

Impact of local management of oligometastasis in Breast Cancer

Design of clinical trials integrating
local treatments with systemic
therapy

Oligometastasis : different from widespread metastasis?

-A malignancy that has progressed to a limited number of haematogenous metastases, 1–5 metastatic lesions.

-whose disease does not seem to progress to a widespread distribution of cancer.

→ oligometastasis? (Hellman, JCO 1995).

→ In truly oligometastatic disease, subsequent disease progression should not occur

Impact of local management of oligometastasis

- What do we know from other tumors than breast cancer?

Oligometastasis : evidence from randomized trials?

- Brain mets
 - 1 lesion :
_surgery or radiosurgery improve survival after WBRT, (1 lesion),
 - 2 -3 lesions :
_impact on neurological death, not OS?
- > clear evidence for monometastatic disease!
(Patchell, NEJM 1990, Andrews, Lancet 2004)

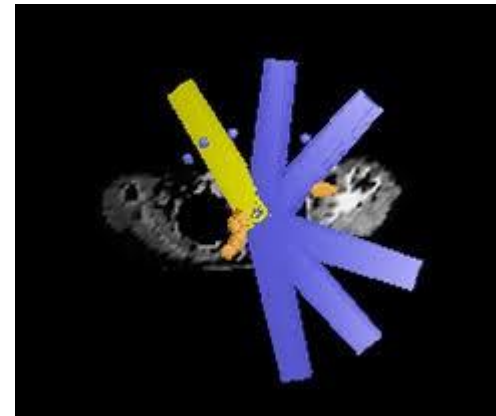
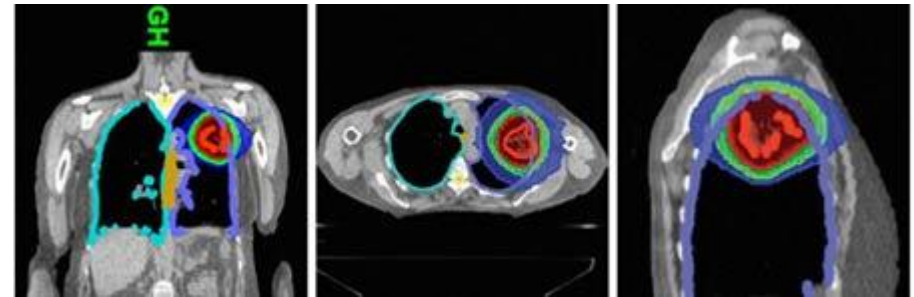
Oligometastasis nonrandomized datas

Surgery series

- Lung :
36% at 5 years, 26% at 10 years, and 22% at 15 years after metastasectomy
(International Registry of Lung Metastases, J Thor Card Sur, 1997)
 - CRC :
 - Hepatic metastasectomy for 5 years OS 15-50% (*Nordlinger, Cancer 1996*).
 - Hepatic metastectomy for breast cancer 22% OS @ 5 years (*Selzner, Surgery 2000*).
 - Oligometastases to multiple organs from CRC 5 years specific survival of 31% (*Miller, J Am Coll Surg, 2007*).
- metastasectomy “acceptable care” for selected cases
but level 1 evidence only in SNC.

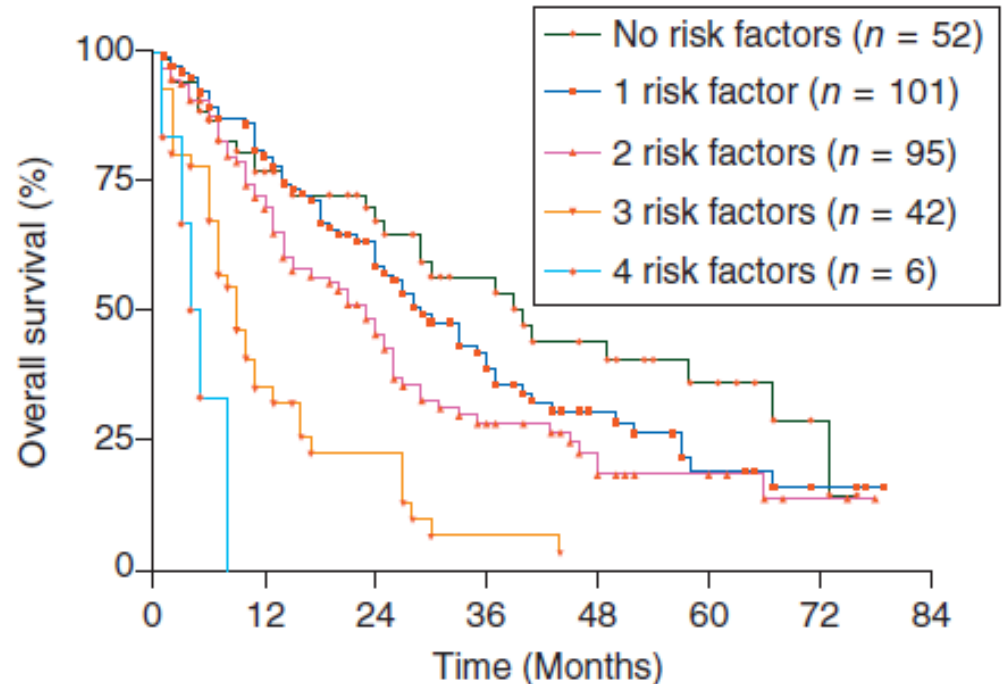
Stereotactic Ablative Radiotherapy, an alternative to surgical resection?

- Safety and feasibility for multiple mets in more than 80% cases.
- Volumes > 50cc can be treated.
- Local control achieved in breast, NSCLC, CRC, sarcoma, RCC, melanoma..
- Non invasive
- From head to toe..



