con il Patrocinio di

AIOM
Associazione Italiana di Oncologia Medica

Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

ESMO
Designated Centers of Integrated Oncology and Palliative Care

8ª edizione

Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2018?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:
Stefania Gori
Giovanni L. Pappagallo

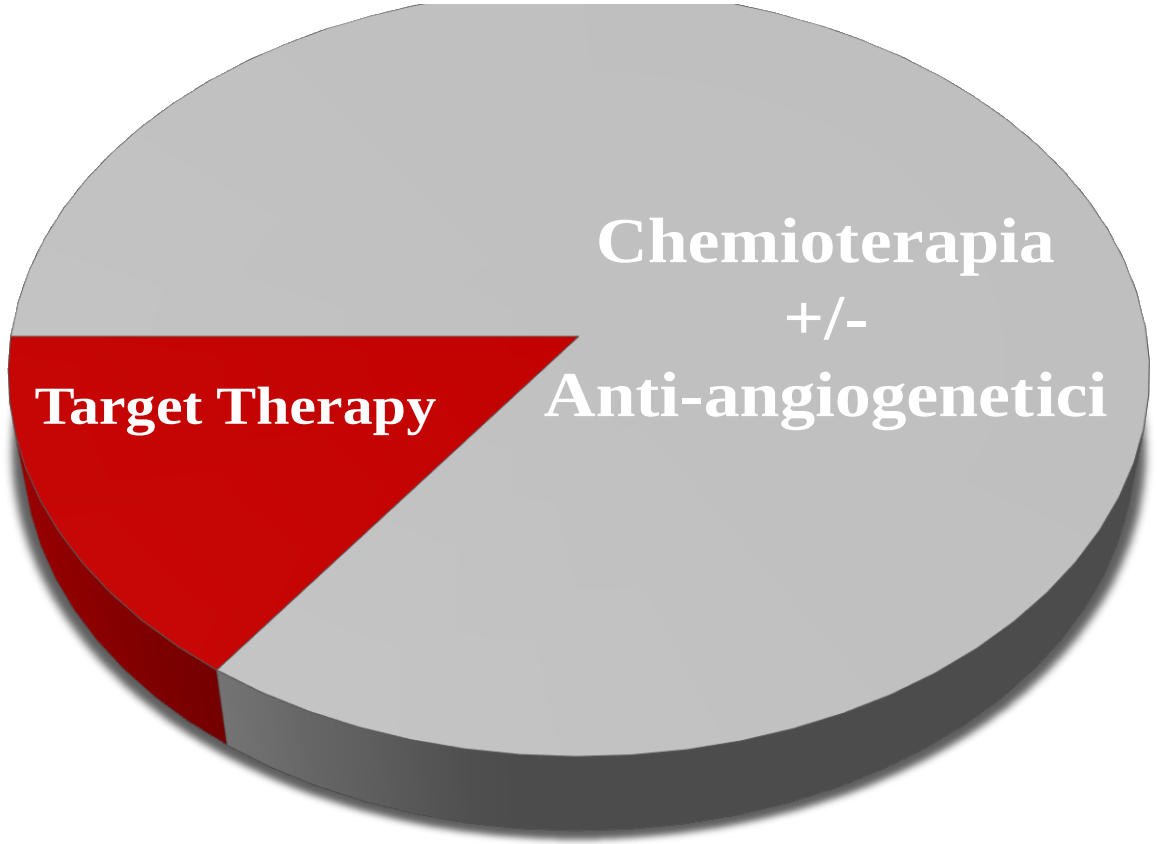
Ospedaletto di Pescantina (VR) 23/24 Marzo 2018
Villa Quaranta Park Hotel

Facciamo il punto su…"*Immunoterapia nel carcinoma mammario*"

I criteri di Risposta: usiamo sempre gli stressi?

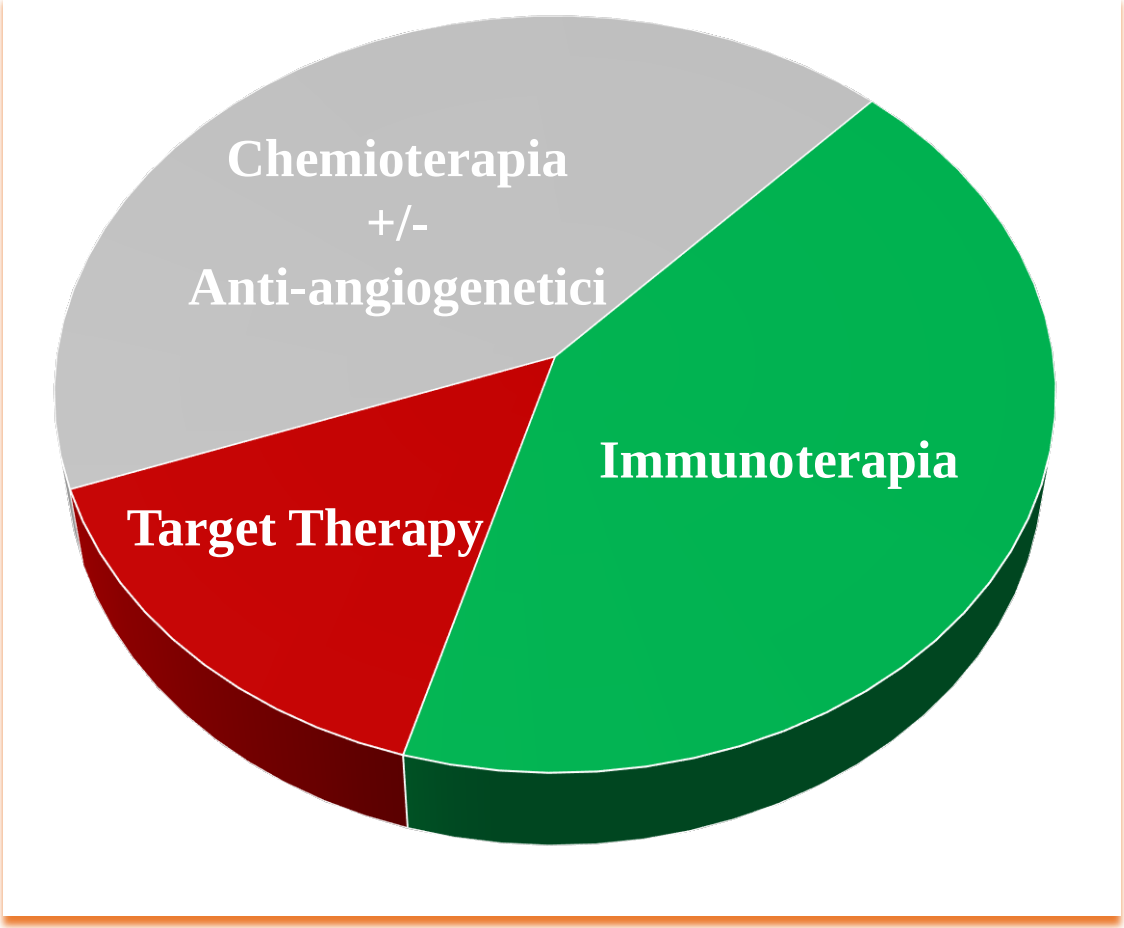
Alessandra Fabi
Oncologia Medica
Istituto Nazionale Tumori Regina Elena
(IFO) Roma

