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Society for Immunotherapy of Cancer

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SITC 2017

CX-839-004: A phase 1/2 study of CB-839, a first-in-class glutaminase inhibitor, combined with nivolumab in patients with advanced Melanoma (MEL), Renal Cell Carcinoma (RCC), or Non-Small Cell Lung Cancer (NSCLC)

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Presenter Disclosure Information

Funda Meric-Bernstam, MD

Nature of Relevant Financial Relationship	Commercial Interest
Grant or research support	Novartis, AstraZeneca, Taiho, Genentech, Calithera, Debiopharma, Bayer, Puma, Aileron, CytoMx, Effector Therapeutics, Zymeworks, PUMA, Curis, Pfizer
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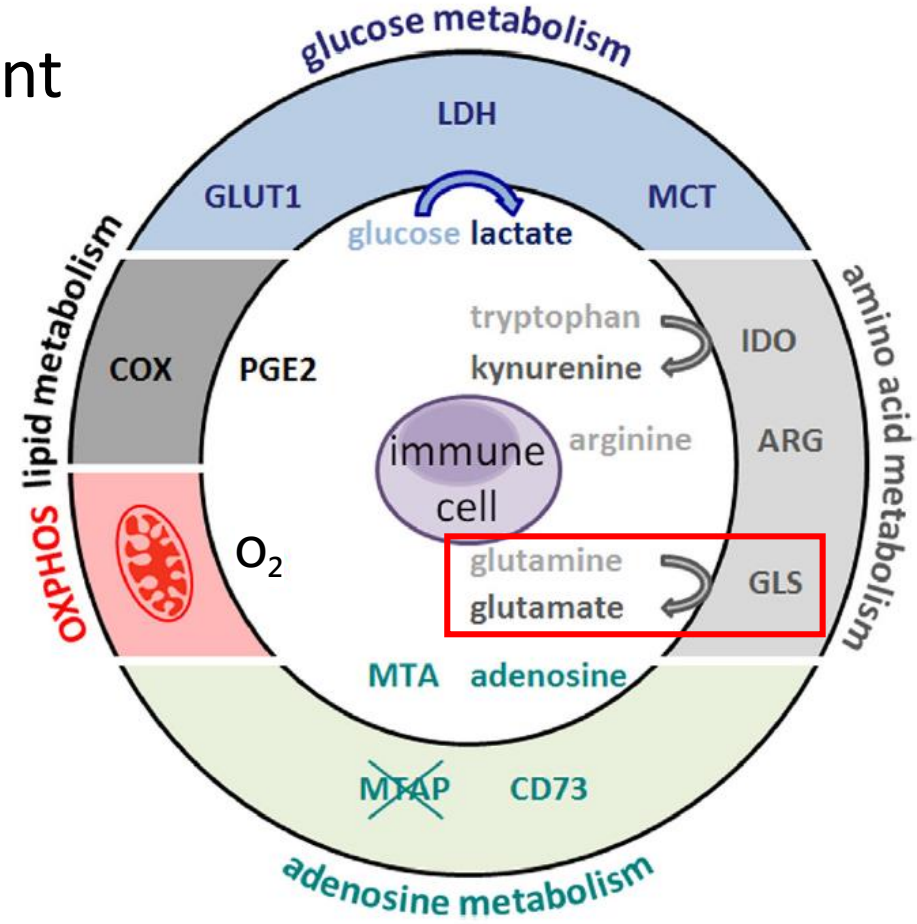
Membership on advisory committees or review panels, board membership, etc.	Inflection Biosciences, Clearlight Diagnostics, Pieris, Darwin Health, GRAIL
Employee	MD Anderson Cancer Center

Metabolic Hallmarks of Tumors

Interplay between tumor cells and immune cells

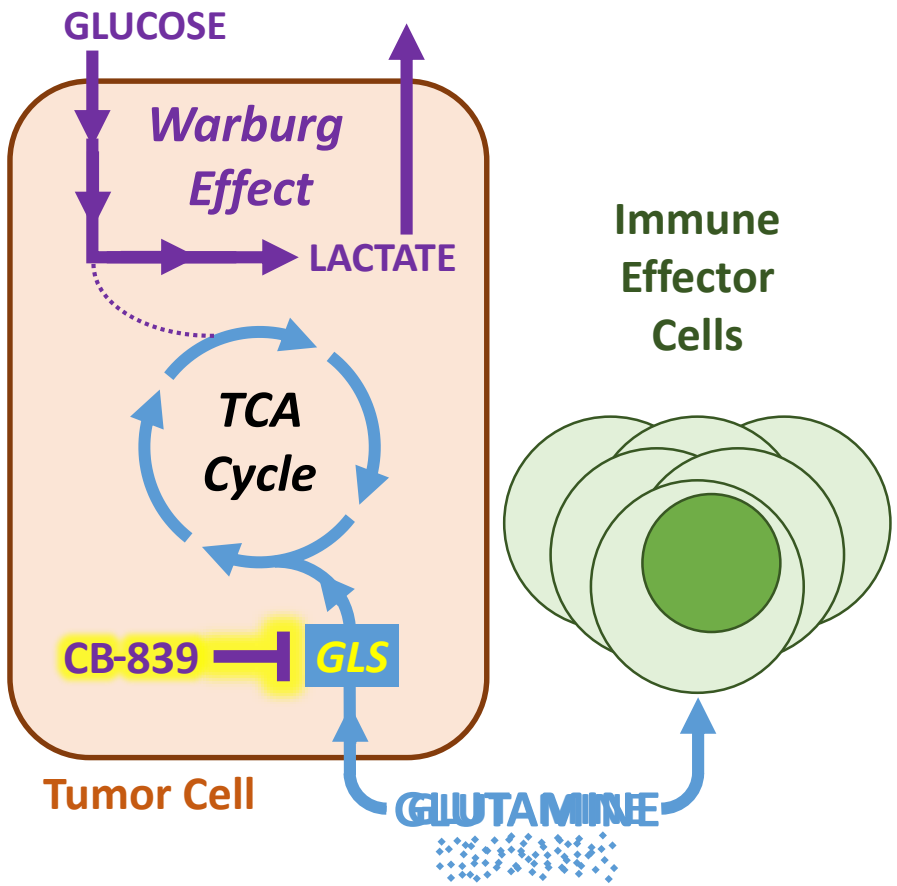
- Altered metabolism in tumor microenvironment
- Depleted essential T-cell nutrients
  - Glucose
  - Arginine
  - O_2
  - Glutamine
- Elevated T-cell suppressive metabolites
  - Lactate
  - Kynurenine
  - Adenosine



