Trends in basic research & technology impact for clinical research in radiotherapy.

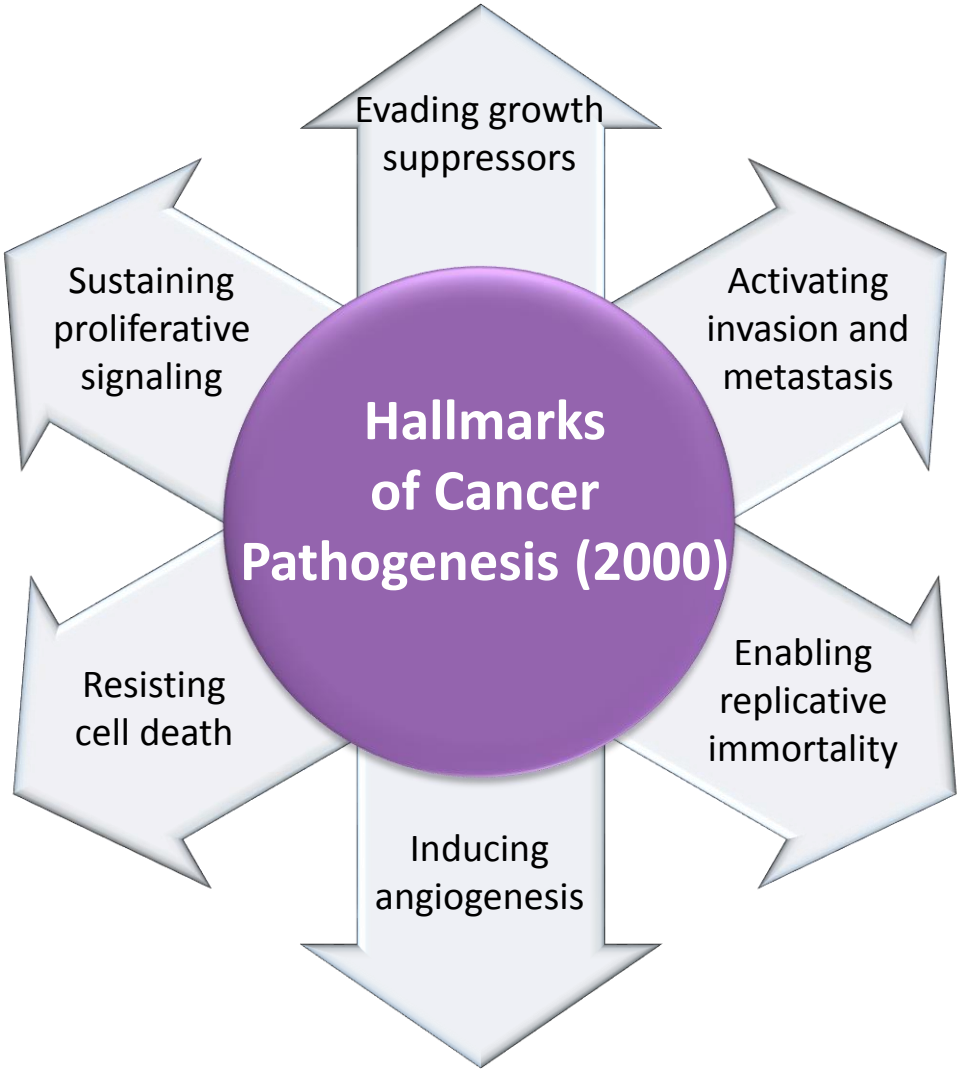
Eric Deutsch MD PhD

Gustave Roussy Cancer Campus

Outline

- Targeted therapies
- Precision medicine
- Lessons from hypoxia
- Immunology
- Imaging
- Oligometastasis

Cancer Pathogenesis: Formerly Characterized by 6 Hallmarks



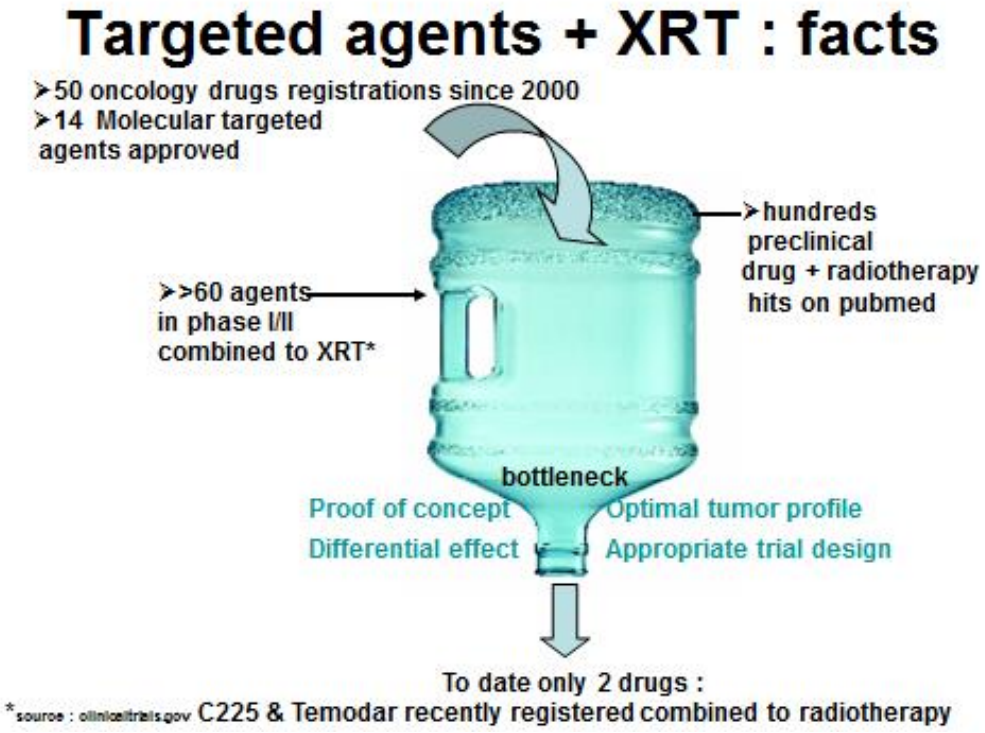
Hanahan D, Weinberg RA. *Cell*. 2000;100(1):57-70.

What have we learned from targeted therapies?

Several targets & drugs tested

- EGFr+HER2 :Lapatinib,
- EGRF : Tarceva,
- VEGF Bevacizumab,
- RAF& VEGF : Sorafenib,
- mTOR Everolimus etc etc

→**Systematic transfer of approved drugs, inefficient??**



We have EGFr targeting..but..

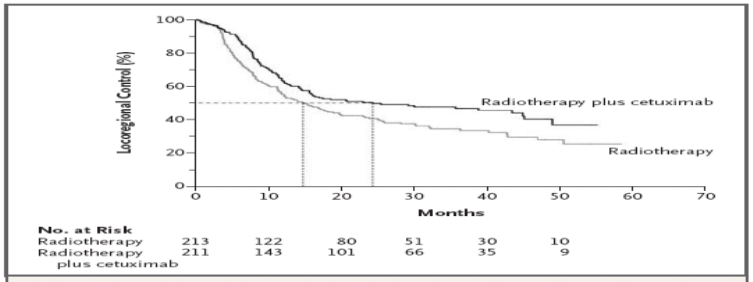


Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
The hazard ratio for locoregional progression or death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; P=0.005 by the log-rank test). The dotted lines indicate the median durations of locoregional control.

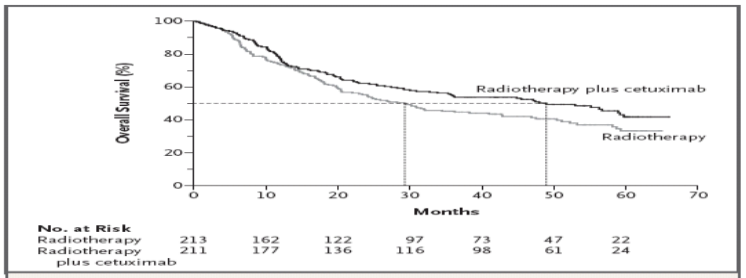


Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.

C225 + radiotherapie :
Bonner NEJM 2006

- C225 = 1st targeted therapy!

But :

→no level-1 evidence in comparison with CDDP

→Triple therapy (C225 & CDDP + RT)

-no improvement in survival

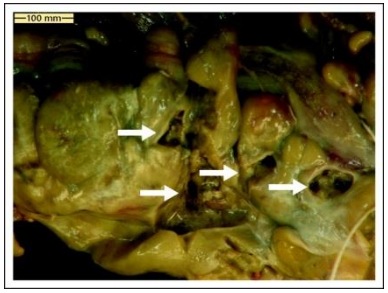
-toxicity increased. (Ang KK, JCO2011)

→No efficacy in lung, oesophagus, anal & cervix

We know drugs may alter the therapeutic ratio of XRT

Bowel perforation

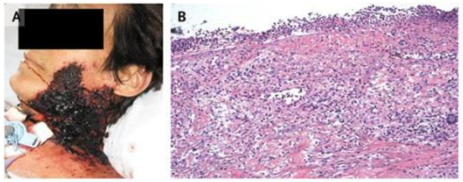
→ Sorafenib (VEGFR2)



Natascha A.J.B. Peters , JCO 2008

Increased Skin toxicity

→ C225 (EGFR)



Budach, NEJM 2007

→ Vemurafenib (RAF)

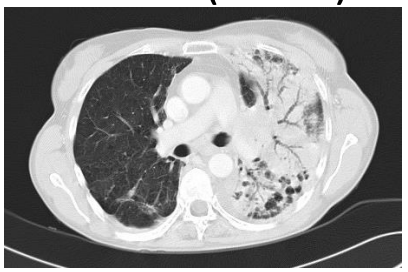
Boussemart, Jama Derm, 2013

Increased Lung toxicity

→ Everolimus (mTOR)

Deutsch, Annals of Oncol, 2015

→ Bevacizumab (VEGF)