Pratica Clinica nel 2010



A. Fabi

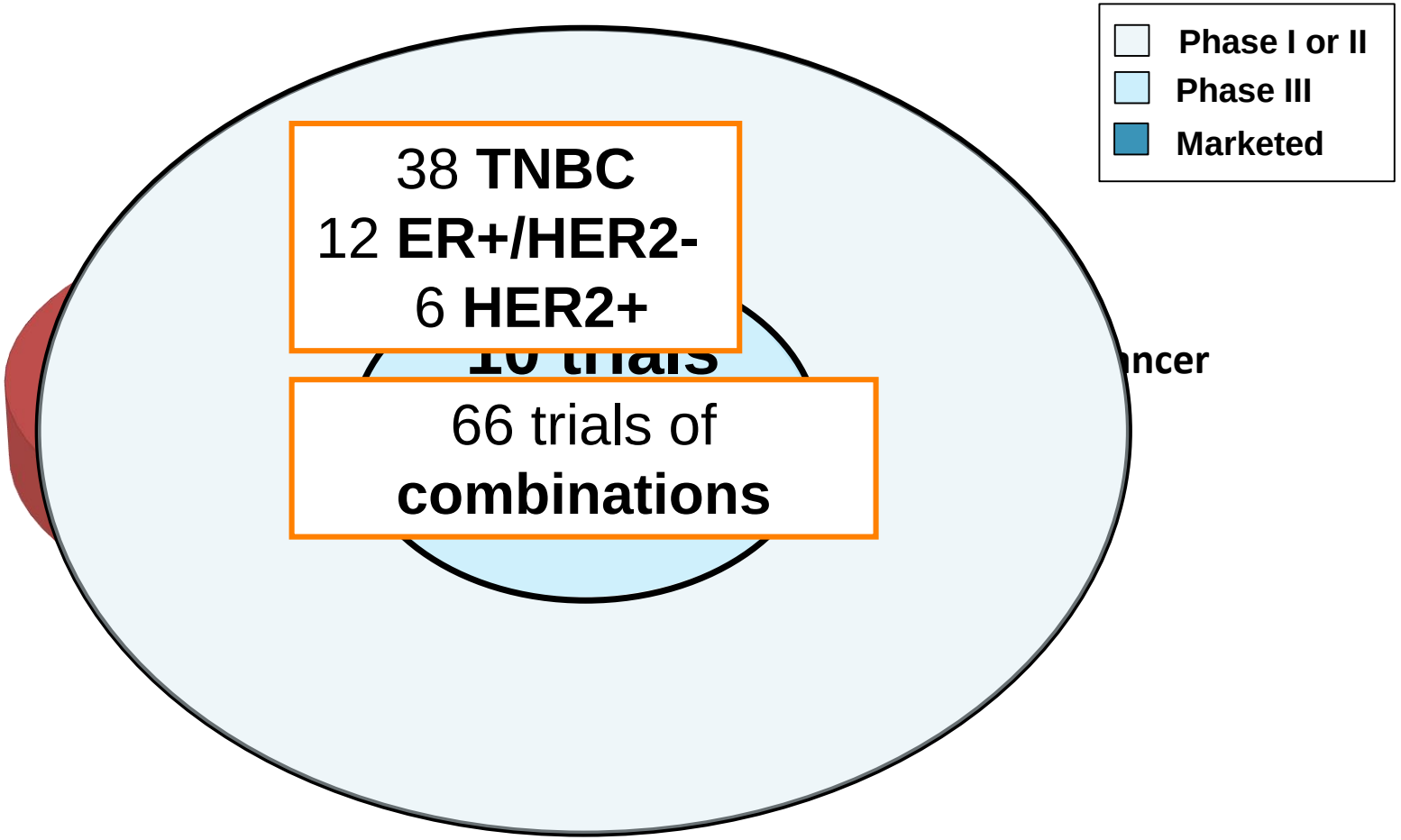
Pratica Clinica Oggi in Oncologia



A. Fabi

Immunotherapy excitement in BC
Trial ongoing with immunechekpoint inhibitors

No use in Clinical Practice



ClinicalTrialsGov (updated 15-01-2018)

Cosa L'Oncologo deve comunicare al Radiologo ?

