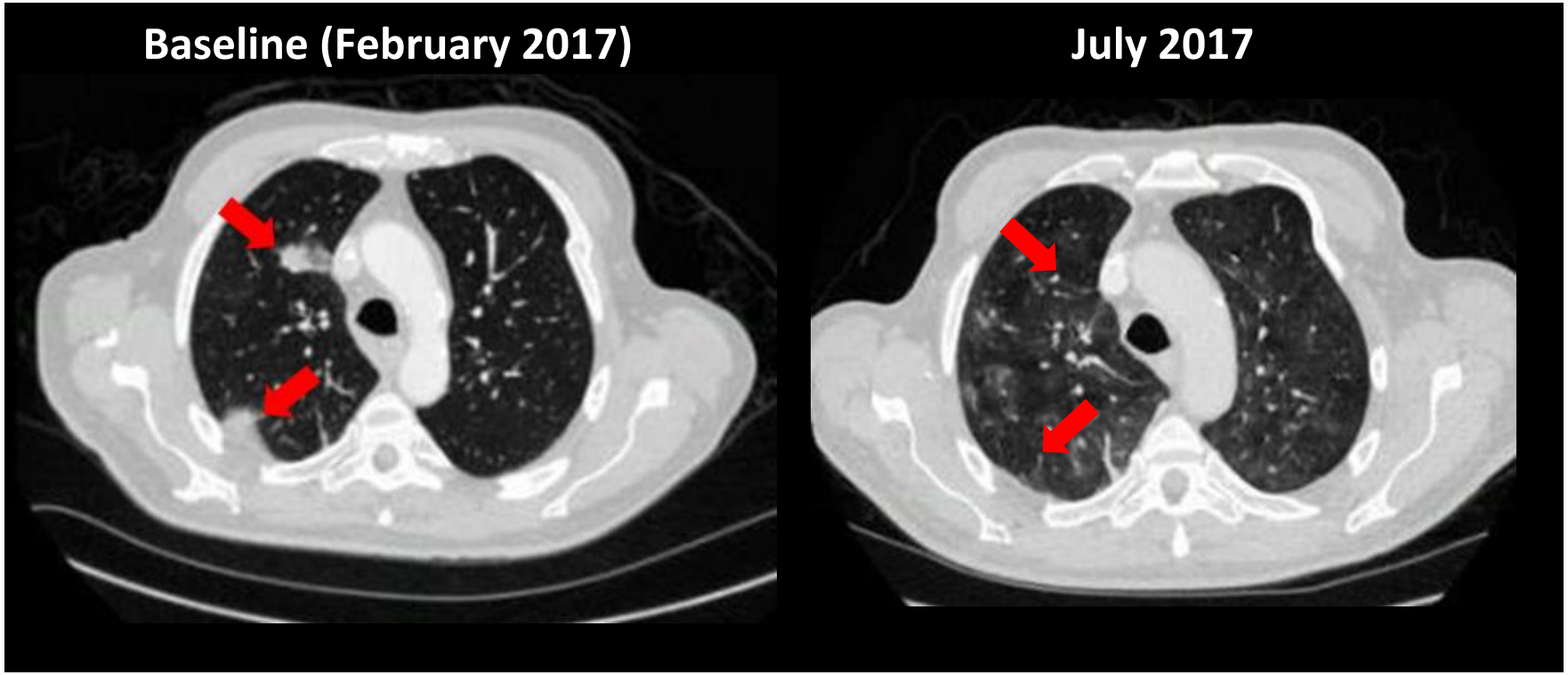


Images provided by James Lee from the University of Pittsburgh Cancer Institute.

- 58-year-old male patient who received 3 prior chemotherapy regimens
  - Neoadjuvant FOLFIRINOX
  - Gemcitabine + *nab*-paclitaxel
  - 5-FU + leucovorin + liposomal irinotecan
- Patient achieved a partial response with a best change in tumor burden of −52%
  - CA19-9 levels declined by 99% from baseline
  - Response is ongoing

5-FU = 5-fluorouracil; FOLFIRINOX = leucovorin + fluorouracil + irinotecan + oxaliplatin

Durable Response in the Lung of a Heavily Pretreated Patient With MSS Pancreatic Cancer



Images provided by Jennifer Johnson from Thomas Jefferson University Hospital.

- 63-year-old male patient who received 4 prior chemotherapy regimens
  - Adjuvant FOLFIRINOX
  - FOLFIRINOX
  - Capecitabine
  - Gemcitabine + *nab*-paclitaxel
- Patient achieved a partial response with a best change in tumor burden of −50%
  - CA19-9 levels declined by 96% from baseline
  - Response is ongoing

Conclusions

- Cabiralizumab is a new immunotherapeutic agent that targets TAMs in the immunosuppressive microenvironment
- Cabiralizumab with or without nivolumab demonstrated:
  - Tolerable safety profile that is comparable to either monotherapy
  - Dose-dependent reduction of circulating $CD14^{+}CD16^{++}$ nonclassical monocytes, reaching maximum at 4 mg/kg Q2W when clearance approaches linear dose range
- Preliminary evidence of durable clinical benefit with cabiralizumab plus nivolumab was observed in heavily pretreated patients with advanced MSS pancreatic cancer
  - Further cohort expansion is ongoing as well as additional biomarker analyses
- These data support further study of cabiralizumab plus nivolumab ± chemotherapy in pancreatic cancer (NCT03336216)

Acknowledgments

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- The clinical study teams who participated in this trial

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- FivePrime Therapeutics, Inc. (South San Francisco, CA), Bristol-Myers Squibb (Princeton, NJ), and ONO Pharmaceutical Company, Ltd. (Osaka, Japan)
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