Renner et al. (2017) *Front Immunol.* 8:248

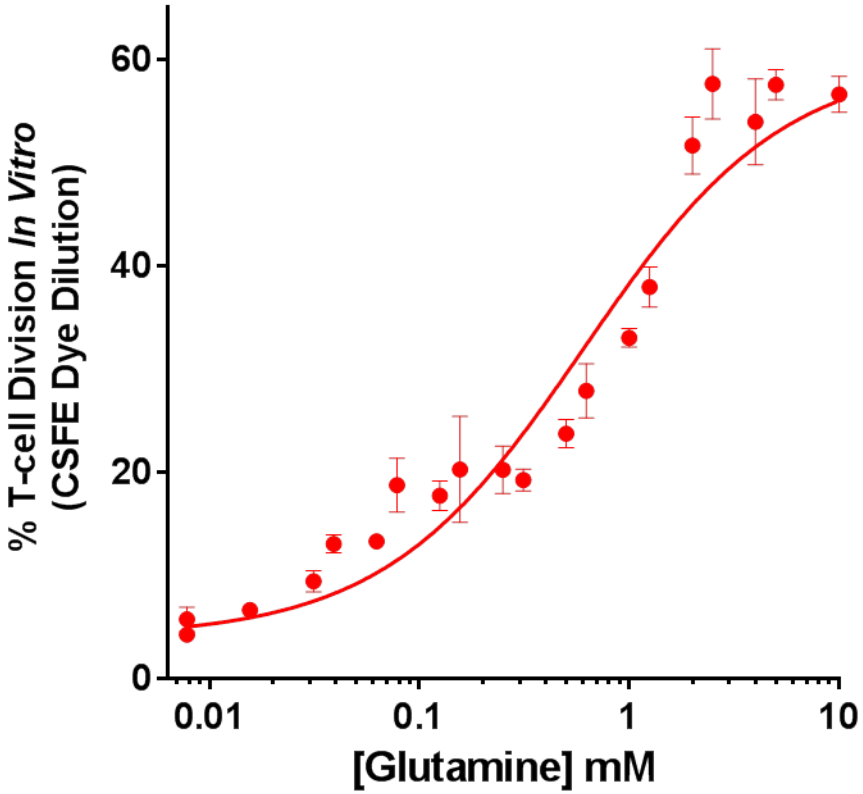
Glutamine Metabolism in the Tumor Microenvironment

- Tumor cells avidly consume glutamine to fuel biosynthesis and proliferation
- Glutaminase converts glutamine to glutamate - a necessary step for glutamine to enter the TCA cycle.
- CB-839 is first in class oral glutaminase inhibitor that:
  - Blocks tumor glutamine consumption
  - Has direct antitumor activity
- Consumption of glutamine by tumors deprives immune cells of this critical nutrient
  - CB-839 elevates glutamine in the tumor microenvironment supporting immune cell function



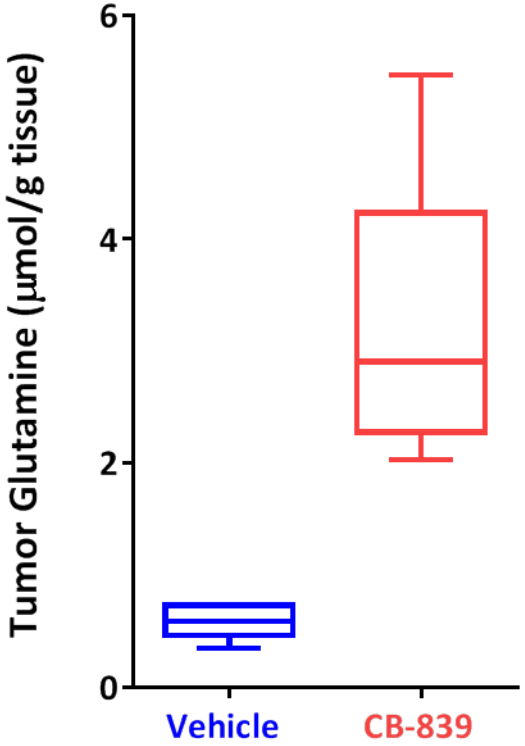
Glutamine is Required by T-Cells and is Elevated by CB-839

T-cell proliferation requires glutamine



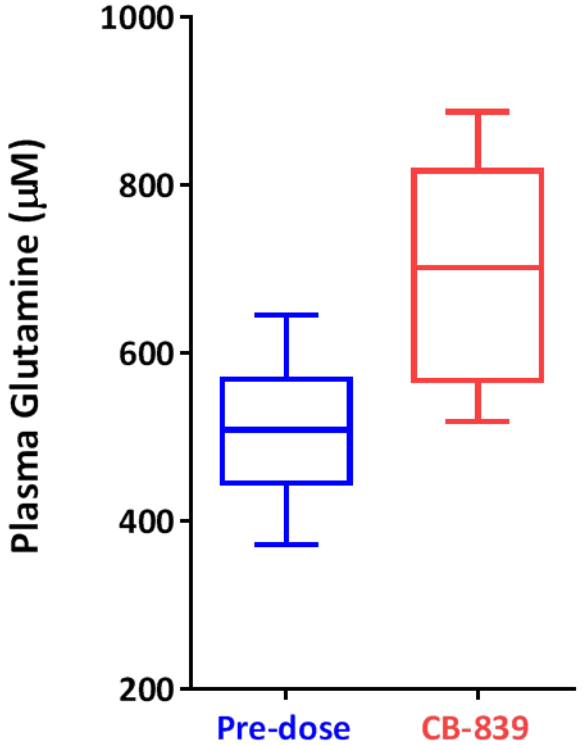
Stimulation – CD3/CD28; Timepoint – 96 hr