Armamentario Terapeutico

Dalla **Chemioterapia** a……..

- **Terapie Biologiche**
- **Immunoterapie alone**
- ***Combinazioni Chemioterapie e T. Biologiche***
- ***Combinazioni T. Biologiche e Immunoterapie***
- ***Combinazioni Chemioterapie e Immunoterapia***
- ***Combinazioni Chemioterapie e Radioterpia***

Perché avere dei Criteri?

Criteri di risposta

- Gruppo di regole atte ad identificare il comportamento di una neoplasia durante un trattamento
- Linguaggio comune standardizzato per la misurazione della risposta dei tumori al trattamento
- Mirano a garantire l'obiettività ed a ridurre la variabilità tra osservatori
- Indispensabili per comparare risultati di studi differenti

? Which are aims of imaging for the oncologist ?

- To define and to improve staging of the cancer
- To address treatment, to guide radioterapic planning
- To improve prognosis
- To define the efficacy of the drug
- To improve evaluation of response
- To provide follow up evaluations
- To address new end-points for clinical studies

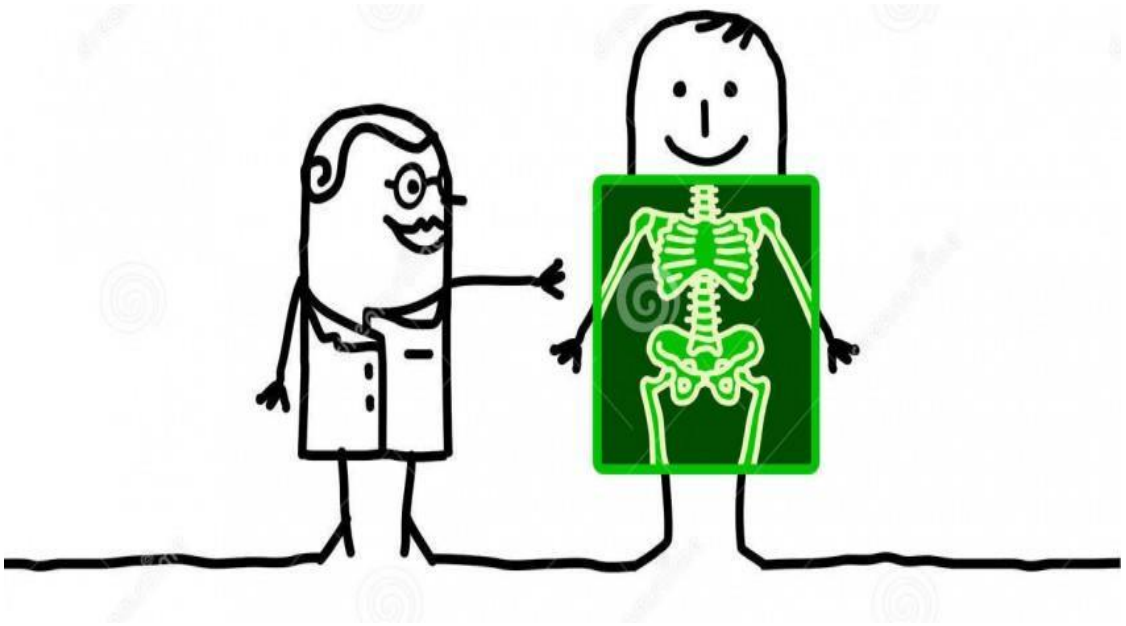
Alonzi and Hoskin, Clin Oncol 2006

CRONOLOGIA DEI CRITERI DI VALUTAZIONE

1979	2000	2009	2009/2013	2017
WHO	RECIST	RECIST 1.1	irRC irRECIST	iRECIST

A. Fabi

Radiologo
->
Oncologo
<-



VIAGGIANO SULLO STESSO BINARIO?

Limiti dei Criteri RECIST

- I criteri RECIST considerano solo le dimensioni dei tumori

- Le variazioni di dimensioni di un tumore non sempre corrispondono alla reale risposta alla terapia

- Necessità di criteri semplici, facilmente riproducibili, di rapida elaborazione che tengano in considerazione anche delle caratteristiche fisiologiche e funzionali del tessuto neoplastico per poter valutare in maniera standardizzata la risposta alla terapia oncologica

A. Fabi

RECIST 1.0 → RECIST 1.1

	RECIST 1.0	RECIST 1.1
Measuring tumor burden	10 targets 5 per organ	5 targets (2 per organ, ≥10 mm)
Lymph node	Measure long axis as for other lesion. Silent on normal size	Measure short axis Define normal size (10 mm)
Progression Definition	20% increase in sum	20% increase and at least 5 mm absolute increase
Non- measurable disease PD	Must be unequivocal	Expanded definition to convery impact on overall burden of disease
Confirmation	Required	Required when respons primary endpoint but not PFS
New lesions	--	New section which includes comment on FDG PET interpretation

A. Fabi

Si chiede al Radiologo ……di diventare più ORGANO-SPECIFICI

mRECIST

Table 2 Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Focus On….

