Optimal therapy for earlier stages of NSCLC

Oligometastatic disease

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Disclosures

Research support Varian Medical Systems

Speakers honoraria Varian Medical Systems.

Advisory board Lilly Oncology

Oligometastatic paradigm

Patients developing a small number of metastatic lesions might achieve long-term survival if all these lesions are ablated with surgery or stereotactic radiotherapy

Hellman and Weichselbaum, JCO 1995

Outline of presentation

- Definitions; available evidence; favorable subgroups
- Where rapid progress is made in systemic therapies
- Using radiotherapy, either conventional or SABR, to elicit distant immune effects (abscopal)
- When safety data for sequencing (or combining) radiation and new agents is lacking

Oligometastatic paradigm: Key terms

Oligometastatic
A malignancy that has progressed to a limited number of haematogenous metastases, defined in most studies as 1–3 or 1–5 metastatic lesions.

Synchronous oligometastasis
A clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour.[111]

Metachronous oligometastasis
The development of oligometastatic disease after treatment of the primary tumour. The interval for classification of 'metachronous' versus 'synchronous' is not standardized.[111]

Oligorecurrence
Oligometastasis in the setting of a controlled primary tumour.[111]

Oligoprogression
Progression of a limited number of metastatic deposits, while all other metastases are controlled with systemic therapy.

Ablative therapy
A term that includes surgical resection, stereotactic radiotherapy, radiofrequency ablation, although these might differ in efficacy and toxicity profiles.

Palma DA, Nat Rev Clin Oncol 2014

Evidence from randomized trials

- In patients with a **single brain metastasis**, addition of surgical resection to whole-brain radiotherapy (WBRT) improved median overall survival from 15 weeks to 40 weeks [Patchell RA, NEJM 1990]

- For patients with **1-3 brain metastases**, radiosurgery in addition to WBRT improved median overall survival from 4.9 months to 6.5 months [Andrews DW, Lancet 2004]

Oligometastases: Who does well ?

An Individual Patient Data Meta-Analysis of Outcomes and Prognostic Factors after Treatment of Oligometastatic NSCLC

Systematic review of the literature to identify reports.

- 757 NSCLC patients with 1-5 synchronous or metachronous mets
- Median patient age at diagnosis was 61 years
- 98% had a good performance status
- 2/3rd of patients had early-stage intra-thoracic disease staged IA-IIB (after excluding metastatic disease)

Ashworth A, Clin Lung Cancer 2014

Individual Patient Data Meta-Analysis after Treatment of Oligometastatic NSCLC

Median OS **26 months**, 1-year OS 70.2%, and 5-year **OS 29.4%**
Surgery was commonest treatment modality for both primary (n=635, 83.9%) and for metastases (n=339, 62.3%)

Predictors of OS: synchronous vs. metachronous metastases ($p<0.001$), N-stage ($p=0.002$) and adenocarcinoma histology ($p=0.036$)

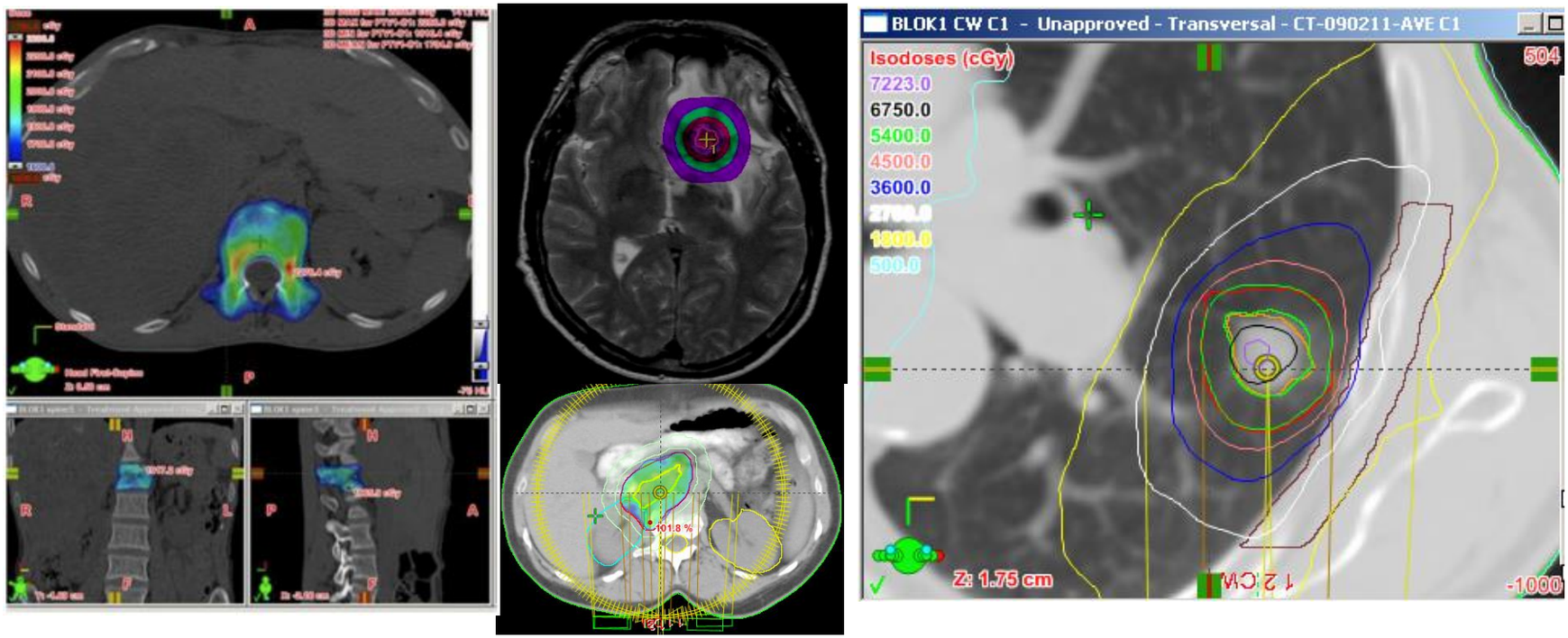
Recursive Partitioning Analysis for risk groups;
Low-risk: metachronous mets (5-year OS 48%);
Intermediate risk: synchronous mets and N0 disease (5-year OS 36%);
High-risk: synchronous mets and N1/N2 disease (5-year OS 14%).

Ashworth A, Clin Lung Cancer 2014

Non-surgical option: SABR

SABR, or SBRT, is a technique for delivering external beam radiotherapy to an **extra-cranial target**

- with high degree of accuracy
- using high doses of irradiation
- delivered in 1-8 treatment fractions



Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases

Mette Marie Fode*, Morten Høyer* Radiother Oncol 2015

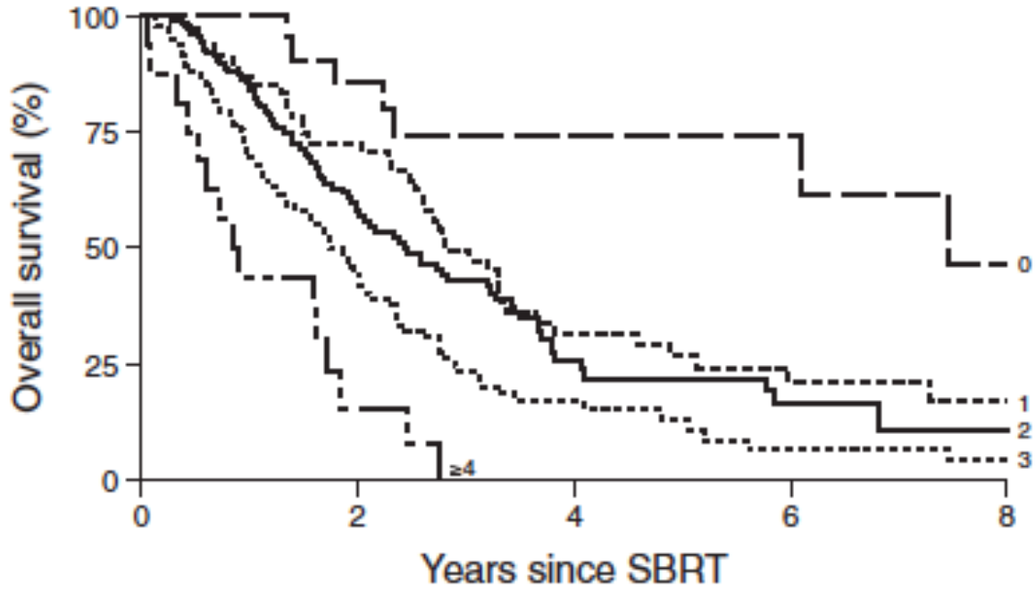
- 321 patients (587 metastases) treated over 13 years
- Commonest metastatic sites were liver and lung

Primary tumor type	
Colorectal	201 (63)
Non-colorectal	120 (37)
Number of metastases	
1	162 (50)
2	95 (30)
3	40 (12)
4–6	24 (8)
Size of the largest metastasis	
1–30 mm	174 (54)
31–88 mm	145 (45)
Unknown size	2 (1)
Treatment sites	
One organ	313 (98)
Liver	212 (68)
Lung	92 (29)
Lymph node	3 (1)
Bone	3 (1)
Supra renal gland	2 (~0.6)
Right atrium	1 (~0.3)
Two organs	8 (2)

Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases

Mette Marie Fode *, Morten Høyer * Radiother Oncol 2015

Favorable prognosis if PS (0–1), solitary metastasis, metastases <30mm, metachronous metastases, and pre-SBRT chemotherapy



No. at risk

0	25	17	10	6	3
1	70	41	14	7	2
2	126	57	15	5	1
3	82	33	10	3	2
≥4	16	2	0	0	0

Fig. 2. Survival by number of unfavorable prognostic factors: performance status, number of metastases, size of the largest metastasis, timing of metastasis and prior chemotherapy.