UZ Brussel's experience

- 309 patients
≤ 5 mets,
SBRT
- Median OS 24 months
- Impaired OS for
 - 1/ non adenocarcinomas,
 - 2/ intracranial lesions,
 - 3/synchronous mets
 - 4/male gender.



De Vin, Annals of Oncol 2014

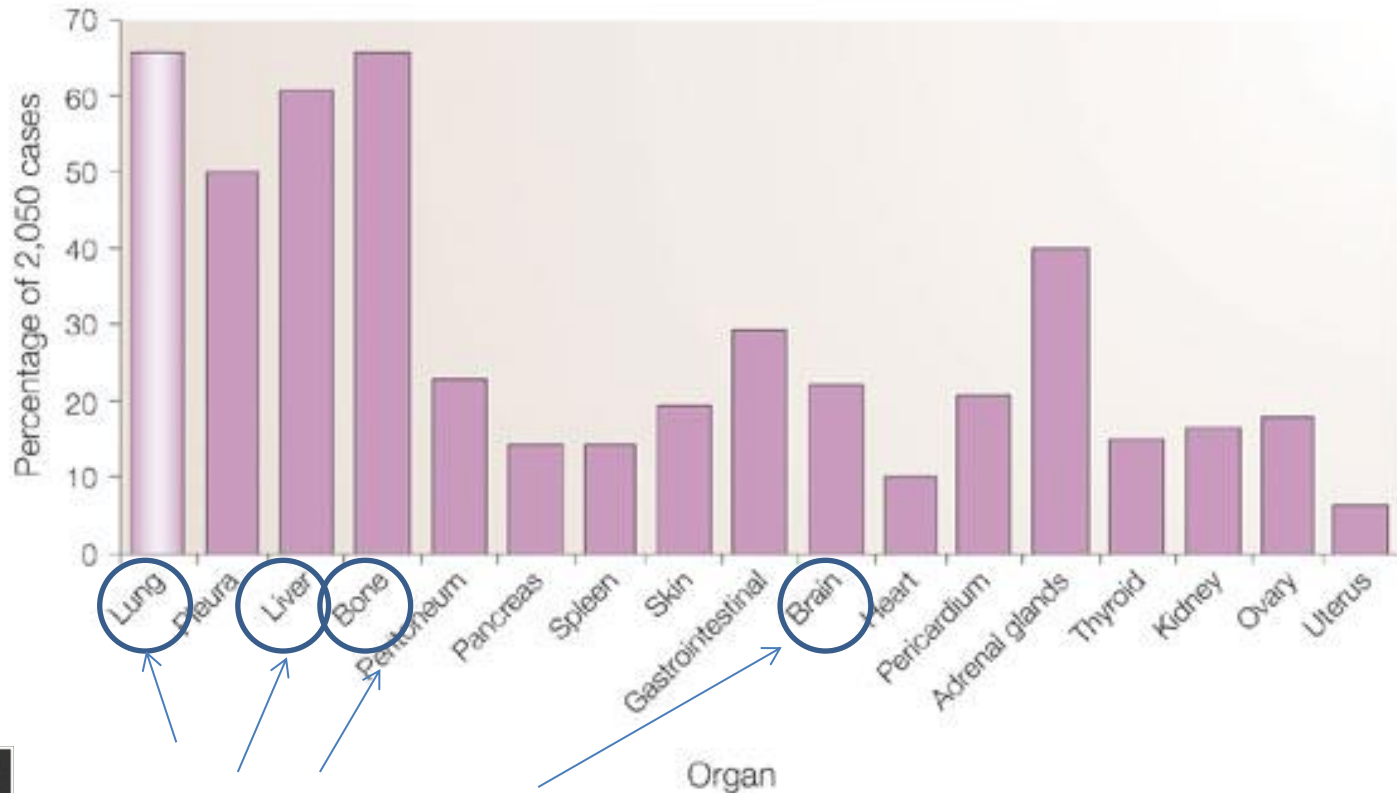
Impact of local management of oligometastasis in BC

- What do we know from other tumors than breast cancer?
- How frequent is oligometastasis in BC?

Stage IV Breast Cancer : Epidemiological facts

- < 10% of BC present stage IV disease at diagnosis (*Howlander SEER*).
- 20-30% of early BC will experience distant metastatic relapse (*EBCTCG, Lancet 2005*)
- ‘potentially curable’ stage IV estimated to be 1–10% of newly diagnosed metastatic BC (*Pagani, JNCI 2010*).

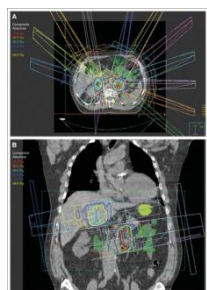
Metastatic BC : distribution of sites



Accessible to focal treatments?

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Nature Reviews | Cancer

Weigelt, Nat Rev Cancer 2005



Impact of local management of oligometastasis in BC

- What do we know from other tumors than breast cancer?
- How frequent is oligometastasis?
- Any evidence for local treatment in metastatic BC?

