Managing Oligometastatis With Stereotactic Radiosurgery

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Frontiers of Radiosurgery

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A Paradigm Shift

- Patients with metastatic disease have historically been treated with a palliative intent, with systemic and local therapies aimed at extending life in the short term or improving quality of life

- A new treatment paradigm is emerging for oligometastatic disease: prolongation of survival or *?cure* is the goal

- *Ablative the*rapy with SBRT is at the forefront of this movement

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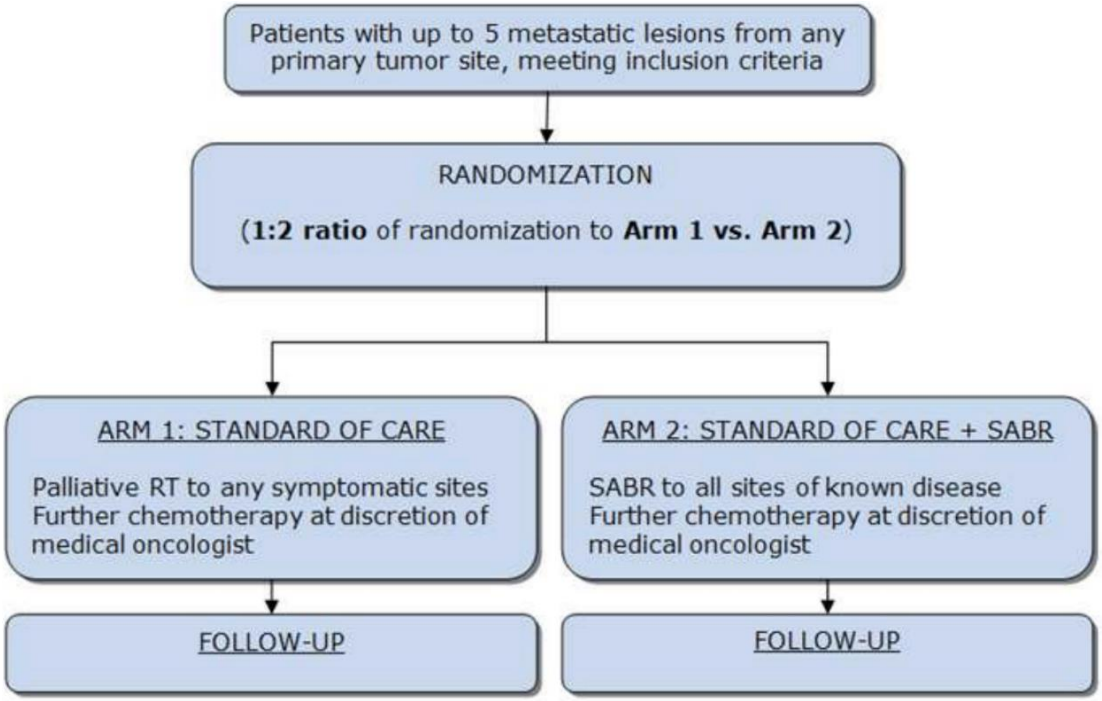
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)



Purpose:

Compare SABR with current approaches of chemotherapy and conventional radiotherapy to assess the impact on overall survival and quality of life.

Palma, et al. SABR-COMET: Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study. ASTRO Annual Meeting, 2018.

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- **Primary Endpoint:** Overall Survival
- **Secondary endpoints:**
  - Progression-free survival
  - Toxicity (CTC-AE 4.0)
  - Quality of life (FACT-G)
  - Lesional control rate at 2 and 4 years
  - Number of cycles of further systemic therapy: Changed to binary variable “Receipt of systemic therapy” (Y/N)

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- **Key Inclusion Criteria:**
  - Controlled primary tumor of any primary site
  - Up to 5 metastasis (definition of oligometastasis)
  - Maximum three lesions on any one site
  - All disease sites safely treatable

- **Exclusion Criteria:**
  - Serious medical comorbidities precluding radiotherapy
  - Bone metastasis in a femoral bone
  - Patients with 1-3 brain metastasis and no disease elsewhere Prior radiotherapy to a site requiring treatment
  - Complete response to first-line chemotherapy (i.e. no measurable target for SABR)
  - Malignant pleural effusion
  - Inability to treat all sites of active disease
  - Clinical or radiologic evidence of spinal cord compression OR tumor within 3 mm of spinal cord on Magnetic Resonance Imaging (MRI).
  - Dominant brain metastasis requiring surgical decompression
  - Pregnant or lactating women

