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Phase I Study of Stereotactic Body Radiotherapy (SBRT) Plus Nivolumab and Urelumab or Nivolumab and Cabiralizumab in Patients with Advanced Solid Tumors

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Disclosures

- CCF has no conflicts to disclose.

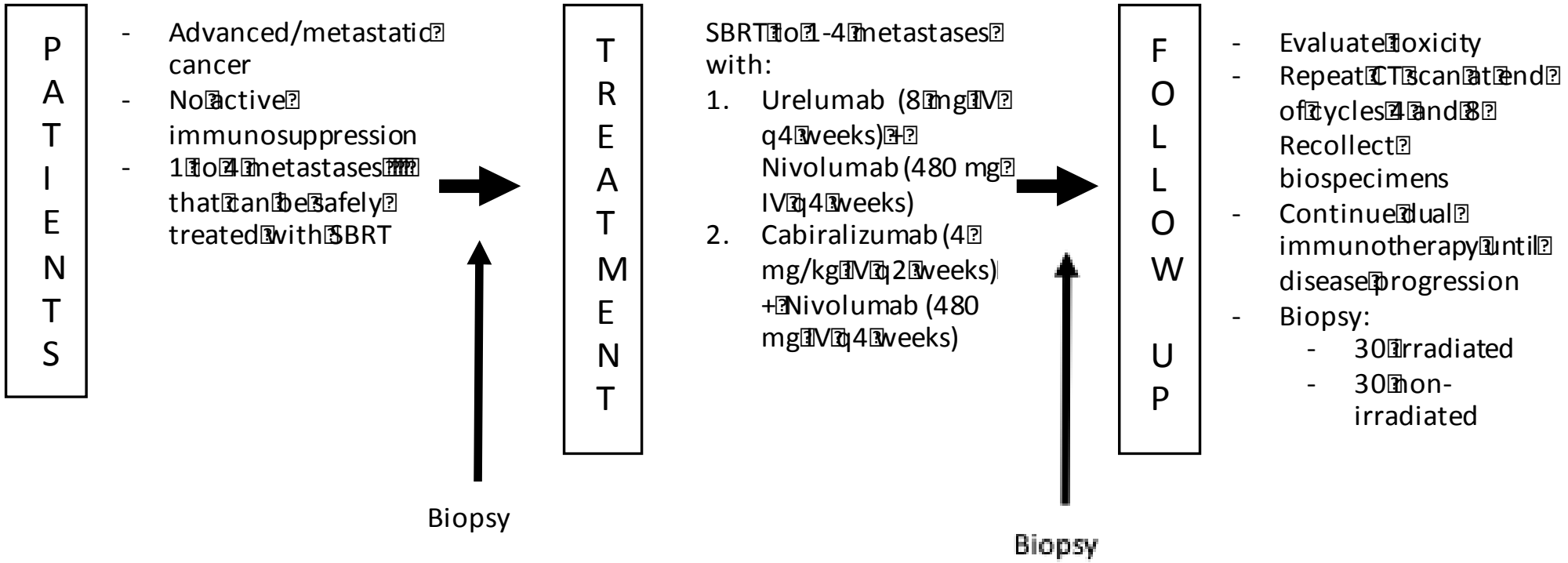
Background

- SBRT alone has been safely administered to multiple metastatic sites.[1]
- SBRT + single-agent immune checkpoint inhibition is associated with a favorable toxicity profile in phase I and II studies.[2,3]
- The safety and efficacy of high-dose, multisite SBRT combined with dual-agent immunotherapy remains unknown.

Study Rationale

- Urelumab, an agonistic anti-4-1BB antibody, may deepen and prolong anti-tumor responses.
- Cabiralizumab, an antagonistic anti-CSF-1R antibody, may overcome resistance to immunotherapy by limiting macrophage-associated immunosuppression.

