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Early FDG-PET Response Correlates With Dose and Efficacy in Patients With Microsatellite Stable mCRC Treated With Carcinoembryonic Antigen T-cell Bispecific (CEA-TCB) Antibody Plus Atezolizumab

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Presenter Disclosure Information

Jose Saro

The following relationships exist related to this presentation:

- *Roche employee*
- *Roche stockholder*

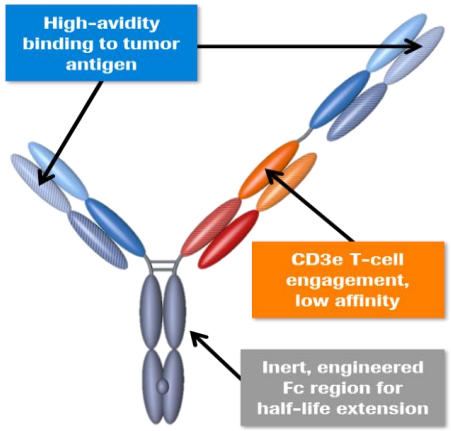
Introduction

- CEA-TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody under investigation as monotherapy and in combination with atezolizumab (anti–PD-L1) in CEA-expressing tumors, including mCRC, of which > 90% of patients express high levels of CEA[1-5]
- CEA-TCB showed manageable toxicity and encouraging signs of clinical activity in combination with atezolizumab in patients with ≥ 3L MSS mCRC,[4,5] which is a disease setting with high unmet medical need[6-8]
  - Atezolizumab enhances anti-cancer immunity, resulting in durable responses as monotherapy across a range of diseases and survival benefit as monotherapy in cancer such as NSCLC[9,10]
- The use of FDG-PET as a pharmacodynamic biomarker for immunotherapy in mCRC has not been established previously
- We report preliminary results of FDG-PET imaging as an early pharmacodynamic marker for CEA-TCB in combination with atezolizumab in patients with MSS mCRC

3L, third line; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; MSS, microsatellite stable; NSCLC, non-small cell lung cancer. 1. Bacac M, et al. *Clin Cancer Res.* 2016; 2. Hammarström S. *Semin Cancer Biol.* 1999; 3. Tiernan JP, et al. *Br J Cancer.* 2013; 4. Tabernero J, et al. ASCO 2017 [abstract 3002]; 5. Argiles G, et al. ESMO GI 2017 [abstract LBA-004]; 6. Grothey A, et al. *Lancet.* 2013; 7. Mayer RJ, et al. *N Engl J Med.* 2015; 8. Le DT, et al. *N Engl J Med.* 2015; 9. TECENTRIQ [package insert] 2017; 10. Rittmeyer A, et al. *Lancet.* 2017.

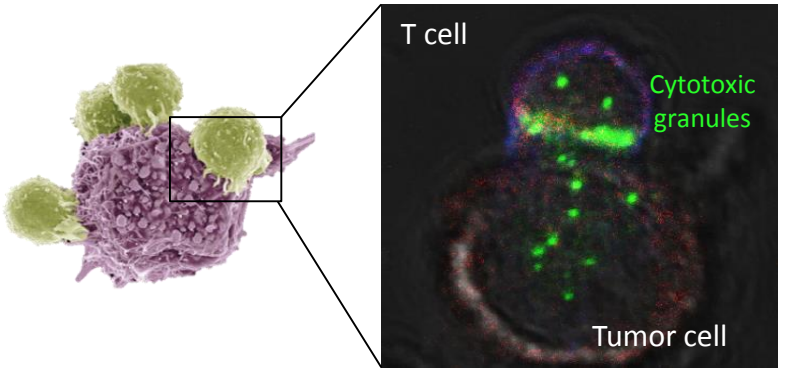
CEA-TCB 2-to-1 Format and Mechanism of Action