Lind, JCO 2012, Mangoni BJC 2012

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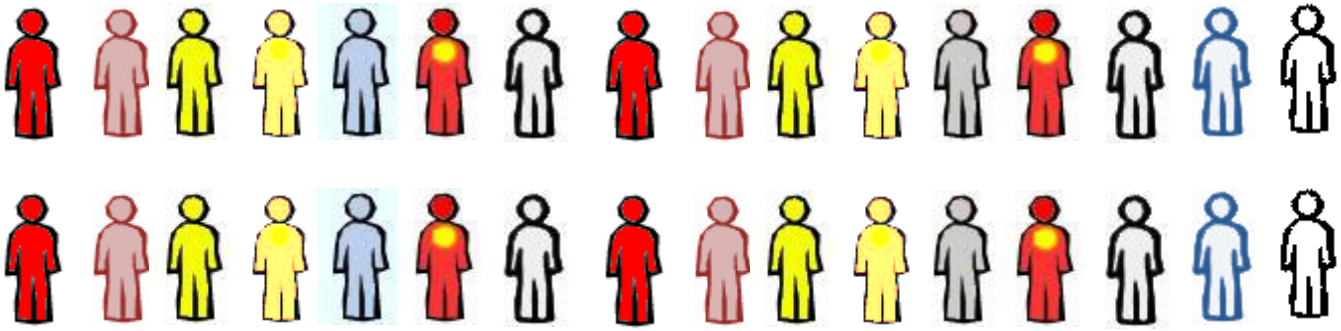
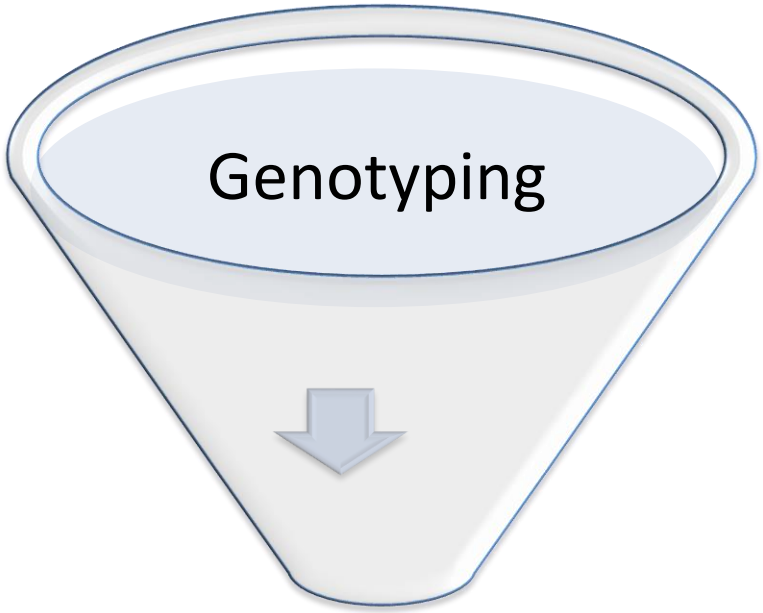
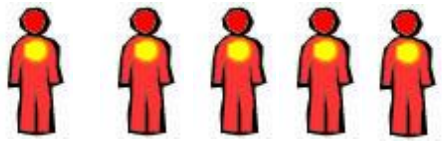




Unselected population

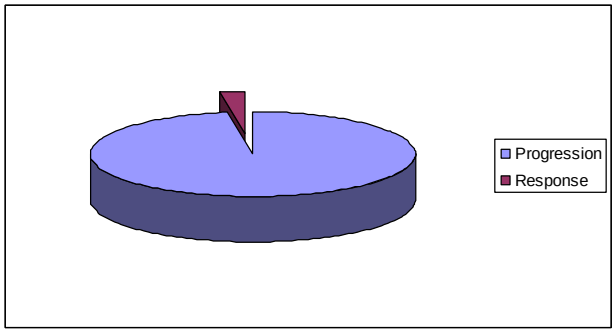
ORR below 10%

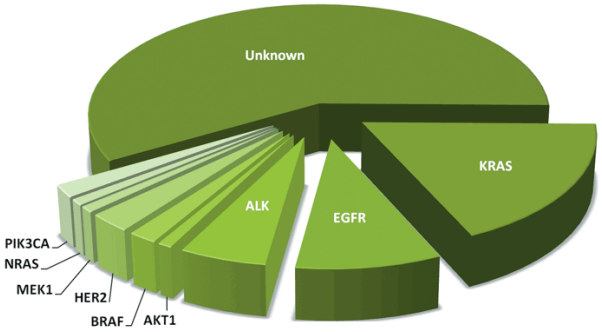


Enriched population

ORR > 30%, and even > 50%
if true oncogene de-addiction

Serendipity versus molecular driven trials EGFR inhibitors

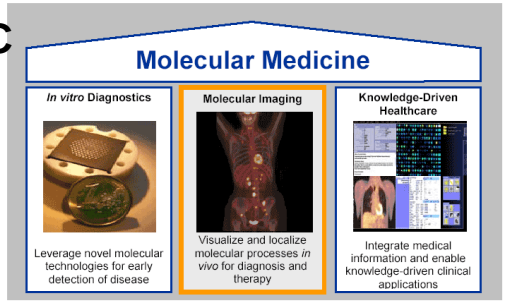


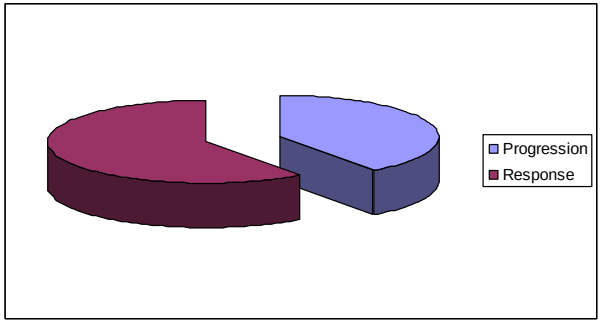


N Tatcher, *Lancet 2005* 1692 randomized patients

No effect

Molecular landscape of NSCLC





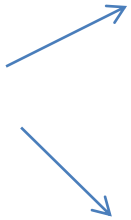
Rosell, Lancet Oncol 2012, 174 patients

Bingo!!

Individualized Therapy for NSCLC

- **RTOG 1210/Alliance 31101, NSCLC stage III**

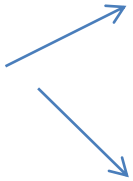
→ EGFr mut R



Erlotinib then Chemoradiation

Chemoradiation

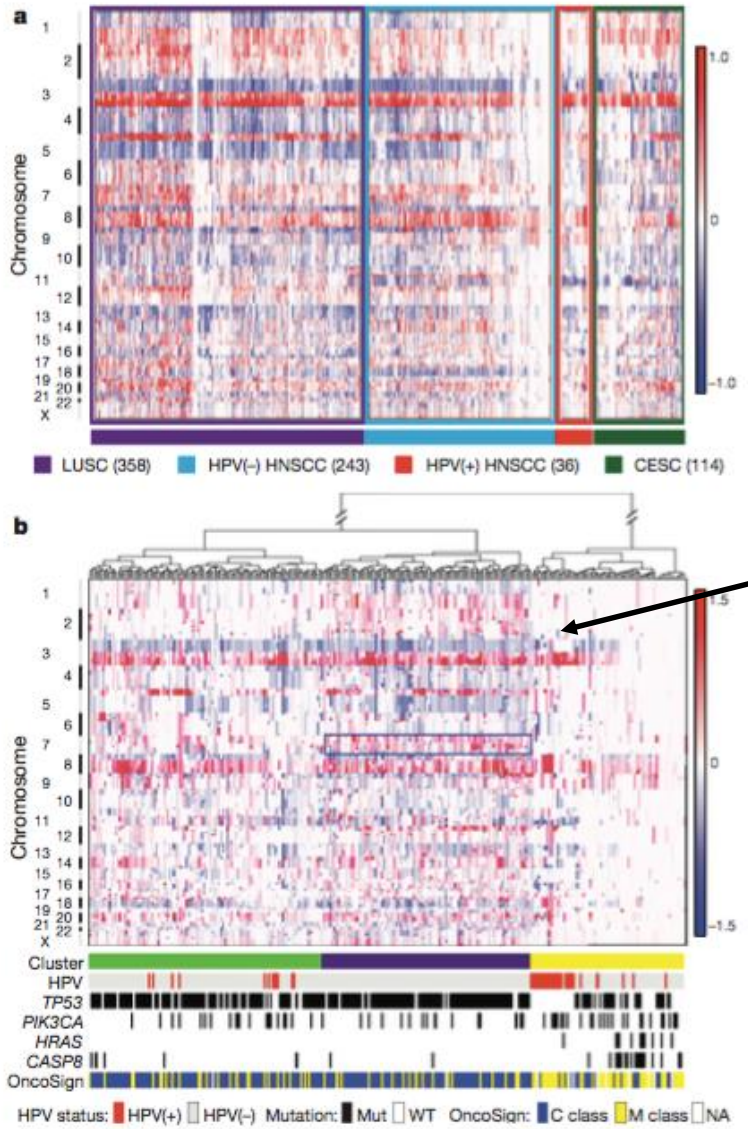
→ ALK trans R



Crizotinib then Chemoradiation

Chemoradiation

Molecular pathology will dictacte new combinations!



HNSCC HPV –
similar to SCC NSCLC

Chr 7 (EGFR) amplification cluster
HPV-

Low CAN cluster
HPV+
HRAS, CAPS8

TCGA, Nature 2015

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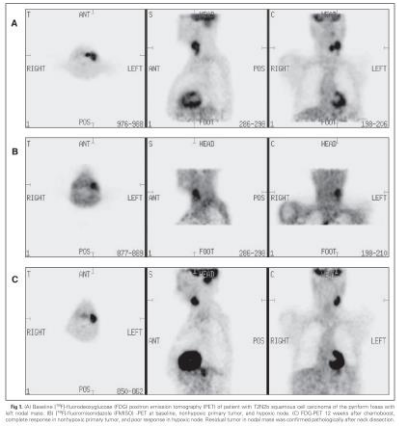
Tirapazamine trial : any lessons learnt?

1-Need for patient selection

- Bioreductive agent hypoxic
- Radiosensitizer



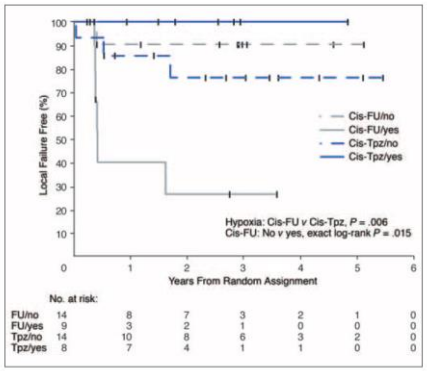


Fig 2. Time to local failure (Kaplan-Meier method) by treatment arm and hypoxia in the primary tumor (censored times are indicated as tick marks on the curves). Cis, cisplatin; FU, fluorouracil; TPZ, tirapazamine.

Rischin, JCO 2006

Randomized phase III

RT + CDDP **RT + CDDP + Tyrapazamine**

Overall results : 2 arms similar!!

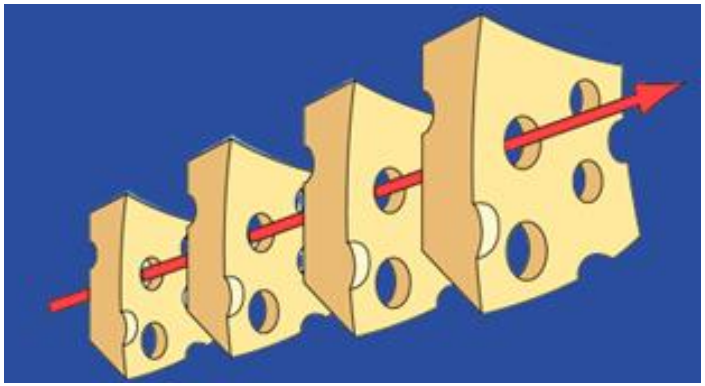
2-Biomarker discovery
QT L, Clin Can Res 2012

3- Need for compliance!
Peters, JCO 2010

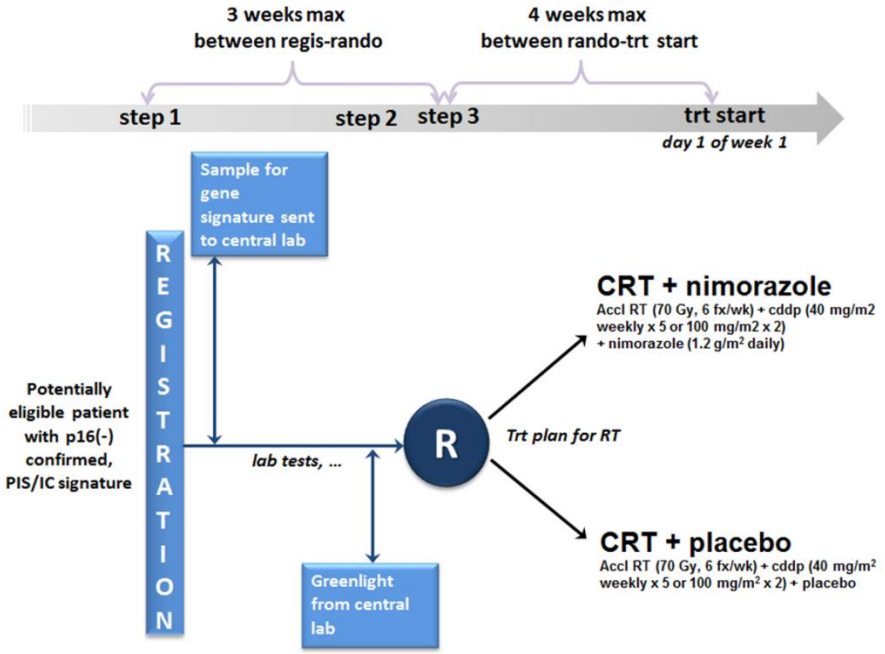
Hypoxic modifications : selection is key!

