

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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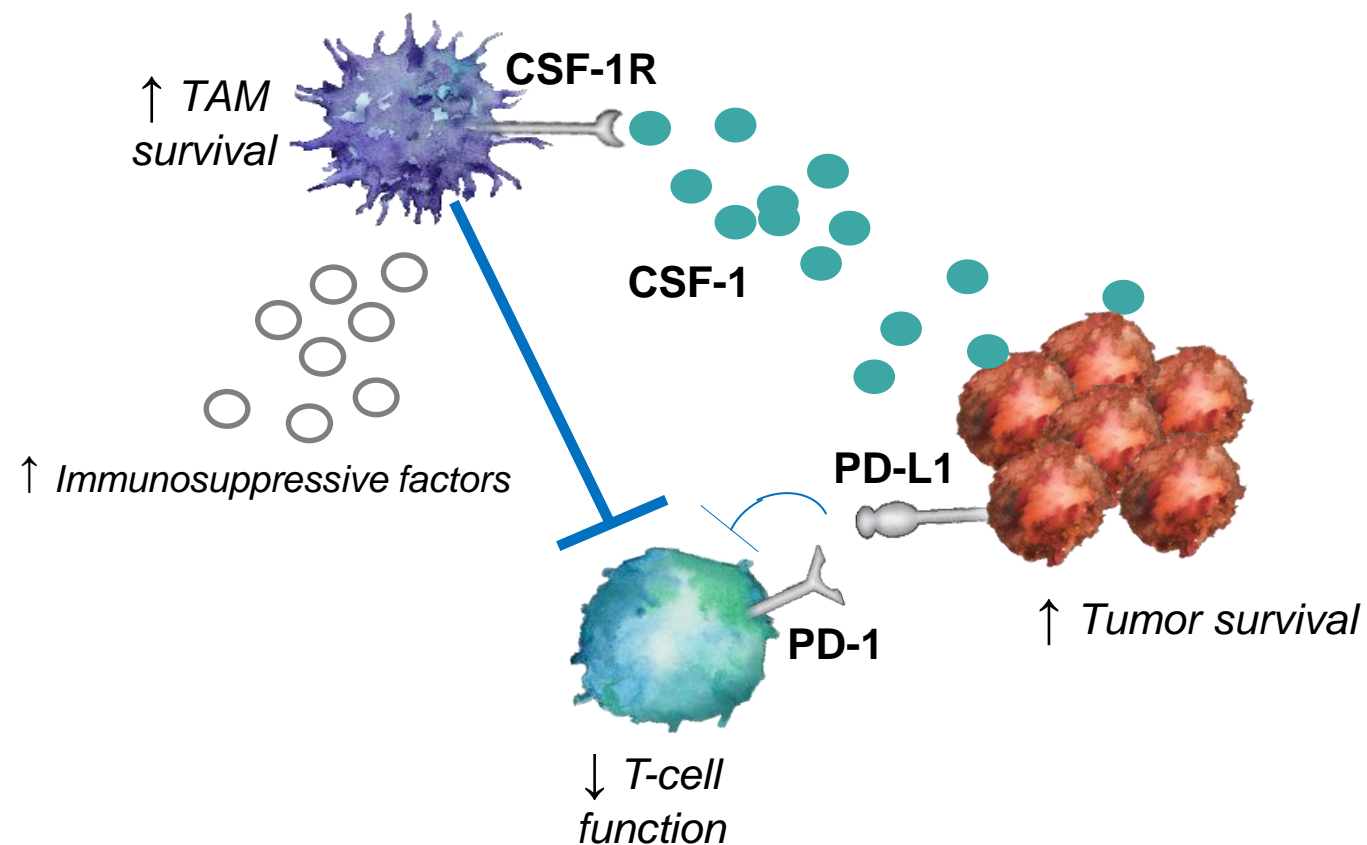
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Presenter Disclosures