Schema



Immunotherapy-refractory histologies preferentially assigned to cabiralizumab arm

Study Design

- Primary endpoint: Dose-limiting toxicity defined as grade 3+ toxicity within 90 days of SBRT day 1.
- Recommended organ-specific SBRT dose will be associated with DLT rate ≤33%.
- Secondary endpoints: RECIST v1.1 response, progression-free survival, overall survival.
- Pre- and post-SBRT biospecimens for molecular correlative studies.

Key Eligibility Criteria

- ECOG 0 or 1
- Advanced solid malignancy progressing on standard therapy (may include prior immunotherapy)
- Unselected for PD-L1 expression
- No active CNS disease
- SBRT targets have not received >10% prescription from prior radiation therapy

Treatment Details

Radiation Therapy (SBRT) Dose

Tumor Location	Initial Starting Dose	Decreased DLT Dose
Lung-Peripheral	45 Gy (3 fractions)	42 Gy (3 fractions)
Lung-Central OR Mediastinal/Thoracic (axillary or cervical) Lymph Node	50 Gy (5 fractions)	47.5 Gy (5 fractions)
Liver	45 Gy (3 fractions)	42 Gy (3 fractions)
Spinal/Paraspinal OR Osseous	30 Gy (3 fractions)	27 Gy (3 fractions)
Abdominal-Pelvic metastases (Lymph Node/Adrenal Gland)	45 Gy (3 fractions)	42 Gy (3 fractions)

Patient Characteristics

Characteristic	All patients (*N* = 59)	Cabiralizumab (*N* = 36)	Urelumab (*N* = 23)
Age, Mean (Range)	58 (25-85)	54 (25-85)	64 (35-78)
Male – No. (%)	20 (34)	13 (36)	7 (30)
Distinct Anatomic SBRT Sites – No. (%)			
1	39 (66)	23 (64)	16 (70)
2	19 (32)	13 (36)	6 (26)
3	1 (2)	--	1 (4)
Smoking Status – No. (%)			
Current/Former	17 (29)	8 (22)	9 (39)
Never	42 (71)	28 (78)	14 (61)

Patient Characteristics

Characteristic	All patients (*N* = 59)	Cabiralizumab (*N* = 36)	Urelumab (*N* = 23)
No. prior therapies – Median, IQR	5 (3-7)	5 (3-7)	5 (2-7)
Prior immunotherapy – No. (%)	10 (17)	5 (14)	5 (22)
Primary Cancer – No. (%)			
Colorectal	13 (22)	6 (17)	7 (30)
Breast	7 (12)	6 (17)	1 (4)
Pancreatic/Ampullary	7 (12)	7 (19)	--
Ovarian/Fallopian	6 (10)	2 (6)	4 (17)
Endometrial/Leiomyosarcoma	7 (12)	3 (8)	4 (17)
Other	19 (32)	12 (33)	7 (30)