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Dose and Fractionation

Metastatic Disease Site	Allowed Fractionation Schemes
Lung	54 Gy / 3 fx 55 Gy / 5 fx 60 Gy / 8 fx
Bone	35 Gy / 5fx 30Gy / 3fx 16-20Gy / 1fx
Brain	SRS 18-24 Gy / 1fx SABR 40 Gy / 5fx WBRT optional
Liver	45-60 Gy / 3-8 fx
Adrenal	60 Gy / 8 fx

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Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Site of Original Primary Tumor – n(%)				0.204
Breast	18 (18.2)	5 (15.2)	13 (19.7)	
Colorectal	18 (18.2)	9 (27.3)	9 (13.6)	
Lung	18 (18.2)	6 (18.2)	12 (18.2)	
Prostate	16 (16.2)	2 (6.1)	14 (21.2)	
Other	29 (29.3)	11 (33.3)	18 (27.3)	
Location of Metastases – n(%)				0.181
Adrenal	9 (4.7)	2 (3.1)	7 (5.5)	
Bone	65 (34.0)	20 (31.3)	45 (35.4)	
Liver	19 (10.0)	3 (4.7)	16 (12.6)	
Lung	89 (46.6)	34 (53.1)	55 (43.3)	
Other	9 (4.7)	5 (7.8)	4 (3.2)	
Number of Metastases – n(%)				0.591
1	42 (42.4)	12 (36.4)	30 (45.5)	
2	32 (32.3)	13 (39.4)	19 (28.8)	
3	18 (18.2)	6 (18.2)	12 (18.2)	
4	4 (4.0)	2 (6.1)	2 (3.0)	
5	3 (3.0)	0 (0.0)	3 (4.6)	

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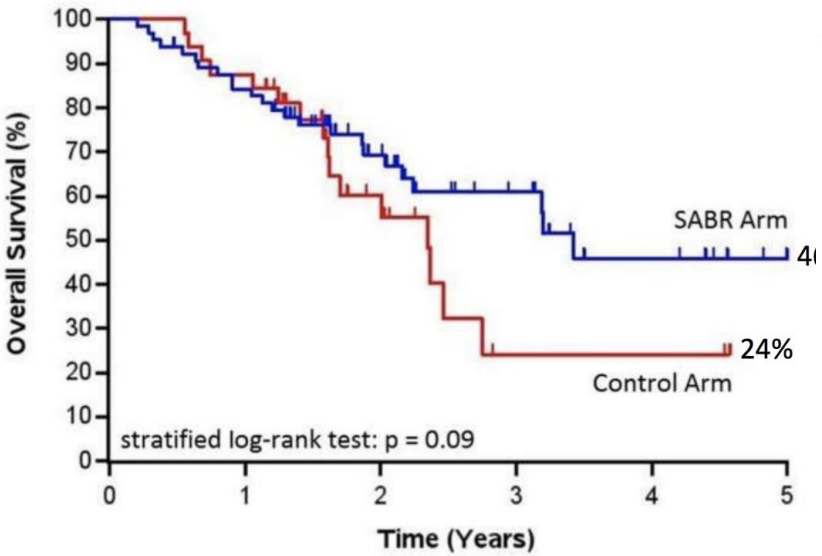
Median OS

Control Arm: 28 months
(95% CI: 19-33 months)