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

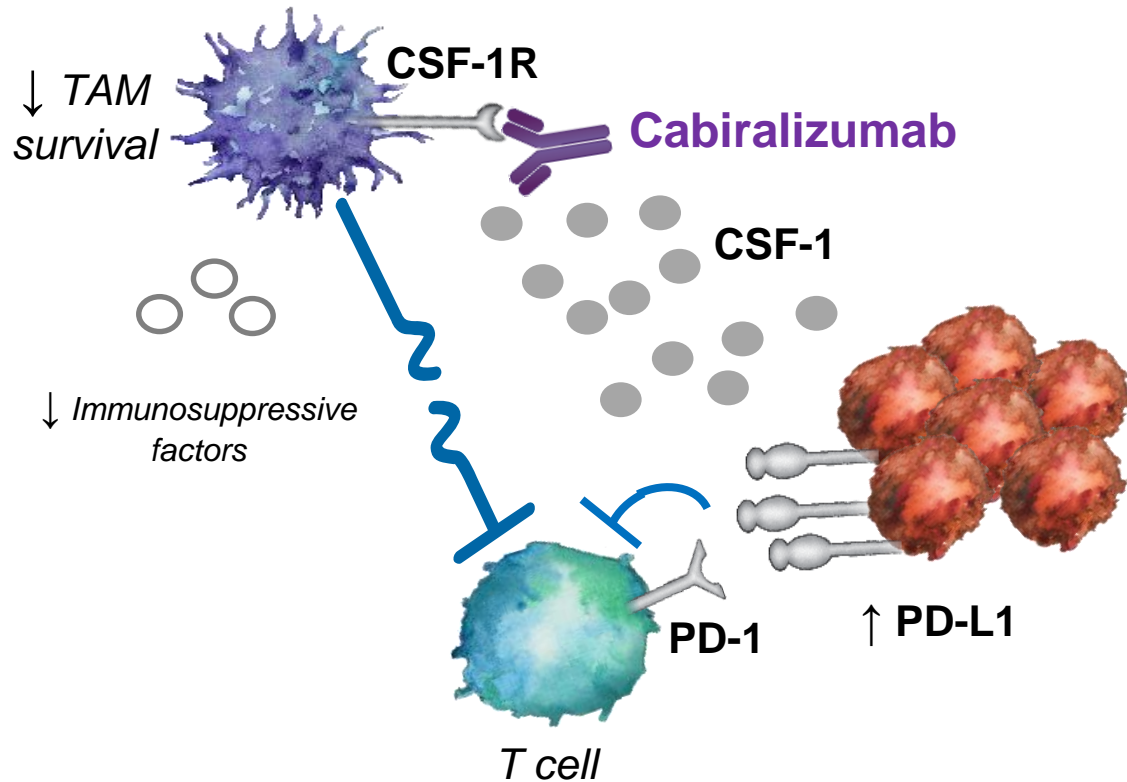
There will be discussion about the use of products for non-FDA-approved indications in this presentation

