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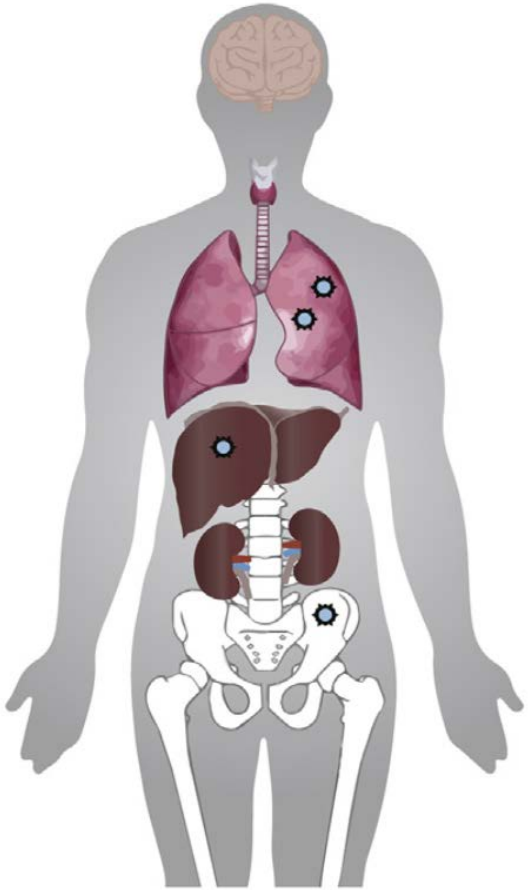

SABR-COMET:
Stereotactic Ablative Radiation (SABR) for the Comprehensive Treatment of Oligo-metastatic Cancers – Results of a Randomized Study

D. Palma, R. Olson,

S. Harrow, S. Gaede, A. Louie, C. Haasbeek, L. Mulroy, M. Lock, G. Rodrigues, B. Yaremko, D. Schellenberg, B. Ahmad, G. Griffioen, S. Senthi, A. Swaminath, N. Kopek, M. Liu, K. Moore, S. Currie, G. Bauman, A. Warner, S. Senan

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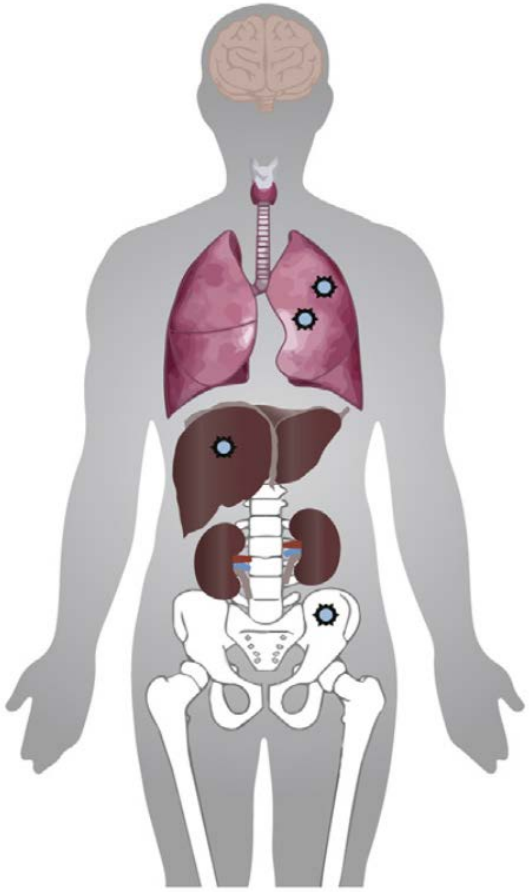
OICR Ontario Institute for Cancer Research

Disclosures

- I have received funding from Varian Medical Systems (radiotherapy equipment manufacturer), which was not related to this research