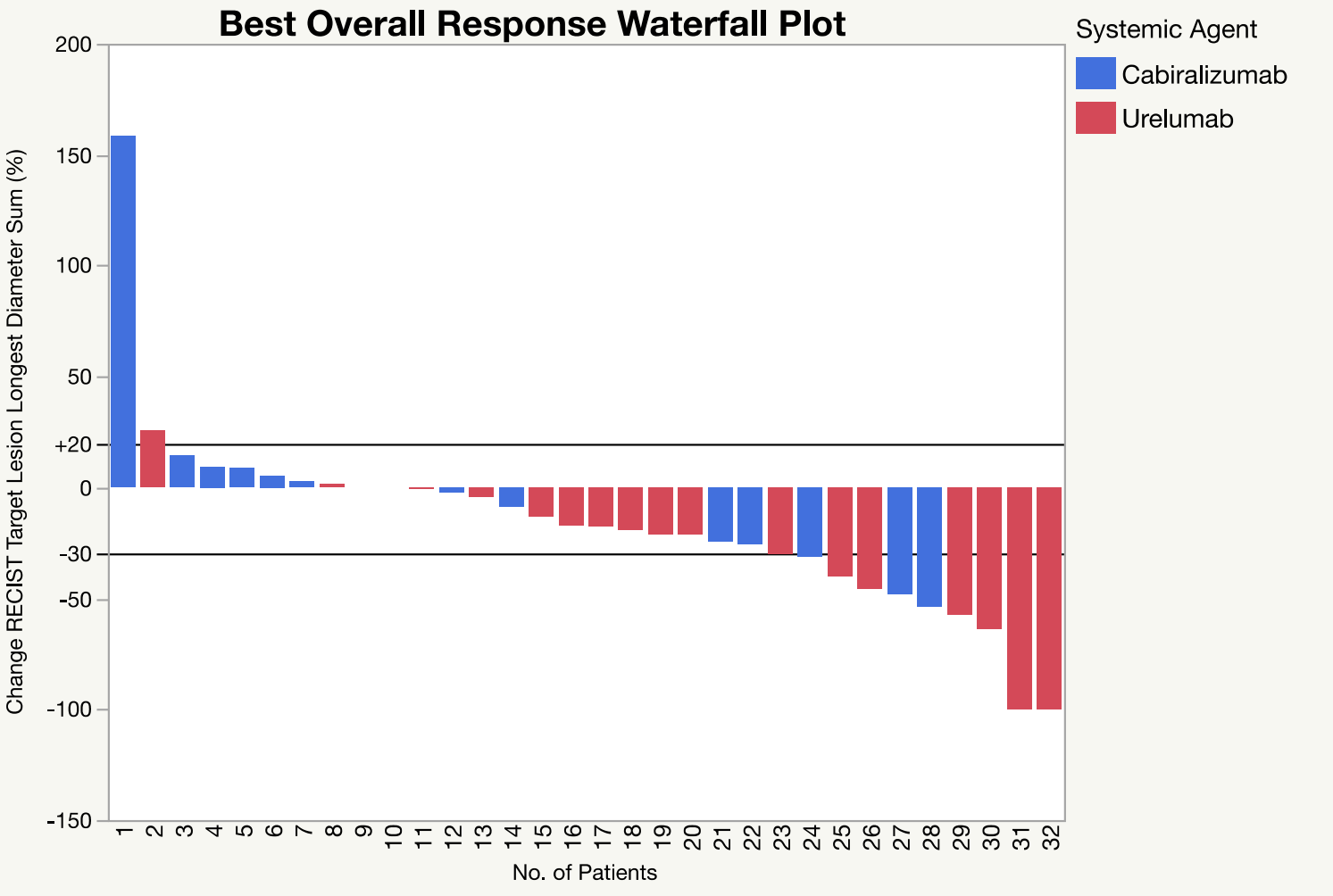
Results

- Median follow-up is 7.7 months for 36 living patients and 5.3 months for 56 treated patients
- Forty patients are evaluable for DLTs 90 days post-SBRT with 5 experiencing at least 1 DLT (13%).
- No SBRT dose reductions based on DLT rates for each of 5 anatomic SBRT cohorts.

Dose-Limiting Toxicity

- **DLTs by anatomic cohort:**
- Peripheral lung: 1/7 (14%, grade 3 maculopapular rash)
- Central lung: 1/10 (10%, grade 4 CPK elevation)
- Liver: 1/9 (11%, grade 3 colitis)
- Osseous: 0/3 (0%)
- Abdomen/Pelvic: 2/11 (18%, grade 3 CPK elevation, grade 4 hyperglycemia)
- **DLTs by systemic agent:**
- Nivolumab + cabiralizumab: 5/19 (26%)
- Nivolumab + urelumab: 0/21 (0%)