Rationale for Cabiralizumab in Combination With Nivolumab



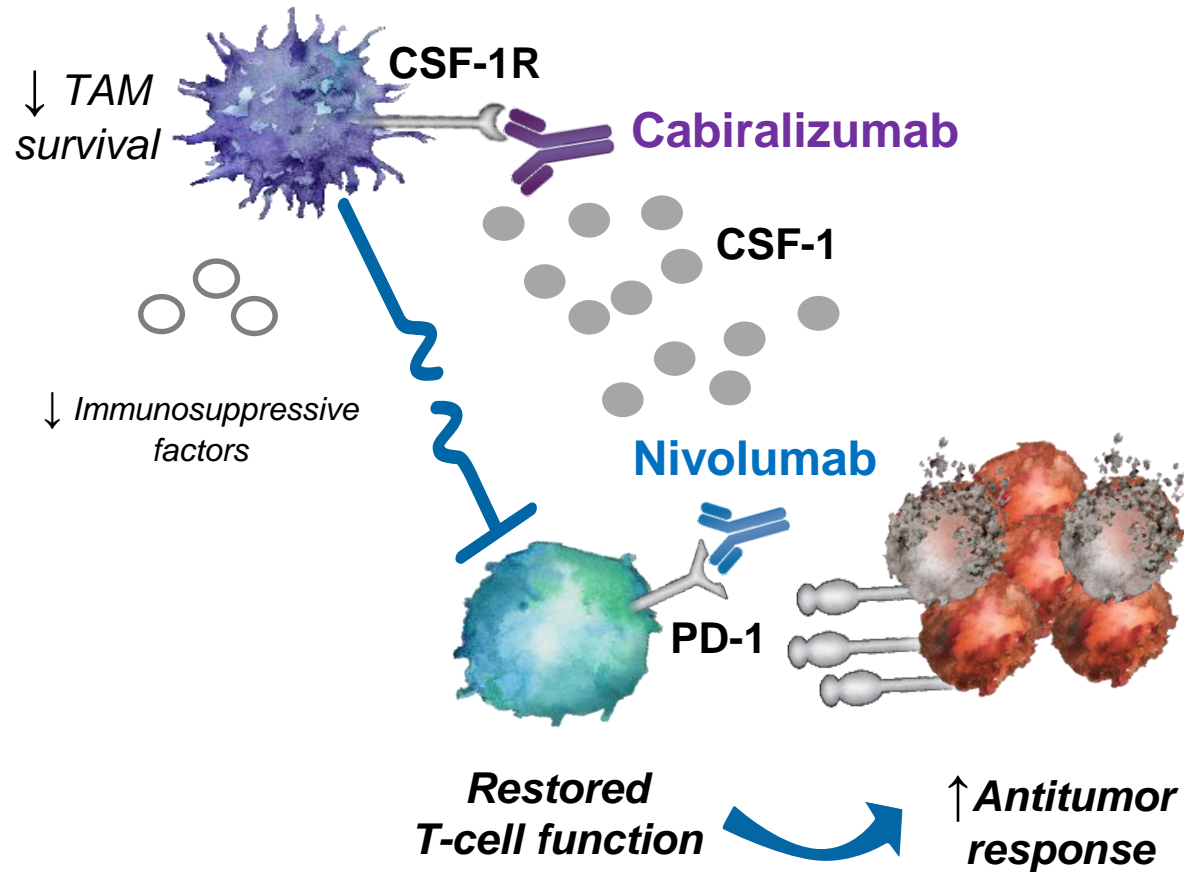
- TAMs inhibit antitumor T-cell activity in the tumor microenvironment^{1,2}
 - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis³⁻⁵
 - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs^{1,2}

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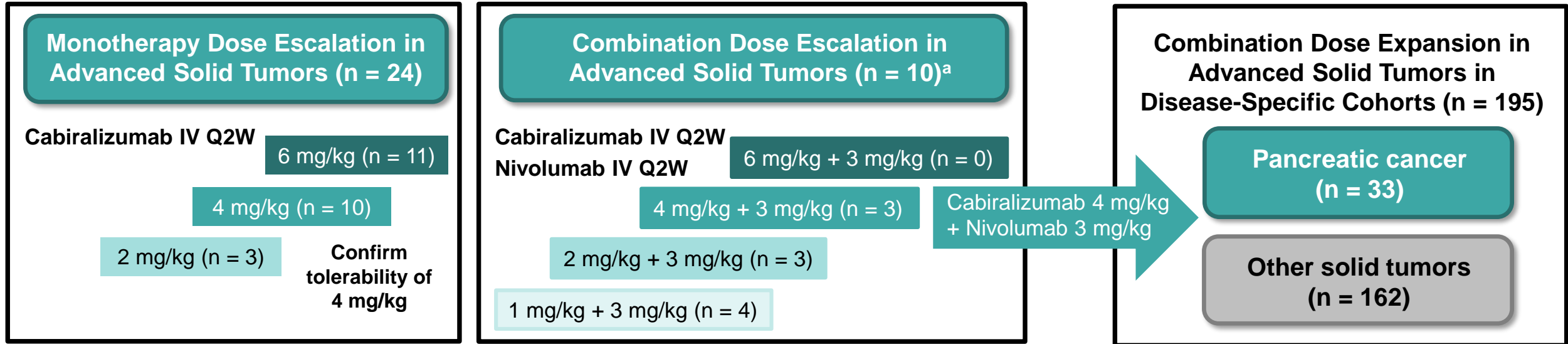
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- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R⁶ and depletes TAMs