IASLC Lung Cancer Staging Project

TABLE 3. Prognostic Impact of Single and Multiple Metastatic Lesions in a Single Organ versus Multiple Metastatic Sites

		Overall Survival		
Proposed Category	**Variable**	**n/N (%)**	**HR (95% CI)**	***P* Value**
M1a	M1a	324/1025 (32)	Reference level	
M1b	M1b, single organ/lesion	225/1025 (22)	1.11 (0.91, 1.36)	0.308
M1c	M1b, single organ/multiple lesions	229/1025 (22)	1.63 (1.34, 1.99)	<0.001
	M1b, multiple organs	247/1025 (24)	1.85 (1.52, 2.24)	<0.001

P value from score χ^2 test in Cox regression.
HR, hazard ratio; 95% CI, 95% confidence interval.

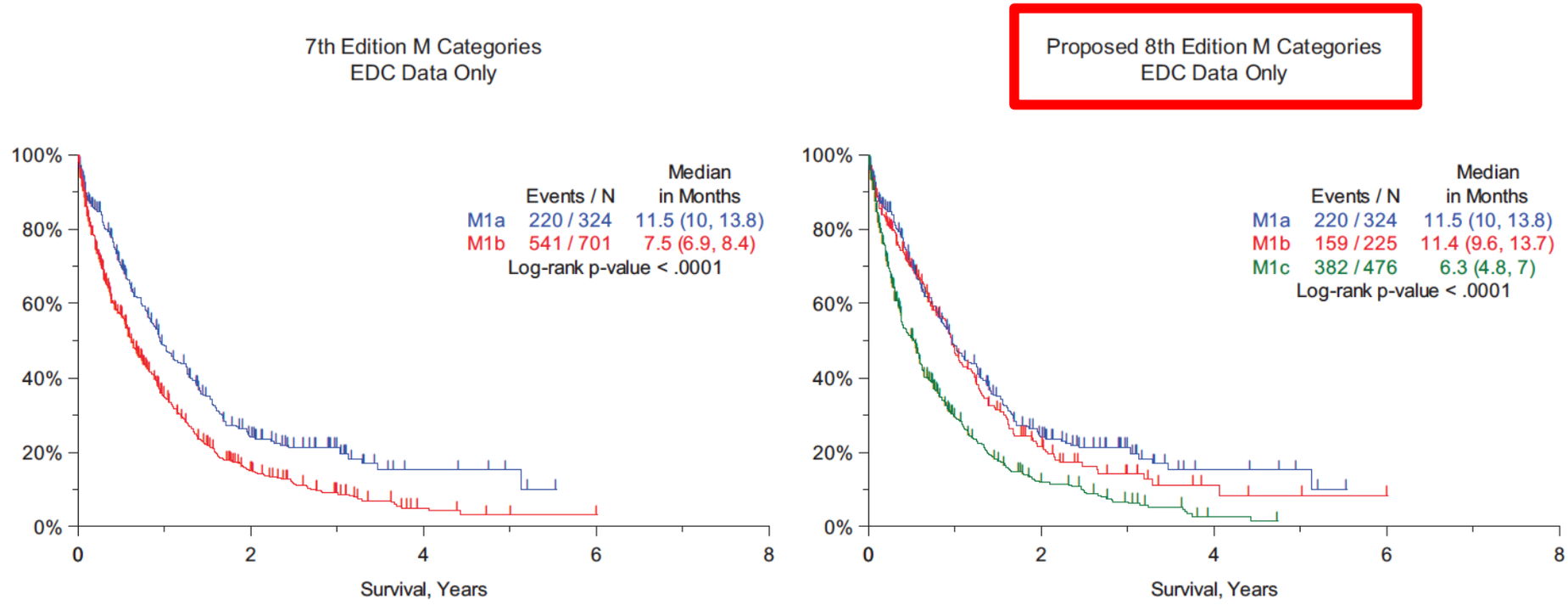
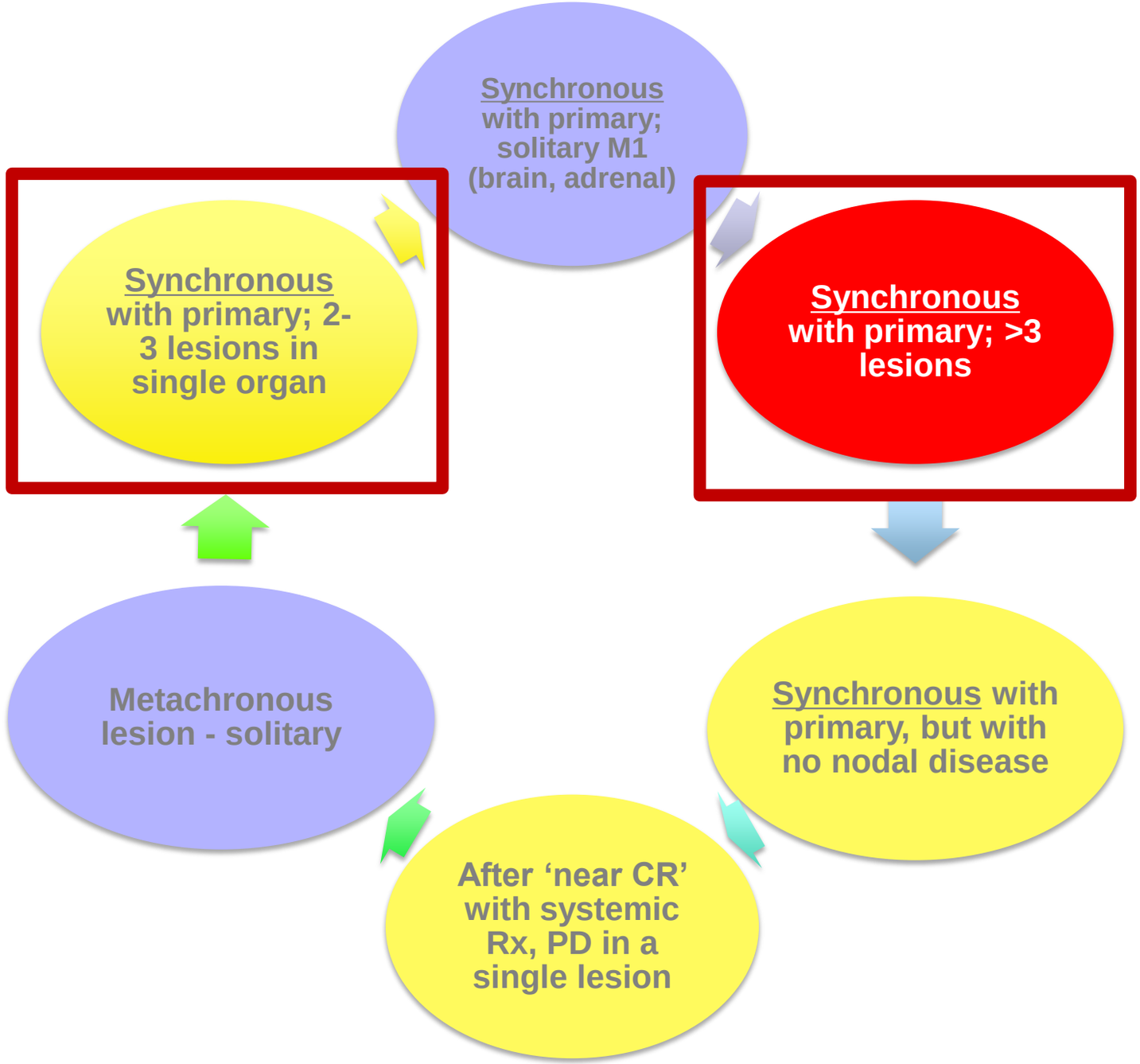


FIGURE 8. The 7th edition and proposed 8th edition M categories.

Eberhardt WE, JTO 2015

Oligometastases: Clinical Subgroups



Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

TABLE 1. Patient and Tumor Characteristics ($n = 39$)

Age (yrs) (mean ± SD) (range)	62.1 ±9.2 (44–81)
Sex	
Male	18 (46.2%)
Female	21 (53.8%)
Comorbidity (modified Charlson)	
None	18 (46.2%)
1	20 (51.3%)
2	1 (2.6%)
WHO performance status	
0	12 (30.8%)
1	26 (66.7%)
2	1 (2.6%)
Localization metastasis	
Adrenal gland	4 (10.3%)
Bone	7 (17.9%)
Brain	17 (43.9%)
Gastro-hepatic ligament	1 (2.6%)
Liver	1 (2.6%)
Lung	1 (2.6%)
Lymph node	2 (5.1%)
Muscle	2 (5.1%)
Ovary	1 (2.6%)
Pleura	3 (7.7%)
Number metastases	
1	34 (87.2%)
2	4 (10.3%)
3	1 (2.6%)

WHO, World Health Organization; NOS, Not otherwise specified.

De Ruysscher D, JTO 2012

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

VUmc

TABLE 2. Treatment for Primary Tumor and Lymph Nodes (n = 39)

Surgery	0
Radiotherapy alone	2 (5.1%)
Sequential chemoradiotherapy	15 (38.5%)
Cisplatin-gemcitabine	11
Carboplatin-gemcitabine	1
Cisplatin-pemetrexed	3
Concurrent chemoradiotherapy	21 (53.8%)
Cisplatin-etoposide	7
Cisplatin-vinorelbine	14
Adjuvant after radiotherapy	1 (2.6%)
Cisplatin-gemcitabine	—
Radiotherapy dose	62.3 ± 10.1 Gy (18–79.2)
Number of fractions	35.9 ± 8.4 [3-44]
Overall treatment time of radiotherapy	30.56 ± 10.3 days [3-44]

De Ruysscher D, JTO 2012

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

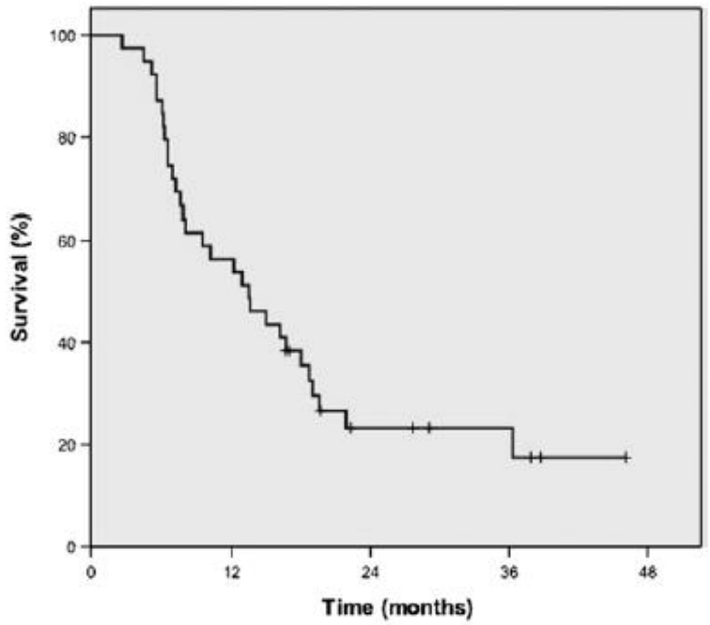


FIGURE 1. Overall survival ($n = 39$).