Immunoterapia nel carcinoma della mammella

A. Fabi

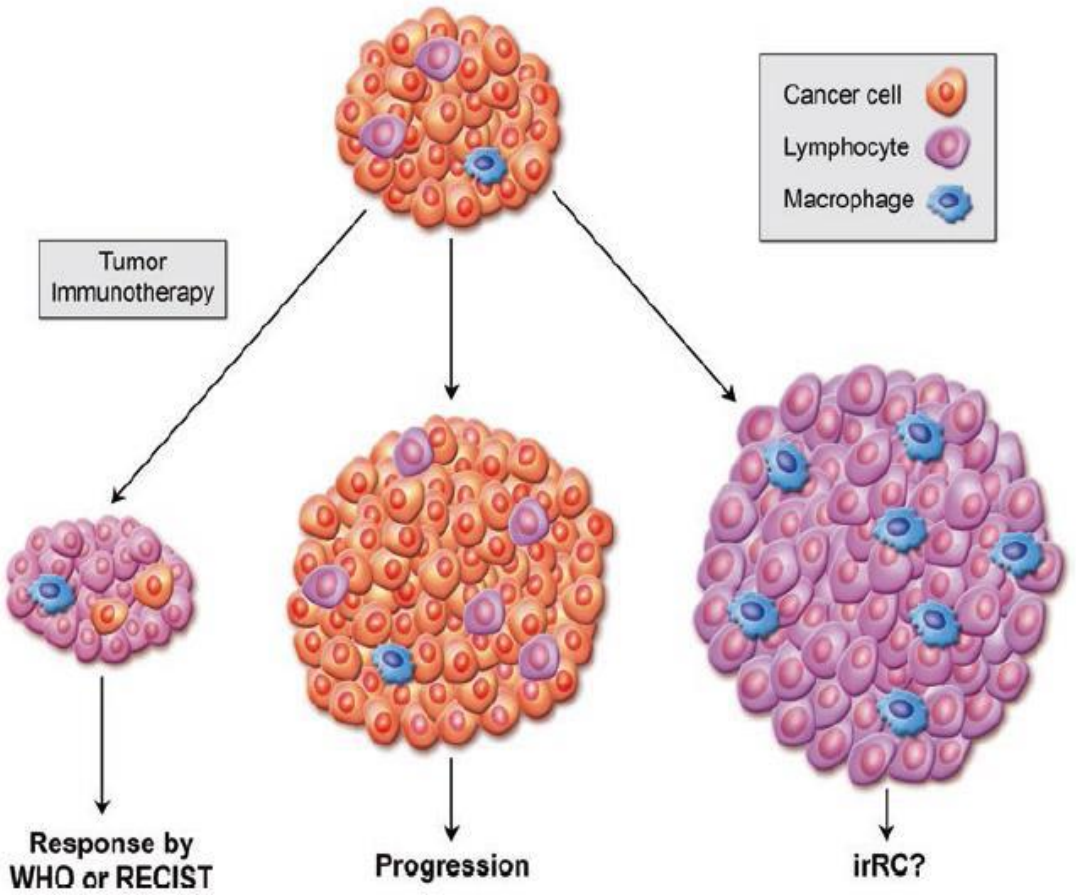
Immunoterapia e risposta al trattamento

Cosa è Importante Sapere !

- Il tempo di risposta può essere più lungo con l'immunoterapia
- Ci può essere una risposta dopo una iniziale pseudoprogressione
- La sospensione del trattamento in caso di progressione può essere inappropria se questa non viene riconfermata a distanza (minimo un mese)
- Una progressione clinicamente non significativa, anche in presenza di nuove lesioni, specie se c'è risposta su altre lesioni, non va considerata
- Le lunghe stabilità di malattia sono un segno di efficacia del trattamento

UNA POSSIBILE SPIEGAZIONE DELLA PSEUDOPROGRESSIONE (…..non solo per l'immunoterapia [RT+CT])

1. Richiamo dei linfociti T citotossici all'interno del tumore dopo trattamenti immunoterapici. La massiva infiltrazione del tumore da linfociti T è dimostrata da varie osservazioni



Tumeh PC et al. Nature 2014

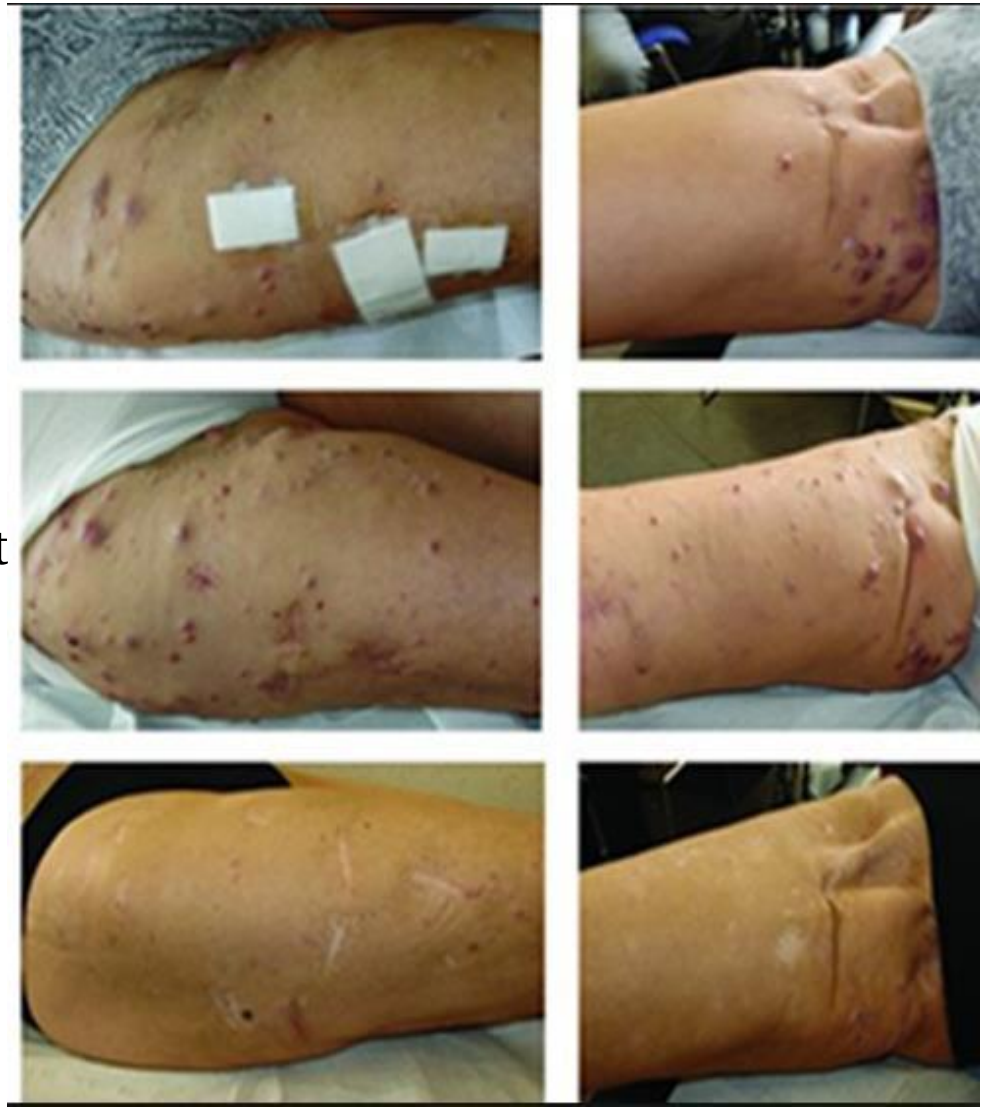
3. Progressione transitoria: Tumori in rapida crescita, che possono aumentare la loro massa fino ad una chiara progressione durante l'intervallo tra l'inizio del trattamento ed il suo effetto biologico