Structure



- Simultaneous binding with 1 arm to CD3 on T cells and 2 arms to CEA on tumor cells
- Flexibility that enables high-avidity binding and selective killing of high–CEA-expressing tumor cells
- A longer half-life compared with other TCB formats
- A silent Fc, which results in a reduced risk of Fcγ receptor–related cytokine release/IRRs

Mechanism of Action[1]



Killing of tumor cells independent of pre-existing immunity through release of cytotoxic granules

- T-cell engagement and activation and tumor-cell killing by delivery of cytotoxic granules[2,3]
- CEA-TCB is uniquely designed to[2,3]:
  - Simultaneously bind to tumor and T cells
  - Engage and activate T cells, inducing potent killing of tumor cells
  - Increase T-cell infiltration, resulting in a more inflamed tumor micro-environment

Fc, fragment crystallizable; IRR, infusion-related reaction.

1. Figure (right) adapted from: Green *The Scientist* April 2014; 2. Bacac M, et al. *Clin Cancer Res.* 2016; 3. Bacac M, et al. *Oncoimmunology.* 2016.

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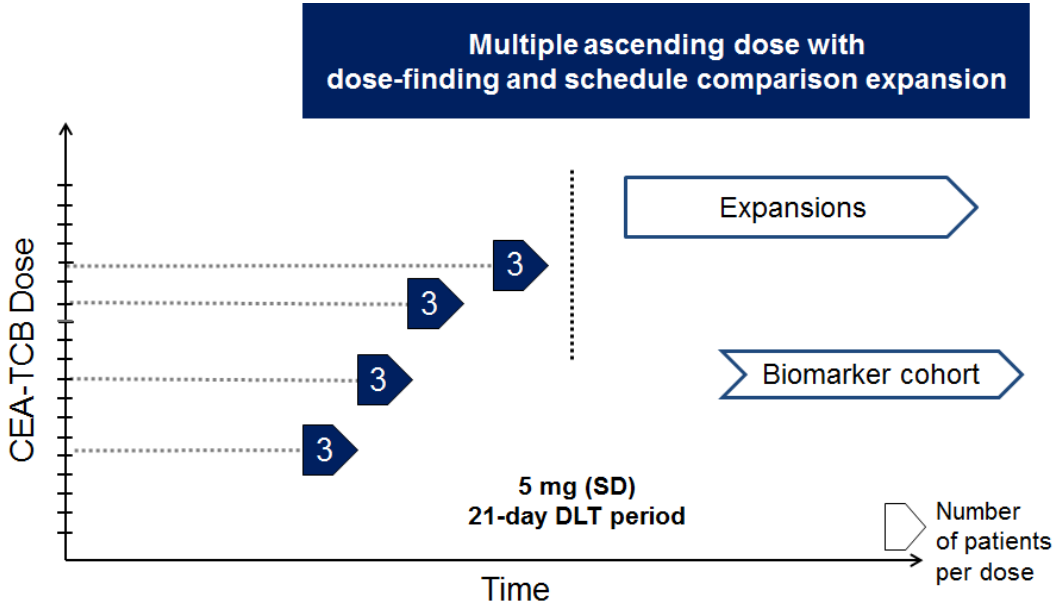
Ongoing Phase Ib Study of CEA-TCB Plus Atezolizumab



- **Key objectives:** Safety/tolerability; MTD and/or recommended dose; preliminary anti-tumor activity and ORR, DOR, DCR and PFS; PK/PD

- **All patients:** locally advanced/metastatic CEA+ solid tumors[a] with ≥ 1 tumor lesion able to be biopsied who progressed on or are intolerant of standard therapy
  - Measurable disease (RECIST v1.1) and ECOG PS 0-1
- **Evaluable patients:** n = 25 of 77 for FDG-PET analyses; n = 24 for RECIST v1.1 vs FDG-PET analyses
  - Median follow-up duration, 119 days (range, 50-360 days); data cutoff, June 6, 2017
- **Treatment:** CEA-TCB at 5 to 300 mg IV qw + atezolizumab 1200 mg IV q3w
- **Methods:** FDG-PET/CT imaging was performed before treatment start and 3 to 7 weeks after treatment start
  - On-treatment changes in SUV_{max}, MTV and TLG were analyzed in ≤ 10 measurable lesions per patient[b]
  - Exploratory statistical analyses used semi-parametric Gaussian regression models and Cox proportional hazards models and Kaplan-Meier landmark analyses (for PFS)[c]