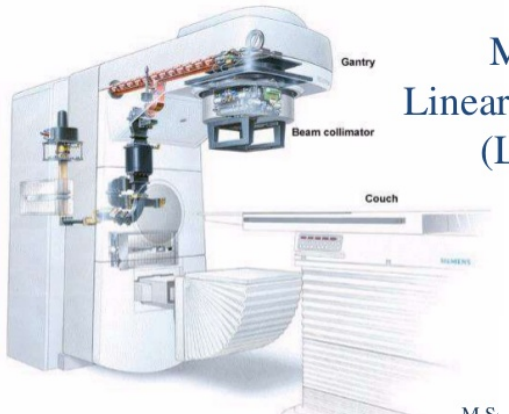
Background: metastases

- Metastatic disease: when cancer has spread from the primary site (e.g. breast) to other distant sites in the body through the blood stream
- Historically treated with systemic therapies to delay progression and extend life, but not “cure”
- radiotherapy reserved for palliation at low doses



Background: radiotherapy

- Common form of cancer treatment used in 30-50% of all cancers
- Commonly used for:
  - cure (e.g. tonsil cancer, cervix cancer)
  - Adjuvant to decrease recurrence (e.g. breast)
  - Palliative (e.g. bone mets, brain mets)
- Most commonly delivered with a linear accelerator



Medical Linear Accelerator (LINAC)

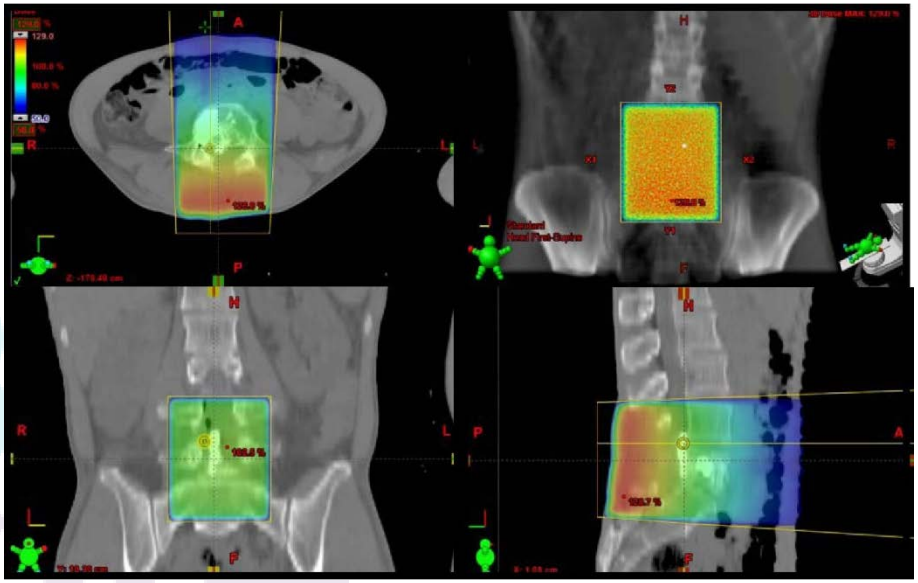
The Oligometastatic Paradigm

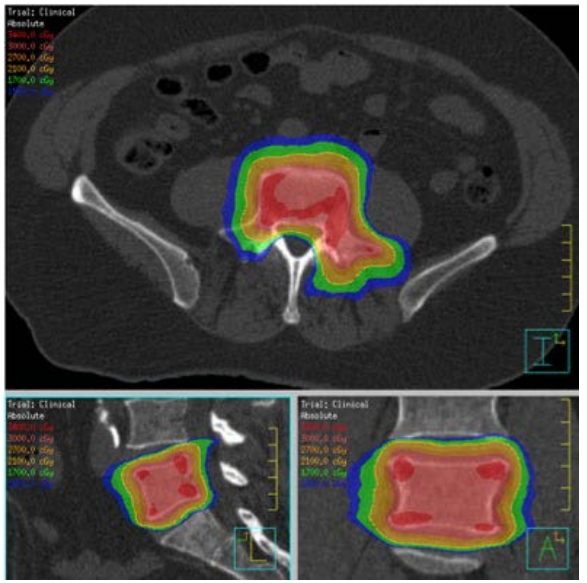
- Variably defined as patients with
  - Limited (1-3 or 1-5) sites of metastatic disease
  - From solid tumours (e.g. breast, colon, prostate, lung)
- Term formally named in the 1990s (Hellman) but anecdotally reported as early as the 1930s (Barney), suggests well selected patients with few metastases should be amenable to a curative approach, such as:
  - Surgery
  - Stereotactic Ablative Radiotherapy