Synchronously metastatic BC : impact of local surgery

- *Khan, Surgery 2002* : 16,023 breast cancer patients with synchronous metastases .
 - Complete surgery of the primary → 39% reduction in the risk of death;
 - 3-year survival rate 35% after complete surgery, VS 26% and 17.3% for positive margins and no surgery, respectively ($P < .0001$).
- + *Rapiditi, JCO 2006, Blanchard Ann Surg 2008, Barbiera Ann Surg Oncol 2006..* Same conclusions

Synchronously metastatic BC : impact of local radiotherapy

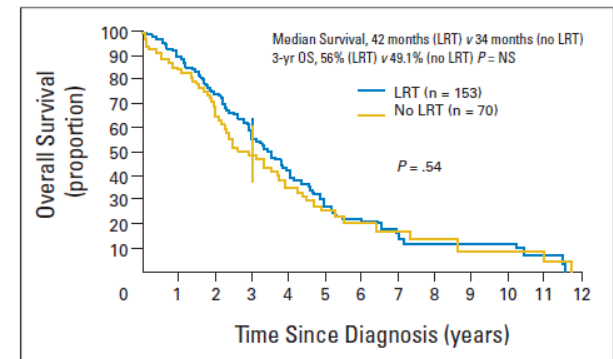
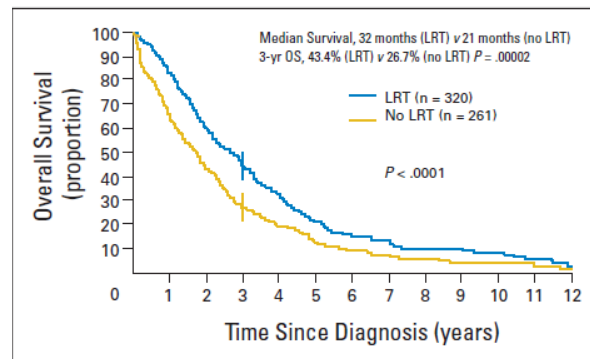
Lescodan et al, JCO 2009

- 581 breast cancer patients, loco regional ttt 320 patients (55%), no loco regional ttt 261 patients (45%), 249 pts (78%) exclusive RT.

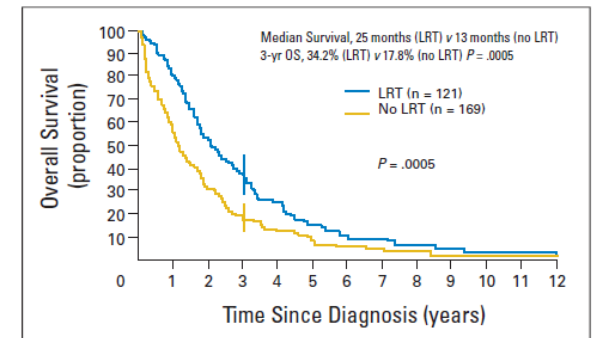
Table 3. Multivariate Analysis of Overall Survival, Cox Model (n = 564)

Characteristic	Hazards Ratio for Death	95% CI	P
Multiple sites			.00005
No	1		
Yes	1.60	1.30 to 2.00	
Medical treatment			.00001
CT alone	1		
HT ± CT	0.53	0.40 to 0.70	
LRT			.0002
No	1		
Yes	0.70	0.58 to 0.85	
Age, years			.003
24-54	1		
55-94	1.27	1.10 to 1.60	
Visceral metastases			.03
No	1		
Yes	1.27	1.00 to 1.60	
Clinical node stage			.0003
N0	1		
N1-3	1.50	1.20 to 1.85	

Abbreviations: CT, chemotherapy; HT, hormonal treatment; LRT, locoregional treatment.



Bone mets



Visceral mets

Breast + nodes : 45 to 50 Gy + 20 to 30 Gy to GTV

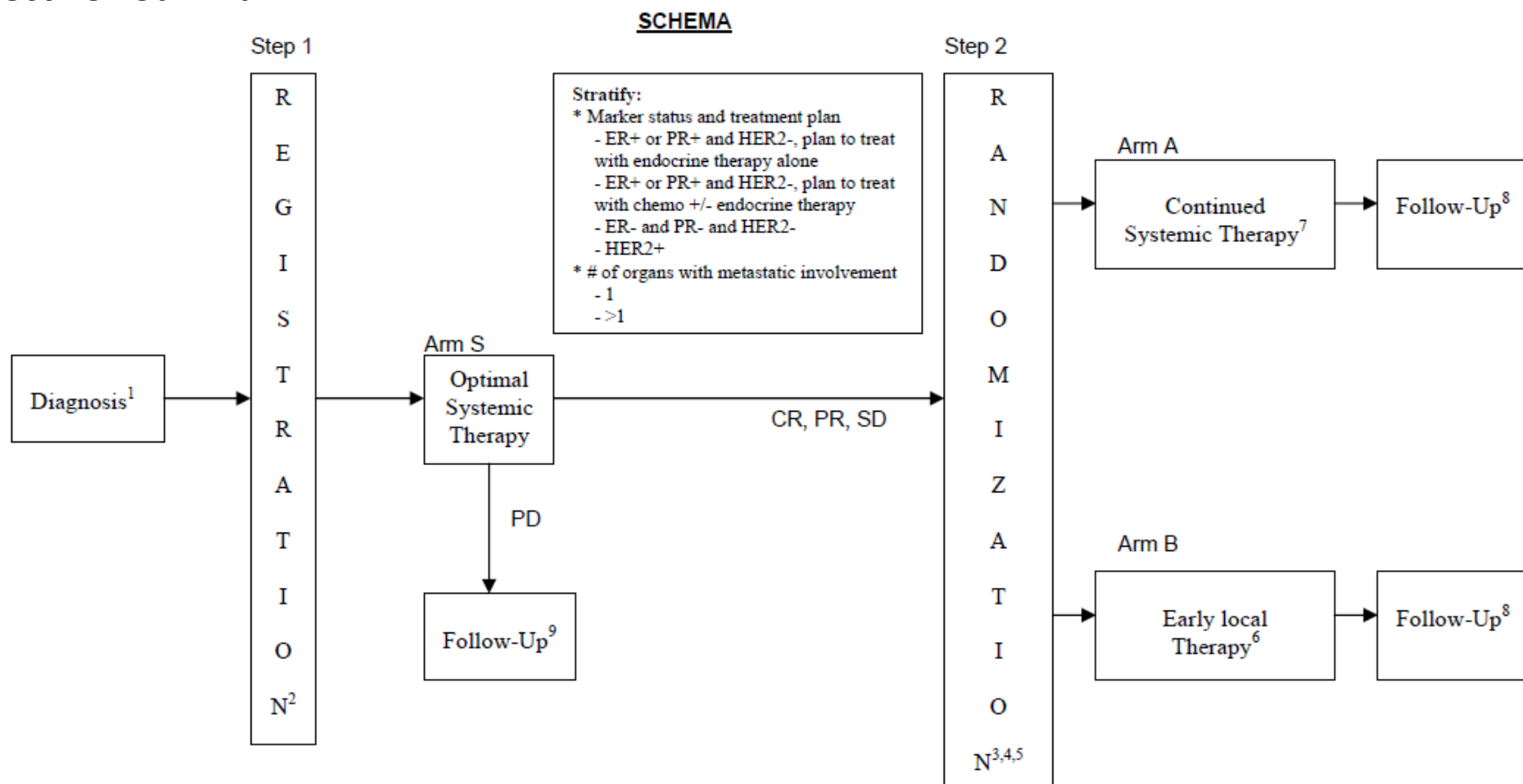
Impact of local management of oligometastasis in BC