CT, computed tomography; MTD, metabolic tumor volume; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis. [a] Moderate to high CEA expression in ≥ 20% of tumor cells by IHC using CEA-specific antibody. [b] As identified by an independent reviewer at baseline. [c] PFS was defined as the time from post-baseline FDG-PET assessment to progressive disease by RECIST v1.1. or death, whichever occurred first. NCT02650713.

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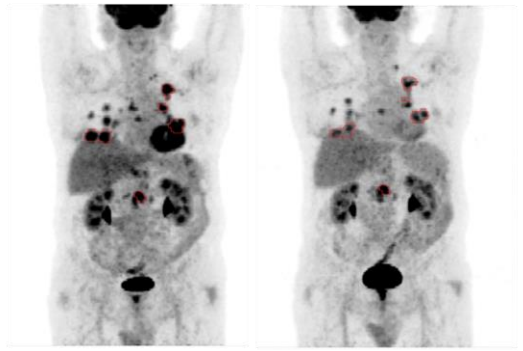
FDG-PET Measured CEA-TCB–Induced Pharmacodynamics

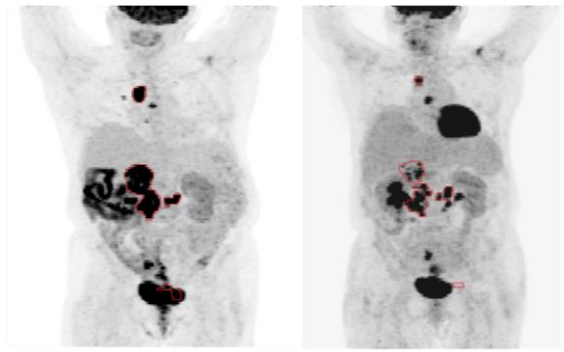
Change in FDG Uptake from Baseline

CEA-TCB 80 mg IV qw + atezolizumab 1200 mg IV q3w



Baseline C2D8 (week 4)

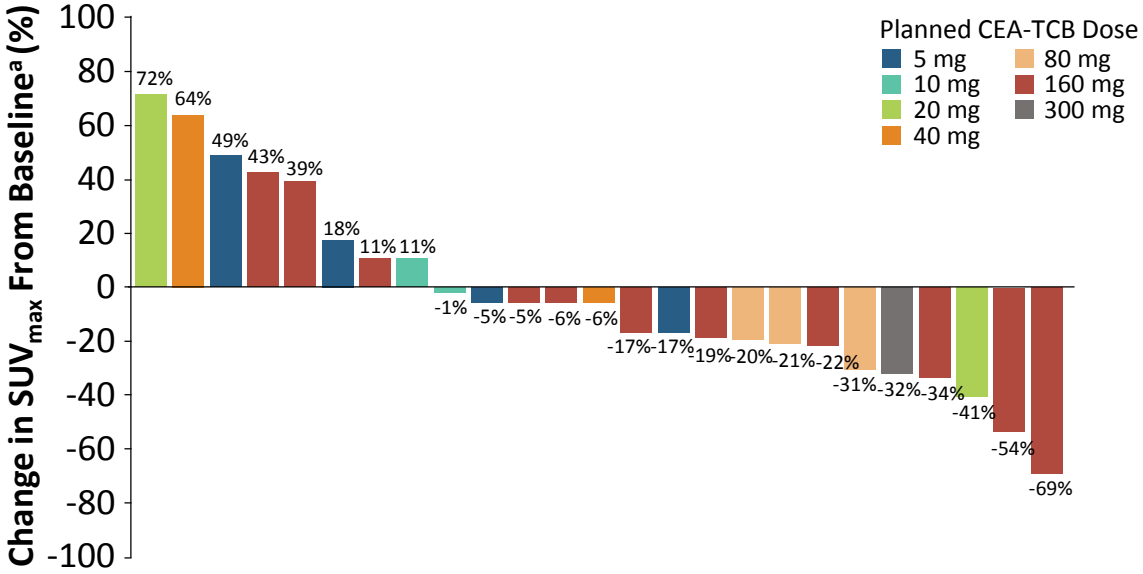
CEA-TCB 160 mg IV qw + atezolizumab 1200 mg IV q3w