1. Hellman et al, JCO 1995. 2. Barney et al J Urol 1939

Stereotactic Ablative Radiotherapy (SABR)

- High doses of radiotherapy achieved by:
  - Limiting the volumes to conformal areas in and around tumours while avoiding normal tissues / organs at risk
  - Using imaging devices attached to linear accelerators to position accurately every day





Randomized Data is Lacking

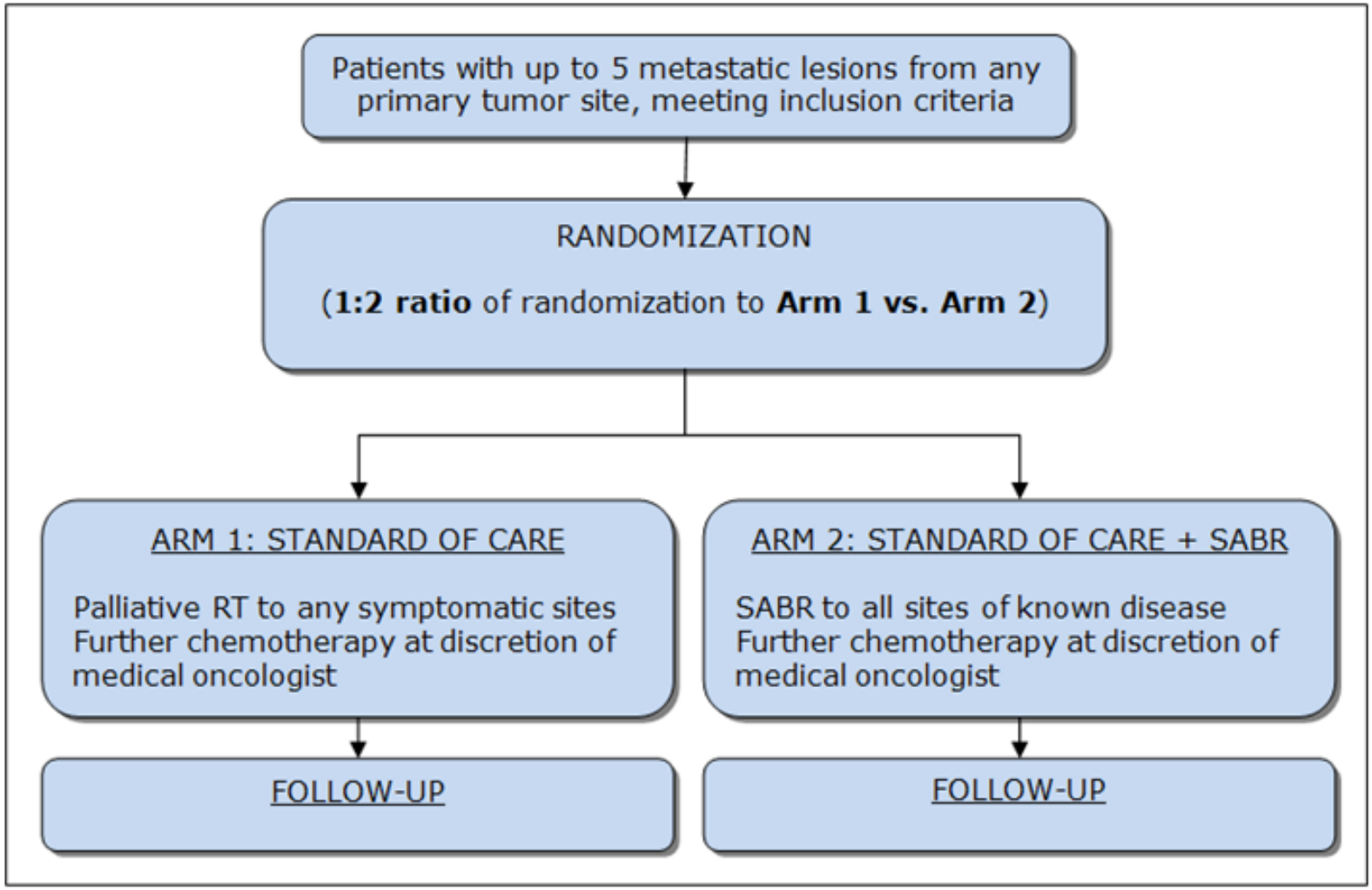
- To our knowledge, the oligometastatic paradigm has not been directly tested before in a randomized trial
- Specifically, there are no completed RCTs with a primary endpoint comparing OS between any ablative approach vs. a palliative approach in patients with oligometastases
- Some clinical scenarios without randomized data include:
  - Surgical resection of lung, liver metastases from colorectal cancer
  - SABR for oligometastases at any body site