- What do we know from other tumors than breast cancer?
- How frequent is oligometastasis?
- Any evidence for local treatment in metastatic BC?
- Trials addressing strategy in BC?

Metastatic breast cancer : local treatment to the primary?

E2108 – A Randomized Phase III Trial of the Value of Early Local Therapy for the Primary Tumor in Patients with Metastatic Breast Cancer Primary

Objective: Survival



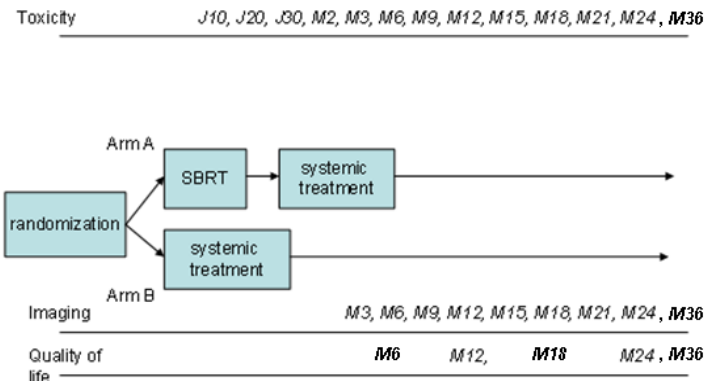
Accrual = 880

Sponsor : **Eastern Cooperative Oncology Group** , PI Seema A. Khan

Metastatic breast cancer

Impact of ablative radiotherapy to the mets ?

- “*Stéresein*” trial
- Multicentric phase III trial of superiority of stereotactic body radiation therapy in patients with metastatic breast cancer
- 1st line treatment
- Max 5 lesions $\leq 10\text{cm}$ or $\leq 500\text{mL}$
- Positive Hormone receptors (IHC), Her2 Negative



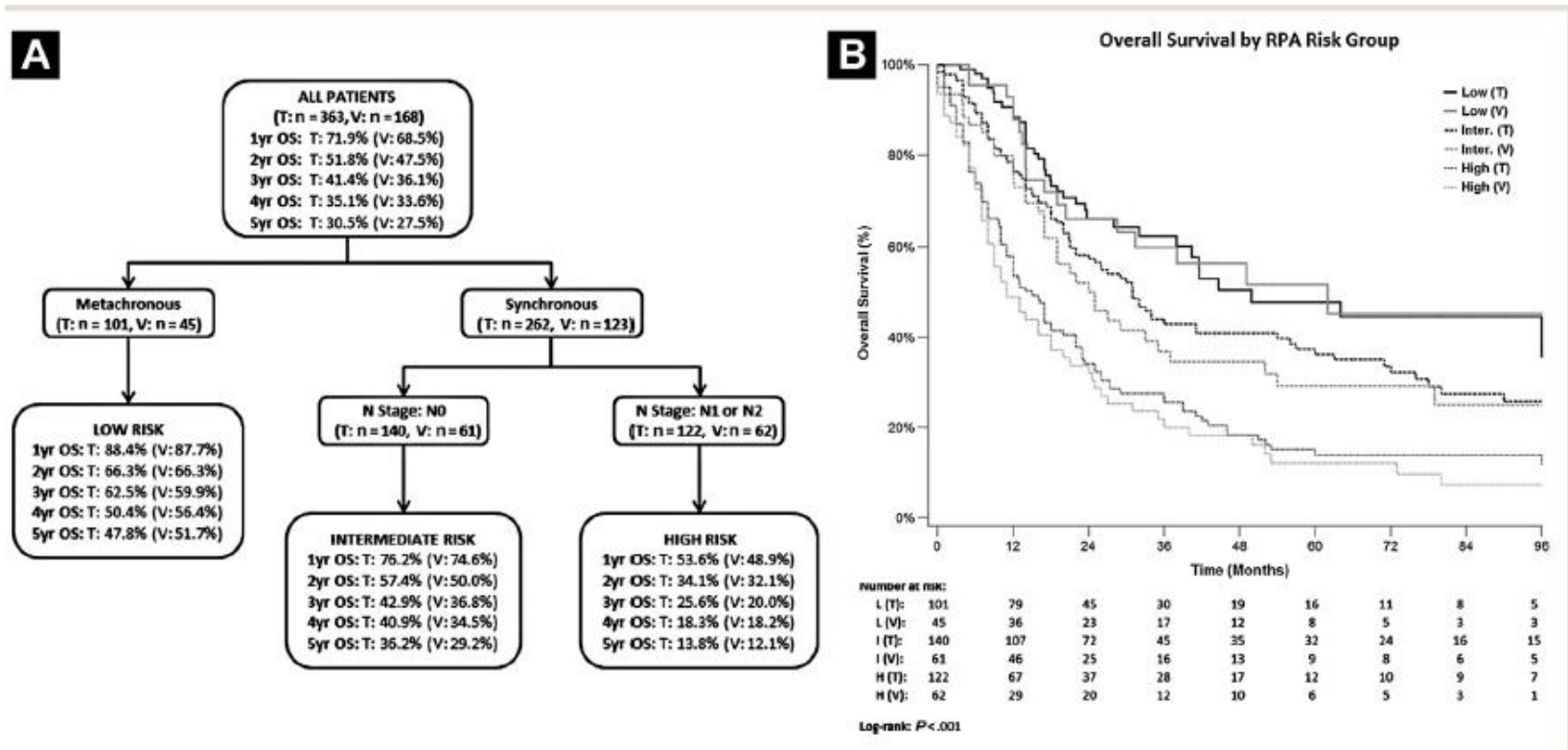
**Sponsor : Gustave Roussy
(C Bourcier, S Rivera)**