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- 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 prognosis³⁻⁵
 - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs^{1,2}
- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R⁶ and depletes TAMs
- Preclinical data suggest that CSF-1R inhibition synergizes with PD-1 blockade to enhance antitumor activity⁷

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

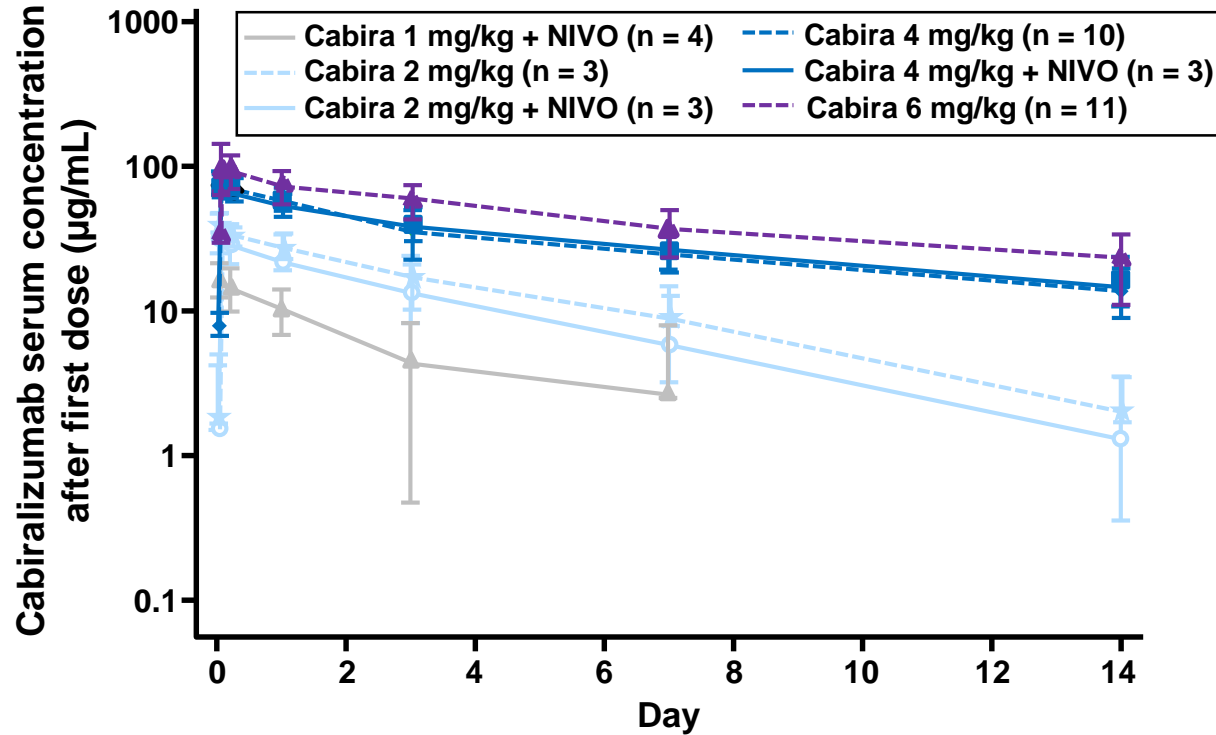
Secondary objectives: immunogenicity, PK, pharmacodynamics, preliminary antitumor activity^b