CB-839 raises glutamine in tumor xenografts



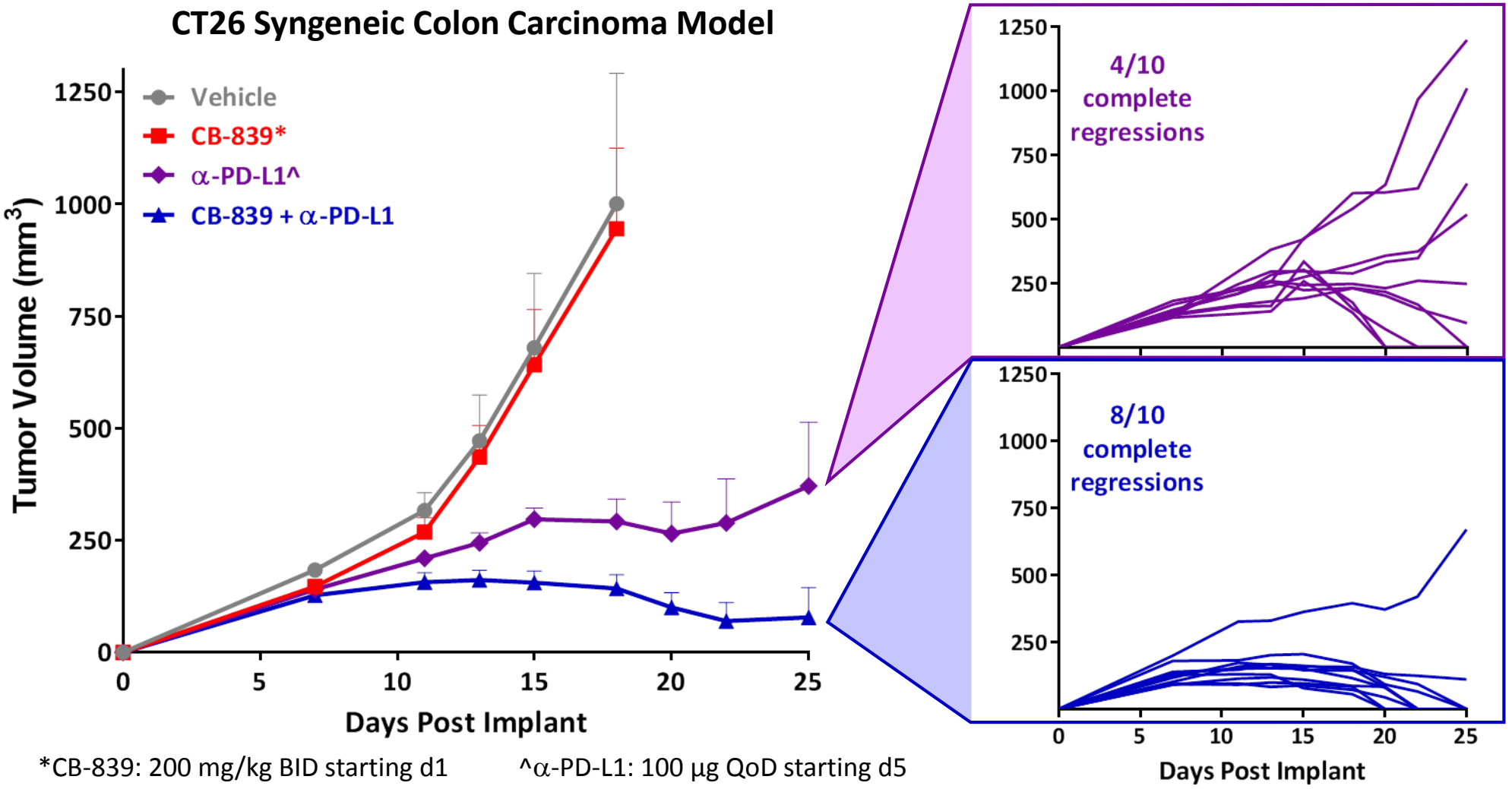
CB-839 dose – 200 mg/kg
Timepoint – 4 hr after single dose

CB-839 raises systemic glutamine in patients



CB-839 dose – 600-800 mg BID
Timepoint – Cycle 1/Day 15

Activity of CB-839 + α-PD-L1 in CT26 Syngeneic Tumor Model



*CB-839: 200 mg/kg BID starting d1 ^α-PD-L1: 100 µg QoD starting d5

CX-839-004: Overall Study Design

Phase 1 Dose Escalation

- 3+3 design
- Standard dose nivolumab
- Two CB-839 dose levels
  - 600 mg PO BID
  - 800 mg PO BID
- Melanoma, NSCLC, RCC pts

RP2D

Phase 2 Expansion Cohorts (Simon two stage design)

Cohort	Prior IO Requirement
Melanoma Rescue	*At study entry,* progressing on α-PD-(L)1*
NSCLC Rescue	*At study entry,* progressing on α-PD-(L)1* or SD ≥ 6 mo without response
RCC Rescue	
RCC Prior IO	α-PD-(L)1 in any prior line with no response
RCC IO Naïve	No prior checkpoint inhibitors

*radiographic or RECIST progression per investigator assessment within 2 months of study entry with no intervening therapy

Demographics

	Cohort	Melanoma Rescue (N=22)	NSCLC Rescue (N=11)	RCC Rescue (N=11)	RCC Prior IO (N=10)	RCC IO Naïve (N=28)
Age, median (range)		64 (30-81)	70 (49-84)	66 (51-86)	66 (51-76)	59 (37-77)
Male, n (%)		12 (55)	5 (45)	9 (82)	8 (80)	20 (71)
ECOG PS, n (%)	0	12 (55)	3 (27)	3 (27)	2 (20)	13 (46)
	1	10 (45)	8 (73)	8 (73)	8 (80)	14 (50)#
LDH > ULN, n (%)		14 (64)				
Stage M1c, n (%)		22 (100)				
IMDC prognosis, n (%)	Favorable			3 (27)	2 (20)	2 (7.1)
	Intermediate			7 (64)	8 (80)	23 (82)
	Poor			1 (9.1)	0	3 (11)
Metastases, n (%)	Liver	11 (50)	3 (27)	1 (10)^	3 (30)	4 (14)
	Other viscera	17 (77)	10 (91)	10 (100)^	10 (100)	26 (93)
	Bone	5 (23)	2 (18)	5 (50)^	6 (60)	12 (43)
	Brain‡	4 (18)	0	2 (20)^	2 (20)	2 (7.1)
Mutation, n (%)		BRAFmt: 6 (29)*	EGFR/ALK: 0			

‡stable at study entry *out of 21 pts (1 unknown) ^out of 10 pts (1 unknown) #1 pt had ECOG PS = 2