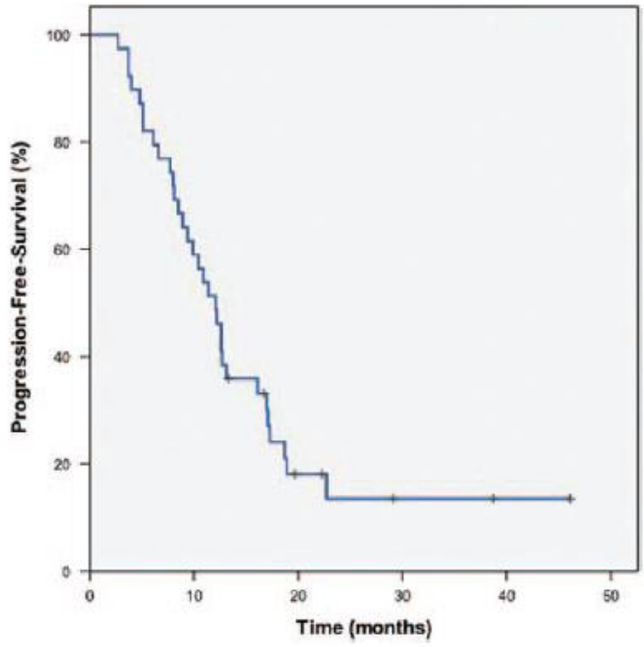


FIGURE 2. Progression-free survival.

- No extracranial stereotactic radiotherapy applied
- 6 patients (15.4%) had no disease recurrence
- 33 patients with a recurrence: 80% outside radiotherapy field or surgical bed, **5.1% in-field recurrence**

De Ruysscher D, JTO 2012

Oligometastases: Caution Advised

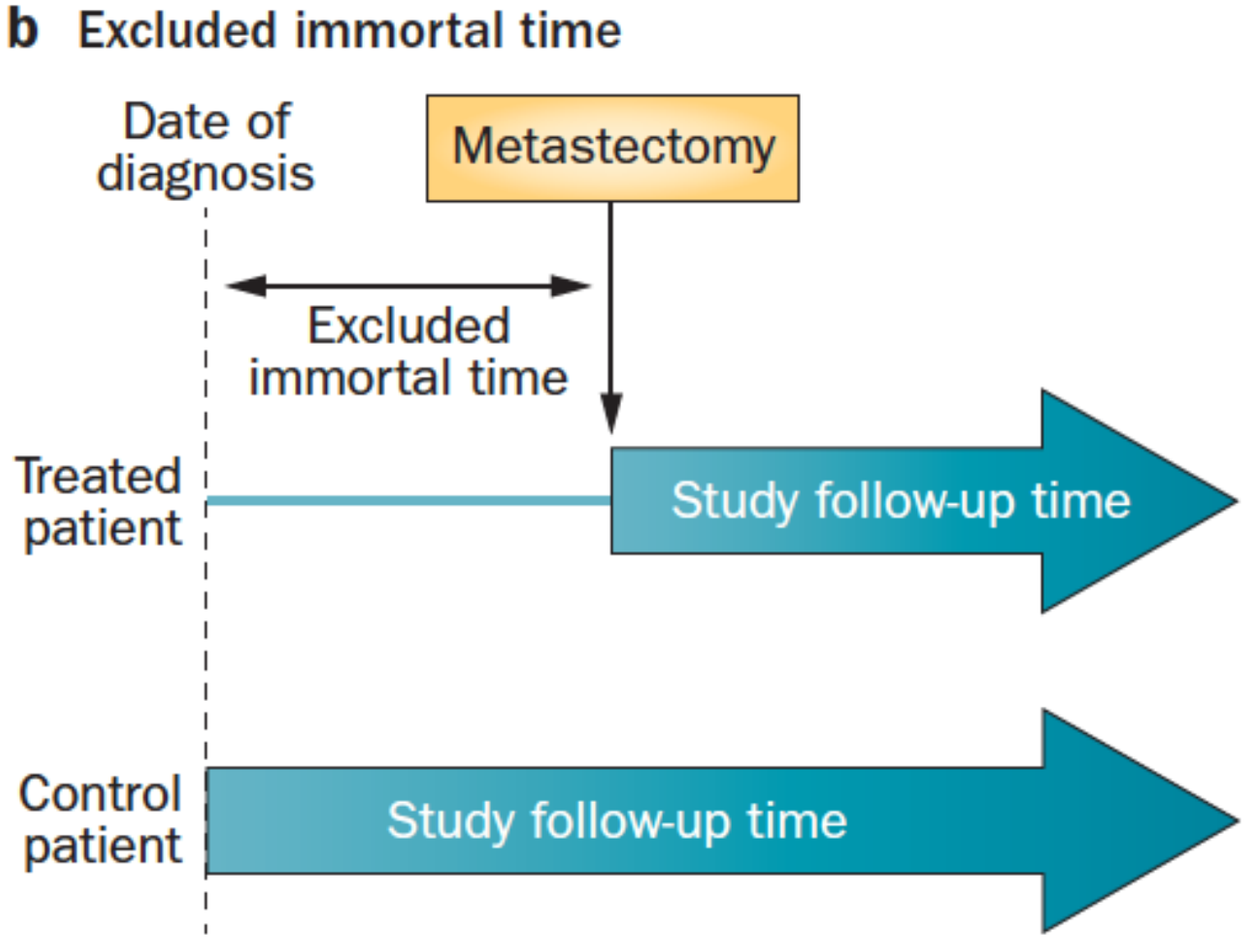
OPINION

The oligometastatic state—separating truth from wishful thinking

David A. Palma, Joseph K. Salama, Simon S. Lo, Suresh Senan, Tom Treasure, Ramaswamy Govindan and Ralph Weichselbaum

***Nature Reviews Clin Oncol.* 2015;11:549-57**

Oligometastatic paradigm

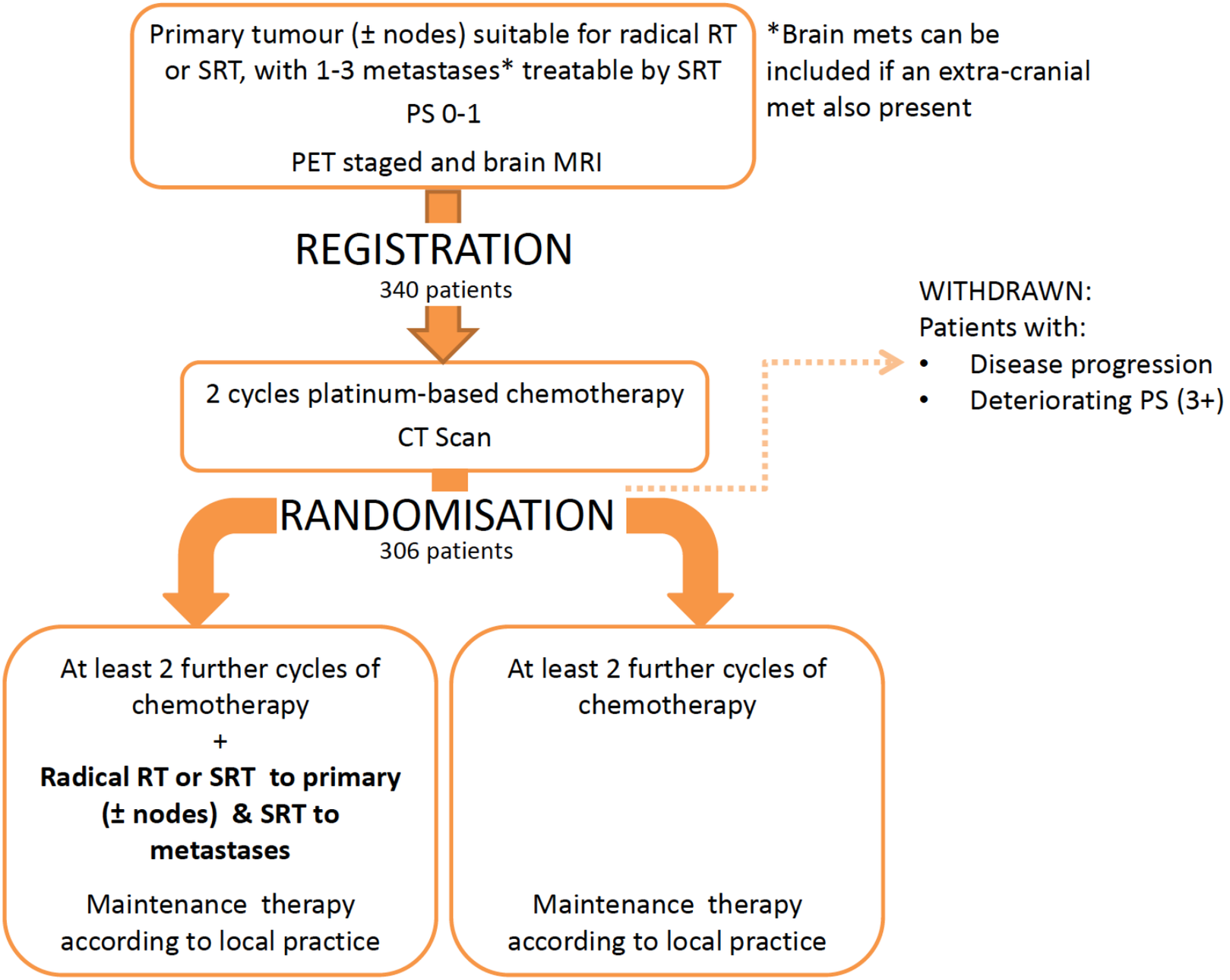


Immortal time bias

This bias arises when a study includes a span of follow-up time during which an outcome (death) could not occur for patients included in the study.[75,76] Immortal time is also known as a 'death-free interval'.