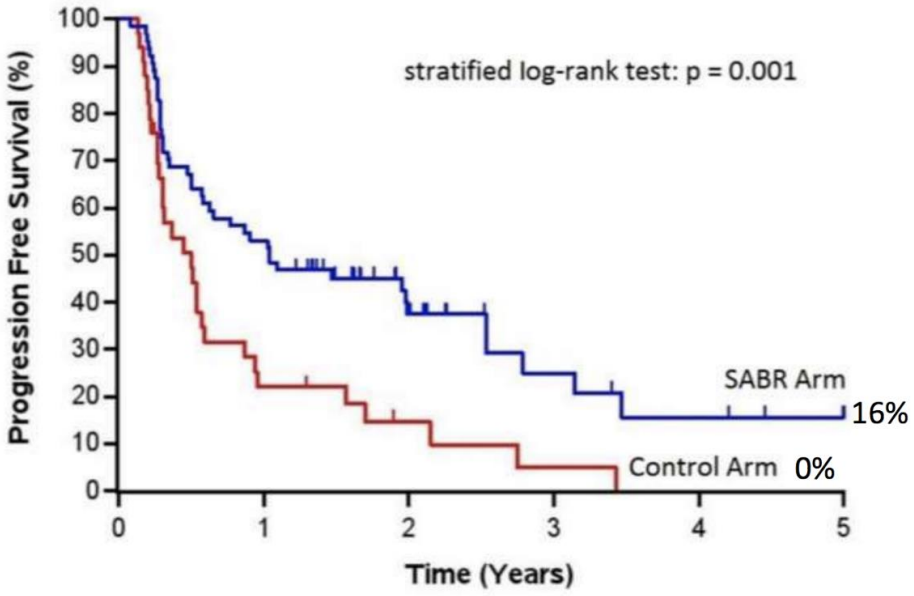
SABR Arm: 41 months
(95% CI: 26 months to 'not reached')



Median PFS

Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)



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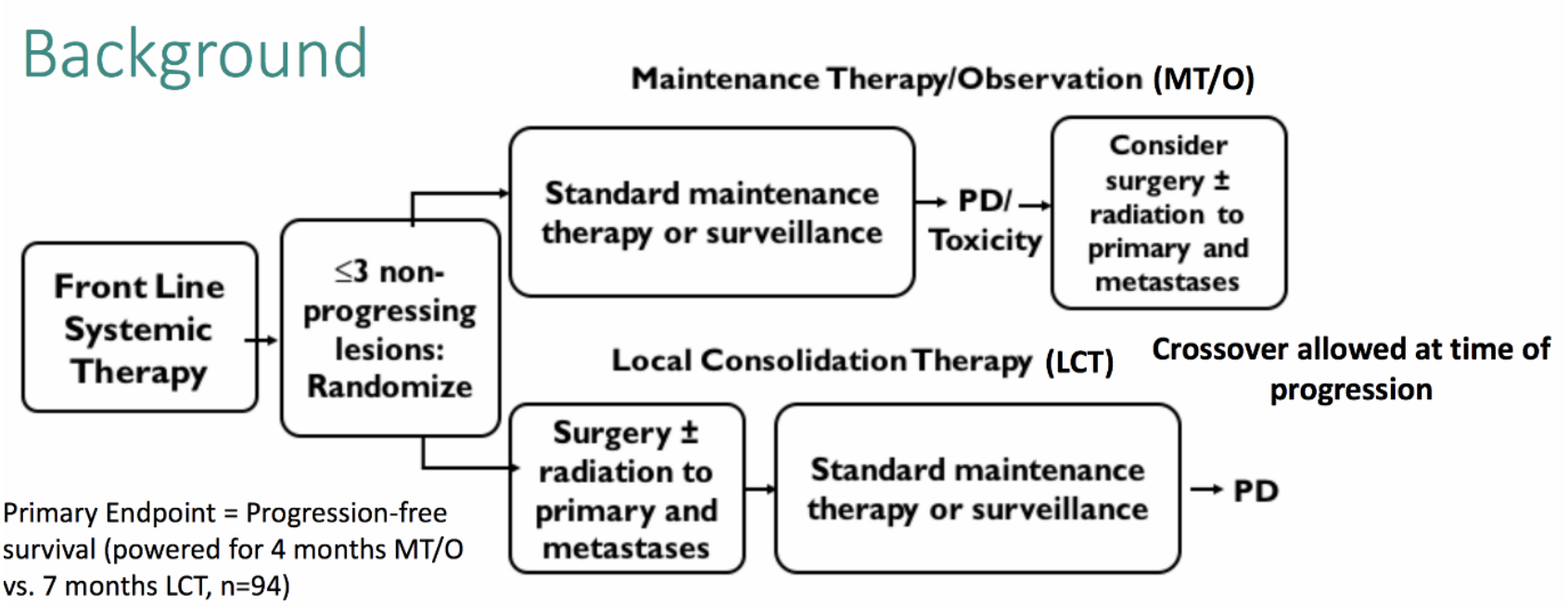
Surgery and/or RT *vs.* Standard Rx and/or Observation in Previously Treated Stage IV NSCLC (MDACC)

Randomized phase II trial to study



Gomez et al., Lancet Oncol 2016.