RECIST Target Lesion Response



Objective response rate = 17.1%

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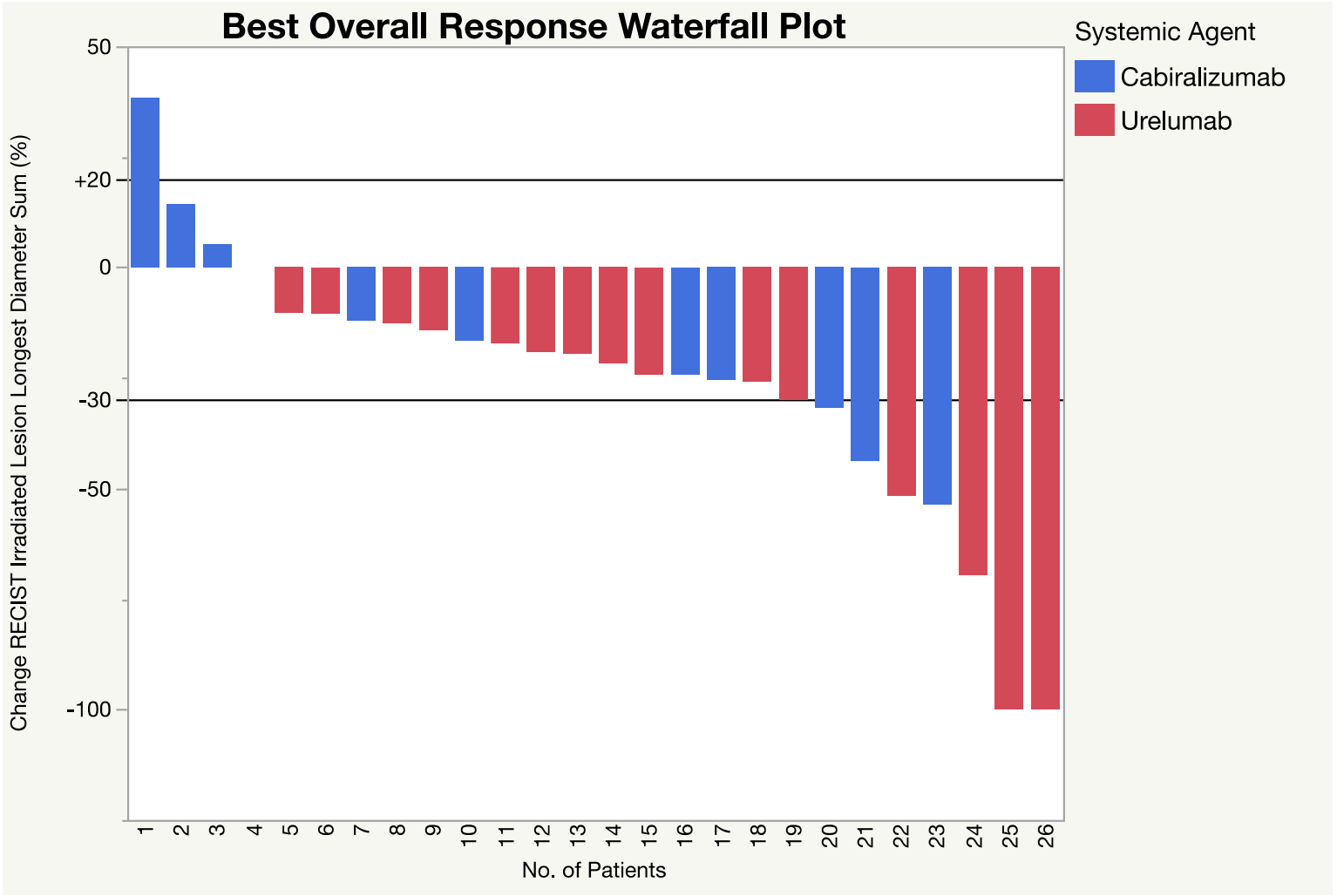
RECIST Irradiated Target Lesion Response



Mean percent change: -26.0% (SD 30.5%)