Palma DA, Nat Rev Clin Oncol 2014

UK-EORTC proposal (SARON trial)



BTOG presentation 2015, accessed on ESMO.org

Oligometastatic paradigm

Changing landscape

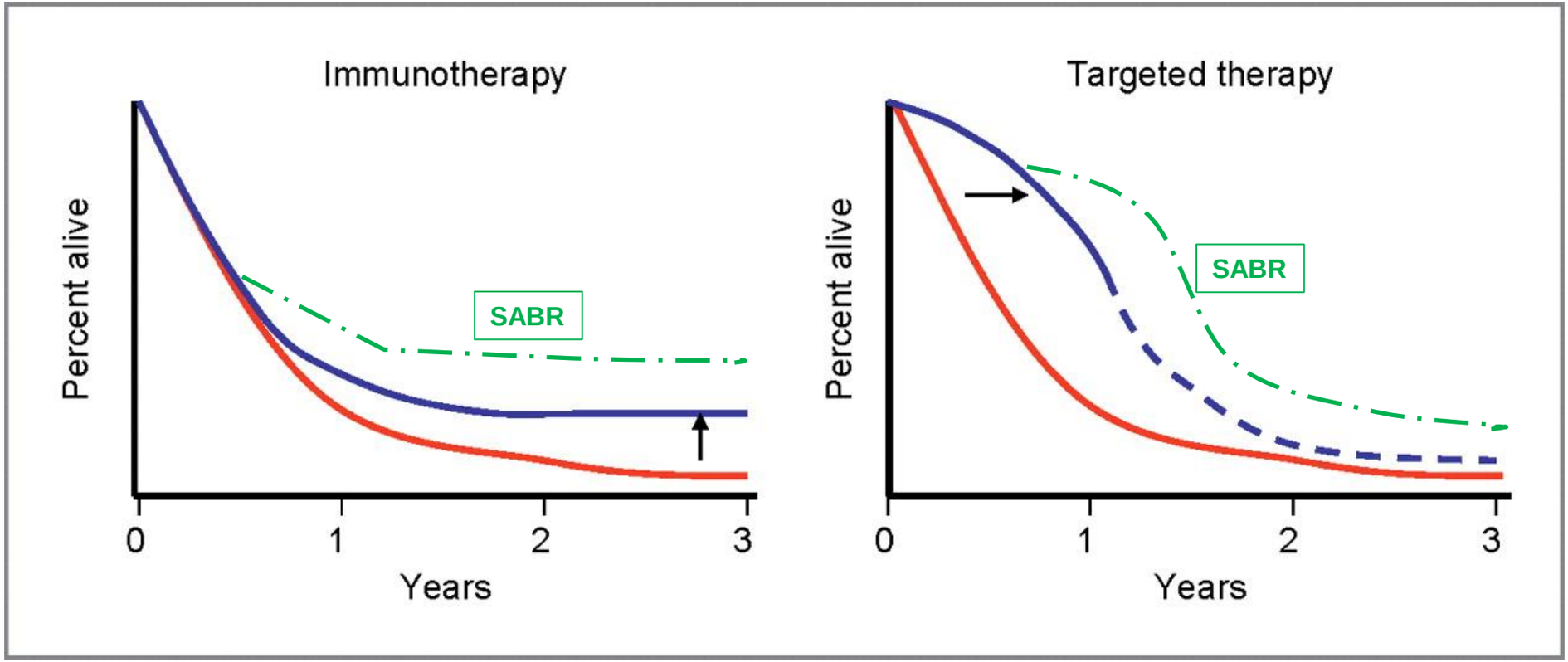
Where rapid progress is made in systemic therapies

Radiotherapy, either conventional or SABR, to elicit abscopal effects

Dilemma's

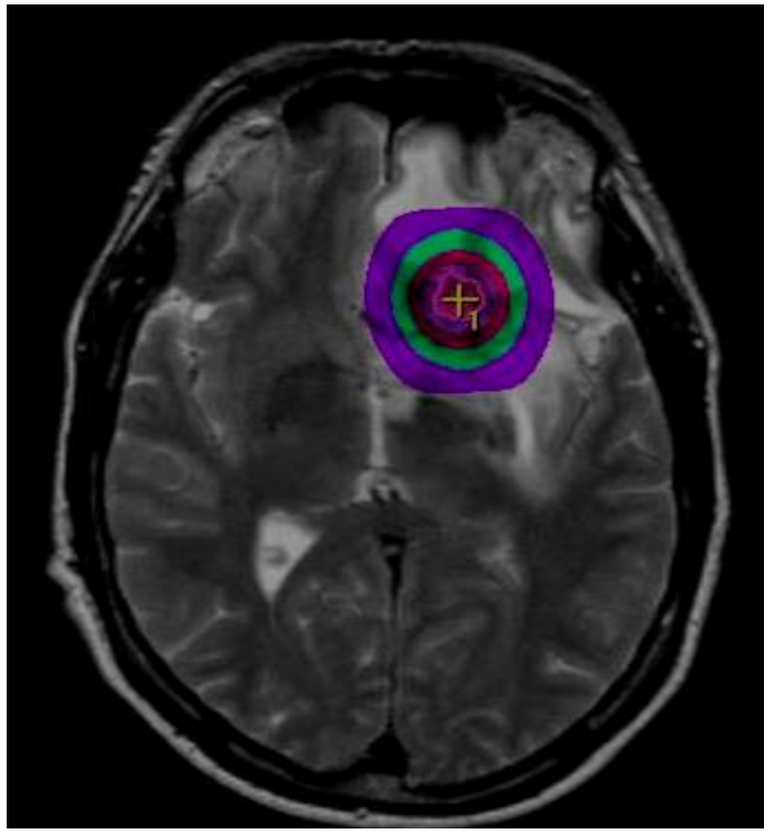
When safety data for sequencing (or combining) radiation and new agents is lacking

Can ablative radiotherapy complement targeted and immune therapies?



Adapted from Ribas A, Clin Cancer Res 2012

Brain metastases



Stereotactic Radiosurgery (SRS)

- SRS is accepted as treatment modality for patients with 1-4 brain lesions, measuring 4 cm or less in diameter

- Good local control can be achieved in patients with BM, either as a stand-alone treatment, or combined with surgical resection or whole-brain radiation therapy (WBRT)

Besse B. Ann Oncol. 2014

Patients with 1-4 Brain Metastases: SRS With/Without WBRT

- Individual patient data meta-analysis of 3 phase III trials of SRS with or without WBRT (n = 264 patients)

- Age was a significant effect modifier for survival (*P* = .04): SRS alone favored in patients ≤50 years of age; no significant differences were observed in older patients

- Age was a significant effect modifier for distant brain failure (*P* = .043), with similar rates in the 2 arms for patients ≤50 of age; risk was reduced with WBRT for patients >50 years of age

Sahgal A, Int J Radiat Oncol Biol Phys. 2015

When science evolves rapidly

Driver mutations
(2014 ASCO Edu Book)

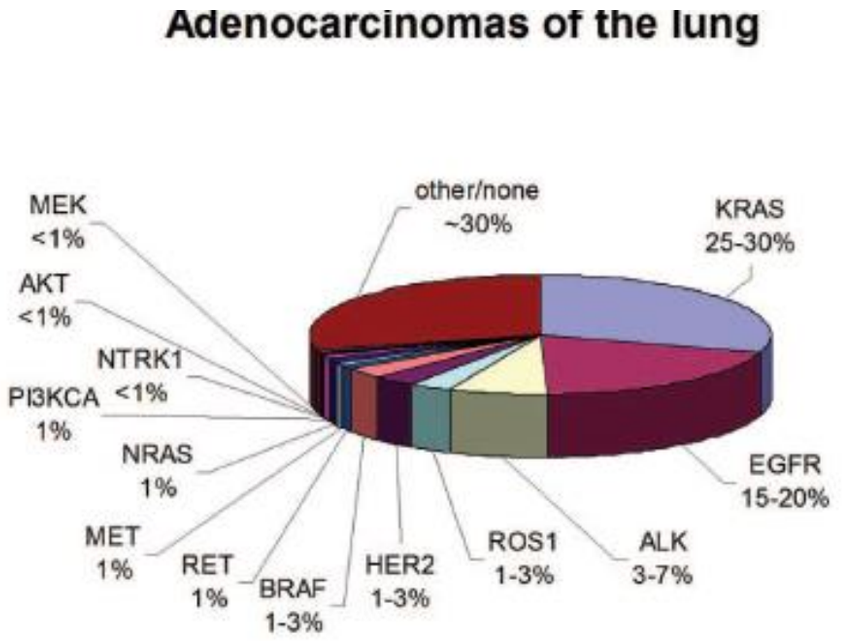


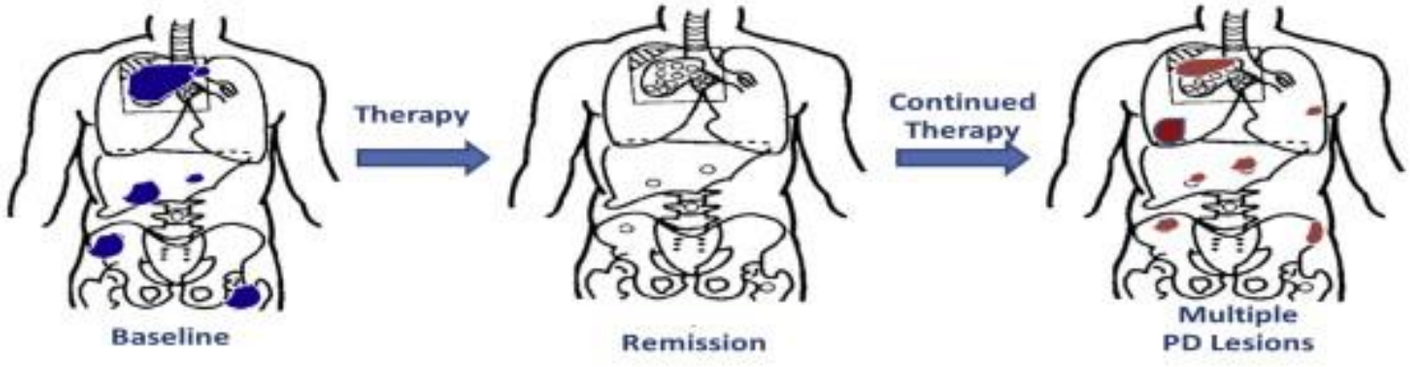
Table 1
Randomized phase III trials comparing chemotherapy with 1st and 2nd generation *EGFR* TKIs.