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Surgery and/or RT *vs.* Standard Rx and/or Observation in Previously Treated Stage IV NSCLC (MDACC)

Experimental arm:

Patients undergo ablation of all residual local and metastatic sites of disease by surgery and/or EBRT.

After completion of LCT, patients undergo either surveillance or maintenance treatment at the discretion of the treating physician.

Key eligibility criteria:
• Diagnosis of stage IV NSCLC
• ≤3 metastases after standard front-line systemic therapy
• Four cycles of platinum-doublet chemotherapy or 3 months of EGFR/ALK targeted therapy for appropriate molecular alterations
• ECOG performance status 0-2
• Eligible for "local consolidative therapy" (surgery/radiation therapy=LCT) to all sites of disease

Gomez et al., Lancet Oncol 2016.

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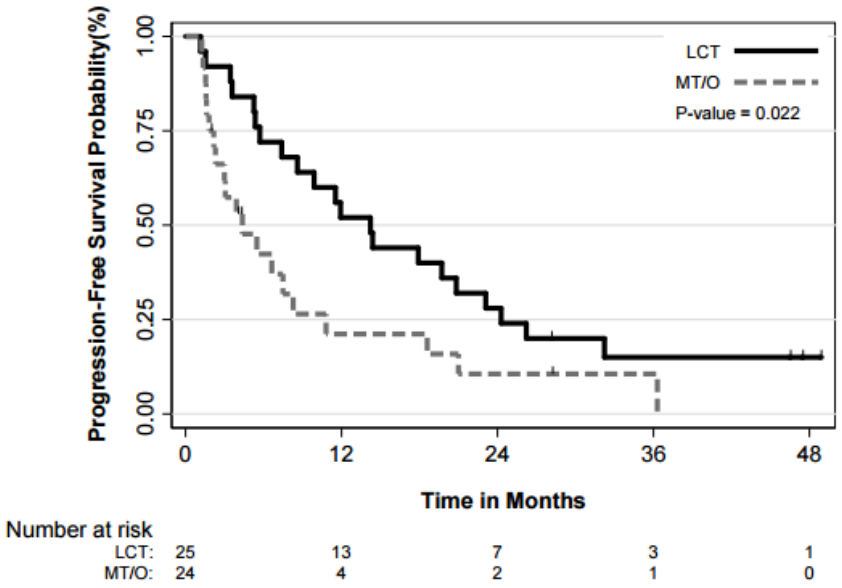
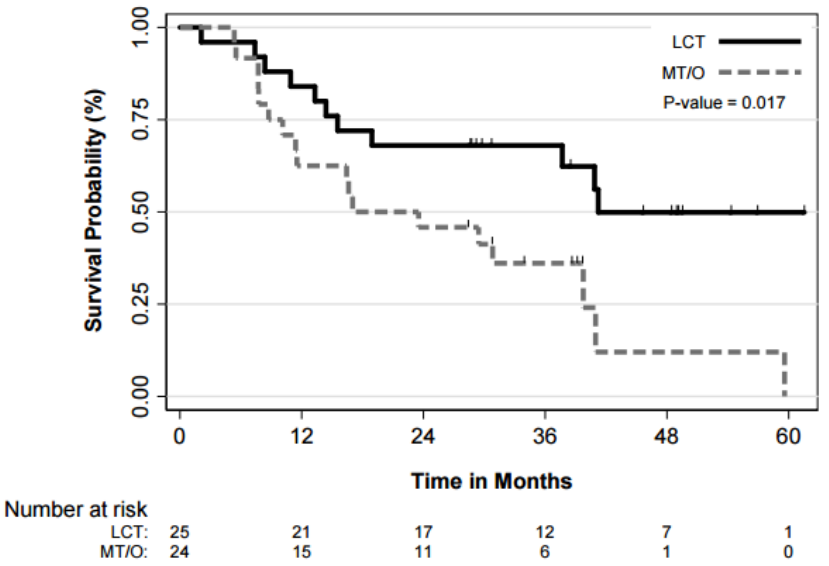
PFS