Prior Therapies

	Cohort (N)	Melanoma Rescue (22)	NSCLC Rescue (11)	RCC Rescue (11)	RCC Prior IO (10)	RCC IO Naïve (28)
# prior lines, median (range)		2 (1-7)	2 (1-5)	2 (2-6)	4 (1-8)	1 (1-4)
# prior lines of IO, median (range)		2 (1-5)	1 (1-3)	1	1 (1-2)	0 (0-1*)
Class of agent, n (%)	α-PD-(L)1	22 (100)	11 (100)	11 (100)	10 (100)	0
	α-CTLA4	14 (64)	0	0	0	0
	α-PD-(L)1 + α-CTLA4	8 (36)	0	0	0	0
	other IO	7 (32)	1 (9.1)	1 (9.1)	2 (20)	1 (3.6)*
	cytokine, vaccine	5 (23)	0	4 (36)	1 (10)	5 (18)
	non-IO targeted agent	BRAFi+MEKi: 3 (14)	0	VEGFi: 10 (91)	VEGFi: 10 (100)	VEGFi: 27 (96)
	chemotherapy	5 (23)	10 (91)	2 (18)	3 (30)	1 (3.6)
Rescue Cohorts immediate prior α-PD-(L)1	PD at study entry, n (%)	22 (100)	11 (100)	9 (82)		
	Best Response, n (%)^ CR/PR	0/1 (4.5)	0/1 (9.1)	0/0		
	SD	2 (9.1)	3 (27)	6 (55)		
	PD	19 (86)	7 (64)	5 (45)		

*one pt treated with OX40 agonist

^per investigator

Safety: Treatment-Related Adverse Events

- CB-839 + nivolumab is well tolerated
- No MTD reached
  - 1 DLT (Gr 3 ALT) at 800 mg
- 800 mg CB-839 BID selected as RP2D
- Two patients discontinued for treatment-related AEs (Gr3 rash and Gr2 pneumonitis)
- No apparent increase in immune related AE (irAE) rate and severity compared to nivolumab monotherapy[1^]
  - irAE All Grades (13.4%)
  - irAE ≥ Grade 3 (3.7%)

Safety Population (N=82)*	Number (%) of Subjects	
Preferred Term	**All Grades**	**≥ Grade 3**
Subjects with Any CB-839 or nivolumab Related AE	61 (75)	8 (9.8)
Fatigue	19 (23)	0
Nausea	16 (20)	1 (1.2)
Photophobia	13 (16)	0
Pruritus	12 (15)	1 (1.2)
Rash or rash macular	11 (13)	1 (1.2)
ALT increased	10 (12)	2 (2.4)
Decreased appetite	10 (12)	0
AST increased	8 (9.8)	1 (1.2)
Constipation	7 (8.5)	0
Diarrhea	5 (6.1)	0
Dyspepsia	5 (6.1)	0
Photosensitivity reaction	5 (6.1)	0
Vision blurred	5 (6.1)	0
Dry skin	4 (4.9)	0
Vomiting	4 (4.9)	1 (1.2)

*includes dose escalation and expansion patients

[1]Nivolumab package insert

^Patients with history of intolerance to prior α-PD-(L)1 therapy were excluded from IO experienced cohorts (54 of 82 safety patients)

Datacut: 9/29/17

Clinical Response

- **ORR of 19% in melanoma patients and disease control in the other IO refractory cohorts**
- **ORR of 21% in RCC IO Naïve cohort with 74% DCR and 50% of enrolled patients remaining on study treatment**

Cohort	Melanoma Rescue	NSCLC Rescue	RCC Rescue	RCC Prior IO	RCC IO Naïve
Total Enrolled	N=22	N=11	N=11	N=10	N=28
RECIST 1.1 Response Evaluable, N (%)*	16 (73%)	6 (54.5)	8 (73%)	7 (70%)	19 (68%)
CR, n (%)	1 (6.3)	0	0	0	0
PR, n (%)^	2 (12.5)	0	0	0	4 (21)
SD, n (%)	4 (25)	4 (67)	6 (75)	4 (57)	10 (53)
PD, n (%)	9 (56)	2 (33)	2 (25)	3 (43)	5 (26)
ORR (CR+PR), n (%)	3 (19)	0	0	0	4 (21)
DCR (CR+PR+SD), n (%)	7 (44)	4 (67)	6 (75)	4 (57)	14 (74)
On study	N=8	N=4	N=4	N=4	N=14

*pts receiving a post-baseline tumor assessment, discontinued due to drug-related AE, or died due to disease having received ≥3 wks of treatment