Study	Year	Regimen		ORR		Median PFS		Median OS	
		TKI (N)	Chemo (N)	TKI (%)	Chemo (%)	TKI (months)	Chemo (months)	TKI (months)	Chemo (months)
Fukuoka et al., 2011; Mok et al., 2009	2009	Gefitinib (132)	Carbo-Taxol (129)	71.2	47.3	9.5	6.3	21.6	21.9
Mitsudomi et al., 2010; Yoshioka et al., 2014	2010	Gefitinib (86)	Cis-Taxotere (86)	62.1	32.2	9.2	6.3	34.8	37.3
Maemondo et al., 2010	2010	Gefitinib (114)	Carbo-Taxol (114)	73.7	30.7	10.8	5.4	30.5	23.6
Zhou et al., 2011, 2012	2011	Erlotinib (83)	Carbo-Gem (82)	83	36	13.1	4.6	22.7	28.9
Rosell et al., 2012	2012	Erlotinib (86)	Platinum Doublet (87)	64	18	9.7	5.2	19.3	19.5
Sequist et al., 2013; Yang et al., 2015	2013	Afatanib (230)	Cis-Pem (115)	56	23	11.1	6.9	28.2	28.2
Wu et al., 2014; Yang et al., 2015	2014	Afatanib (242)	Cis-Gem (122)	66.9	23	11	5.6	23.1	23.5

Sub-typing Resistance to Targeted Therapies

PD Subtype

Systemic PD



Gandara D, Clin Lung Cancer 2014

Managing Oligometastatic Progression during targeted therapies

- Several experiences...support the **use of local therapies** (surgery, stereotactic radiation) with **continued EGFR or ALK inhibition** in cases of oligometastatic progression, resulting in minimal toxicity and in months to years of disease control. Before proceeding with local therapy, patients should have a full evaluation of the extent of disease, including CNS imaging.

- Recommendation: in case of oligometastatic progression during TKI treatment, use a local treatment (such as surgery or radiotherapy) and continue/resume TKI

- Strength of recommendation: C

- Level of evidence: V

Besse B, Ann Oncol. 2014

Crizotinib in *ALK*-Rearranged NSCLC and Brain Metastases

- Previously untreated asymptomatic brain metastases: systemic DCR at 12 weeks was 63% (95% CI, 54% to 72%), the **intracranial DCR was 56%** (95% CI, 46% to 66%), and **median intracranial TTP was 7 months** (95% CI, 6.7 to 16.4)

- Patients with previously treated brain metastases: systemic DCR was 65% (95% CI, 57% to 72%), the **intracranial DCR was 62%** (95% CI, 54% to 70%), and the **median intracranial TTP was 13.2 months** (95% CI, 9.9 to not reached).

Costa J, JCO 2015

Alectinib in Crizotinib-Refractory ALK-Rearranged NSCLC

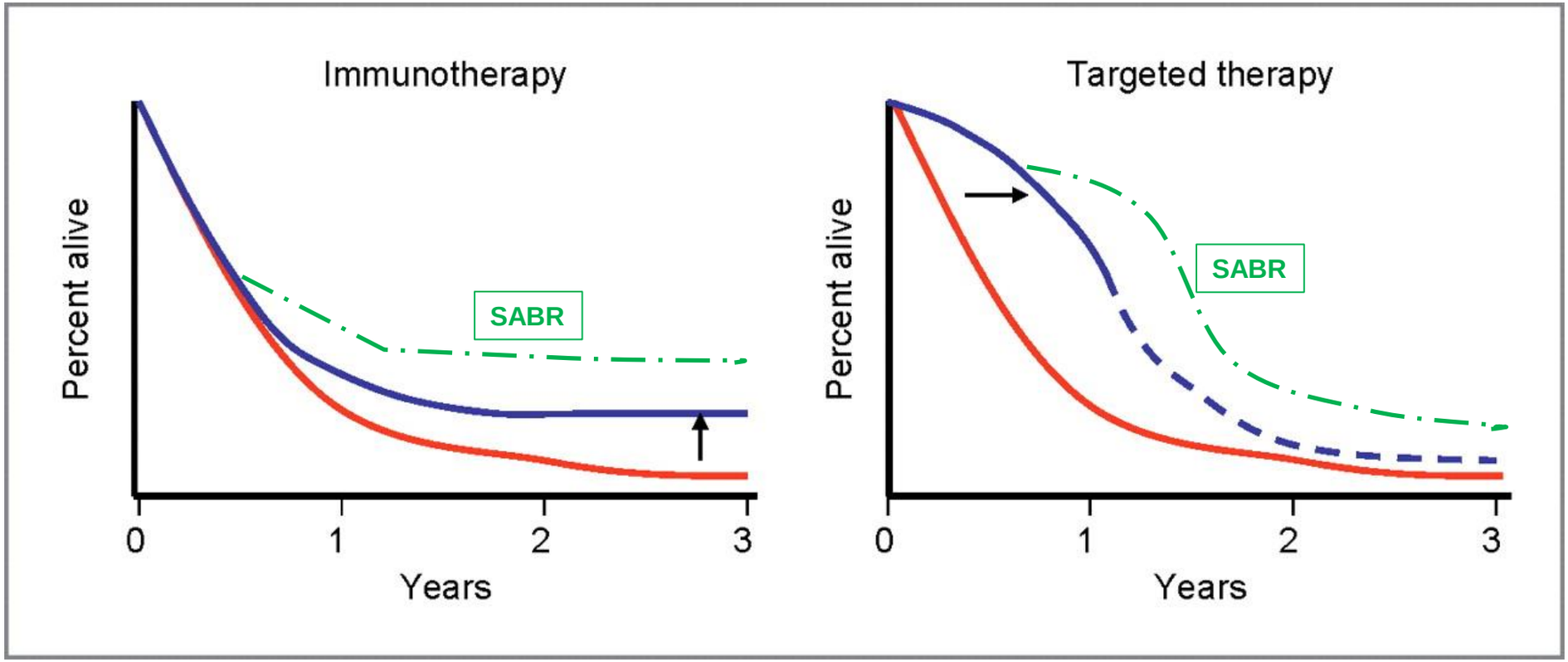
- CNS disease control rate of 83% (95%CI, 74% to 91%); median CNS duration of response of **10.3months** (95% CI, 7.6-11.2 months).

- 35 patients with baseline measurable CNS lesions: **CNS ORR was 57%** (95% CI, 39% to 74%).
- 23 patients with baseline CNS metastases (measurable or nonmeasurable) and no prior radiation: **43% had a complete CNS response**

- 12 month cumulative CNS progression rate was 24.8%

Ou S-H, JCO 2015

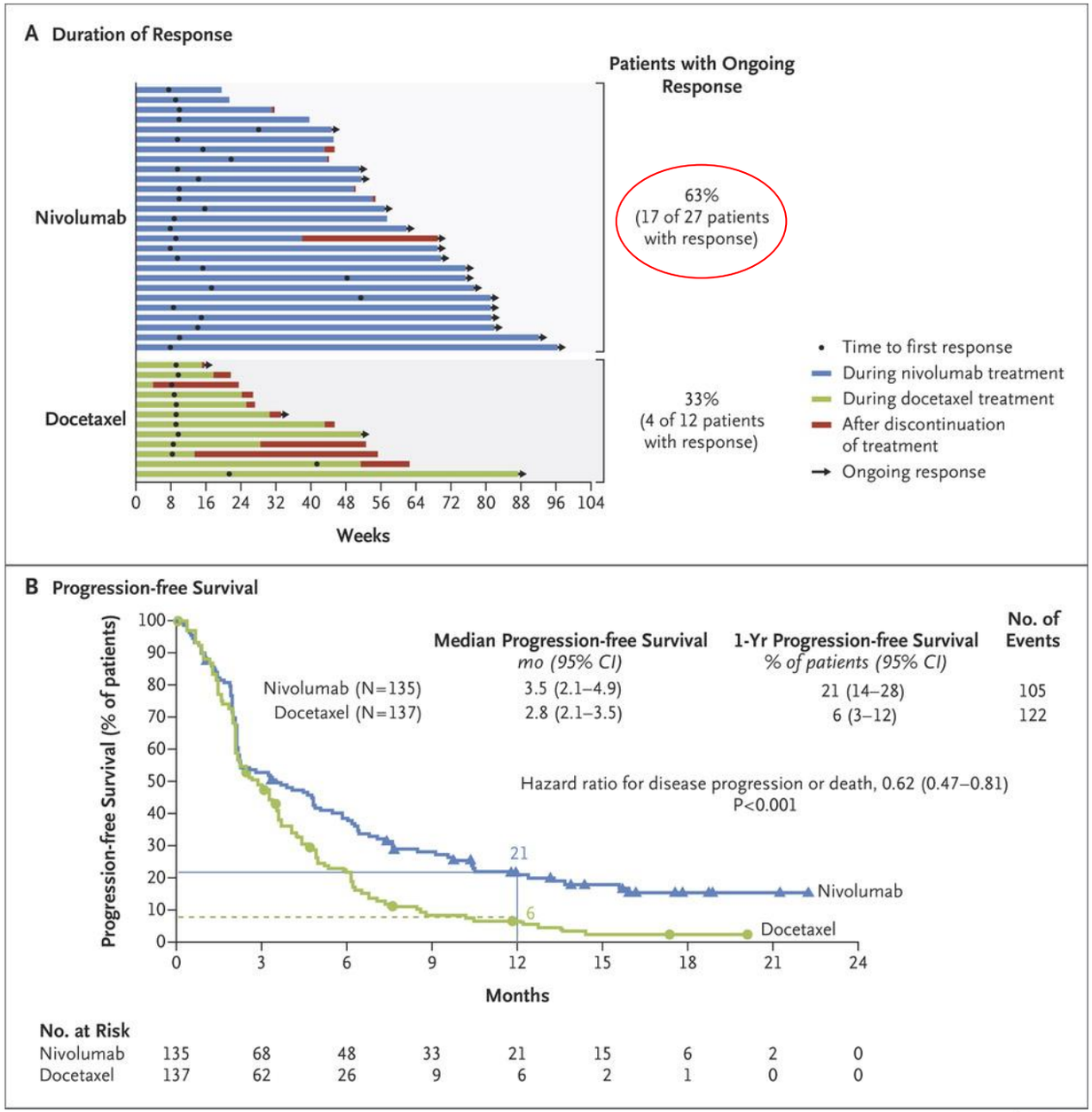
Can ablative radiotherapy complement targeted and immune therapies?