And also :

NRG BR-002 : (NSABP, RTOG, and GOG) :
phase II/III study for patients with 1-2 metastases

Learning from other tumors?

Example of oligometastatic NSCLC :



Ashworth, Clin Lung Cancer 2014

→ highly favorable subset of metastatic NSCLC patients might benefit from more ablative therapies

How to optimize selections?

1- tumor growth kinetics?

2- the clinical scenario?

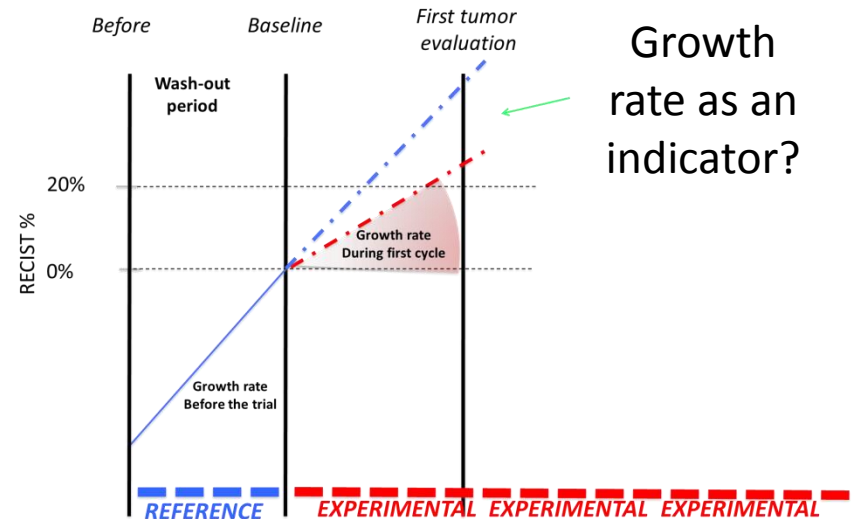
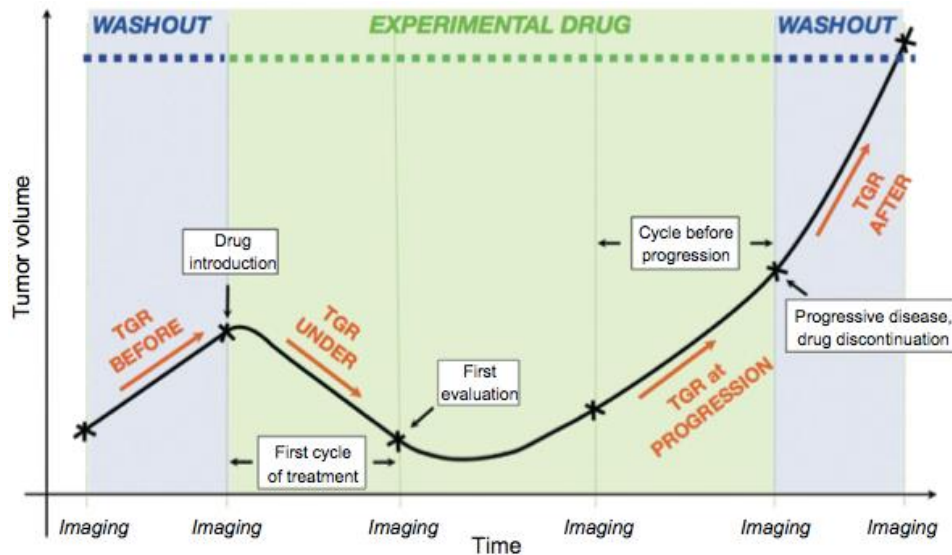
- i) those who present with oligometastases;
- ii) residual oligometastases after systemic therapy
- iii) relapsed oligometastases after curative locoregional therapy.
« *Oligorecurrence* »

3- biology?

Tumor kinetics for patients selection?

Tumor growth rate :

- Tumor volume (V) approximated by $V = 4 \pi R^3 / 3$, where $R = D/2$.