Tumeh PC et al. Nature 2014

Pre-treatment

During treatment (3 weeks)

Post-treatment (1 year)



Published OnlineFirst November 24, 2009; DOI: 10.1158/1078-0432.CCR-09-1624

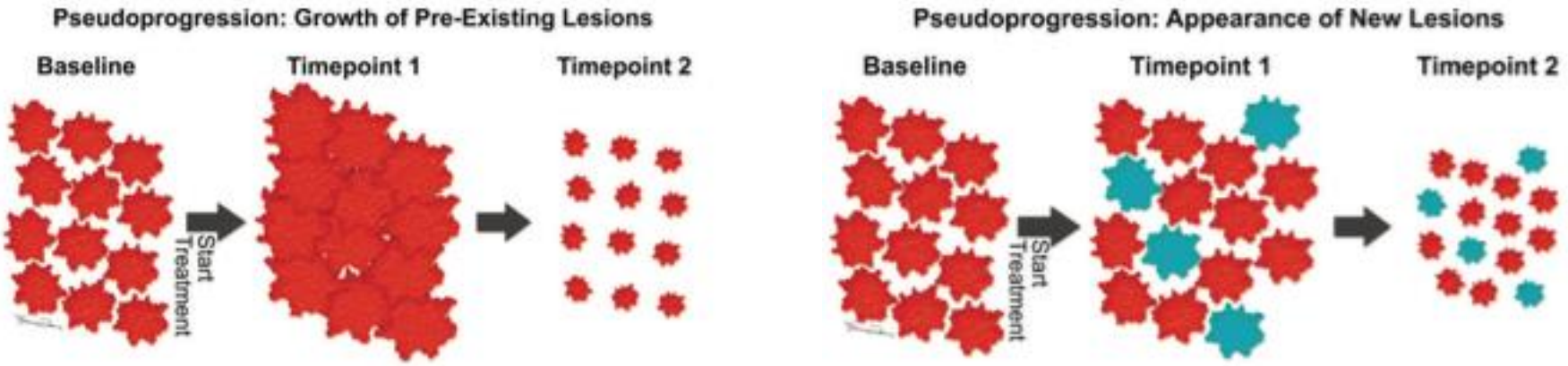
irRC **(Clin Cancer Res 2009)**

Principi base irRC

E’ ancora più importante fare i confronti sull’ indagine Basale più che sull’esame immediatamente precedente precedente

- Le nuove lesioni non necessariamente rappresentano una progressione. Queste vanno incluse nel calcolo del TTB ed il loro significato è subordinato alla successiva conferma radiologica

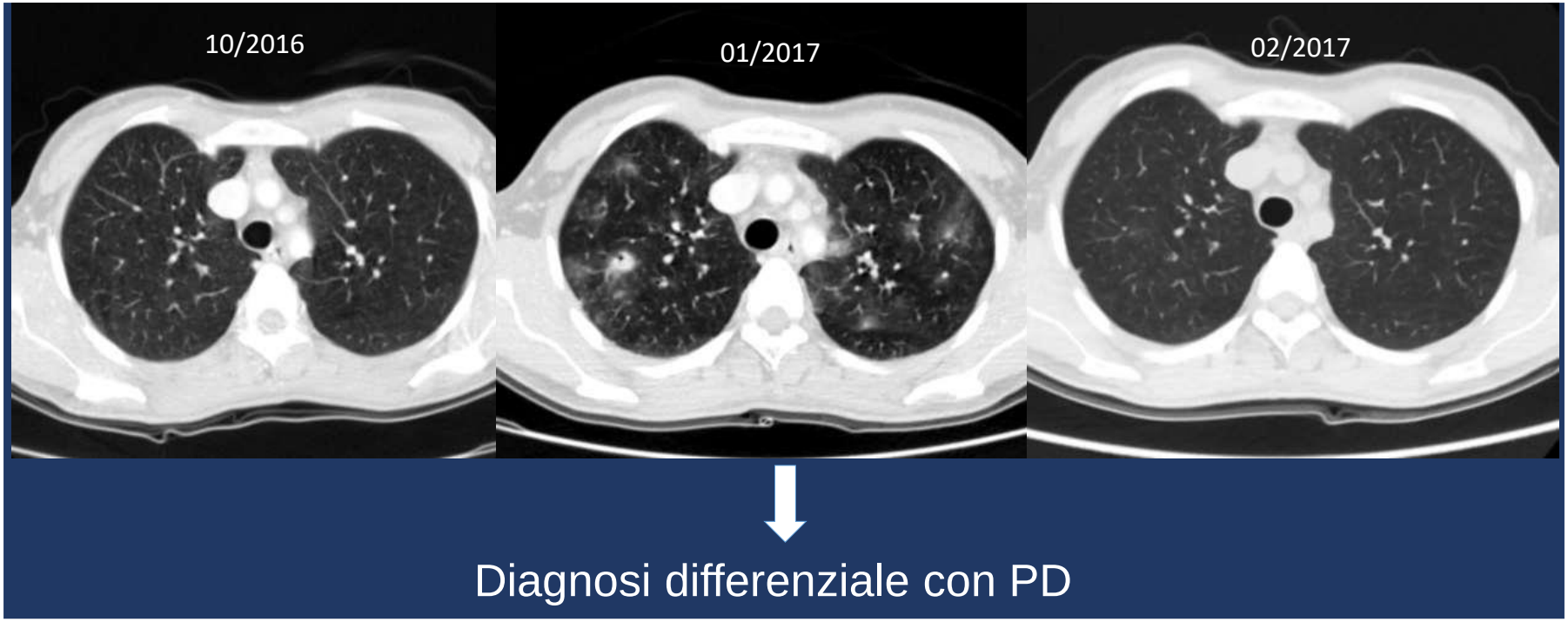
accurate identification of true progression