Adapted from Ribas A, Clin Cancer Res 2012

Nivolumab vs Docetaxel in advanced squamous NSCLC

PFS and Duration of Response (DOR)



Brahmer J 2015 NEJM 2015

Radiation & Local Immune Effects

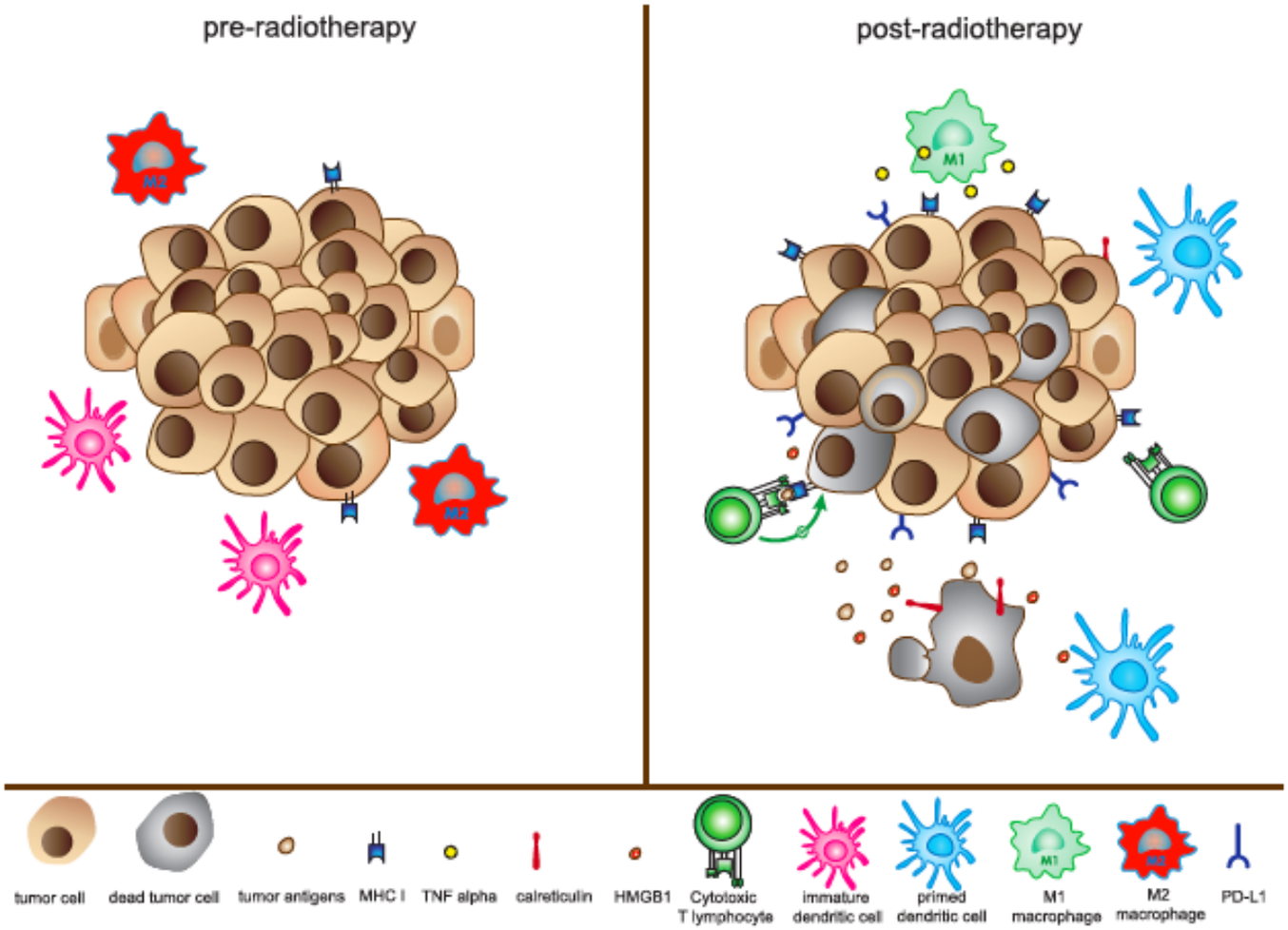
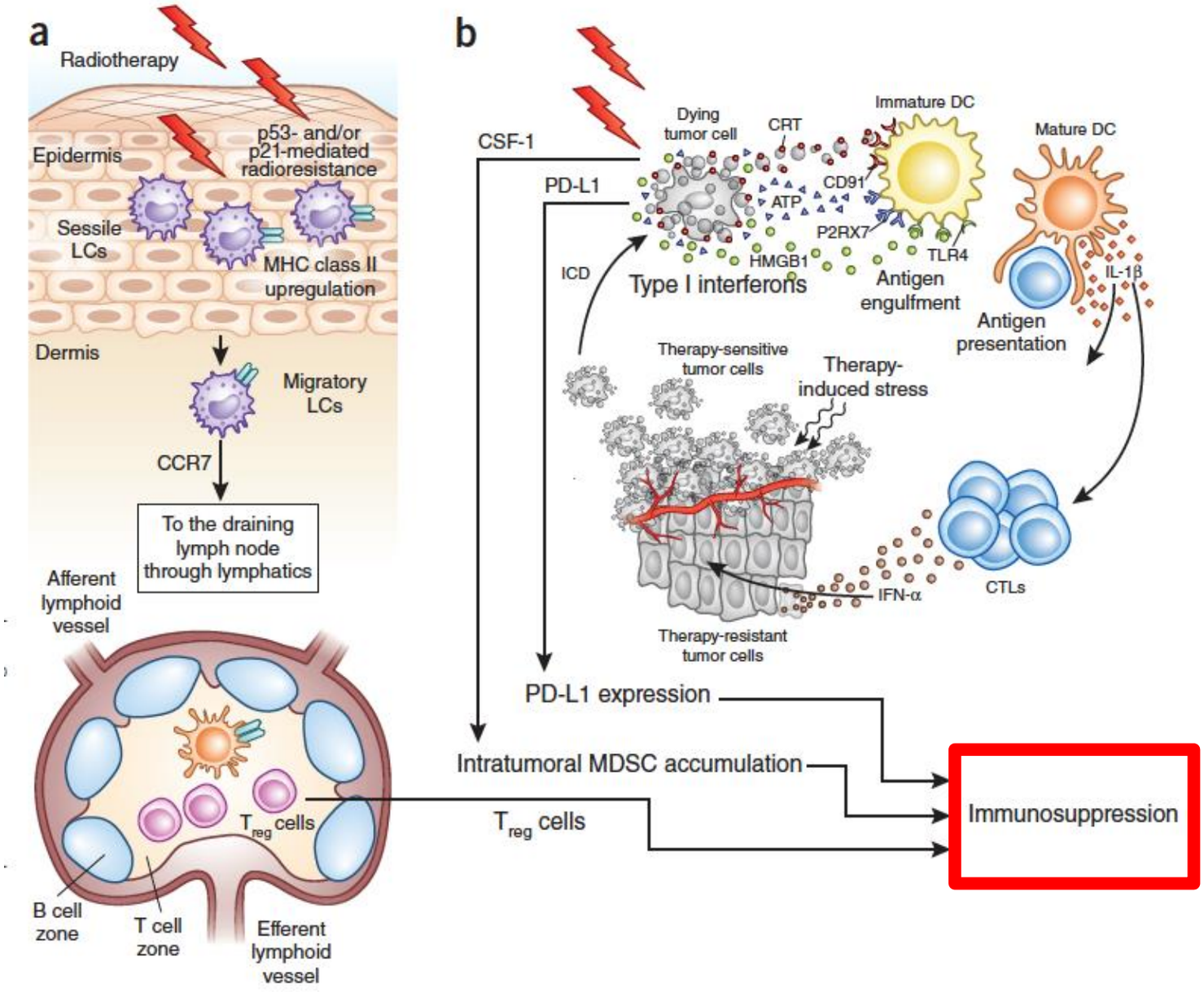


FIGURE 1. Radiotherapy induces multiple immunomodulatory changes that can potentially influence the effectiveness of immunotherapy. Shown above from left to right and in Table 1: radiation may lead to direct tumor cell killing; upregulation of immunogenic cell surface markers, such as MHC-1; secretion of danger signals and cytokines, such as TNF-alpha; induction of immunogenic cell death via calreticulin and HMGB-1, among others; improved homing of immune cells, such as cytotoxic T lymphocytes to tumor; improved antigen presentation by mechanism including priming of dendritic cells; a shift in TAM from the M2 to M1 phenotype; and upregulation of cell surface PD-L1, among others. MHC-1, major histocompatibility complex 1; HMGB-1, high mobility group protein B1; TAM, tumor-associated macrophage; PD-L1, programmed cell death ligand-1.