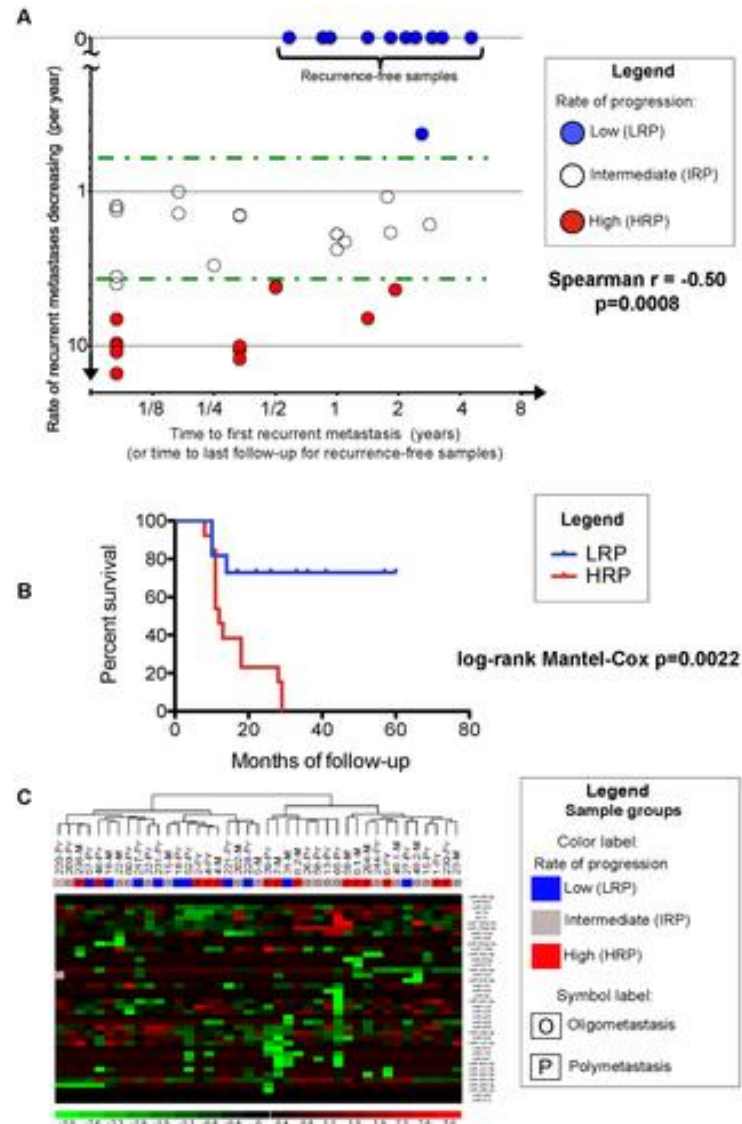


Growth rate as an indicator?

Ferté et al, Clin Cancer Res 2013

Biological selection?

- miRNA to identify « real » oligometastatic patients?





Clinical cases of abscopal effect

A

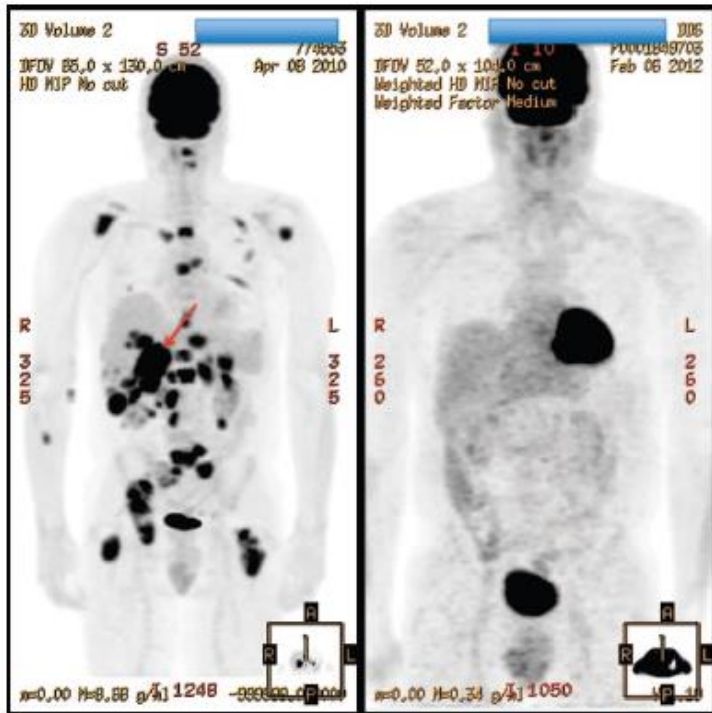
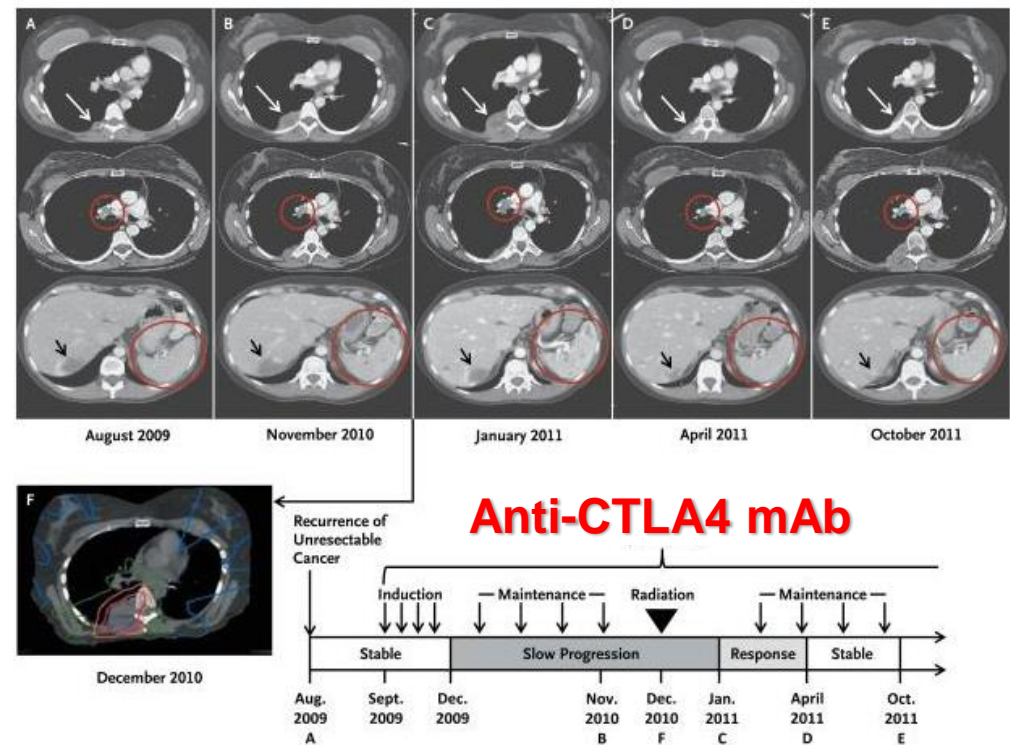