Efficacy

Biomarker



Medical Need Drug



1219 ROG-HNCG

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

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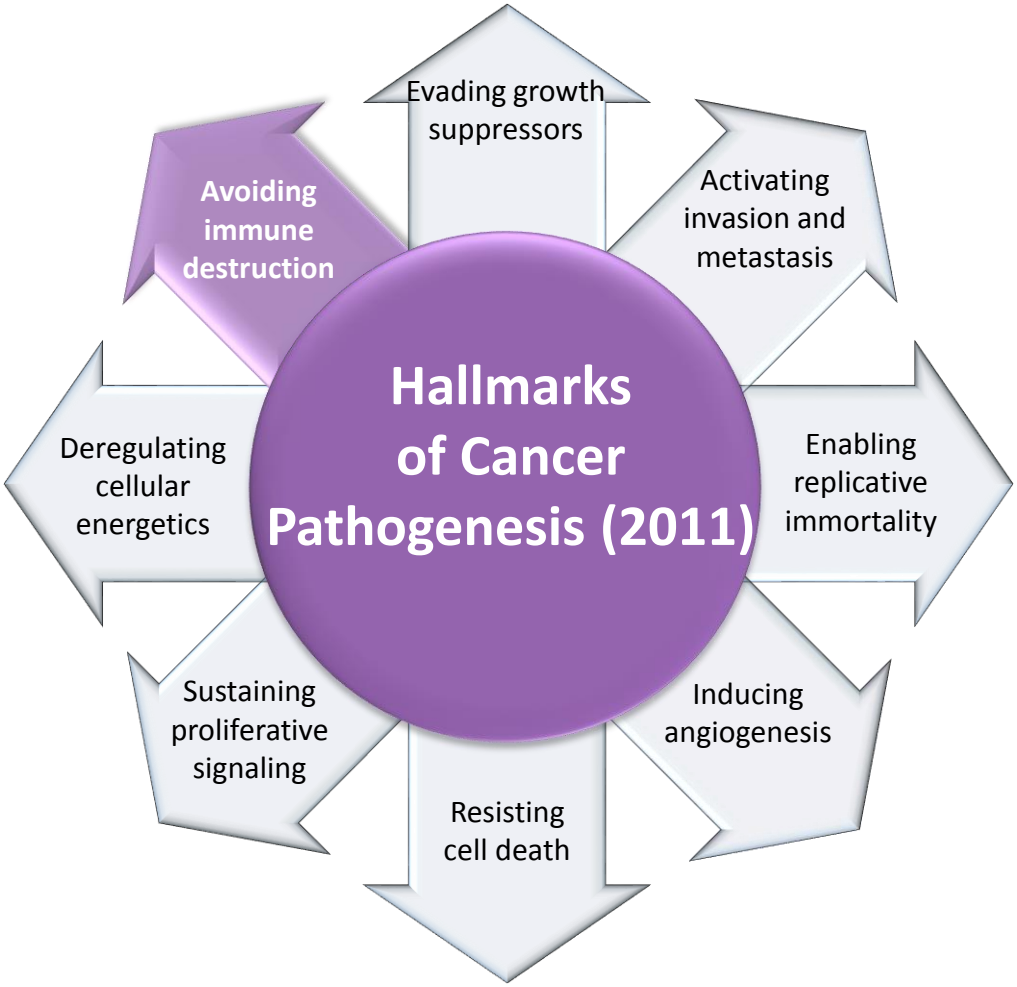
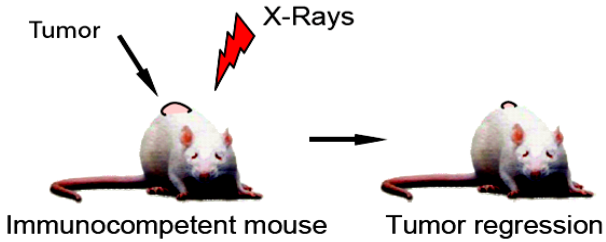
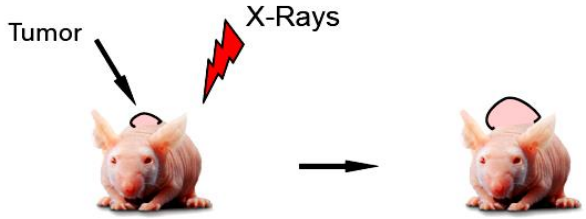
Immune Evasion Now Recognized as a Hallmark

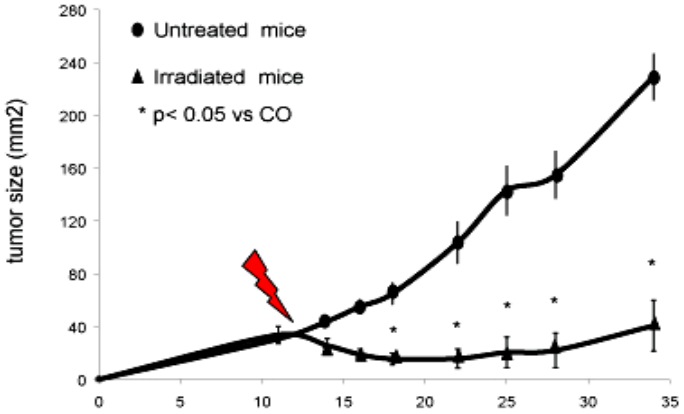


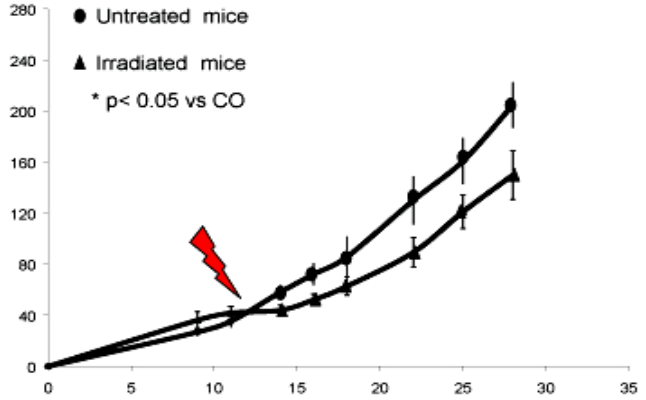
Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646-674.

Tumor microenvironment : more than hypoxia

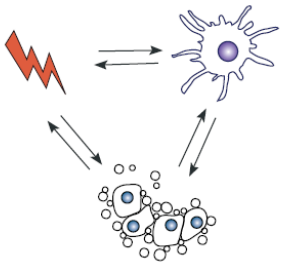








Radiation
-ER Stress
-Apoptosis
-HMGB1 release



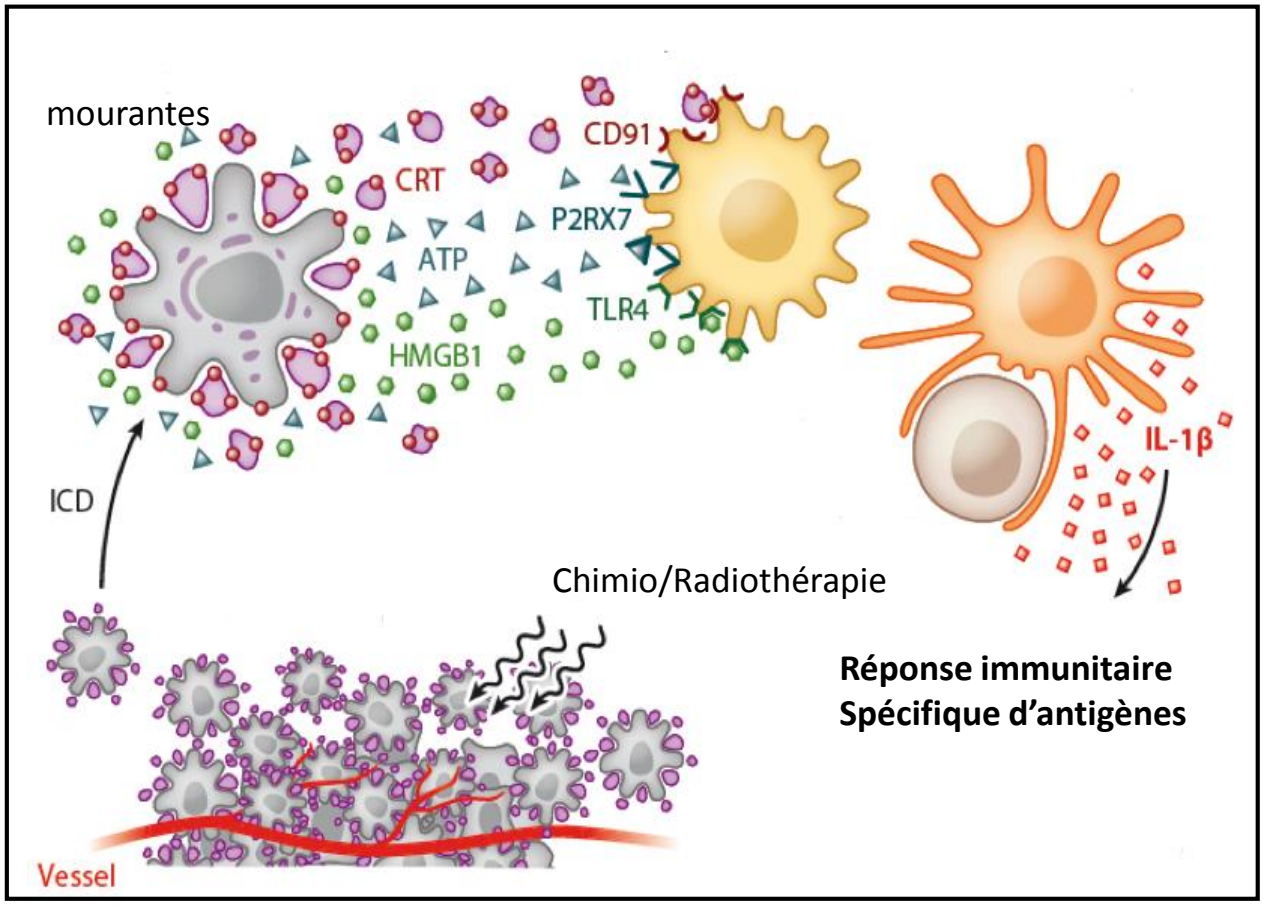
Host
-TLR4 /MyD88
-P2RX7 / NLRP3
-Immunocompetent