Daly ME, *J Thorac Oncol.* 2015

Radiation: Immunosuppresive Effects



Zitvogel L, Nature Immunol 2015

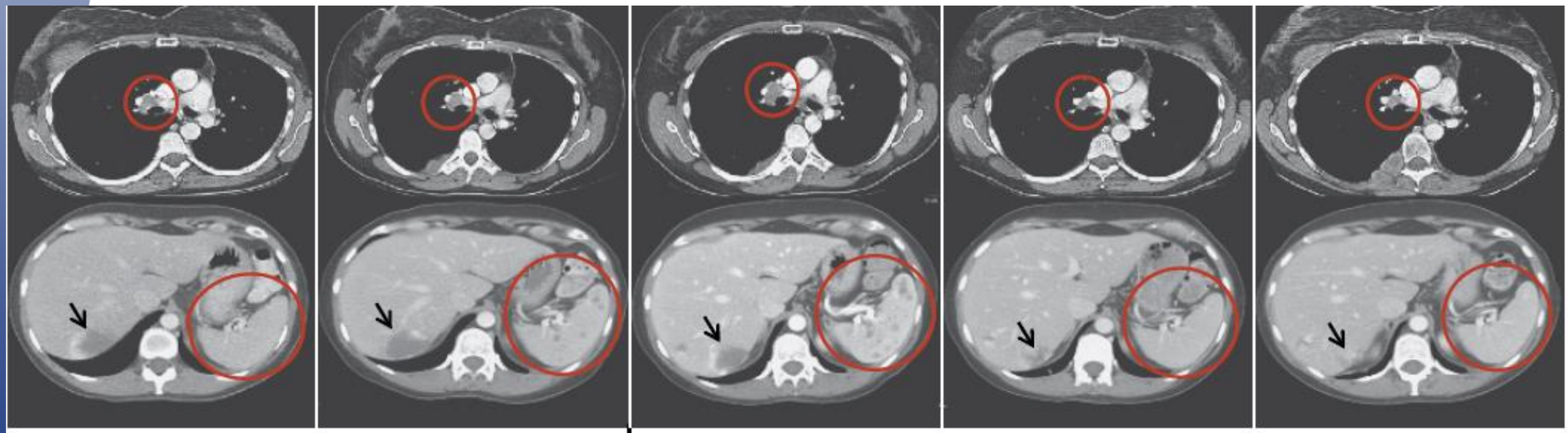
Radiotherapy: Distant ('abscopal') Effects

- 'Abscopal effect' refers to a regression of *non-irradiated* metastatic lesions *distant* from an irradiated tumor site.
- 'Out-of field' effects are uncommon[1], and are believed to be an immune-mediated phenomenon[2]
- Radiotherapy combined with immunotherapy may increase the abscopal effect[3]. However, issues such as optimal sequencing and radiation dose remain uncear.

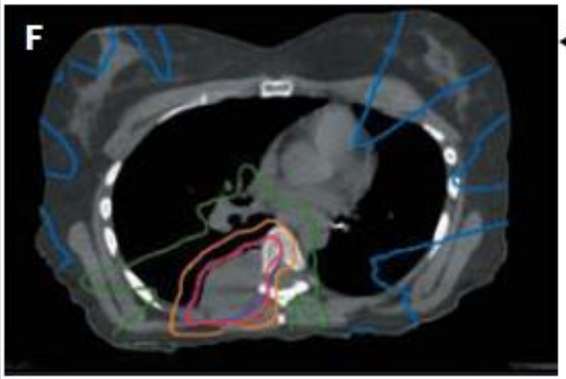
[1]Reynders K, et al. Cancer Treat Rev. 2015 Jun;41(6):503-510; [2] Grimaldi AM, et al. *Oncoimmunology*. 2014;3:e28780. eCollection 2014; [3] Postow MA, et al. *N Engl J Med*. 2012;366(10):925-931

Radiation + Immunotherapy: Abscopal Effect

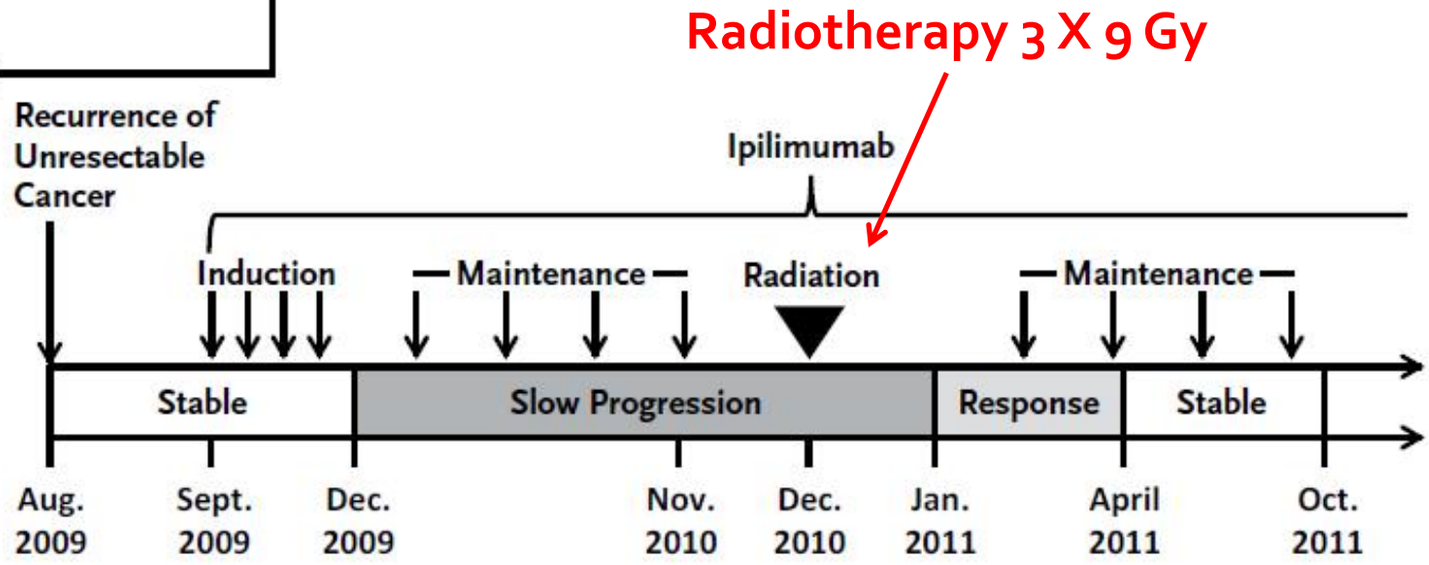
Melanoma Patient



August 2009 | November 2010 | January 2011 | April 2011 | October 2011



December 2010



Postow MA. *N Engl J Med*. 2012;366(10):925-931

Oligometastatic paradigm

Changing landscape

Where rapid progress is made in systemic therapies

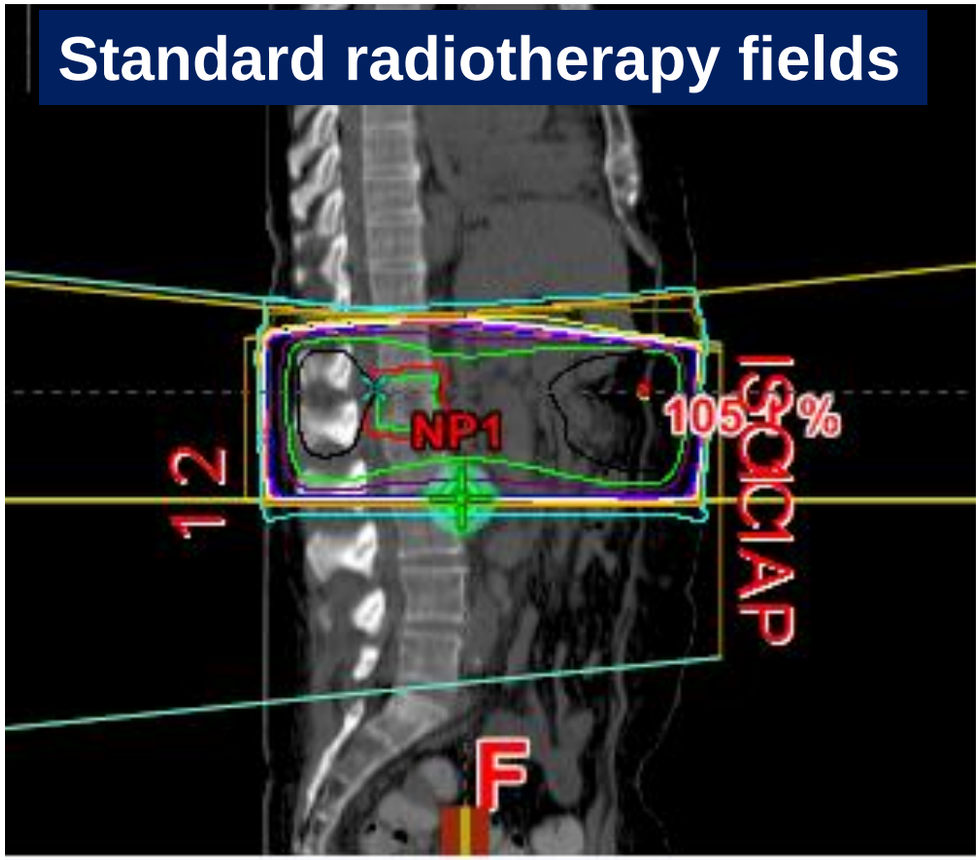
Radiotherapy, either conventional or SABR, to elicit abscopal effects