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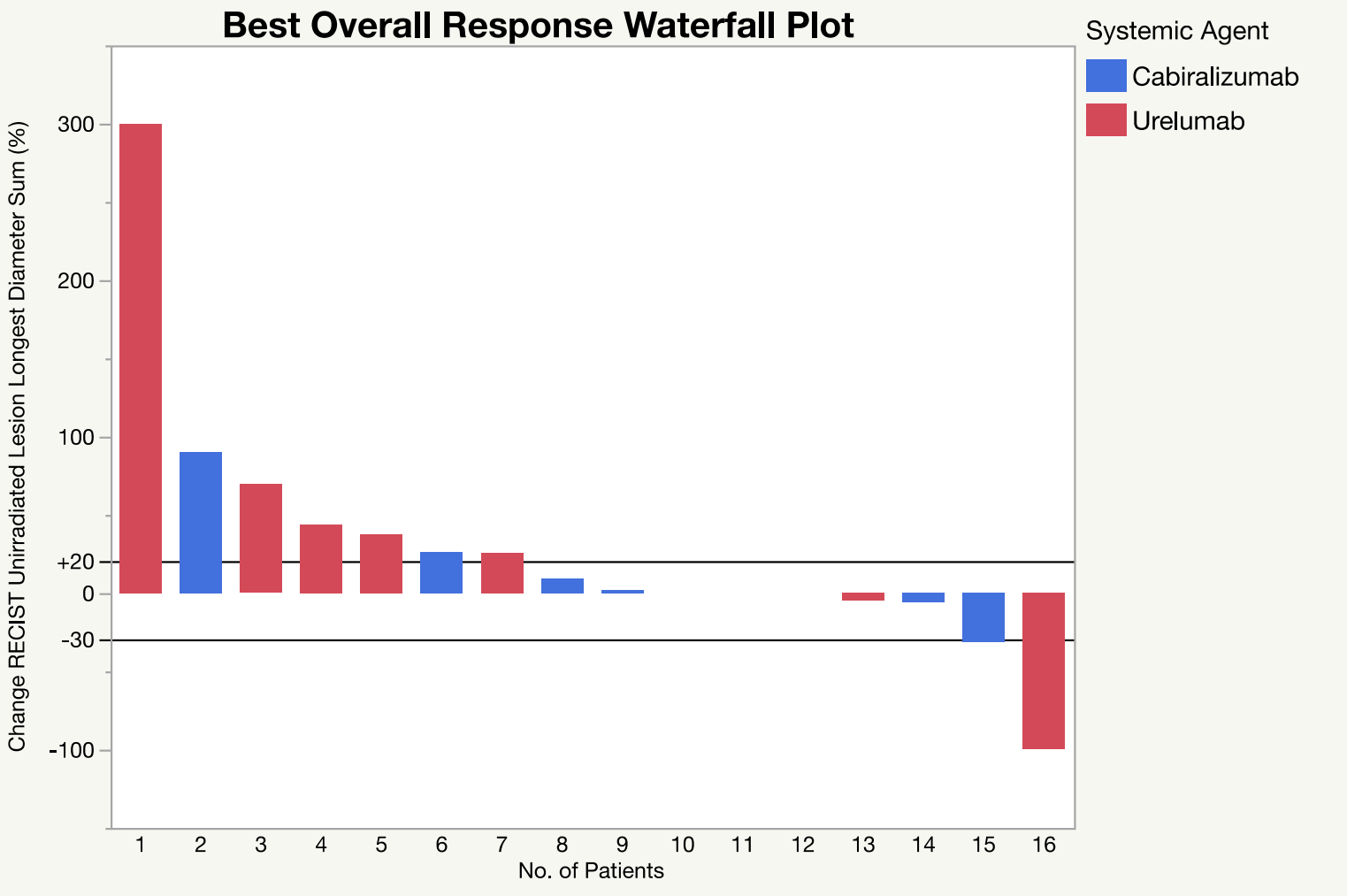
RECIST Unirradiated Target Lesion Response



Mean percent change: +5.8% (SD 83.8%)