^confirmed

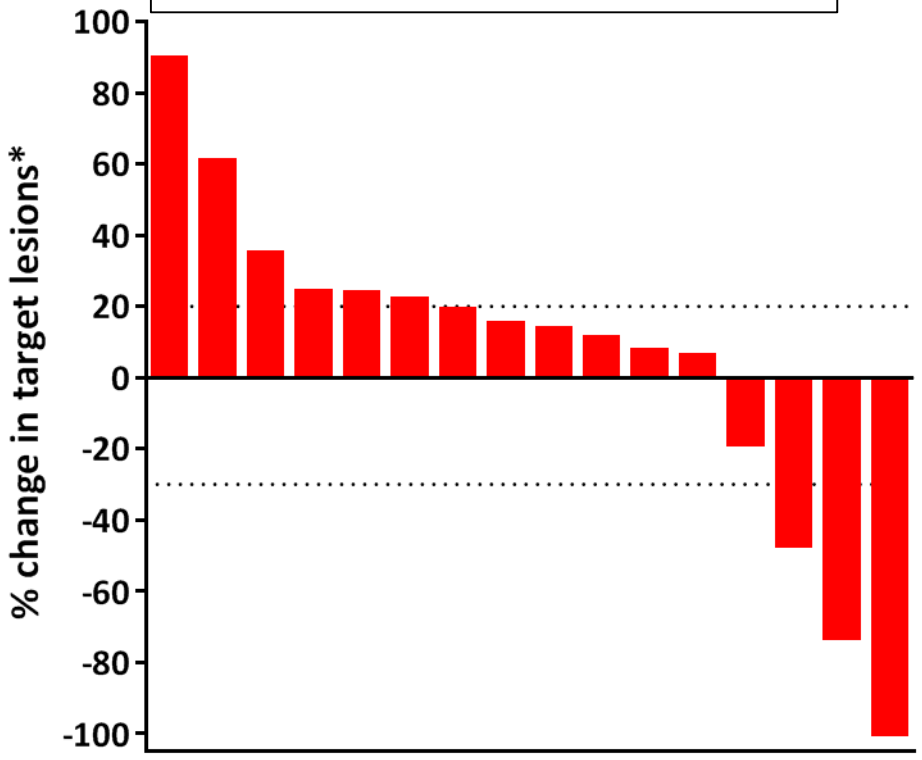
Melanoma Rescue Cohort Responses

Please see poster #O16 for detailed information on all cohorts

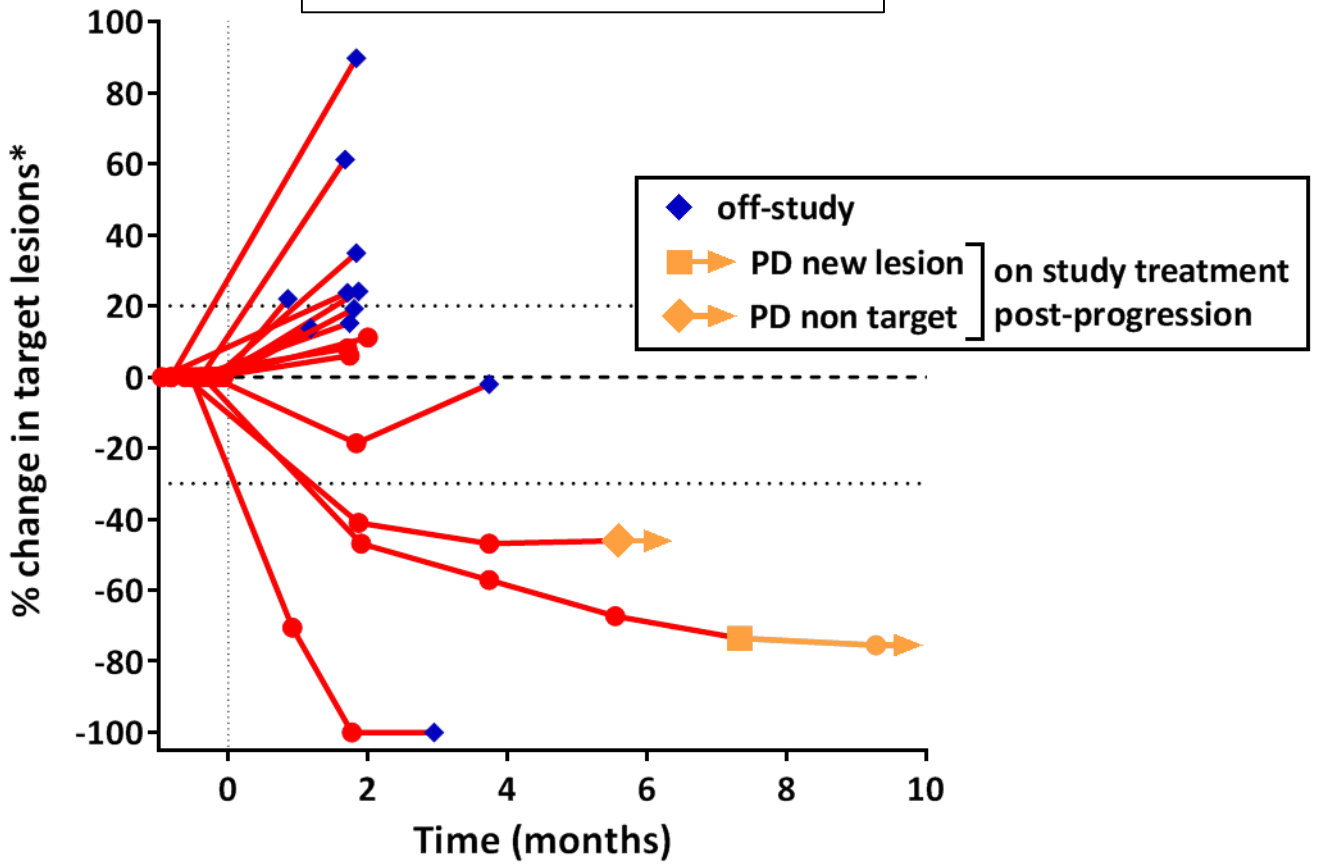
Deep Responses in Melanoma Rescue Cohort