Baseline Demographics and Prior Therapy

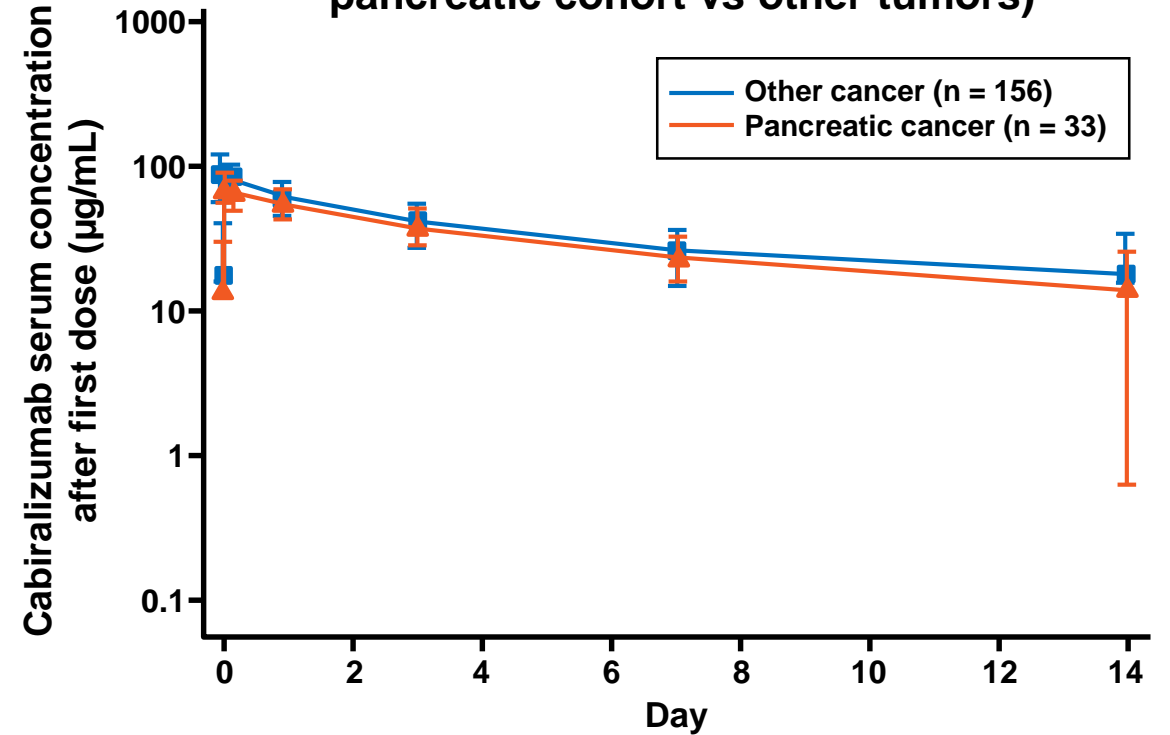
	Cabiralizumab monotherapy (n = 24)	Cabiralizumab + nivolumab (n = 205)
Median age (range), years	65.5 (48–88)	64 (25–85)
< 65 years, n (%)	10 (42)	110 (54)
Male, n (%)	13 (54)	100 (49)
ECOG performance status, n (%)		
0	7 (29)	55 (27)
1	17 (71)	145 (71)
2	0	4 (2)
Not reported	0	1 (<1)
No. of prior regimens, 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)

Cabiralizumab Demonstrated Target-Mediated Clearance and Low Immunogenicity

Dose escalation (n = 34)