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

B



Postow, NEJM2012, Hinicker, NEJM2012

Combination of radiotherapy with immunomodulators may enhance the abscopal effect

Radiotherapy + immunomodulation : MelIPIRX trial

Phase I trial in metatstacic melanoma

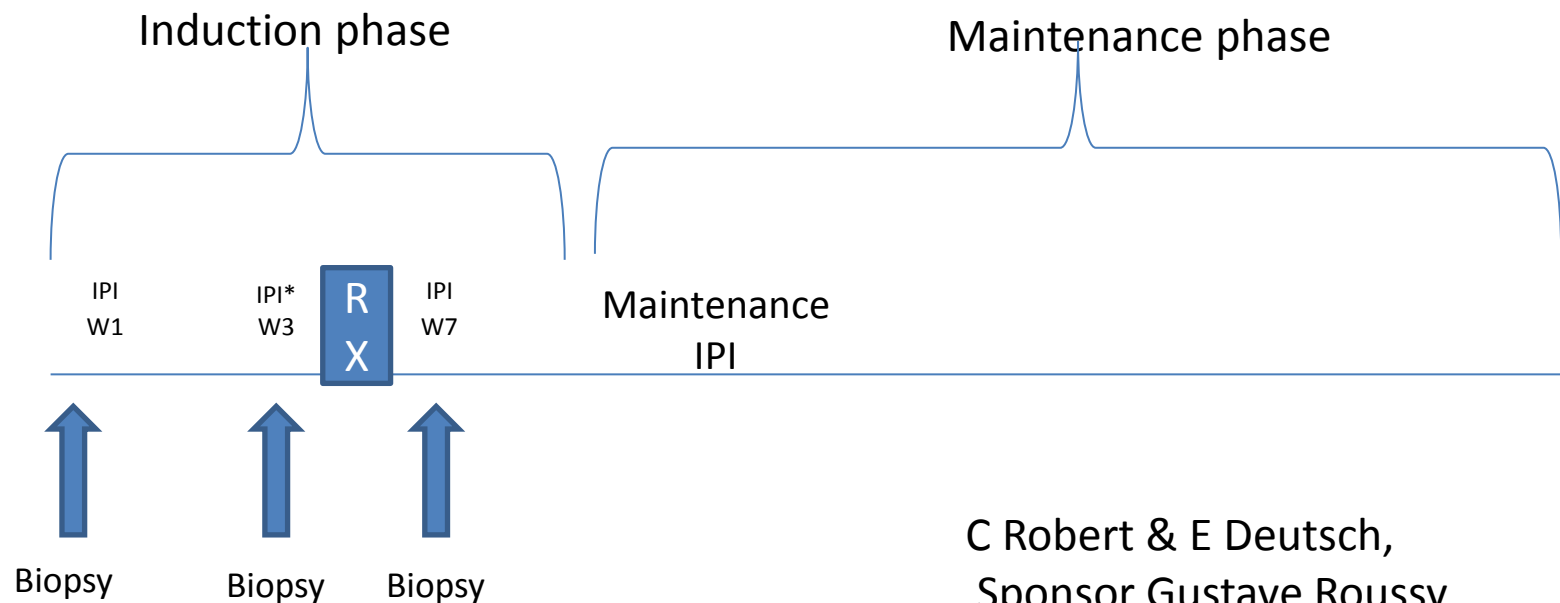
IPilimumab 3mg/kg

Dose escalation of RT dose

Objective Safety and DMT

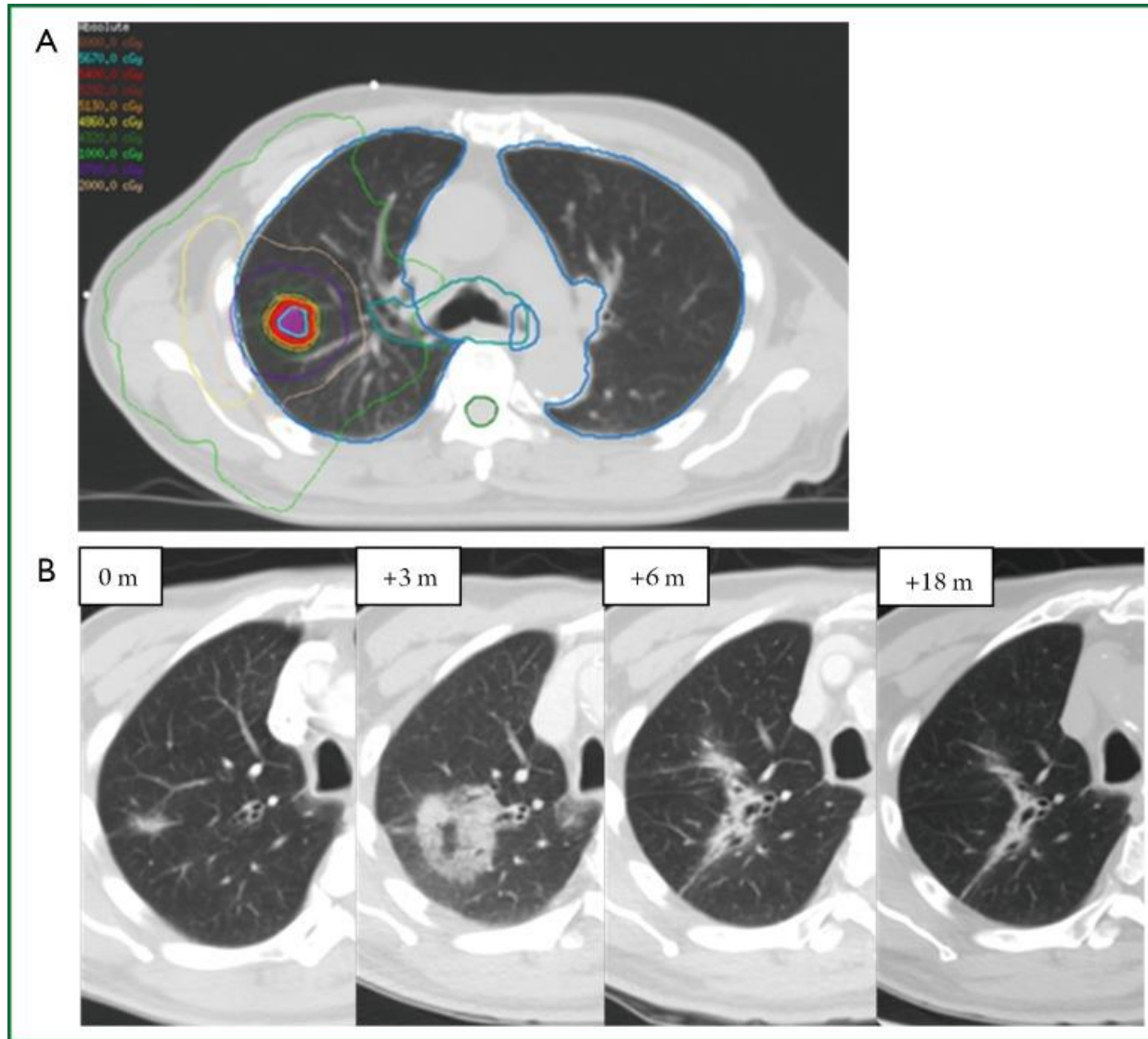
RT on 1 tumor site

→ Local and distant impact of RT? « Immune cell death »?



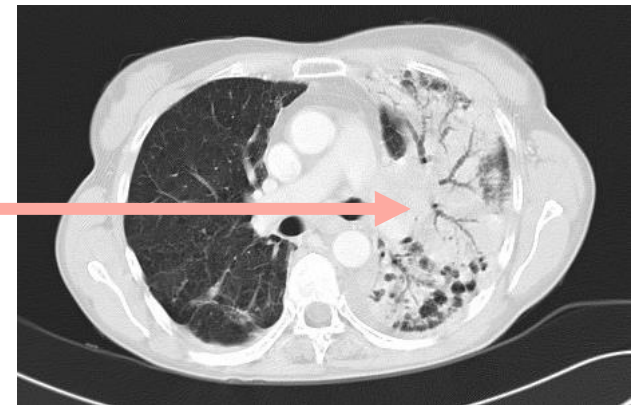
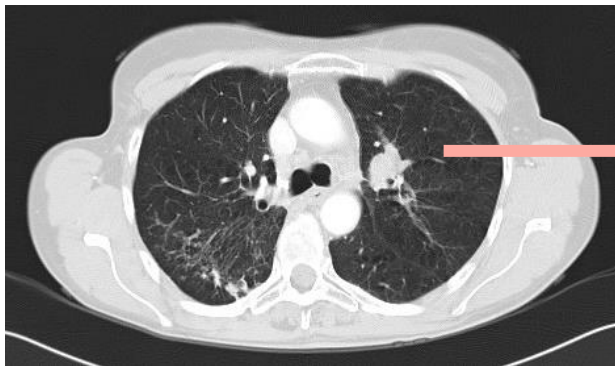
C Robert & E Deutsch,
Sponsor Gustave Roussy

Focal response assesment is a challenge



Safety is a challenge too!

→ example of bevacizumab+RT



Lind, Senan, Smit, JCO 2012

Integration of SBRT with bevacizumab currently tested in CRC
([NCT01569984](https://clinicaltrials.gov/ct2/show/study/NCT01569984), DR Y Joung, Sunnybrook, Toronto)

Still many questions..

- 'better-than-expected' survival after ablative treatment??
- Long term survival?
- Deferring initiation of systemic therapy?
- Immunological response?

..and Level 1 Evidence Based Medicine...!!!!

Oligometastatic breast cancer.. an issue has been raised previously ..

“3% to 30% of selected patients with biopsy-proven distant metastases from breast cancer ...should be approached with curative, not palliative, intent.”

Hortobagyi, JCO 2001