Courtesy A. Tesniere

Tumor
CRT exposure / HMGB1 & ATP release

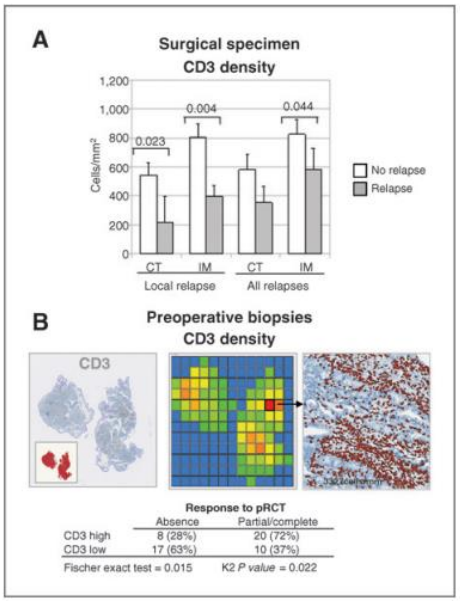
Apetoh, Tesniere*, Ghiringhelli*et al. Cancer Research 2008*

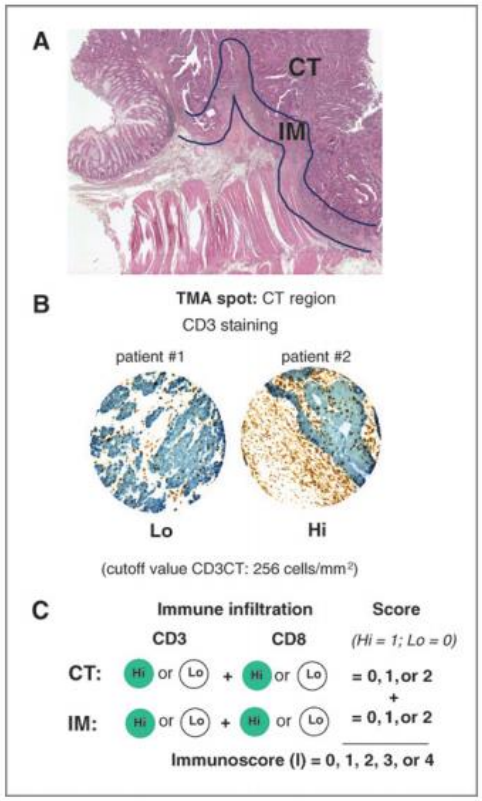
Characteristics of immune cell death

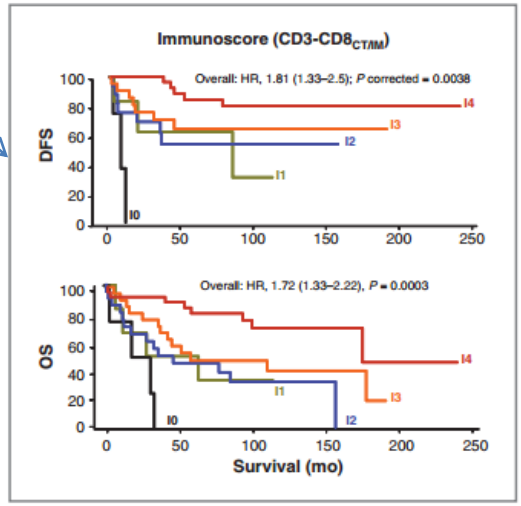


Casares et al, J Exp Med 2005
Obeid et al, Nat Med 2007
Apetoh et al, Immunol Rev 2007
Ghiringhelli et al, Nat Med 2009
Galuzzi et al, EMBO 2012
Martins et al, Ann N Y Acad Sci. 2010
Ko et al, Cell Death and Diff 2014

Immunoscore could be predictive of response to CRT in rectal cancer.

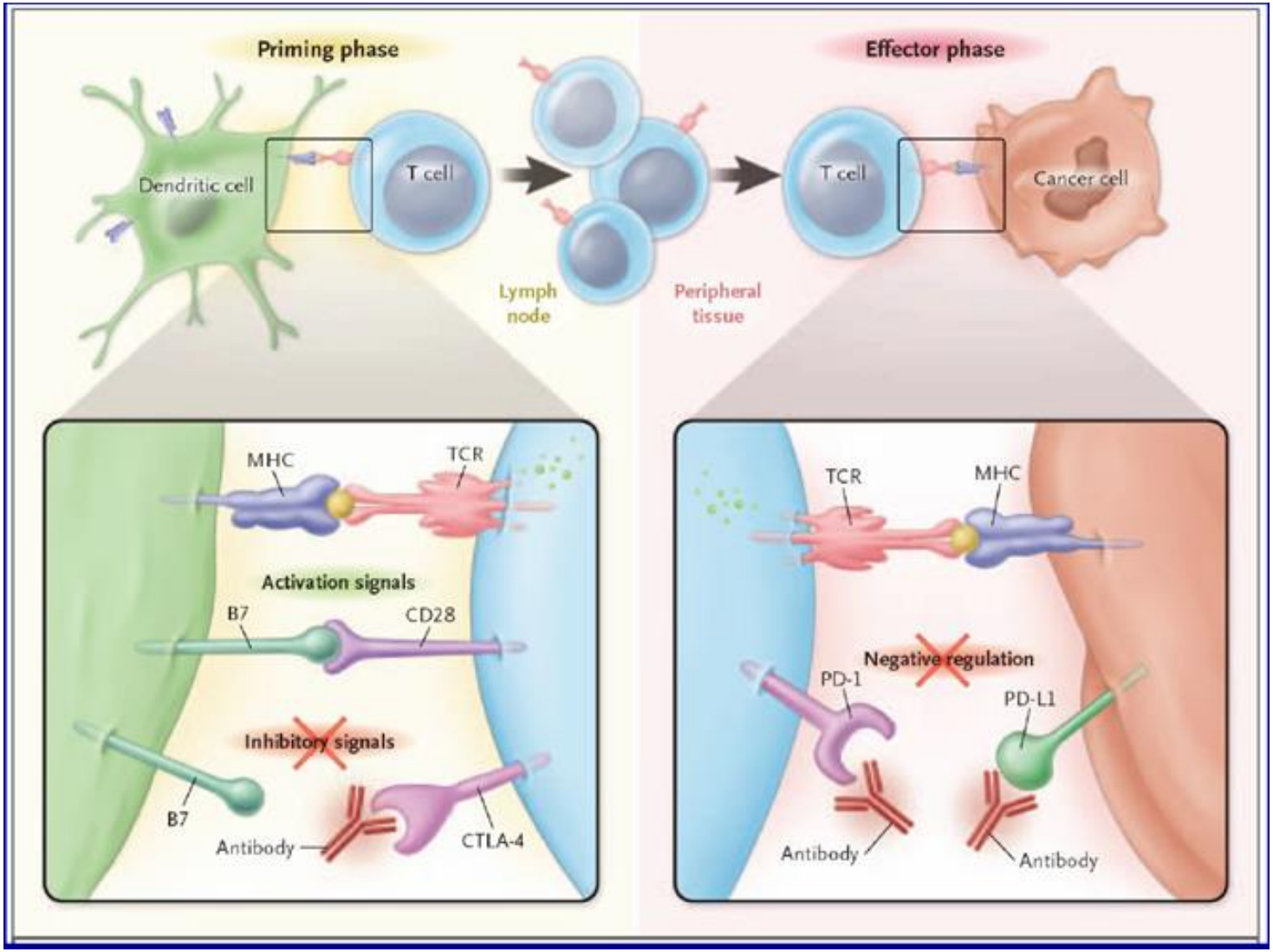






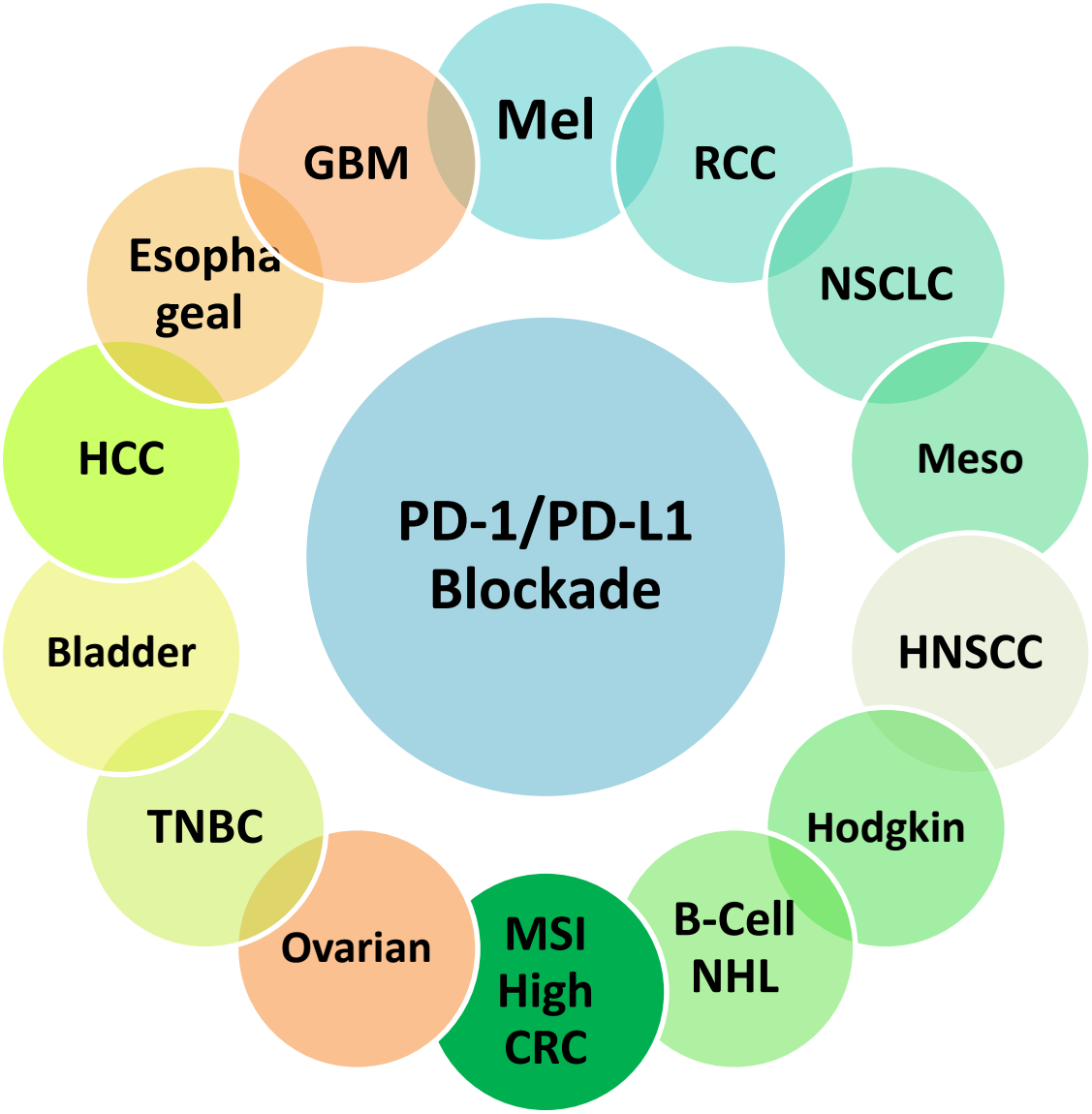
Anitei, Clin Can Res 2014

Blocking of PD-1 or CTLA-4 signaling



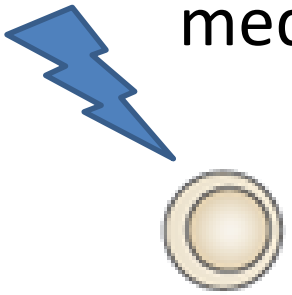
NEJM 2012

Immuno-stimulatory Ab : Spectrum of activity



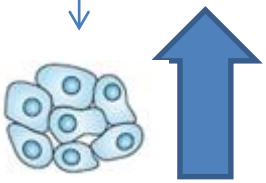
Adapted from A Marabelle

Immune adaptive response by tumor cells mediates resistance to fractionated radiotherapy