Baseline C2D8 (week 4)

- On-treatment maximum-intensity–projection images (right) showed reduction in FDG uptake vs pre-treatment images (left)

Change in SUV_{max} From Baseline by CEA-TCB Dose



- On-treatment decreases in tumor metabolic activity were seen in most patients treated at doses ≥ 80 mg of CEA-TCB + atezolizumab

C2D8, cycle 2 day 8. Data cutoff for CT scan: July 14, 2017.
[a] Measurements were centrally assessed.

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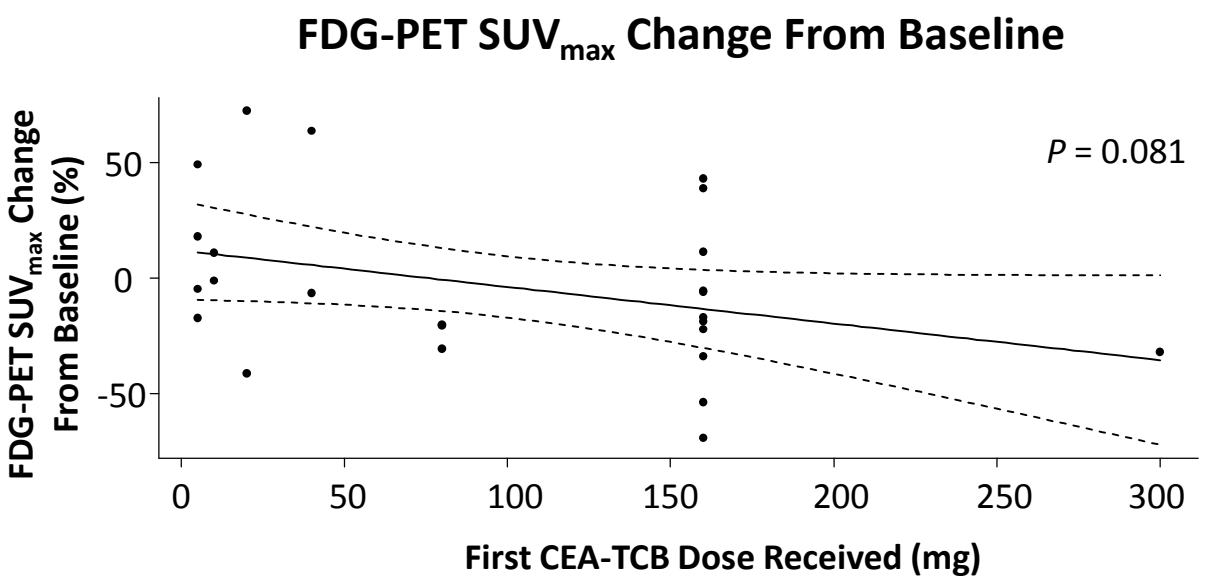
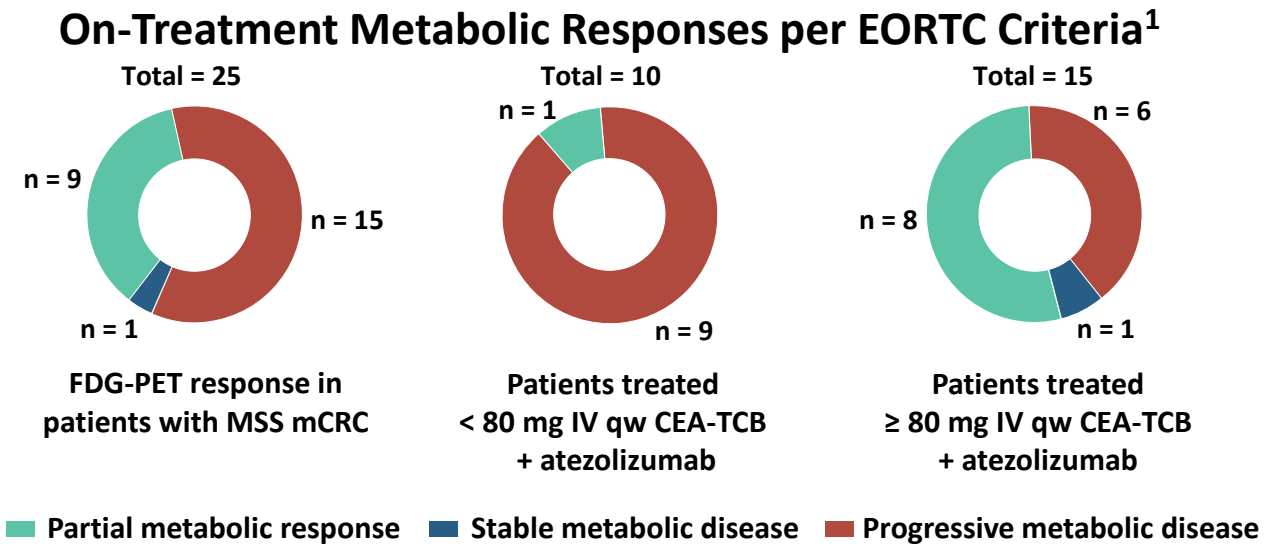
Change in On-Treatment SUV_{max} and Metabolic Responses Appeared to Correlate With CEA-TCB Dose