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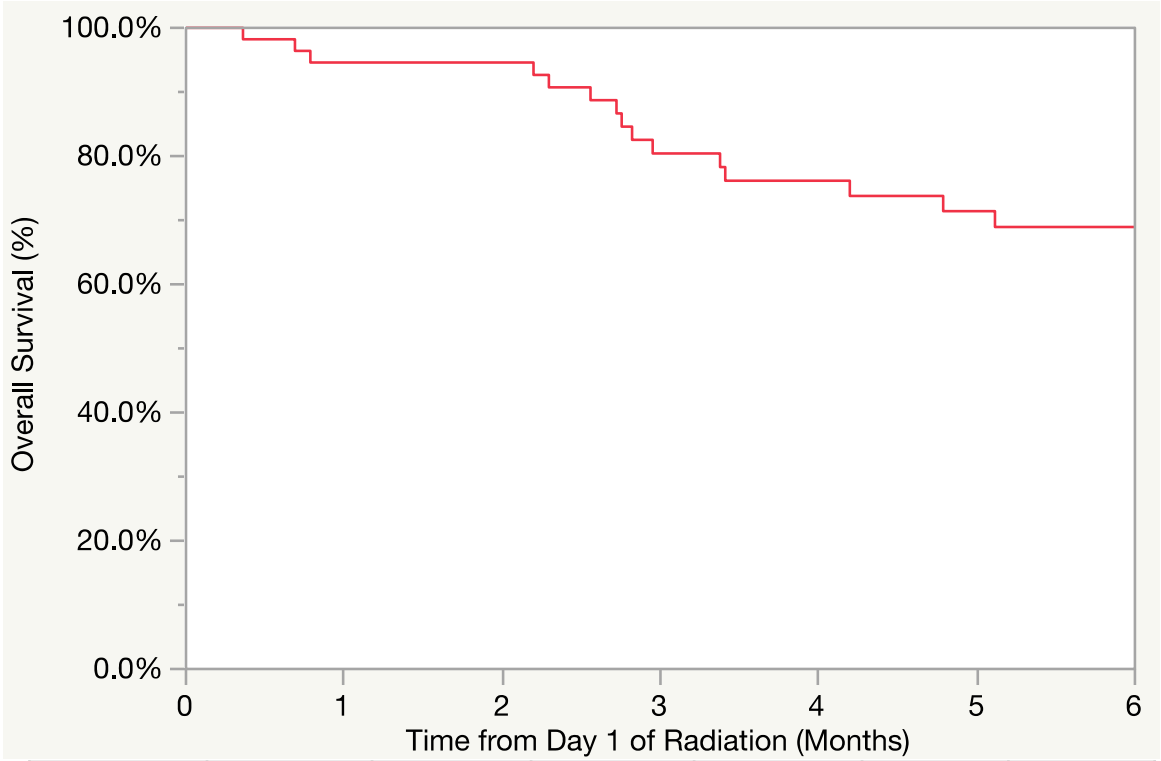