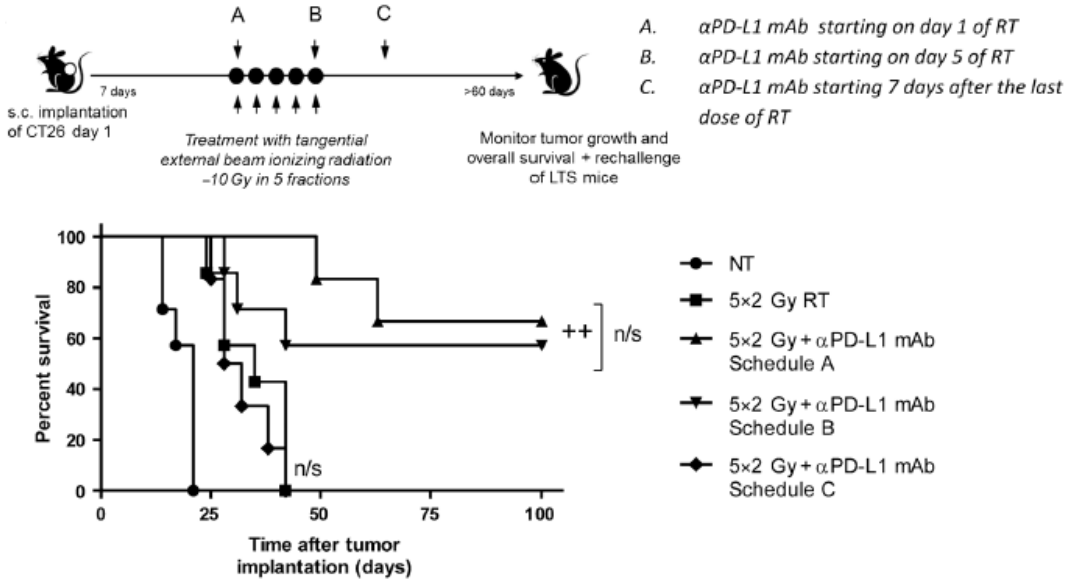
CD8+ lymphocyte

IFN



PDL-1

Tumor cells



Anti PDL-1 & XRT :

Potentiation only observed with concurrent but not sequential aPD-L1 mAb therapy

Dovedi, Can Res 2014

Clinical cases of abscopal effect

A

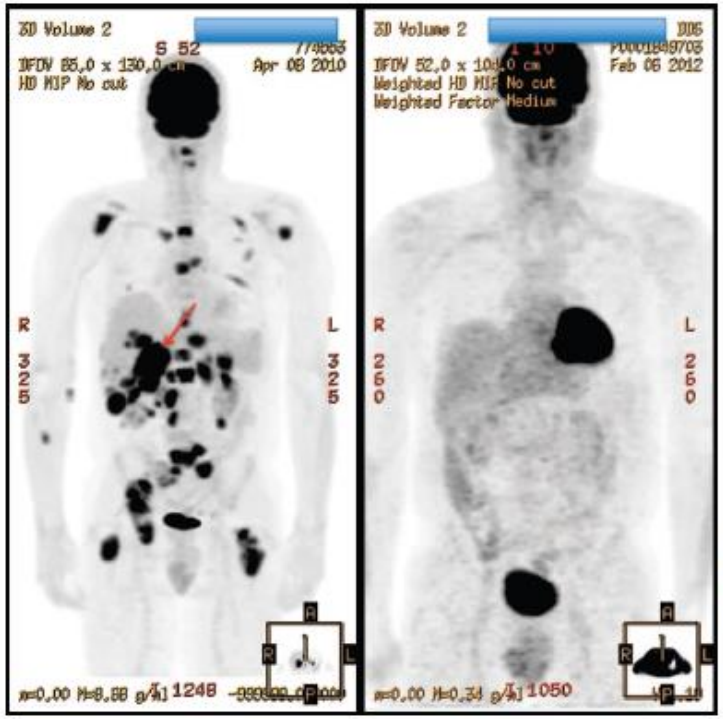
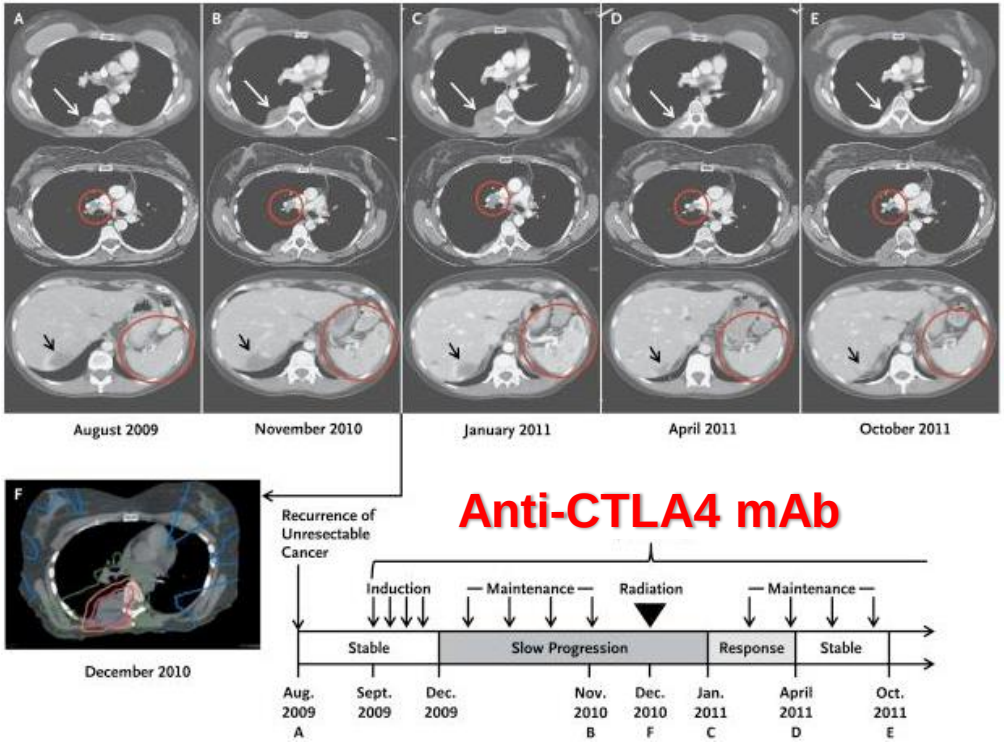


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

B



Postow, NEJM2012, Hinicker, NEJM2012

Combination of radiotherapy with immunomodulators may enhance the abscopal effect

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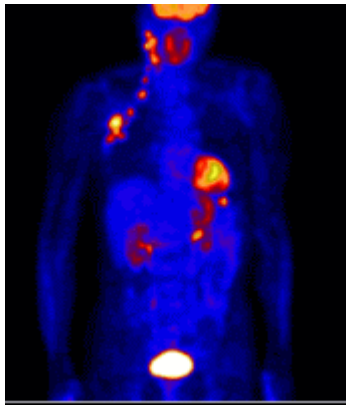
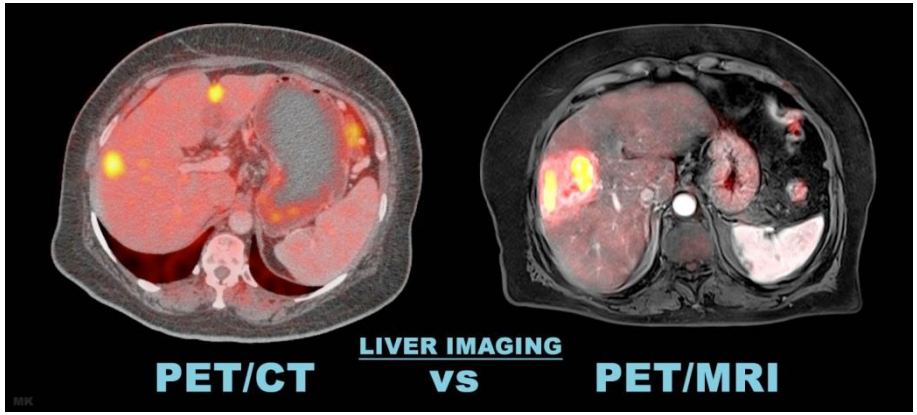
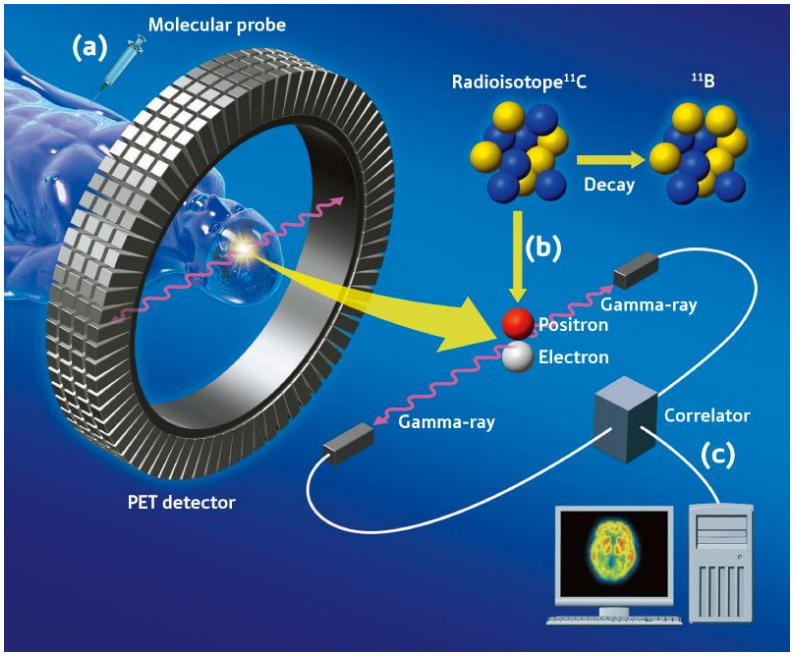
Imaging




LIVER IMAGING
PET/CT
vs
PET/MRI


(a)
Molecular probe
Radioisotope ^{11}C
^{11}B
Decay
(b)
Gamma-ray
Positron
Electron
Gamma-ray
Correlator
(c)
PET detector