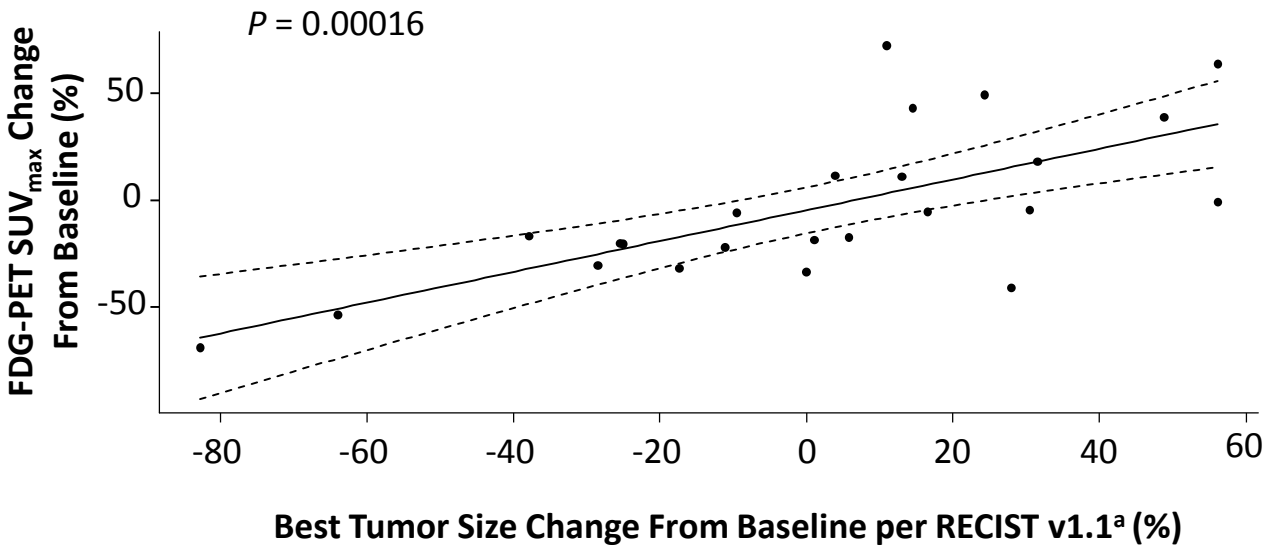
- On-treatment decreases in SUV_{max} appeared to correlate with increasing CEA-TCB doses + atezolizumab (*P* = 0.081)