Purpose

- To assess the impact of a SABR on:
  - overall survival
  - oncologic outcomes
  - Toxicity
  - quality of life

- in patients with up to 5 metastatic cancer lesions and a controlled primary tumor, compared to standard of care treatment alone

Methods: SABR-COMET Schema



Endpoints

Primary Endpoint

- Overall Survival

Secondary endpoints:

- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate
- Number of cycles of further systemic therapy

Main Inclusion Criteria

- Controlled primary tumor
  - defined as: at least 3 months since original tumor treated definitively, with no progression at primary site
- Up to 5 hematogenous metastases
- Maximum 3 metastases in any single organ system
- All sites of disease safely treatable

Main Exclusion Criteria

- Serious medical comorbidities precluding radiotherapy
- Prior radiotherapy to a site requiring treatment
- Malignant pleural effusion
- Tumor within 3 mm of spinal cord on MRI or cord compression

Phase II Randomized Screening Design

VOLUME 23 · NUMBER 28 · OCTOBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

Design Issues of Randomized Phase II Trials and a Proposal for Phase II Screening Trials

Lawrence V. Rubinstein, Edward L. Korn, Boris Freidlin, Sally Hunsberger, S. Percy Ivy, and Malcolm A. Smith

- Moderate sample size to provide an initial, non-definitive comparison between two arms
- Once trial is complete, a finding can be considered definitive if $p<0.005$

Phase III RCT alpha = 0.05

Phase II Screening RCT alpha = 0.20

SABR Details

- Number of fractions dependent on tumor size and location
  - Lung: 54/3, 55/5, 60/8
  - Bone: 35/5, 30/3, 16-20/1
  - Brain: SRS (18-24/1) or SABR (40/5), WBRT optional
  - Liver: 45-60 Gy in 3-8
  - Adrenal: 60/8

- Normal tissue tolerances not to be exceeded
  - PTV coverage compromised wherever needed

Sample Size and Analyses

- Estimated median survival of 9 months in control arm. To detect a 6-month improvement in OS, with 80% power, a two-sided alpha of 0.2, and 5% rate of dropout, 99 patients needed.

- All analyses **intention-to-treat** and **pre-specified**

- Protocol assumed 4 years of accrual and 1 year of additional follow-up. Data locked as of Jan 2018 for this analysis.