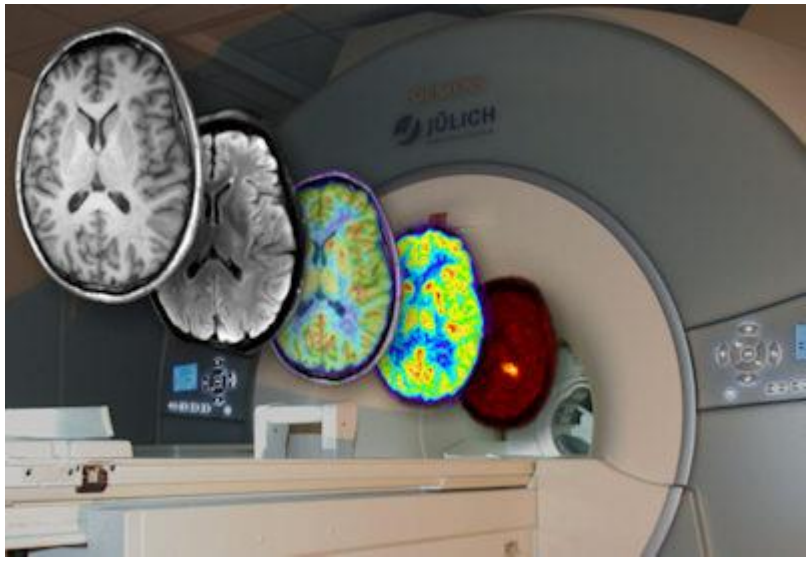
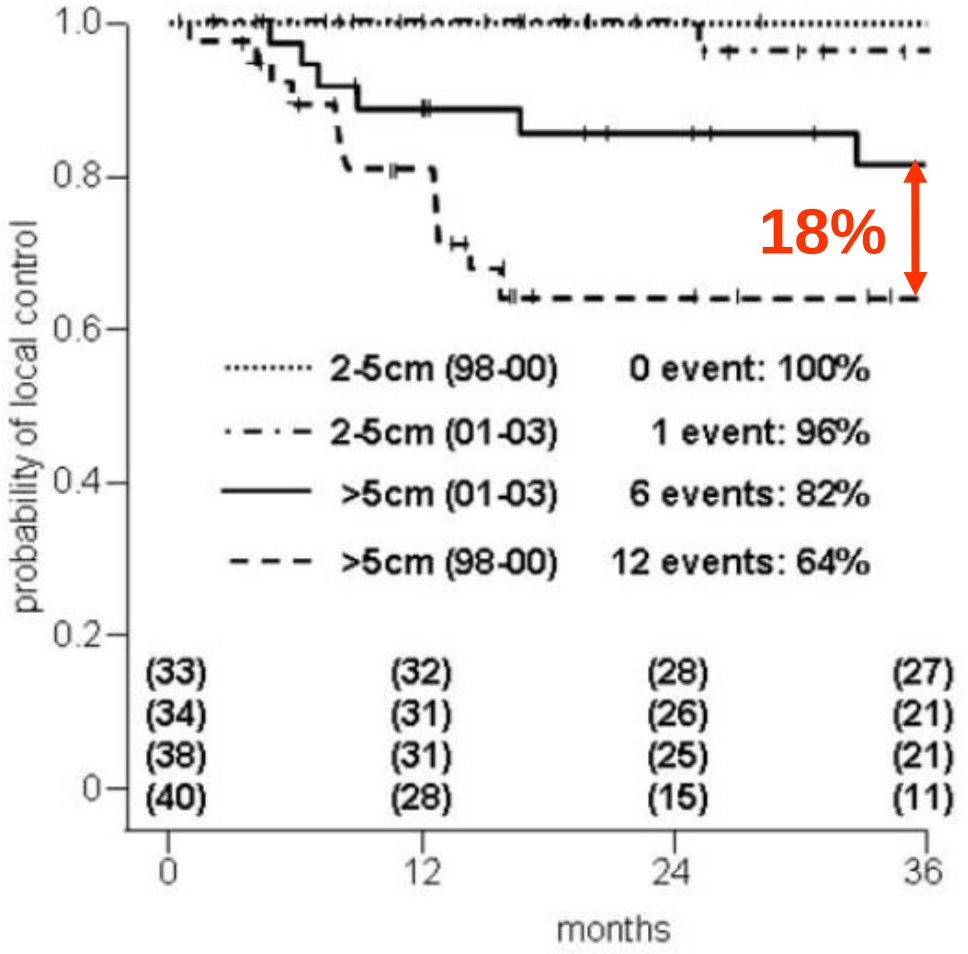
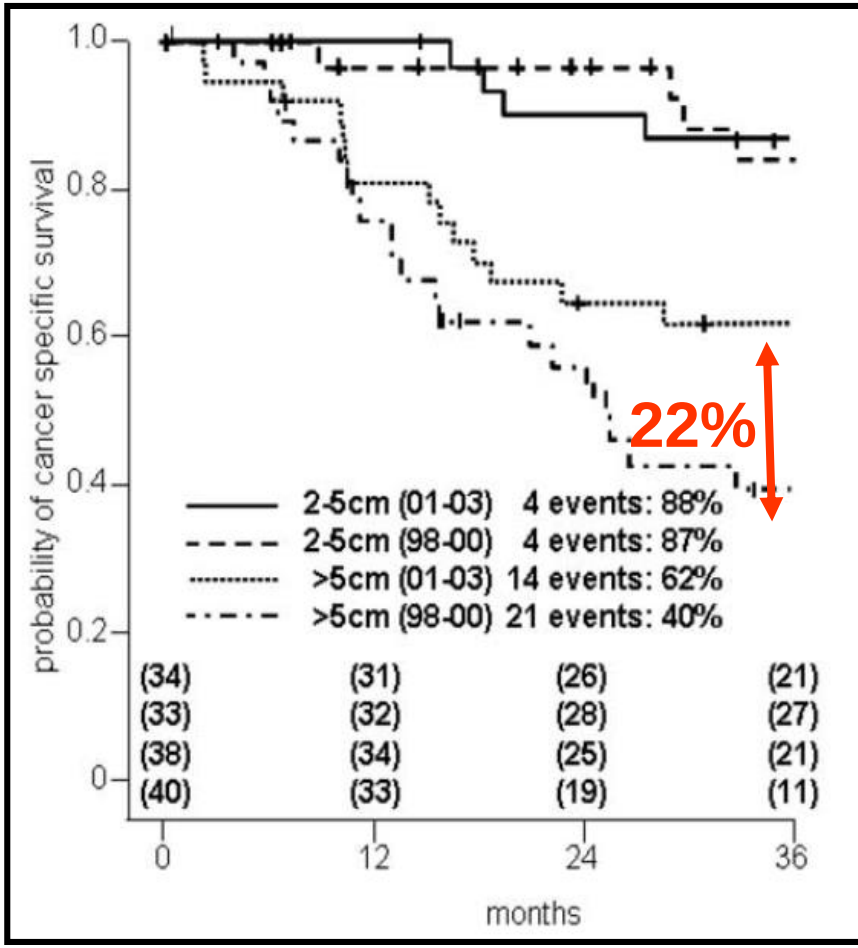


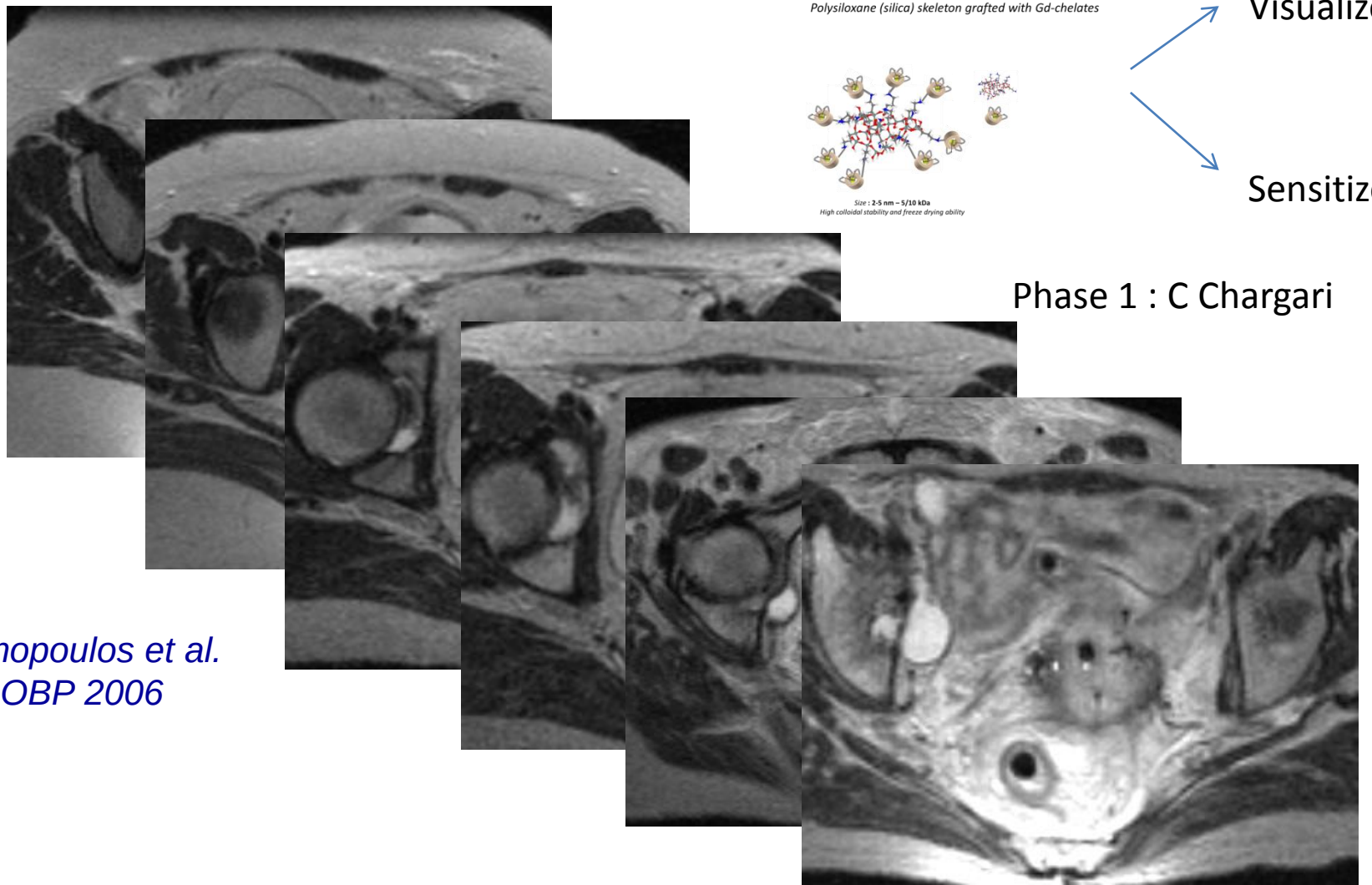
Image guided adaptive brachytherapy for cervix cancer

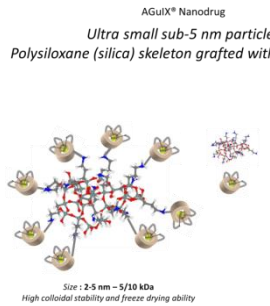




Pötter Radiother Oncol 2007

Adaptive MRI based planning concept
→ Can we do more?