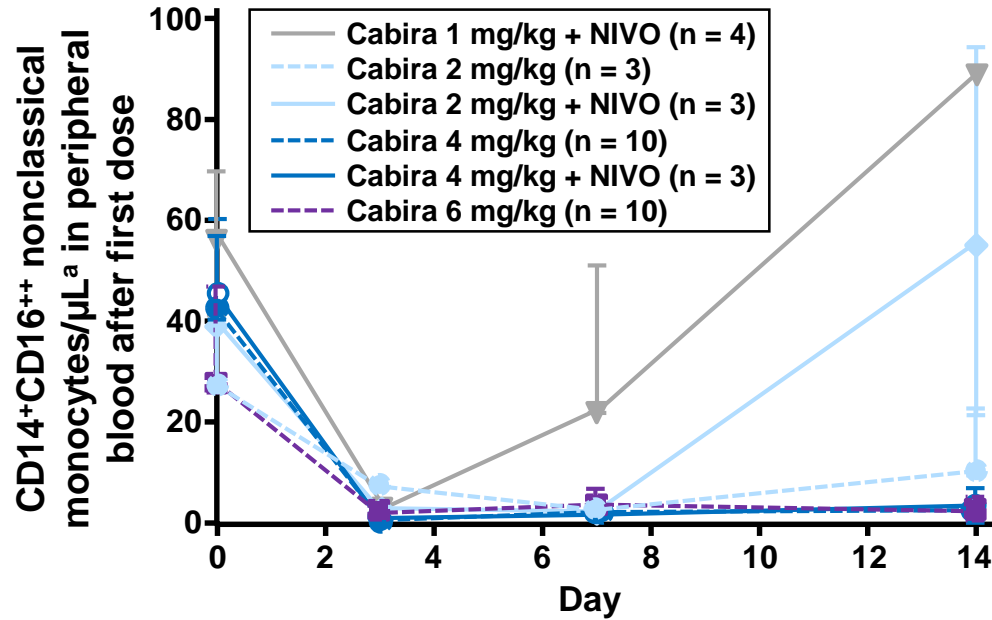
Dose expansion (cabira 4 mg/kg + NIVO 3 mg/kg; pancreatic cohort vs other tumors)



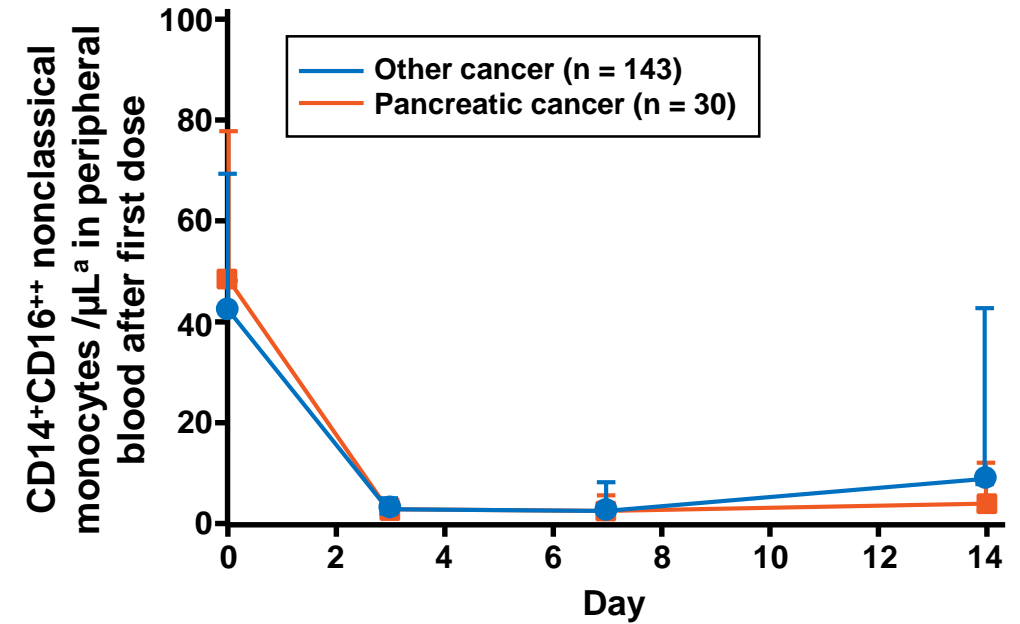
- Cabiralizumab PK is similar when administered as a monotherapy or in combination with nivolumab
- PK of cabiralizumab ≥ 4 mg/kg Q2W approaches the linear dose range, suggesting saturation of target-mediated clearance
- Exposure with the cabiralizumab 4 mg/kg dose in the presence of nivolumab was similar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

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 agents¹⁻³
- 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

^aBars 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 cabiralizumab³ 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 agents⁴⁻⁶
 - 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

^aIncludes AE terms indicative of elevated CPK, AST, ALT, and LDH. ^bIncludes AE terms indicative of elevated amylase and lipase. ^cIncludes 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

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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**

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 < 65 years, n (%)	64 (37–85) 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)
1	4 (12)
2	12 (36)
≥ 3	10 (30)

^aOf 33 patients, 31 were response evaluable. ^bPatient was ineligible or refused standard therapy.