ORR of 19% in melanoma patients progressing on α-PD-(L)1 at study entry

Best Change in Tumor Burden



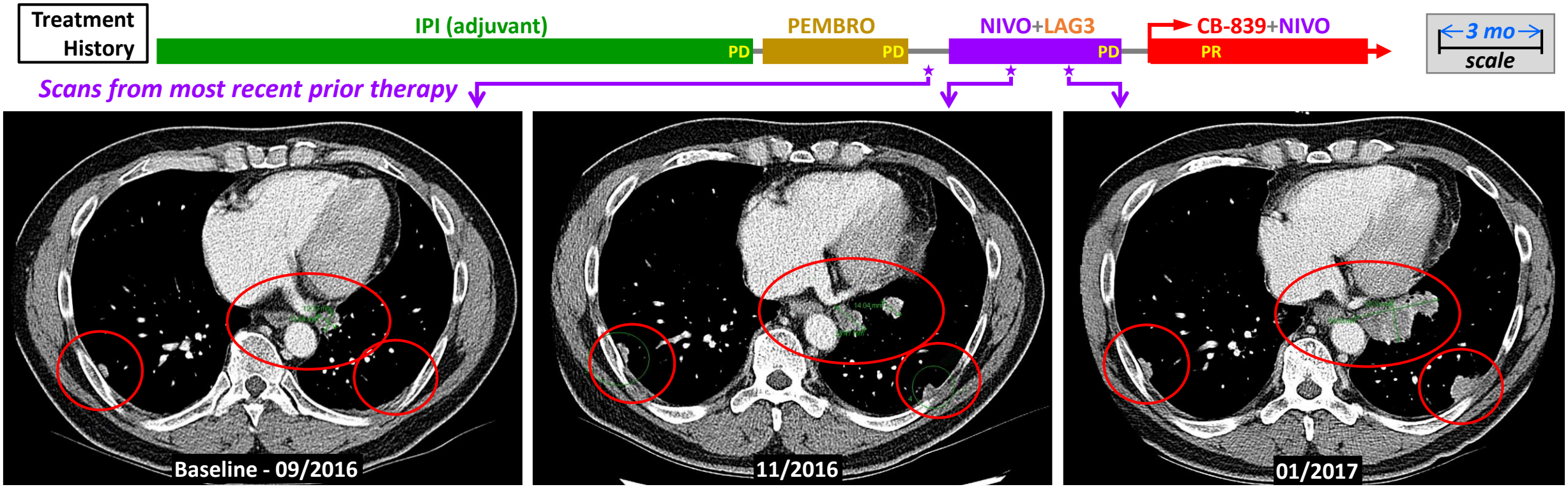
Tumor Burden over Time



*Target lesion Response by RECIST 1.1

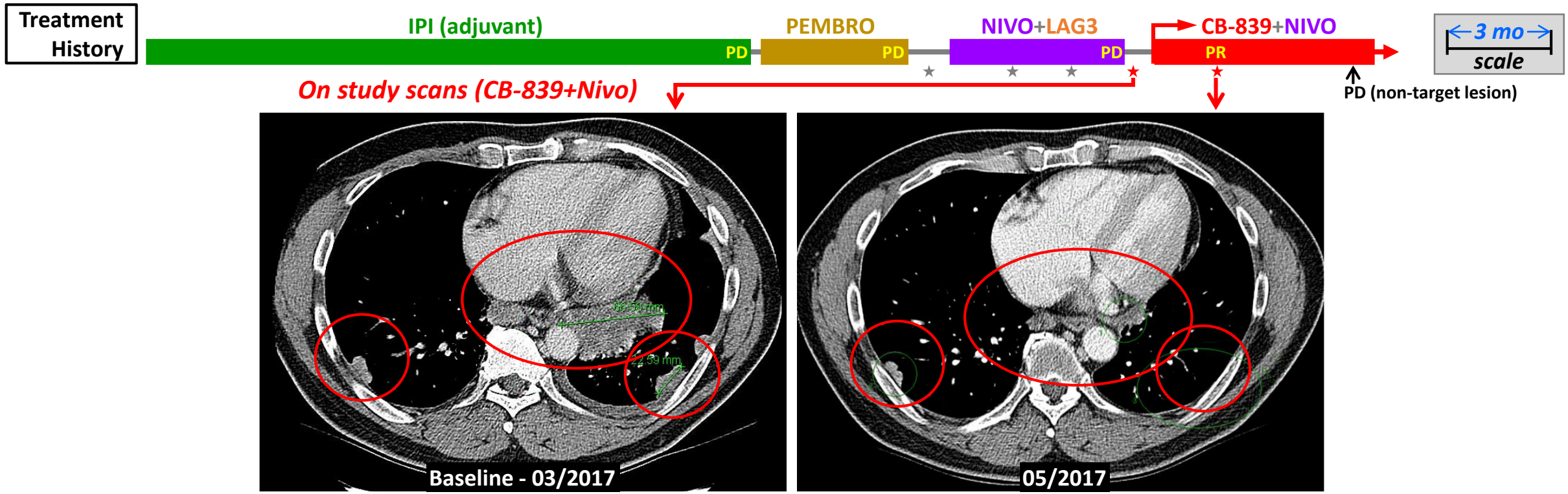
Melanoma Rescue Case Study: Patient 1

- 51 yo M with Stage M1c metastatic melanoma, LDH↑, BRAF wt
- Prior therapy: best response PD on all prior IO regimens
- Immediate prior therapy: ***rapid and symptomatic*** progression on nivolumab + α-LAG3
- Sites of disease: large intestine, lung, pleural cavity, skin, lymph nodes

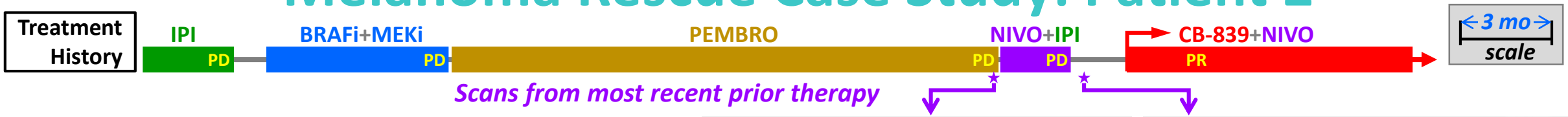


Patient 1: Dramatic and Rapid Response to CB-839 + Nivolumab

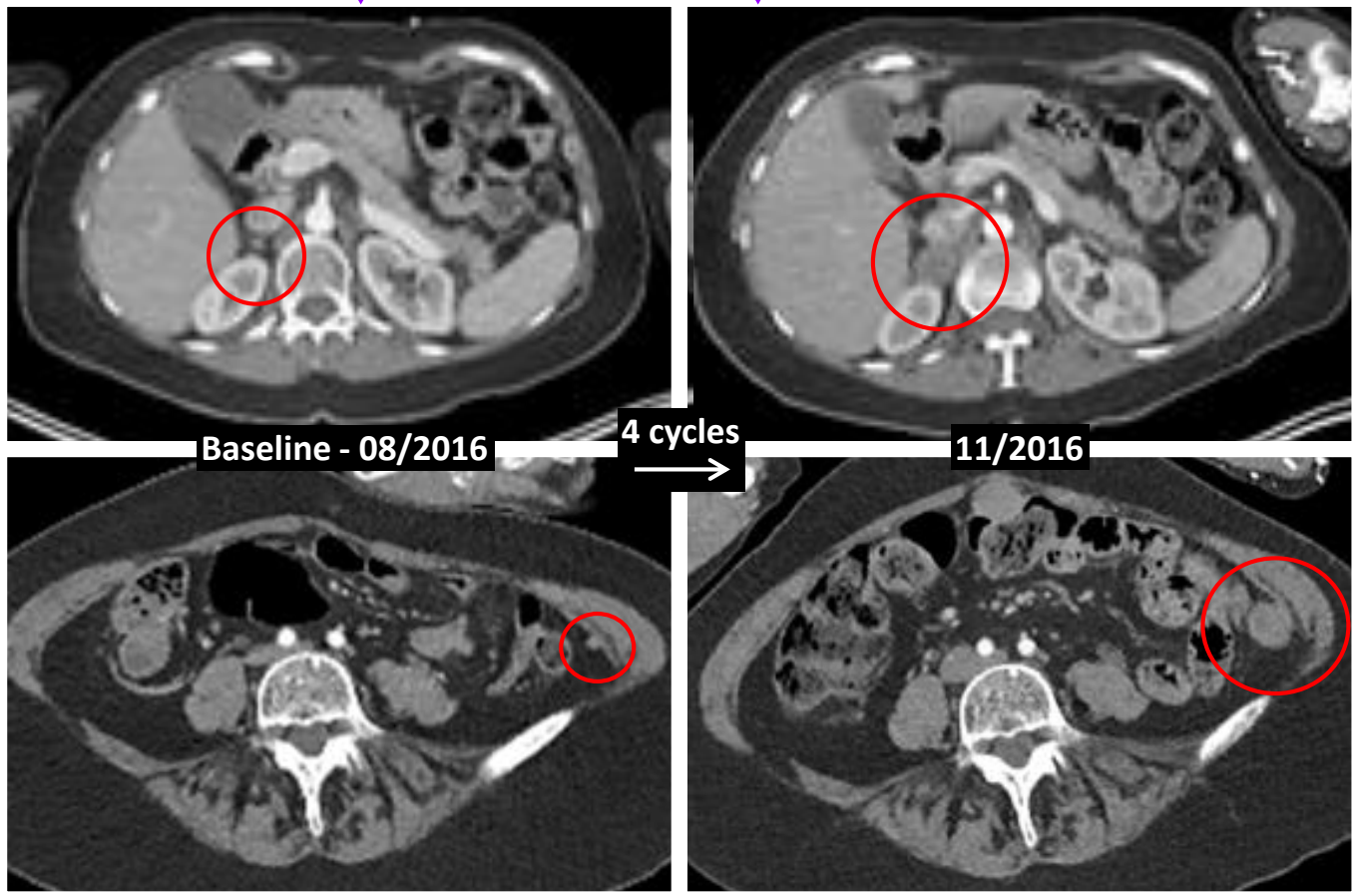
- Time to PR ~8 weeks (-41%); resolution of respiratory symptoms; RECIST response confirmed (-47%)
- DOR 3.7 mo; PD for non-target skin lesions (target still -46%)
- Current status: s/p resection of skin lesions for TIL harvest; pt remains on study for clinical benefit
- TOS 6.3 months