Visualize

Sensitize

Phase 1 : C Chargari

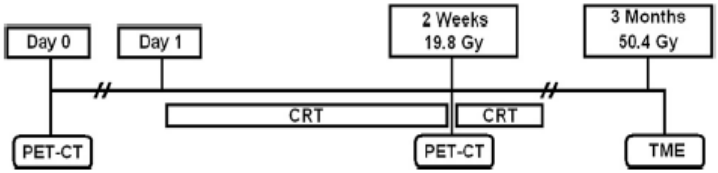
Dimopoulos et al.
IJROBP 2006

Can we use imaging data during treatment to select patients?

PET-BASED TREATMENT RESPONSE EVALUATION IN RECTAL CANCER: PREDICTION AND VALIDATION

Marco H. M. Janssen, M.Sc.,* Michel C. Öllers, M.Sc., Ph.D.,*
Ruud G. P. M. van Stiphout, M.Sc.,* Robert G. Riedl, M.D.,† Jørgen van den Bogaard, M.A.,*
Jeroen Buijsen, M.D.,* Philippe Lambin, M.D., Ph.D.,*‡ and Guido Lammering, M.D., Ph.D.*‡

*Department of Radiation Oncology (MAASTRO), GROW Research Institute, University Medical Centre Maastricht, Maastricht, the Netherlands; and †Department of Pathology, University Medical Centre Maastricht, Maastricht, the Netherlands



VALUE OF DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING FOR PREDICTION AND EARLY ASSESSMENT OF RESPONSE TO NEOADJUVANT RADIOCHEMOTHERAPY IN RECTAL CANCER: PRELIMINARY RESULTS

Maarten Lambrecht, M.D.,* Vincent Vandecaveye, M.D., Ph.D.,† Frederik De Keyzer, M.Sc.,†
Sarah Roels, M.D., Ph.D.,* Freddy Penninckx, M.D., Ph.D.,‡ Eric Van Cutsem, M.D., Ph.D.,§
Claus Filip, M.D., Ph.D.,† and Karin Haustermans, M.D., Ph.D.*

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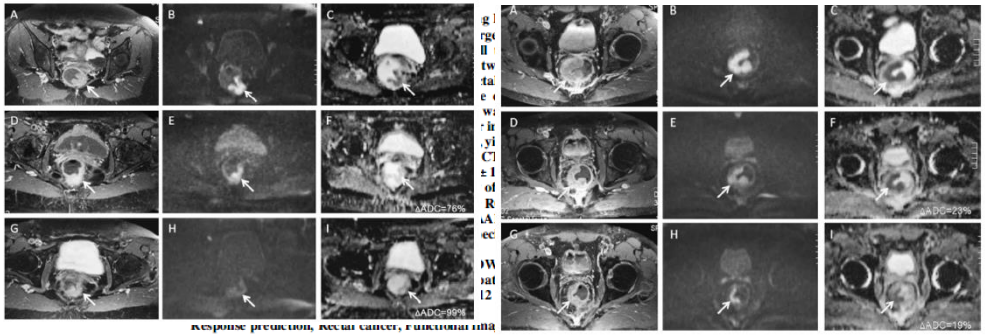
Purpose: To evaluate diffusion-weighted magnetic resonance imaging (DWI) for response prediction before and response assessment during and early after preoperative radiochemotherapy (RCT) for locally advanced rectal



Responder → Standard therapy

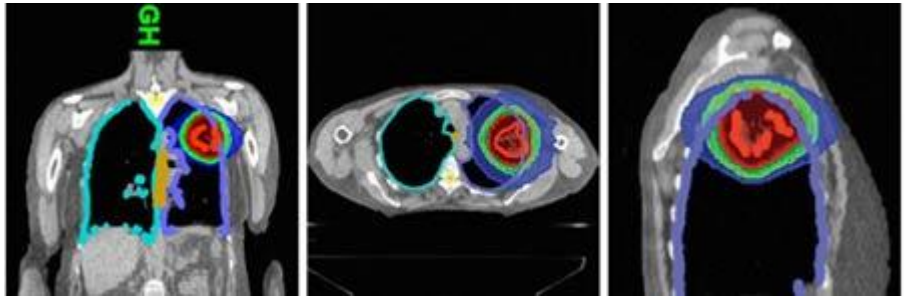
Non Responder → Intensified therapy

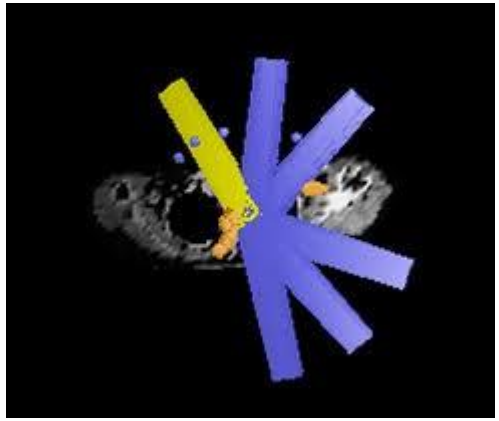
Outline

- Targeted therapies
- Precision medicine in radiotherapy
- Lessons from hypoxia
- Immunology
- Imaging
- Oligometastasis

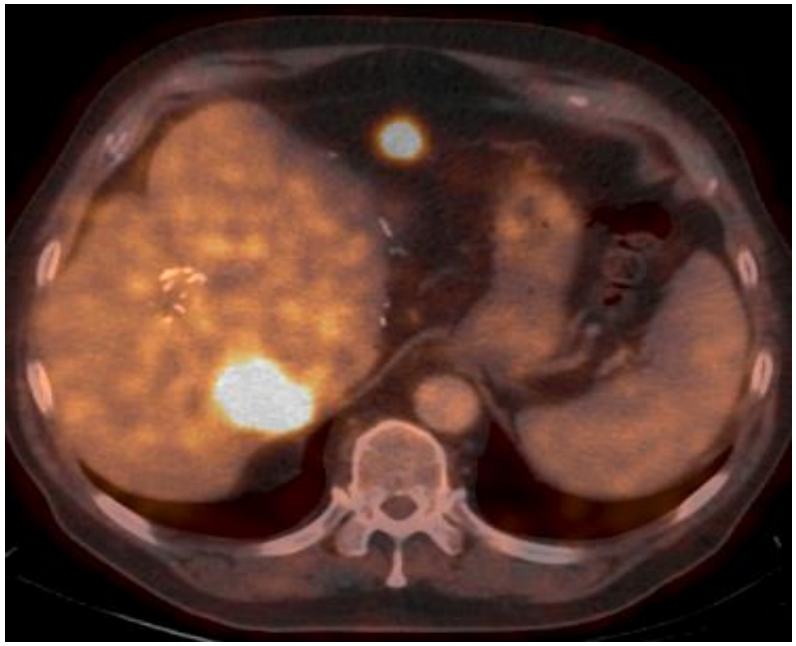
Stereotactic Ablative Radiotherapy, an alternative to surgical resection?

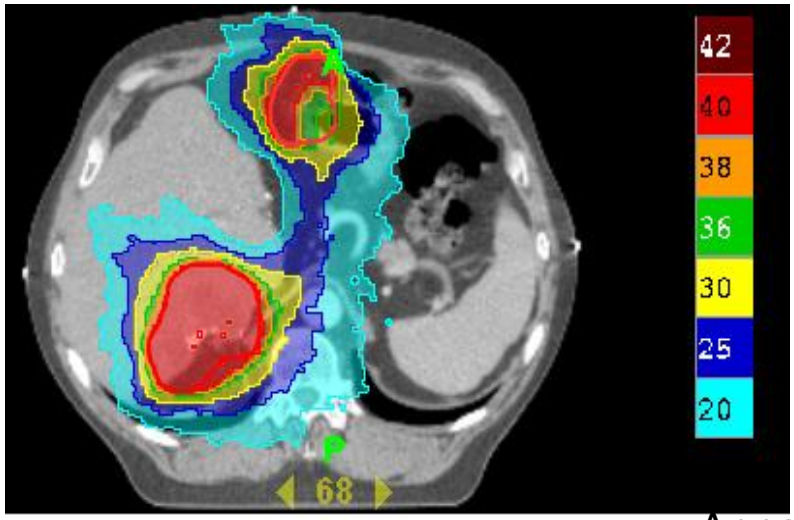
- Safety and feasability for multiple mets in more than 80% cases.
- Local control achieved in breast, NSCLC, CRC, sarcoma, RCC, melanoma..
- Non invasive