Dilemma's

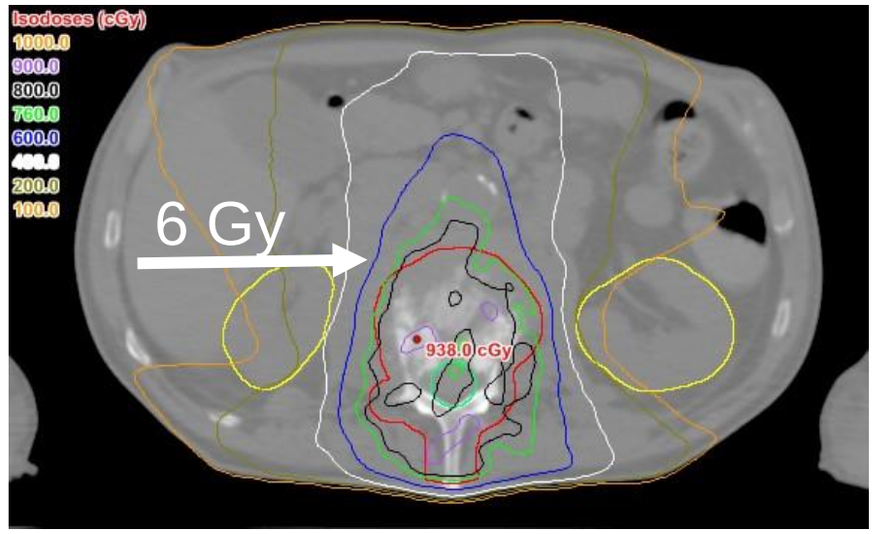
When safety data for sequencing (or combining) radiation and new agents is lacking

‘Safer’ palliative radiotherapy

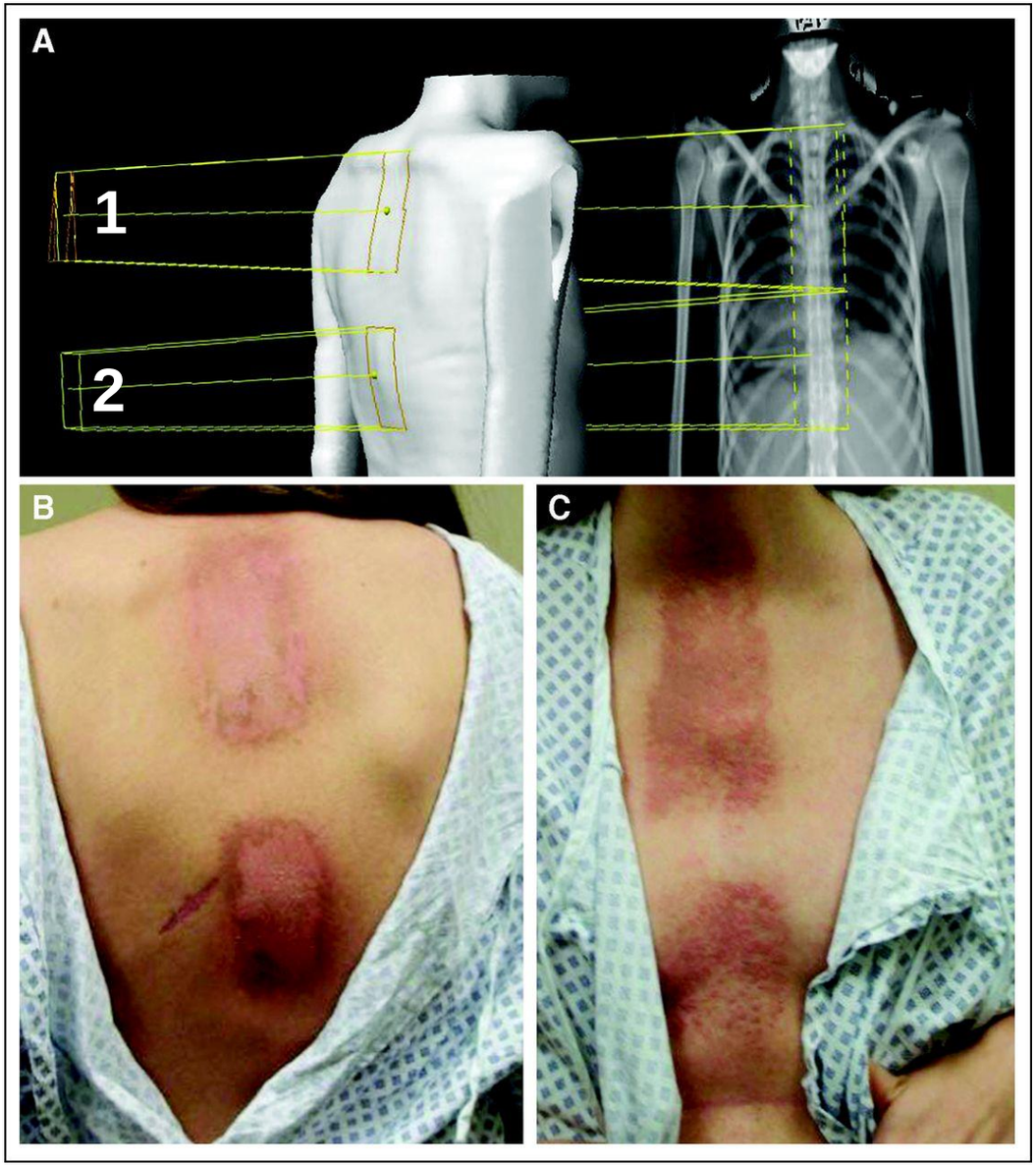
VUmc



Intensity modulated radiotherapy (VMAT) limits normal organ doses



Standard radiotherapy fields + BRAF*i*



Metastatic melanoma with BRAF V600E mutation; Rx **vemurafenib** 960 mg BID

Progressive bone metastase - stop vemurafenib for 4 days,

20 Gy (5F) by posterior beam to T1-T7, T10-L1, and bilateral acetabula (AP/PA)

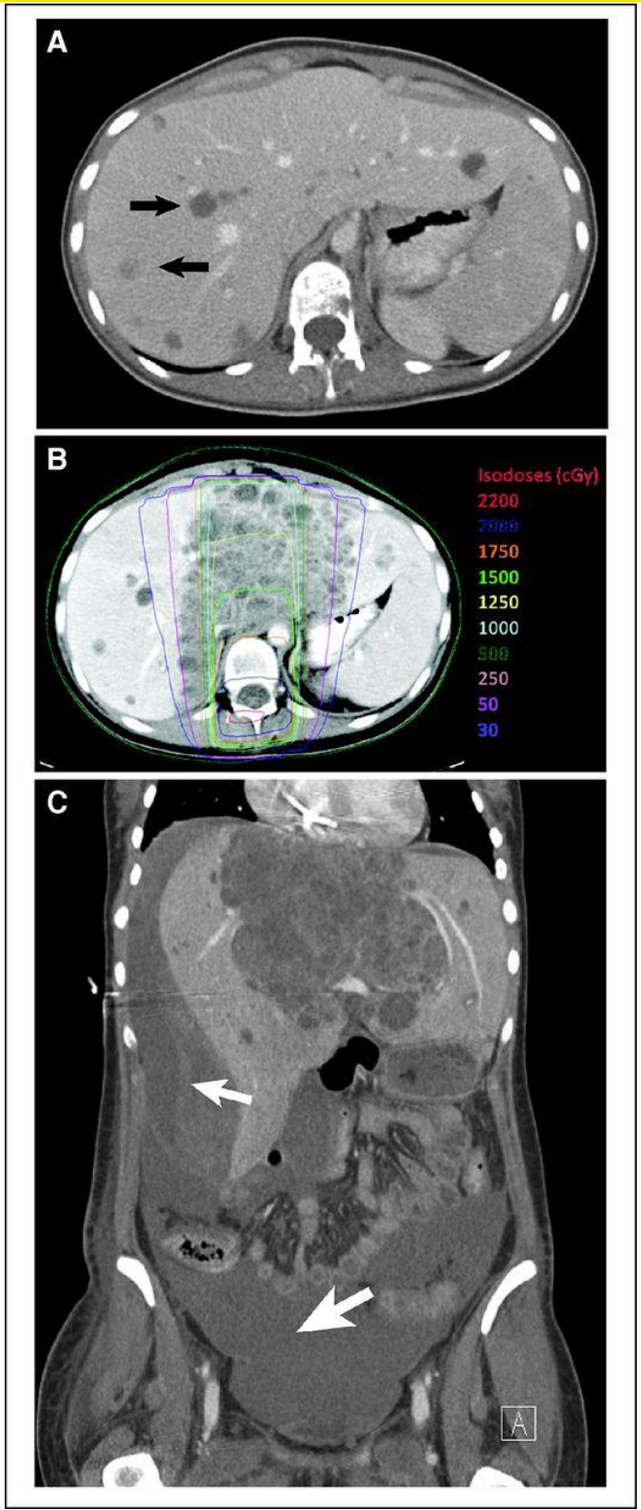
Vemurafenib restarted 2 days after RT

Two weeks after RT, tender, raised rash with well-delineated borders that matched her RT portals

Dry desquamation, and resolution of skin changes occurred within 4 weeks.

Anker CJ. JCO 2013

Standard radiotherapy fields + BRAF*i*



Multiple brain metastases 3 weeks later, followed by cauda equina compression L4

20 Gy SRS to brain metastases
8 Gy RT to L2-L5 using a PA field,

Vemurafenib stop 2 days before; restarted 4 days after SRS (480 mg for 3 days before full doses)

1 week post-RT, **mild erythema** in L2-L5 portal

10 weeks post-RT: multiple hypodense liver lesions in matching previous RT portal

Acute abdomen - pain and acute drop in hematocrit - large subcapsular hepatic hematoma and hemoperitoneum

Anker CJ. JCO 2013

Oligometastatic NSCLC: Conclusions

In unselected populations, favorable prognostic groups of NSCLC may be identified, such as

- Metachronous metastases (5-year OS 48%);
- Synchronous metastases with N0 disease (5-year OS 36%)

With targeted therapies and immunotherapy, there is potential for further improvement in outcomes by adding ablative therapies.

High-quality evidence is lacking; potential benefits must be balanced against risks of unexpected morbidity and mortality.

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