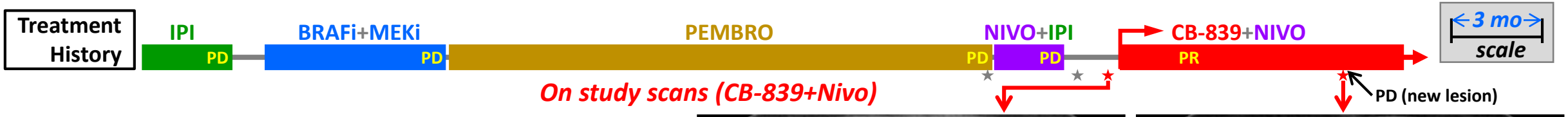
Melanoma Rescue Case Study: Patient 2



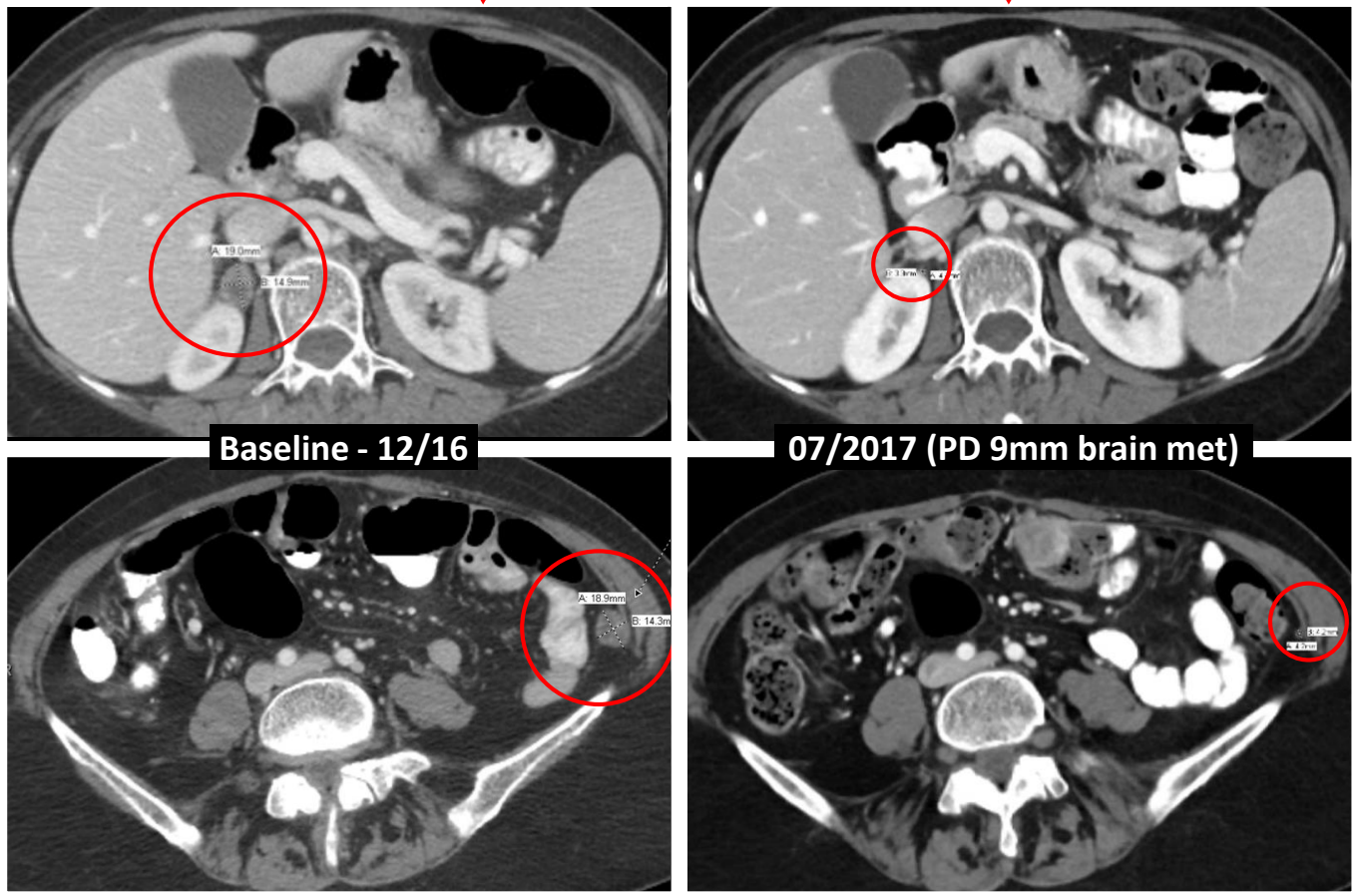
- 61 yo F with Stage M1c metastatic melanoma, BRAF mutant
- Prior therapy: best IO response non-CR/non-PD (pembro)
- Immediate prior therapy: rapid multi-lesion progression on nivo + ipi (4 cycles)
- Sites of disease: chest wall, para-renal, stomach wall, multiple peritoneal metastases