Gary X. Wang, MD, PhD
Vikram Kurra, MD
Justin F. Gainor, MD
Ryan J. Sullivan, MD
Keith T. Flaherty, MD
Susanna I. Lee, MD, PhD
Florian J. Fintelmann, MD

Immune Checkpoint Inhibitor Cancer Therapy: Spectrum of Imaging Findings[1]

Side Effects or Progression?



TNBC patients treated with Pembrulizumab (Clinical Trial)

Limitazioni irRC

- Gli irRC sono basati su dati estrapolati fondamentalmente dal melanoma, dubbia applicabilità per gli altri tumori

- Non viene specificato come misurare le lesioni linfonodali

- La misurazione bidimensionale delle lesioni ed il numero elevato consentito, limita la riproducibilità ed aumenta il tempo speso dall'operatore rispetto alla misurazione unidimensionale dei criteri RECIST 1.1

Nascita degli irRECIST

Wolchok JD, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412–20.
Nishino M et al. Developing a common language for tumor response to immunotherapy: Immune-Related Response Criteria using unidimensional measurements. Clin Cancer Res. 2013;19:3936–43.
Bohnsack O et al. Adaptation of the immune-related response criteria: irRECIST. Ann Oncol 2014;25 (suppl 4):iv361–iv372.
Hodi FS et al. Evaluation of Immune-Related Response Criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 2016;34:1510–7.
Chiou VL et al. Pseudoprogression and Immune-Related Response in Solid Tumors. J Clin Oncol 2015;33:3541–3543

IMMUNOTERAPIA: iRECIST vs RECIST1.1

Unchanged

RECIST 1.1	iRECIST
Definitions of measurable, non-measurable disease	√
Definitions of target (T) and non target (NT) lesions	√
Measurement and management of nodal disease	√
Calculation of the sum of measurement (SOM)	√
Definitions of CR, PR, SD and their duration	√
Confirmation of CR and PR	√
Definition of progression in T and NT (iRECIST terms i-unconfirmed progression (iUPD))	√

Changed

RECIST 1.1	iRECIST
Management of new lesions	NEW
Time point response after RECIST 1.1 progression	NEW
Confirmation of progression required	NEW
Collection of reason why progression cannot be confirmed	NEW
Inclusion and recording of clinical status	NEW

http://www.eortc.org/recist/irecist/

IMMUNOTERAPIA: iRECIST

Terminologia:

- CR → iCR
- SD → iSD
- PR → iPR
- PD → iUPD – Unconfirmed PD

  PD → iCPD – Confirmed PD

✓ 4-8 weeks
✓ Clinicamente stabile

New lesions:

- Fino a 5 NL-T (2 x organo)
- Oltre 5 NL-T: non-target (NL-NT)
- Non incluse in SOM
- iSOM

irRECIST: Imaging and Treatment after 1st Radiologic Evidence of PD or SD, CR or PR

(from Keynote 119 protocol)

	Clinically Stable		**Clinically Unstable**	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor image by site	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor images confirms PD	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required	N/A
Repeat tumor images shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 9 week (63 ± 7 days) imaging schedule.

Limitazioni irRECIST

- Sono stati sviluppati basandosi solo su dati provenienti da pazienti trattati con anti CTLA-4 ed anti PD-1/PDL-1, dubbia applicabilità per i nuovi trattamenti immunoterapici (IDO inhibitors , agonist mAbs targeting CD137) e le associazioni chemioterapia-immunoterapia

- Dubbia riproducibilità, accuratezza, applicabilità su tutte le neoplasie

- Necessita di ulteriori studi, non sono standard per FDA e EMA

- La maggioranza dei trials clinici continua ad usare i RECIST1.1 anche per l'immunoterapia, in alcuni casi vengono usate varianti diverse degli irRECIST e spesso la valutazione della risposta immunocorrelata è un end-point secondario

Come l'Oncologo può aiutare il Radiologo?
Quali suggerimenti pratici suggerire al Radiologo ?