OS



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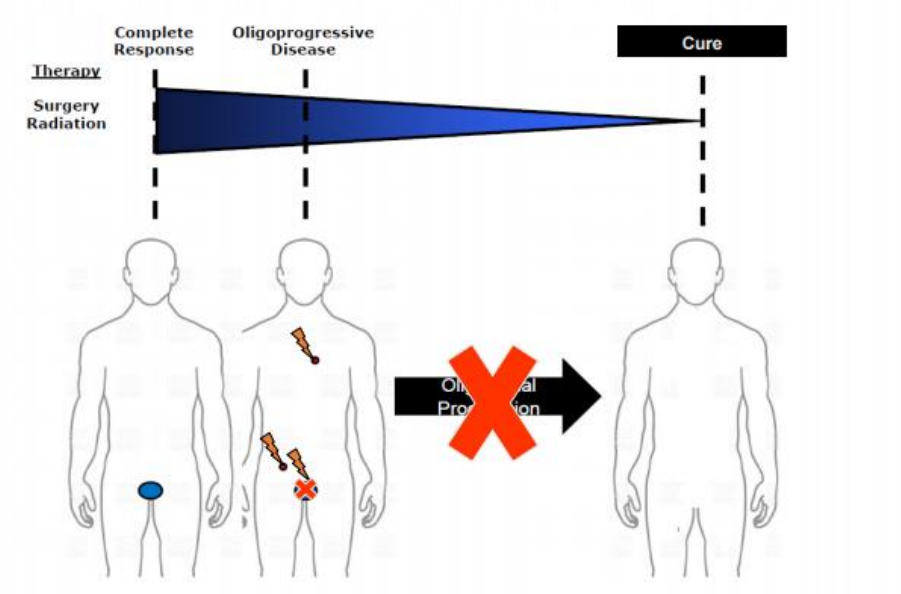
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)



Purpose:

To study the effects of stereotactic body radiation treatment on patients with five or fewer prostate cancer bone metastases to determine if we can stall the use of hormonal therapy and/or prevent other bone metastases from developing elsewhere in the body.

Phillips, R. Johns Hopkins, ASTRO 2019

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Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

Trial Design

- Eligibility:
  - Recurrent hormone-sensitive prostate cancer
  - 1-3 metastatic lesions ≤ 5 cm by CT, MRI, or bone scan
  - PSA doubling time < 15 months
  - ECOG performance status ≤ 2
- 54 men were randomized 2:1 to stereotactic ablative radiation (SABR) or observation for 6 months
- Follow-up every 3 months including H&P and PSA, with CT and bone scan performed at 6 months
- Correlative studies included prostate-specific membrane antigen (PSMA)-PET scans as well as analysis of T-cell repertoires and circulating tumor DNA.

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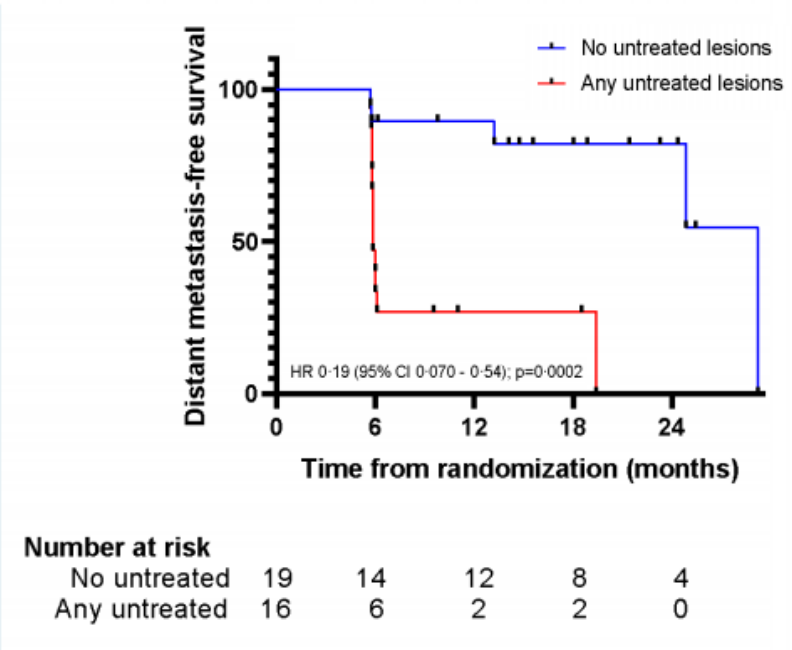
Total consolidation of PSMA-PET detected lesions at decreased risk of new metastasis formation