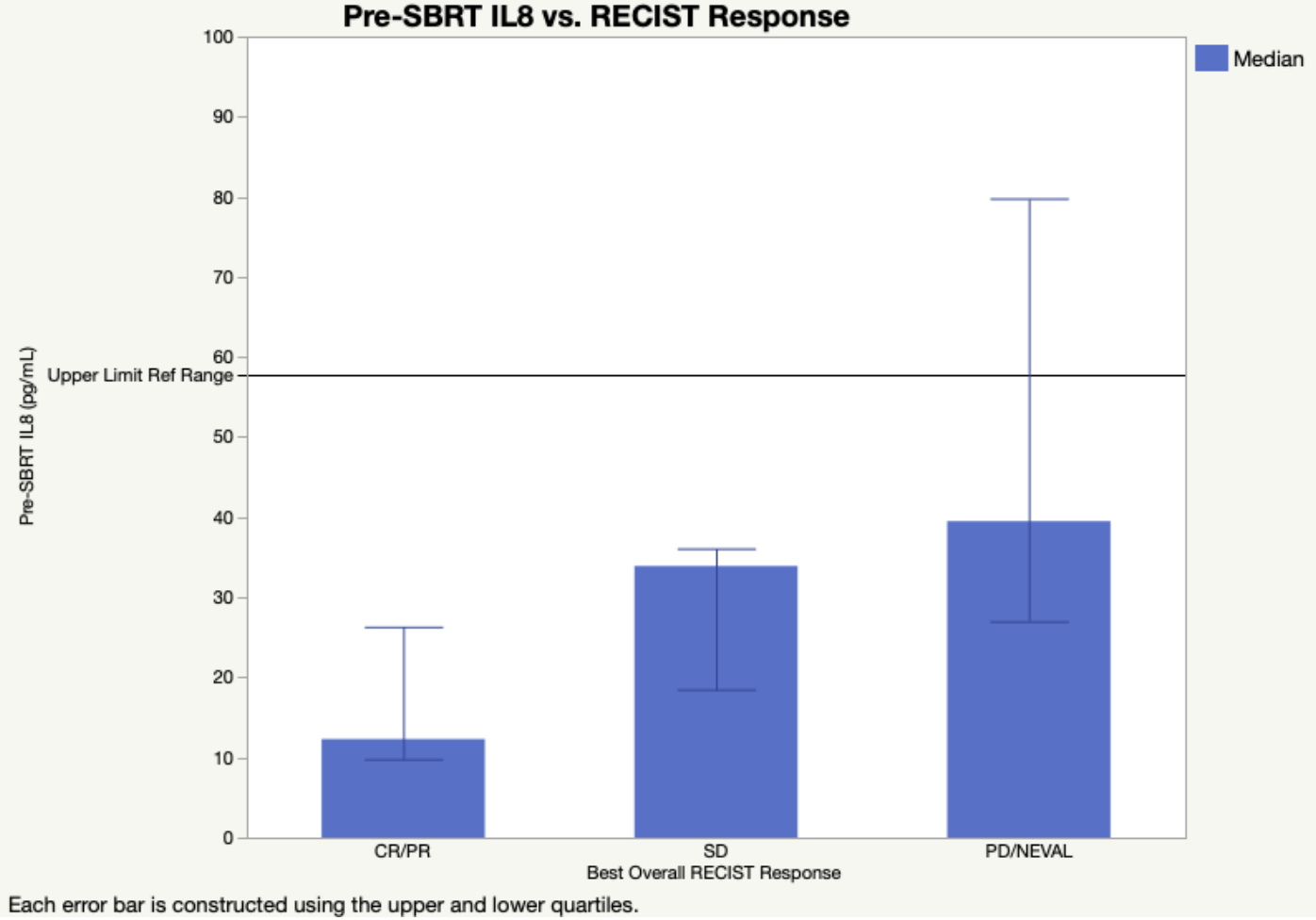
Overall Survival