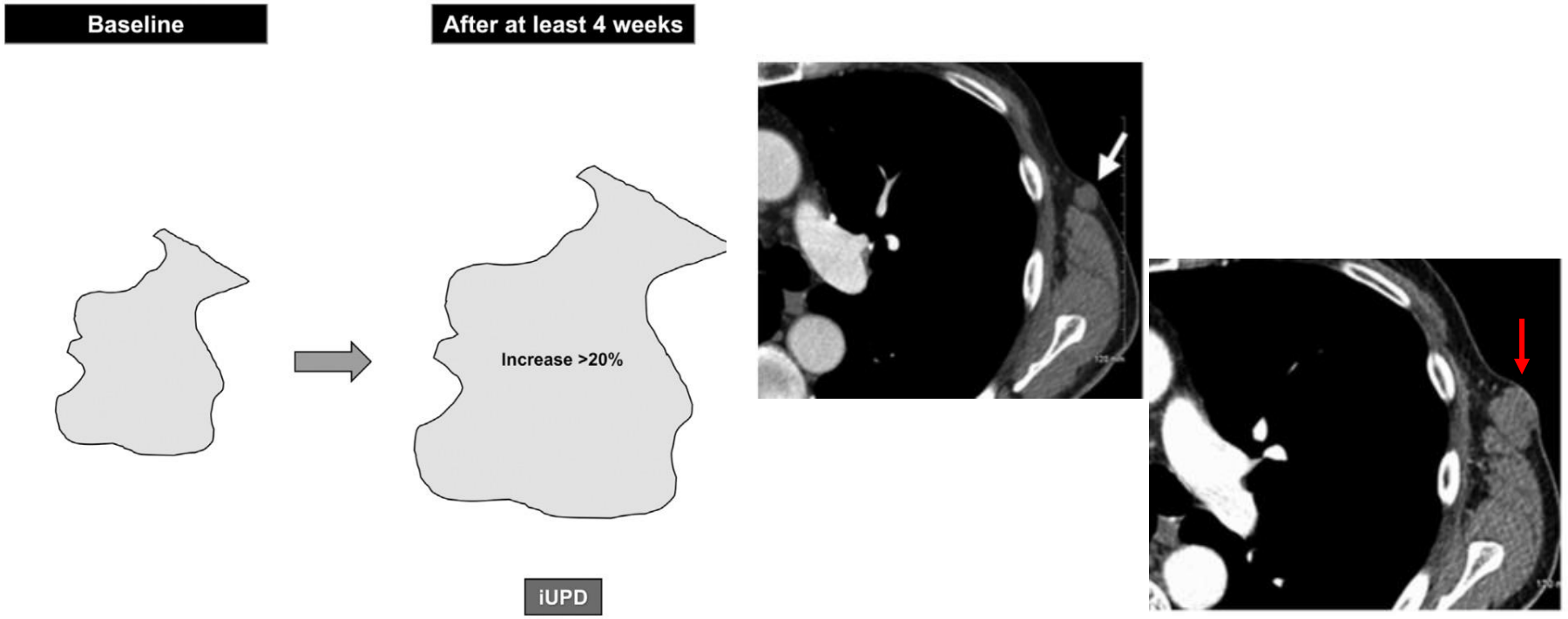
- Importanza di un'attenta valutazione clinica del paziente in progressione alla prima TC

- La TC di conferma va sempre fatta dopo almeno 4 settimane

- Se dopo una iniziale PD sopravviene una PR od SD, anche la seconda PD necessita di conferma radiologica (Stesse regole)

- La PD è confermata sia se le precedenti lesioni in PD continuano ad aumentare di diametro (>5 mm), sia se le lesioni precedentemente in SD vanno in PD RECIST, sia se c'è una inequivocabile PD sulle lesioni non target

accurate identification of true progression



accurate identification of true progression…… the Radiologist point of view

Critical Reviews in Oncology / Hematology 120 (2017) 13–21

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journal homepage: www.elsevier.com/locate/critrevonc

Review article

Critical features and challenges associated with imaging in patients undergoing cancer immunotherapy

Cinzia Solinas[a,1], Michele Porcu[b,*,1], Zuzana Hlavata[c], Pushpamali De Silva[a], Marco Puzzoni[d], Karen Willard-Gallo[a], Mario Scartozzi[d], Luca Saba[b]

One of the questions raised from our review would be whether there is ***an ideal imaging method*** for the evaluation of tumor burden in cancer patients treated with immunotherapy.

At the moment, we have no clear information in this regard

inflammatory response might be achieved by novel approaches including diffusion, perfusion, and metabolic imaging