Consolidation	New metastases at 6 months	P-value
Total (n = 19)	16%	0.006
Subtotal (n = 16)	63%	



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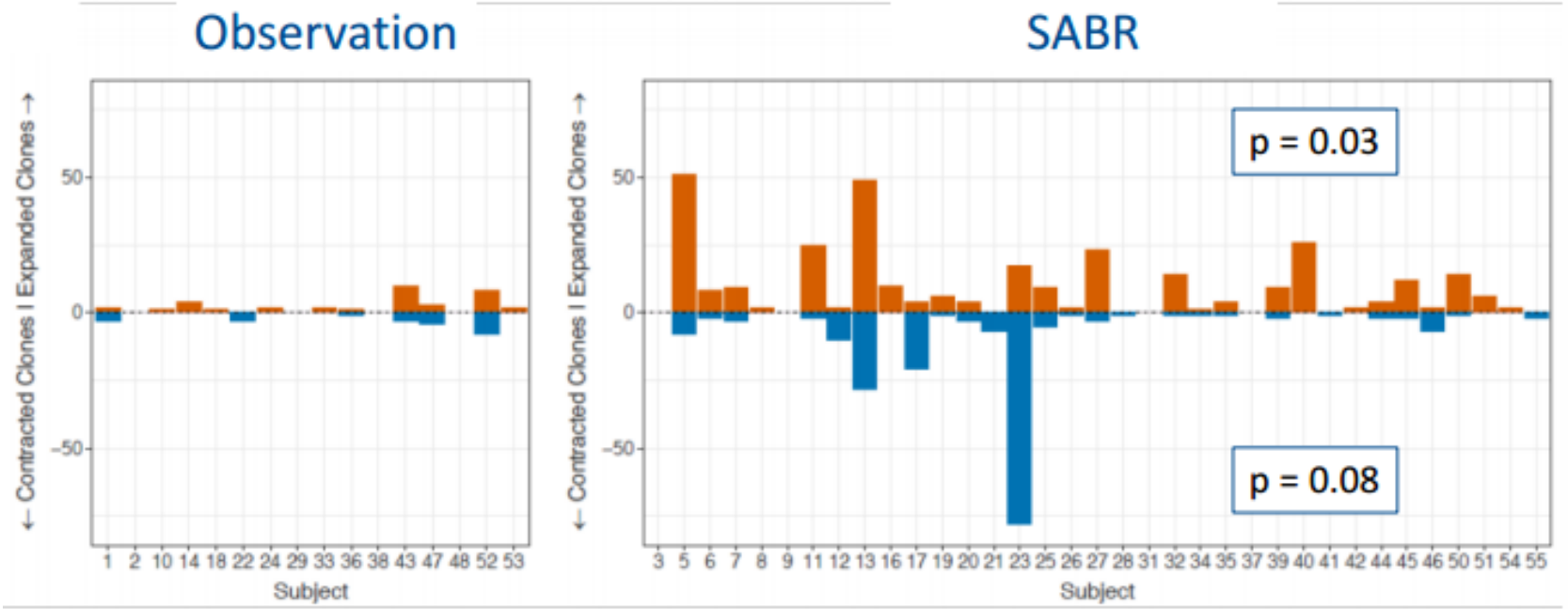
Clonal T-cell expansion in SABR cases