- Partial metabolic response was reported in 10% (1 of 10) of patients treated with CEA-TCB < 80 mg + atezolizumab
- Partial metabolic response was reported in 53% (8 of 15) of patients treated with CEA-TCB ≥ 80 mg + atezolizumab

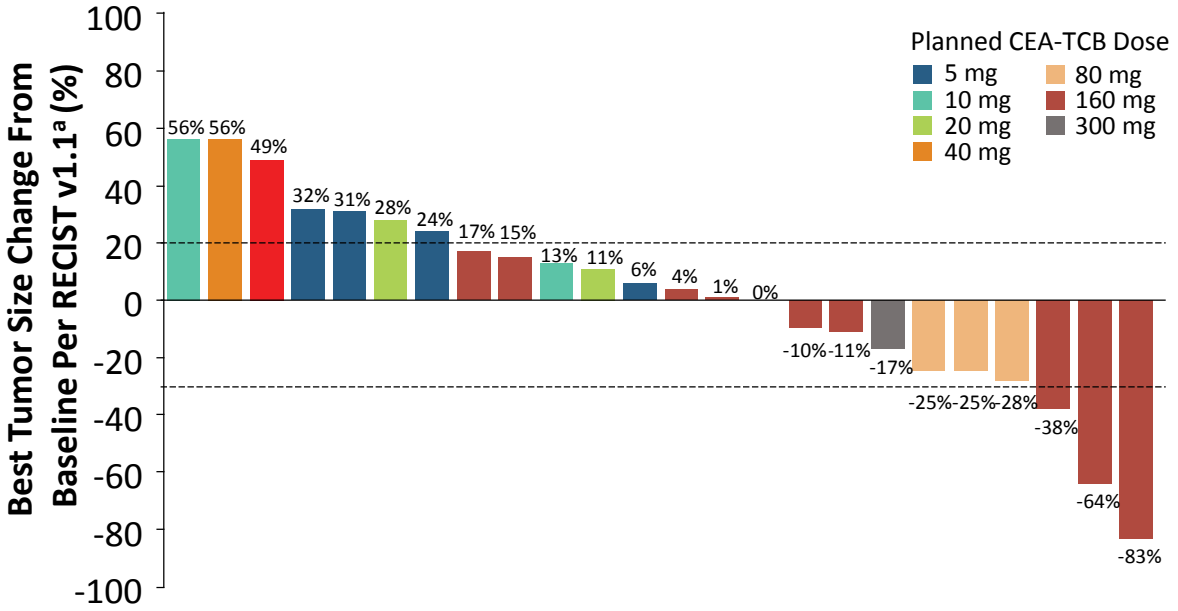
1. Young H, et al. *Eur J Cancer*. 1999.

Change in On-Treatment FDG-PET SUV_{max} Appeared to Correlate With Best Tumor Size Change From Baseline

FDG-PET SUV_{max} Change From Baseline by Best Change in Tumor Size From Baseline Per RECIST v1.1



Best Change in Target Lesion(s) From Baseline per RECIST v1.1 by CEA-TCB Dose[a]



- On-treatment decreases in SUV_{max} appeared to correlate with reduction in tumor size ($P < 0.001$)
- Reduction in tumor size was seen mainly in patients treated with CEA-TCB ≥ 80 mg + atezolizumab

[a] Investigator assessed.