No. at Risk						
56	53	50	39	35	31	27

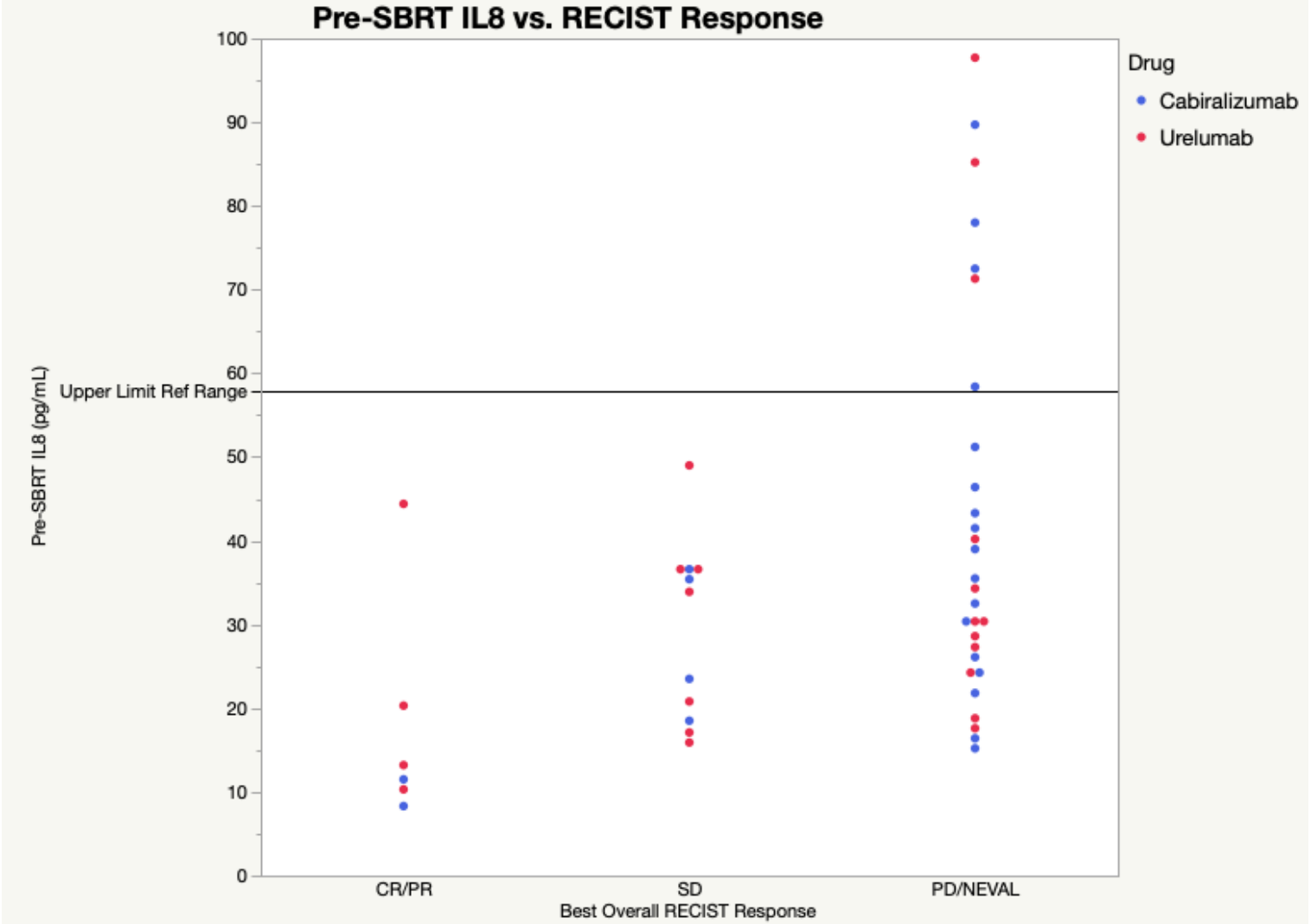
Median OS not reached (95% CI 8.4 months – not reached)

Pre-SBRT IL8 vs. RECIST Response



Pre-SBRT IL8 is associated with RECIST response category (p=0.008)

Pre-SBRT IL8 vs. RECIST Response



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Conclusions

- Multisite SBRT plus nivolumab/cabiralizumab or nivolumab/urelumab preliminarily demonstrates acceptable toxicity.
- Preliminary data suggest potential for clinically meaningful anti-tumor activity.
- Ongoing investigation with molecular correlative studies is warranted.

Acknowledgements

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- Robyn Hseu, CCRP, MLIS
- Linda Janisch, APNP
- Gini Fleming, MD
- Steven J. Chmura, MD, PhD

References

1. Chmura SJ, Winter K, Salama JK, et al. Phase I trial of stereotactic body radiation therapy (SBRT) to multiple metastatic sites: a NRG Oncology study. Int J Radiat Oncol Biol Phys 102:S68-S69, 2018.
2. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. J Clin Oncol 36:1611-1618, 2018.
3. Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs. pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol DOI: 10.1001/jamaoncol.2019.1478, 2019.