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

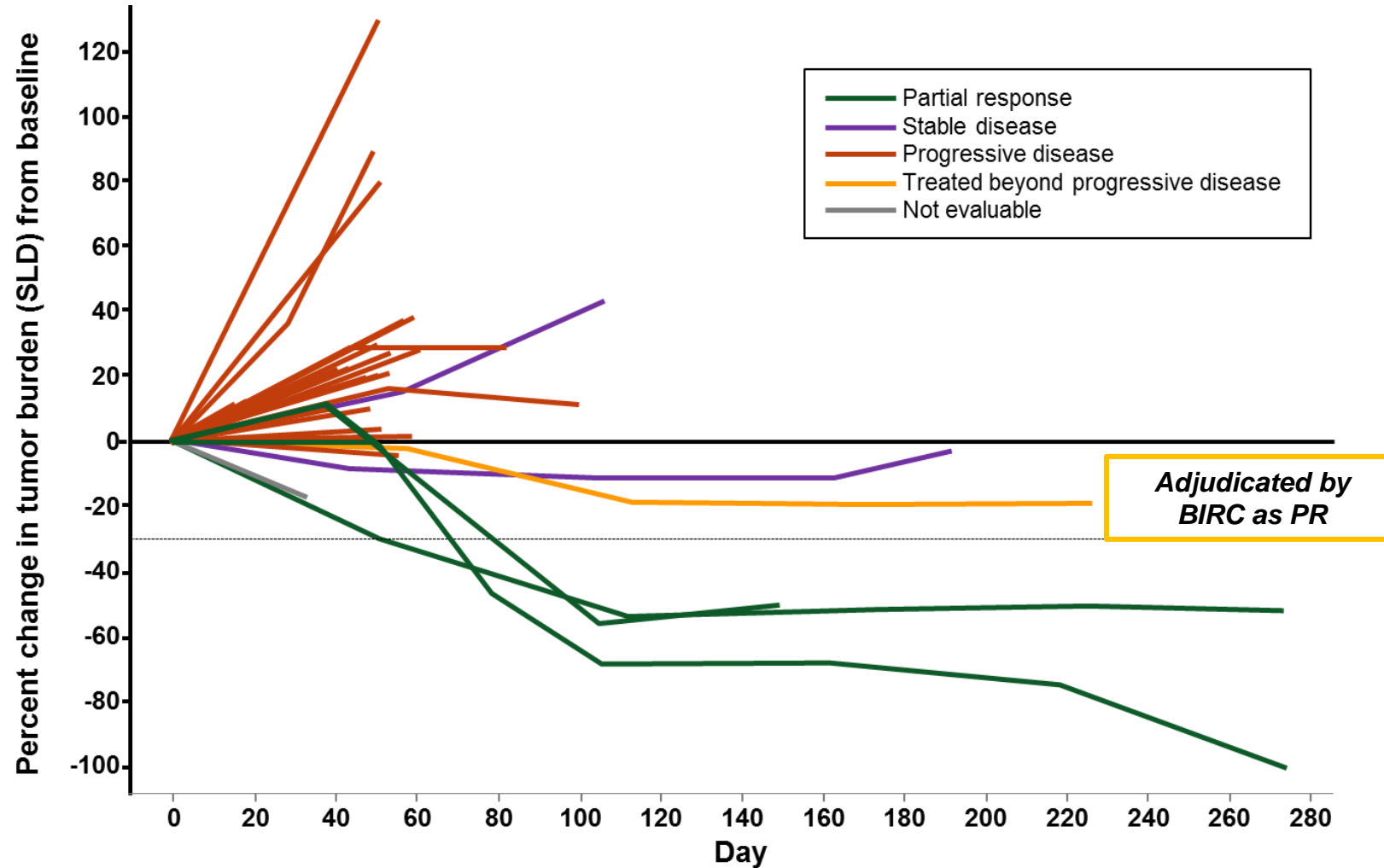
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ECOG performance status, n (%)		
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≥ 3	15 (45)	
No. of prior regimens for metastatic disease, n (%)		
0	7 (21)	
1	4 (12)	
2	12 (36)	
≥ 3	10 (30)	

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	

^aOf 33 patients, 31 were response evaluable. ^bPatient was ineligible or refused standard therapy. ^cIncludes AE terms indicative of elevated CPK, AST, ALT, and LDH. ^dIncludes 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

^aPlot 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.