Patient 2: Dramatic and Rapid Response to CB-839 + Nivolumab



- Time to PR ~8 weeks (-47%, confirmed)
- Best RECIST response -73%
- DOR 5.4 mo
- PD new 9 mm brain met (target lesion response -73% at time of PD); received SRS to brain lesion
- Current status: Remains on study treatment for clinical benefit; RECIST target lesion response remains -73% and TOS 9.3 mo

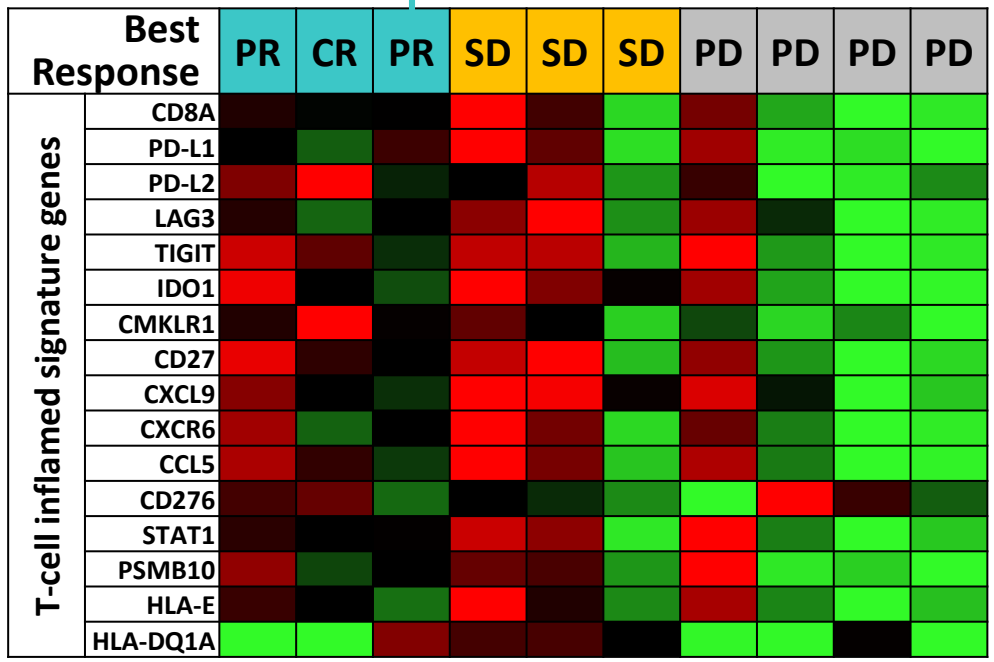


Disease Control in Melanoma Rescue Patients with Inflamed Tumors

- Gene expression analyzed in tumor biopsies from Melanoma Rescue cohort
  - 10 baseline, 1 paired (pre- and post-dose) from responding patient

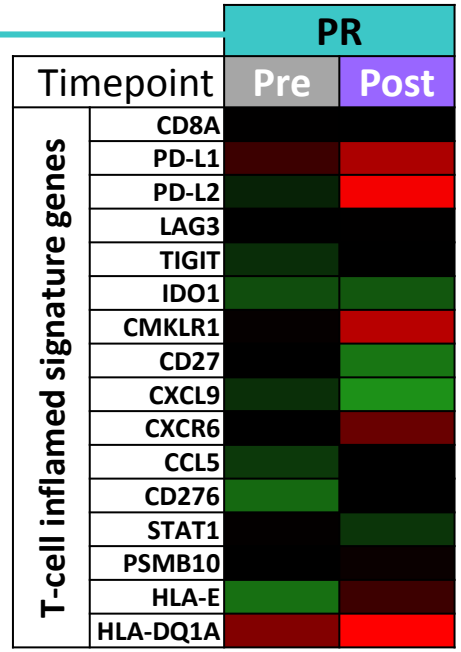
Pre-treatment biopsies

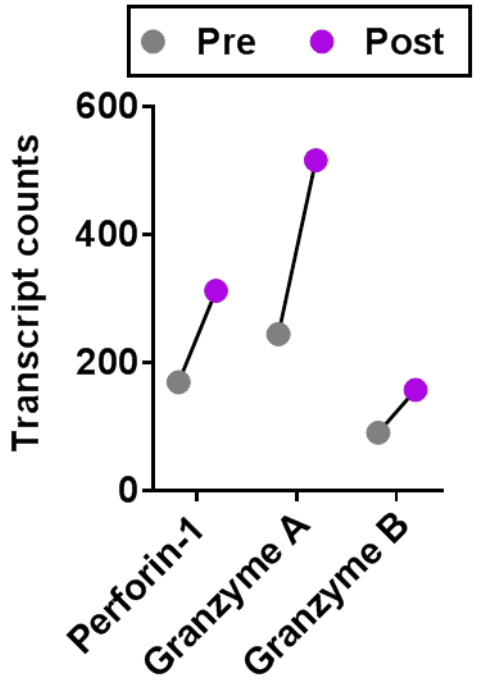
- Elevated T-cell inflamed signature* in pre-treatment biopsies (despite progressive disease) associated with clinical benefit from addition of CB-839



Paired biopsies from responding patient

- Post-treatment (C2D1) increase in T-cell inflamed signature* and T-cell effector genes





*predictive of pembrolizumab response [Ayers et al (2017) *J Clin Invest.* 127:2930]

Conclusions

- The combination of CB-839 + nivolumab is well tolerated
- This ongoing study is designed to stringently test for benefit of adding CB-839 to nivolumab in IO refractory patients
- Melanoma responders (ORR 19%) demonstrate clinical activity and suggest that resistance to α-PD-(L)1 can be overcome by the addition of CB-839
- Disease control seen in the majority of NSCLC and RCC patients progressing on α-PD-(L)1 therapy at study entry is encouraging
- ORR is 21% in RCC IO Naïve cohort with 74% DCR and 50% of enrolled patients remaining on study treatment
- The Melanoma Rescue cohort has been expanded to explore the encouraging signal of this new mechanism of action

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