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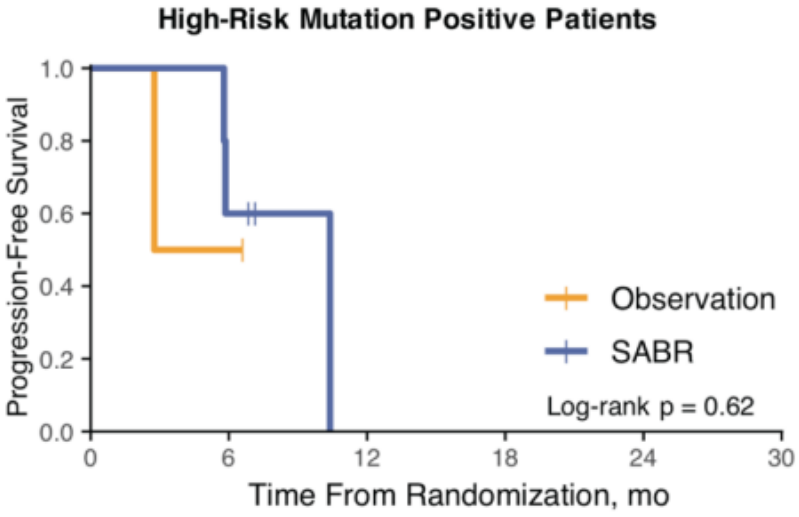
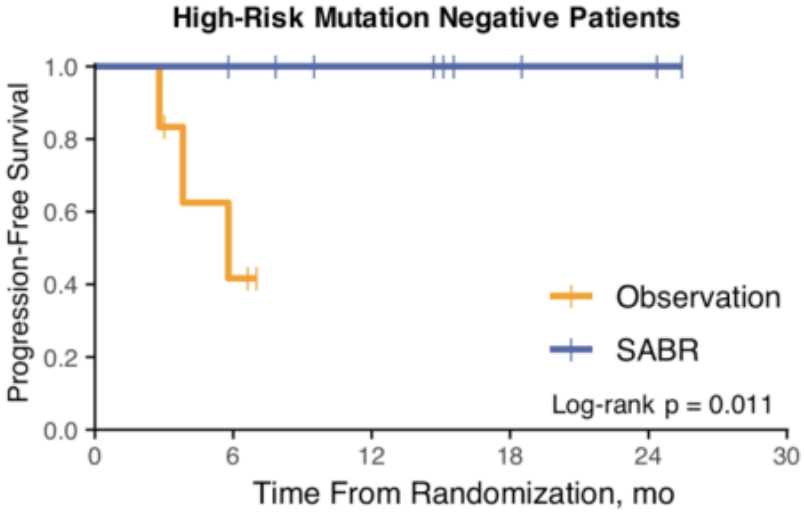
High-risk mutation associated with progression in SABR patients





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Conclusions

- SABR improves PFS in men with oligometastatic prostate cancer compared to observation alone.
- Total consolidation of PSMA radiotracer-avid lesions may decrease risk of new metastases and alter the natural history of this disease.
- SABR induced a systemic immune response in a prototypically "cold" tumor type.
- Continued biomarker development and validation may help us tailor individualized treatment approaches.

Phillips, R. Johns Hopkins, ASTRO 2019

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Published and Ongoing Clinical Trials

Clnical Trial	Design	Primary Disease	Key Inclusion Criteria	Treatment Arms	Results	Status
UT Southwestern	Phase IIR	NSCLC	Received 1st line chemo with partial response or stable disease; up to 6 sites extracranial disease	Maintenance chemo vs. SBRT + maintenance chemo	Increase in PFS in SBRT arm, 9.7 months vs. 3.5 months	JAMA Oncology, 2018.
NRG LU002	Phase IIR/III	NSCLC	Received 1st line chemo and/or immunotherapy with partial response or stable disease; up to 3 extracranial mets amenable to SBRT	Maintenance chemo vs. SBRT + maintenance chemo	N/A	Open
NRG BR002	Phase IIR/III	Breast	Up to 2 mets, at least 5cm apart; primary tumor control; all known disease amenable to resection or SBRT	Planned systemic treatment vs. Planned systemic treatment + 1-5 fraction SBRT and/or surgery	N/A	Open

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Potential for Cure?

- The jury is still out…
  - Median follow up in SABER-COMET was 25 months
    - OS and PFS benefit
    - Various tumor types
  - Median follow up in MDACC Oligometastatic NSCLC trial was 38.8 months
    - OS and PFS benefit
    - Included pts who did not progress after first line therapy
- Areas needing attention:
  - Potential for cure remains with improved OS, though is not proven
  - Need data on patients alive without disease not just without progression
  - Timing of consolidative therapy
  - Total ablative therapy to all lesions or not

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Some Key Takeaway Points

- Oligometastatic disease treatment paradigm changing from palliative to potentially curative
- SBRT as a key component of this therapeutic approach
- Growing body of randomized and cooperative data with ongoing clinical trials
- Better imaging may yield better results
- Body of knowledge should include immune and genetic parameters of primary tumor and oligometastasis
- Registry and “big data” key component to best scientific approach

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