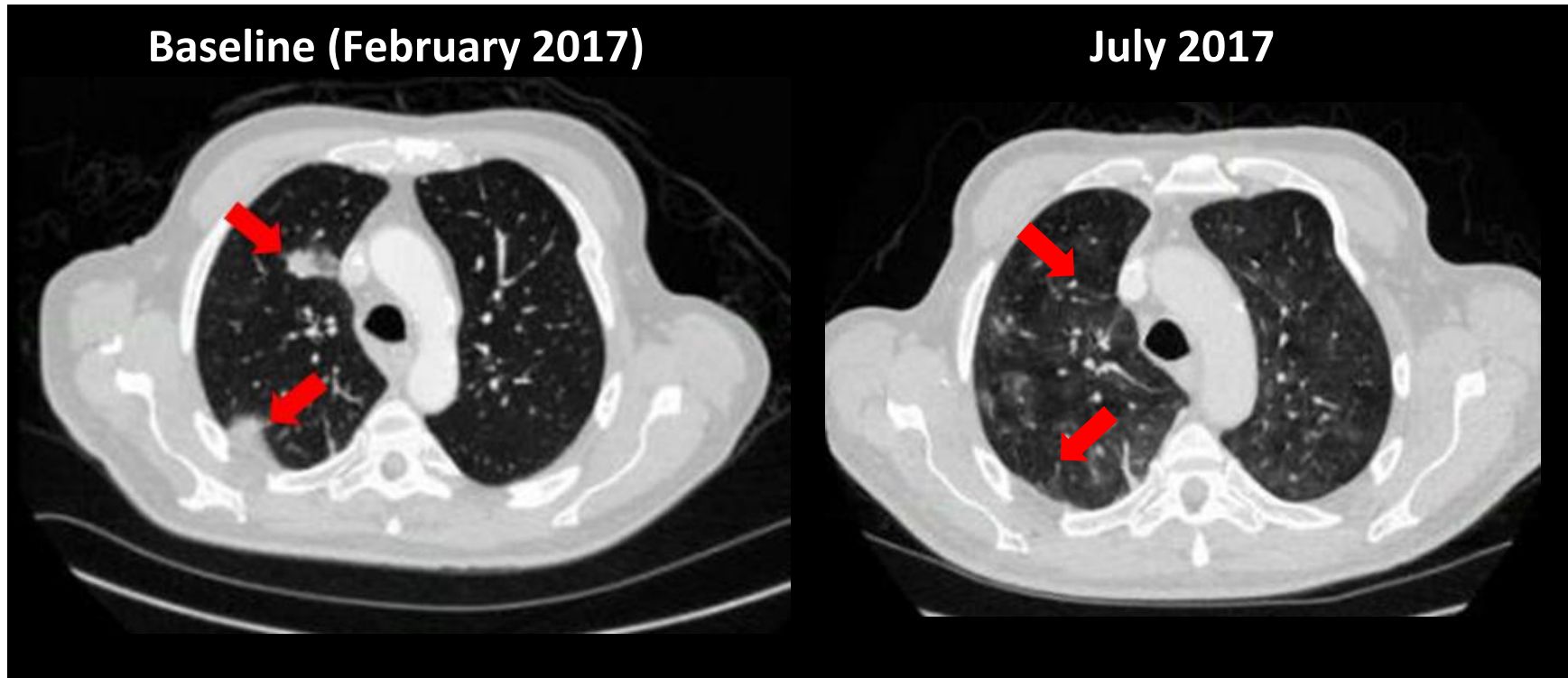
Durable Response in the Liver of a Heavily Pretreated Patient With MSS Pancreatic Cancer



- 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

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

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)

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