Results: Baseline Characteristics

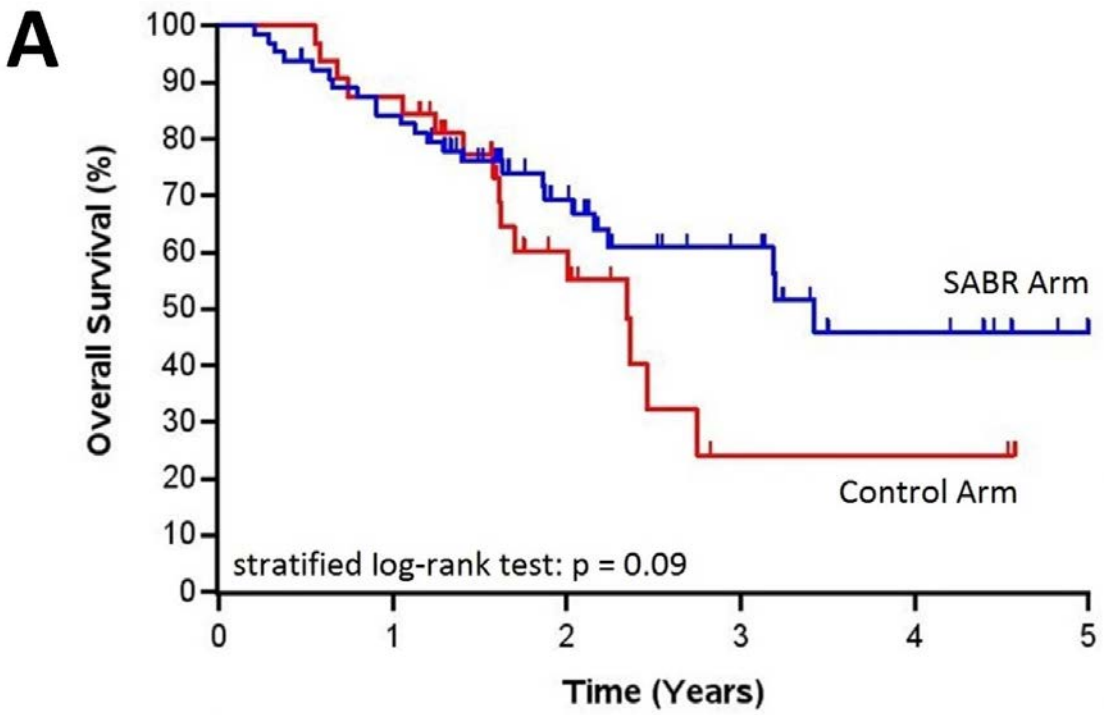
Between February 2012 and August 2016, 99 patients were randomized at centres in Canada, Scotland, Netherlands and Australia

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Age – median, (min, max)	68 (43, 89)	69 (44, 87)	67 (43, 89)	0.494
Sex – n(%)				0.772
Male	59 (59.6)	19 (57.6)	40 (60.6)	
Female	40 (40.4)	14 (42.4)	26 (39.4)	
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	16 (16.2)	6 (18.2)	12 (18.2)	
Prostate	29 (29.3)	2 (6.1)	14 (21.2)	
Other		11 (33.3)	18 (27.3)	

Results: Baseline Characteristics

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
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)	
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)	

Overall Survival



Number at risk:

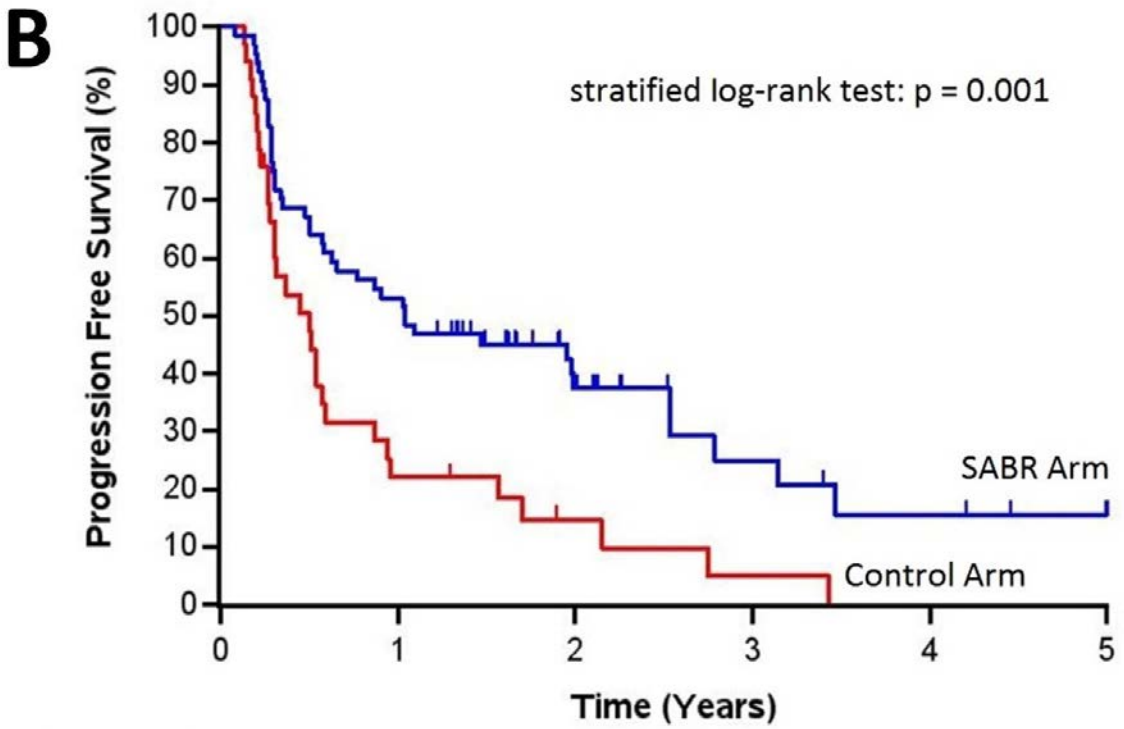
Control	33	28	12	2	2	
SABR	66	53	29	15	7	1

Median OS

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

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

Progression-Free Survival



Number at risk:

Control	33	7	3	1		
SABR	66	34	15	6	3	1

Median PFS

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

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

Adverse Events

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Related AE Grade ≥ 2 – n(%)	22 (22.2)	3 (9.1)	19 (28.8)	0.03
AE Associated with Death (Grade 5) – n(%)	3 (3.0)	0 (0.0)	3 (4.5)	0.55
Fatigue – n(%)				
Grade 2	6 (6.1)	2 (6.1)	4 (6.1)	0.45
Grade 3	1 (1.0)	1 (3.0)	0 (0.0)	
Dyspnea – n(%)				
Grade 2	1 (1.0)	0 (0.0)	1 (1.5)	1.00
Grade 3	1 (1.0)	0 (0.0)	1 (1.5)	
Pain (any type) – n(%)				
Grade 2	5 (5.1)	0 (0.0)	5 (7.6)	0.14
Grade 3	3 (3.0)	0 (0.0)	3 (4.6)	

Sensitivity Analyses (not pre-specified)

Excluded all prostate patients to see if HR for OS and PFS remain <1

- OS HR = 0.83
- PFS HR = 0.61

2) Multivariable analyses for OS and PFS (to control for histology):

OS		
Factor	HR	P-value
Lung Primary (vs. other)	4.05	<0.001
SABR Arm (vs control)	0.60	0.12

PFS		
Factor	HR	P-value
Prostate Primary (vs. other)	0.14	<0.001
SABR Arm (vs control)	0.58	0.02