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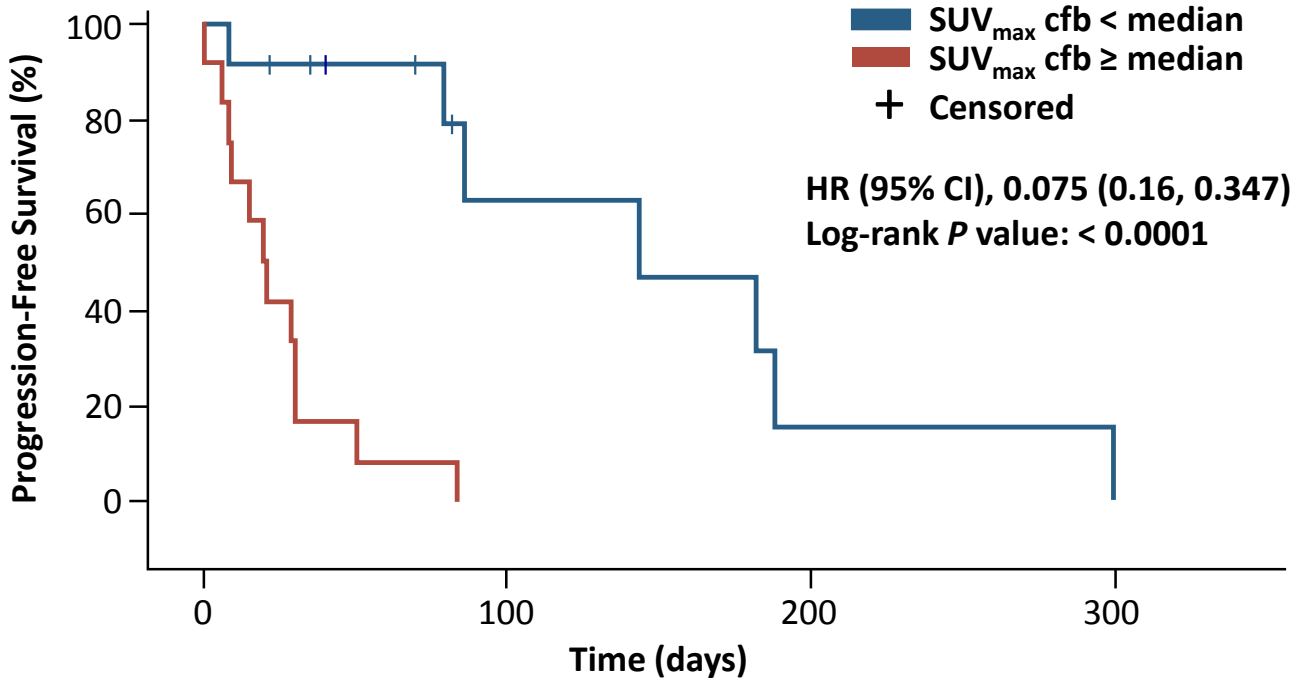
Change in On-Treatment FDG-PET Appeared to Correlate With Longer PFS



- On-treatment reduction in SUV_{max} appeared to correlate with prolonged PFS[a] ($P < 0.0001$)

cfb, change from baseline. FDG-PET SUV_{max} cfb median cutoff = -6.39.

[a] PFS was defined as the time from post-baseline FDG-PET assessment to progressive disease by RECIST v1.1. or death, whichever occurred first.

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Conclusions

- SUV_{max} reduction after CEA-TCB + atezolizumab appeared to correlate with:
  - Higher CEA-TCB doses
  - Tumor size reduction
  - Longer PFS following FDG-PET assessment
- Early on-treatment changes in FDG-PET may act as a pharmacodynamic biomarker related to treatment efficacy and potentially guide dose selection in patients with MSS mCRC
- Further analyses to validate the use of FDG-PET and CT scans are ongoing

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