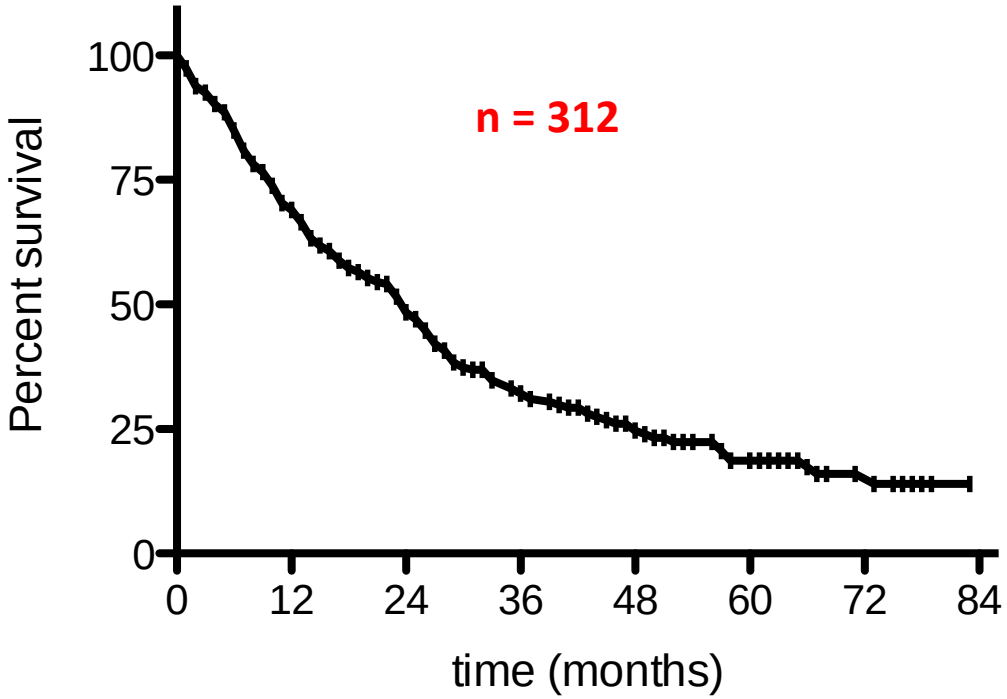




Radiotherapy for oligometastatic cancer







Courtesy M De Ridder

M. De Ridder

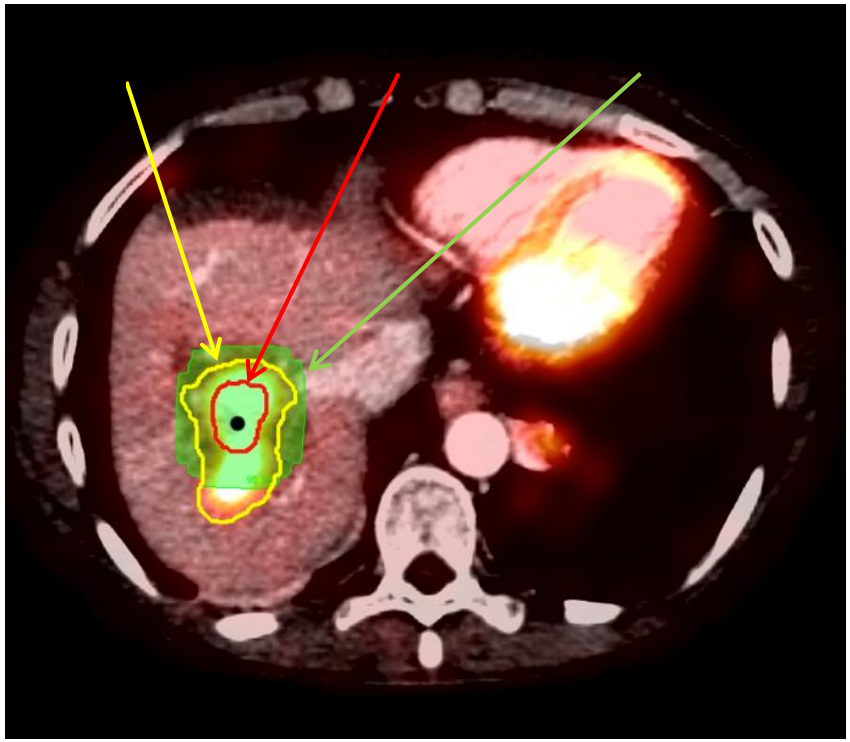
Annals of Oncology 2014

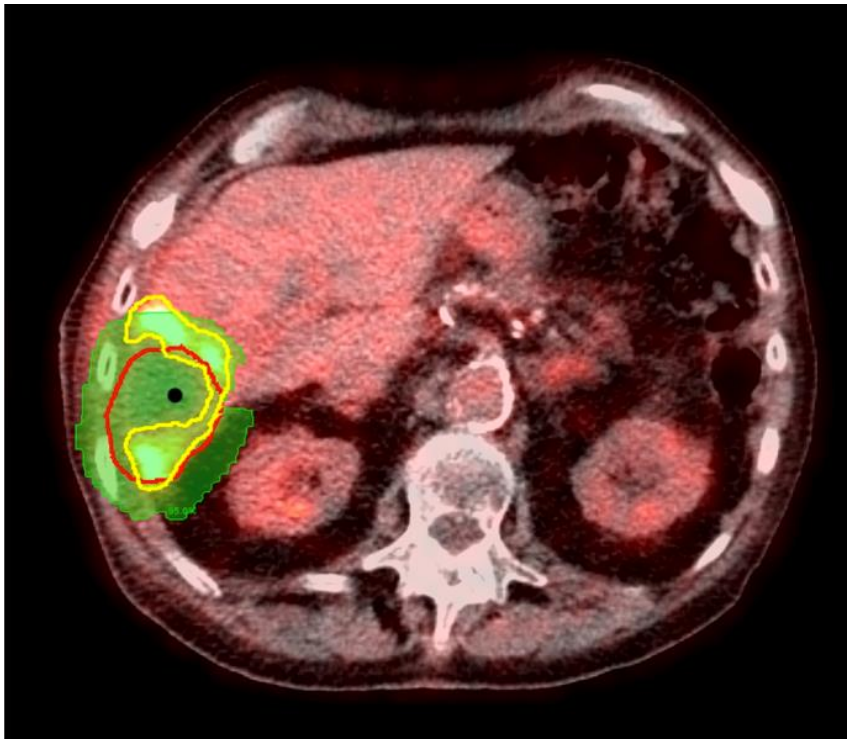
February 2016

Patterns of local failure

In-GTV Relapse: Insufficient dose

Marginal Relapse: Geographical miss

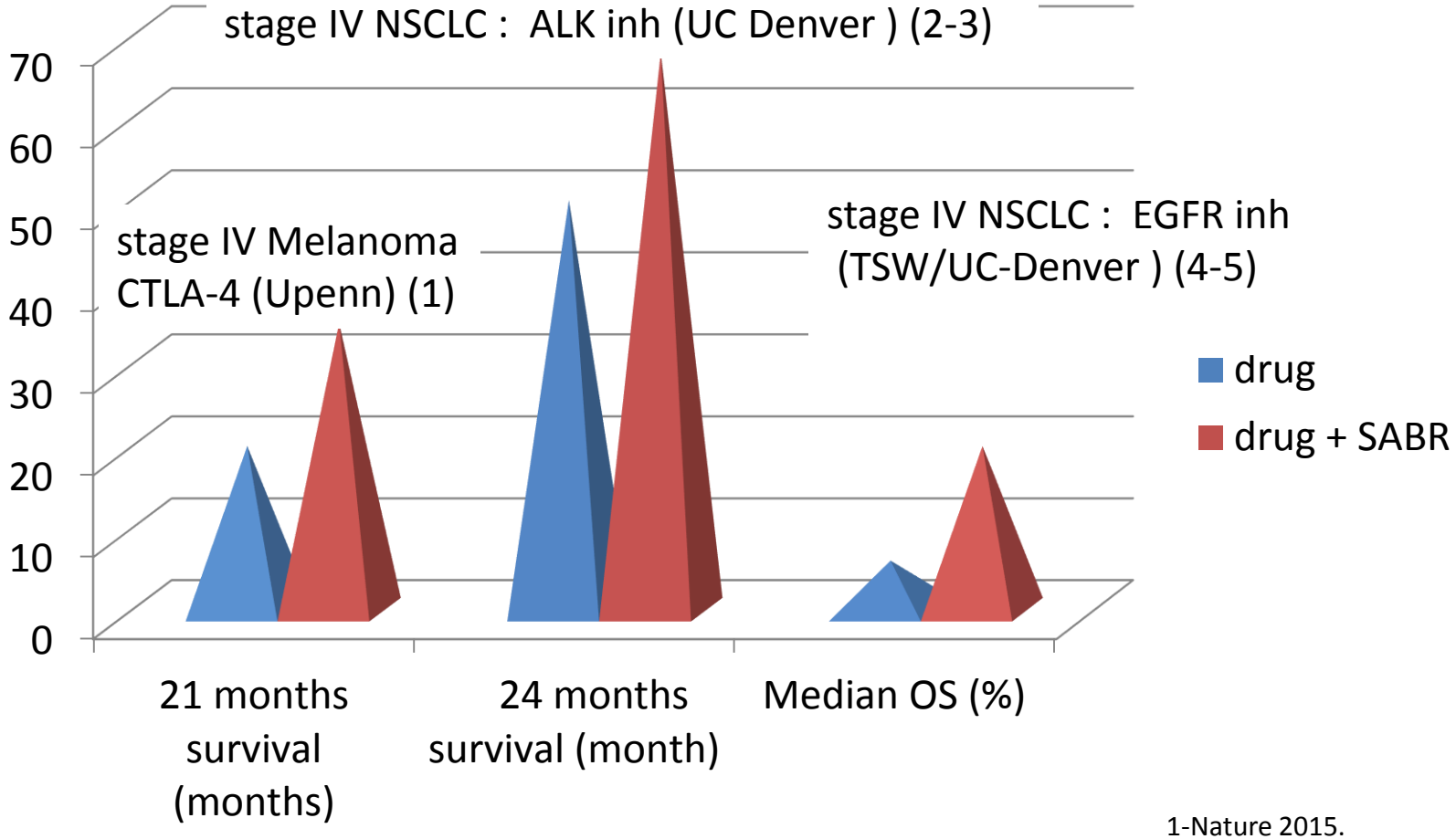




Radiotherapy & Oncology 2014
Van den Begin et al, Radiother Oncol 2013 under review

New drugs + SABR in stage IV desease

positive trend from 'back to back' comparisons?



> 20 trials combining SABR + targeted or immuno therapies

1-Nature 2015.
2-Int J Radiat Oncol Biol Phys. 2014).
3- Lancet Oncol. 2011
4-J Clin Oncol. 2014.
5-N Engl J Med. 2005

PD-L1 blockade + SBRT trial

→PDL1 ‘responsive’ tumors :

NSCLC, Renal, CRC

→Ablative SBRT of 1-3 sites

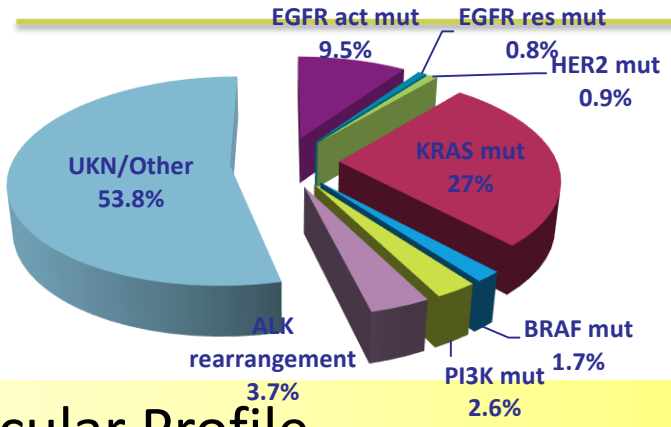
→At least 1 un-irradiated lesion

« In field response »

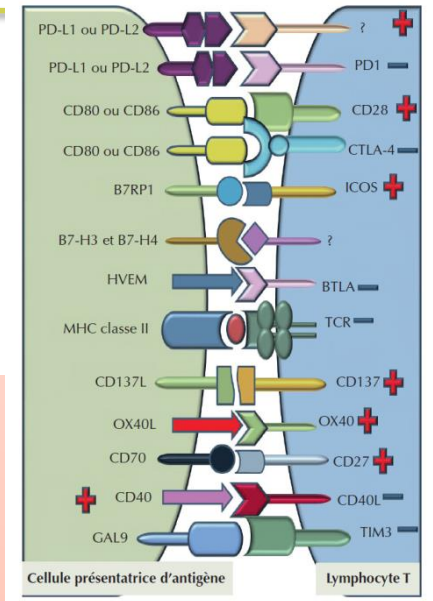
« abscopal reponse »

Time to progression

Sponsor : Gustave Roussy

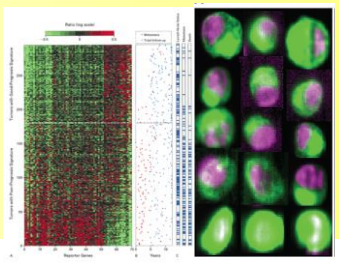


Molecular Profile

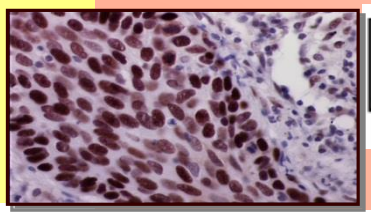


Immunological Profile

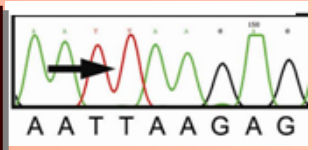
RT sensitivity



Chemotherapy sensitivity



Targeted therapy sensitivity



→ Optimal drug-radiotherapy combination

Precision medecine in RT : we mean accuracy **and** biology

- Biomarkers
- Accuracy/balistics
- Immune profile
- Proof of concept
- High level evidence

Acknoledgements :

Radiation therapy department & INSERM1030