Discussion

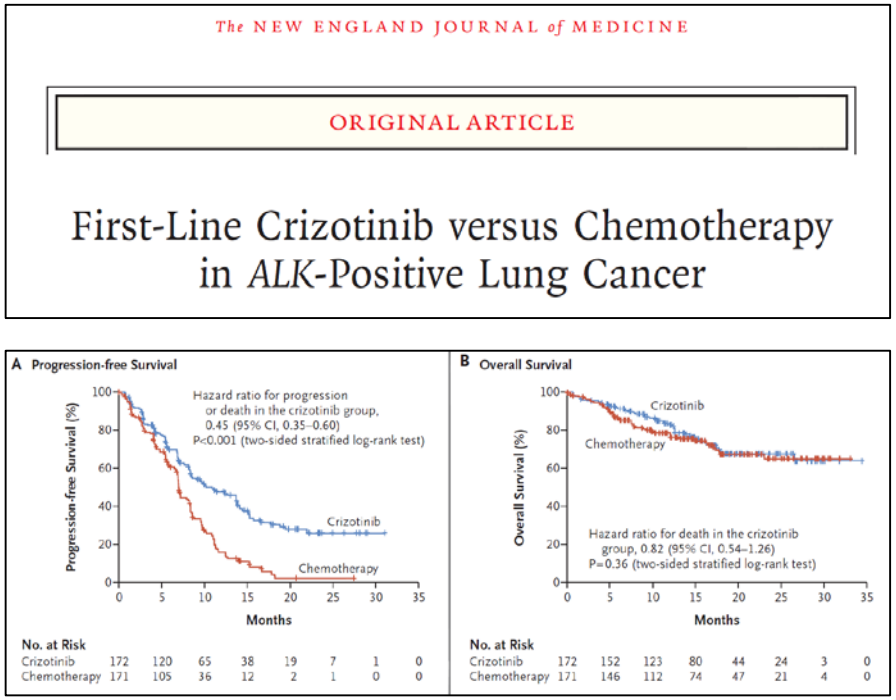
Limitations

- **Not Histology Specific**
  - Most SRS/SABR trials for metastases are not (brain, spine)
  - Histology specific trials have not accrued well, as numbers are lower
- **Pragmatic Selection of Systemic Agents**
  - It was impossible to mandate specific systemic therapy, given the multiple disease sites and expected changes in SOC over time
- **Phase II Design**
  - OS results not definitive

Is a Clear PFS Benefit Enough to Treat?

- There is ample precedent in oncology
  - Aromatase Inhibitors for Breast Cancer
  - Crizotinib in ALK-rearranged NSCLC

- Majority of FDA approvals for cancer drugs are not based on OS.[1,2]



Next Steps

SABR-COMET 3

Phase III RCT for patients with a controlled primary tumor & 1-3 metastatic lesions

PI: Robert Olson

Being evaluated for funding

SABR-COMET 10

Phase III RCT for patients with a controlled primary tumor & 4-10 metastatic lesions

PI: David Palma

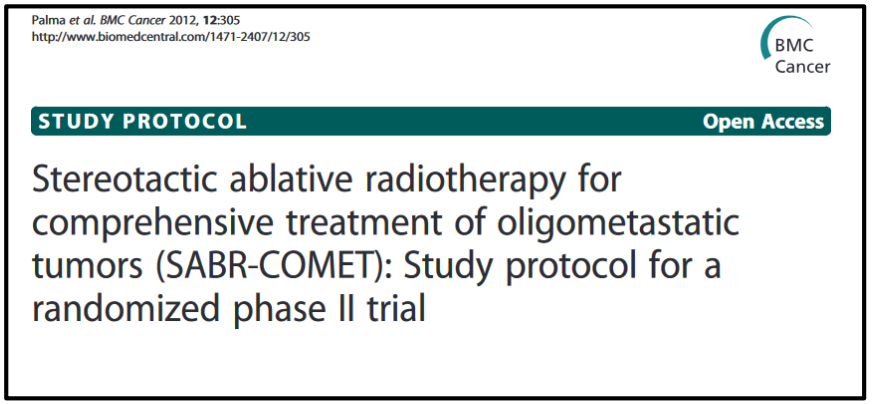
Opening in a few months

Conclusions

- SABR was associated with an improvement in OS, meeting the primary endpoint of this trial, and PFS was doubled.
- Toxicities were more common with SABR, with a 4.5% risk of treatment-related death
- To our knowledge, these findings represent the strongest clinical evidence available in support of the oligometastatic state across multiple tumor types
  - This is a higher level of evidence than exists for any surgical intervention for oligometastatic disease

Further Information

Protocol



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