Courtesly by A.Vidiri

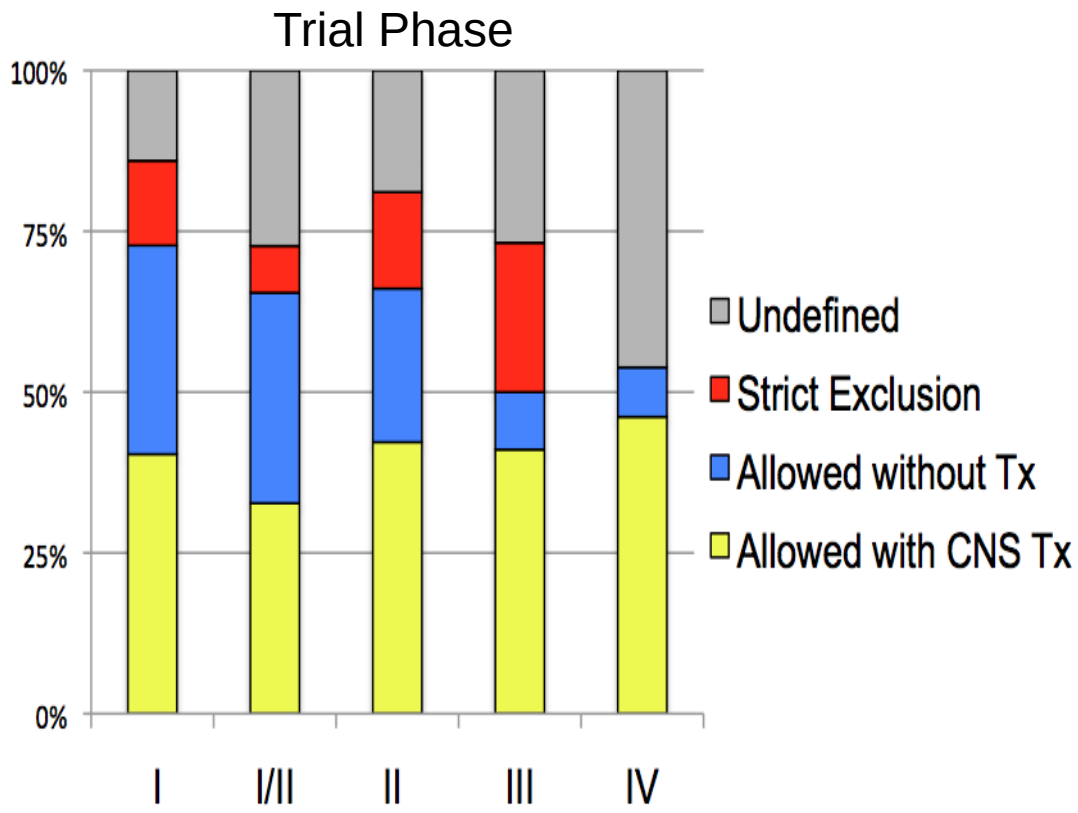
Metastasi Cerebrali

Perchè i RECIST/iRECIST non sono adeguati?

Considerazioni:
tipo di misurazione (unidimensionale, bidimensionale o volumetrica), grado di cambiamento del tumore necessario per la risposta e la progressione, requisiti per scansioni confermative, inclusione dell'uso di corticosteroidi e sintomi neurologici e considerazione dello stato della malattia extracranica.

Open issue

Pochi pazienti con meta cerebrali inclusi in studi clinici



Category	Odds Ratio (95% CI)	P-value
Industry vs University	2.262 (1.063-4.808)	0.0342

Open issue

Methodologia di assessment della risposta

Author (year)	Regimen	Assessment of CNS response
Chargari (2011)	**Trastuzumab + WBRT**	WHO
Bachelot (2013)	**Lapatinib/capecitabine**	CNS composite criteria
Costa (2015)	**Crizotinib**	RECIST 1.1
Long (2012)	**Dabrafenib**	RECIST 1.1

RANO-BM

Imaging	Target lesion	Maximum no. of CNS target lesion	Measurament technique	Shrinkage required for PR	Confirmatory scans	Steroids	Neurological symptoms	Extracranial disease
MRI	≥ 10 mm	5	Unidimensional	≥ 30%	Required in non-randomized trials where response is the primary endpoint	Stable or decreased compared with time of baseline scan	Stable to improved clinically	Included

Lin et al., Lancet Oncol 2015

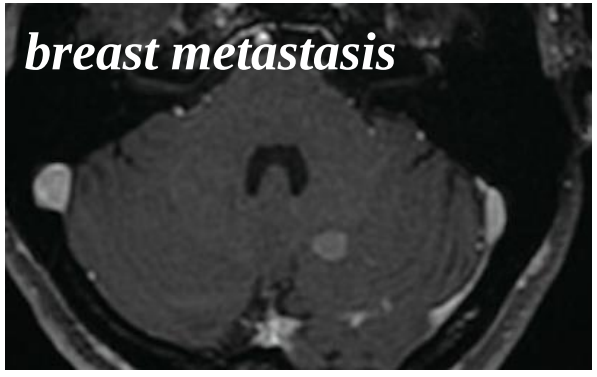
RECIST 1.1 vs RANO

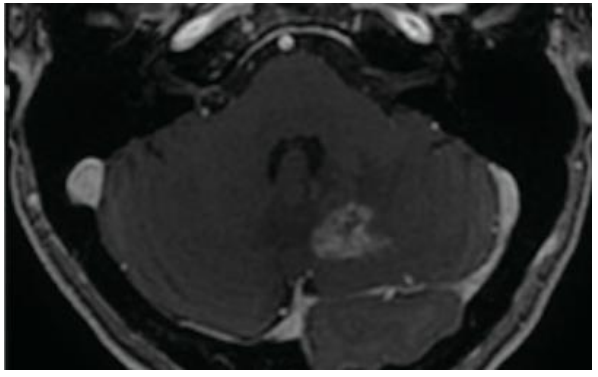
Efficacy of alectinib in central nervous system metastases in crizotinib-resistant *ALK*-positive non–small-cell lung cancer: Comparison of RECIST 1.1 and RANO-HGG criteria

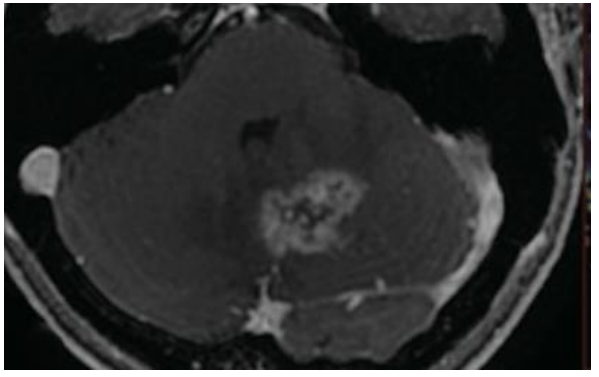
Of the 39 patients with measurable CNS disease by both RECIST and RANO-HGG, only three (8%) had CNS progression according to one criteria but not the other (92% concordance rate)

Ghandi et al, Eur J Cancer 2017

accurate identification of true progression







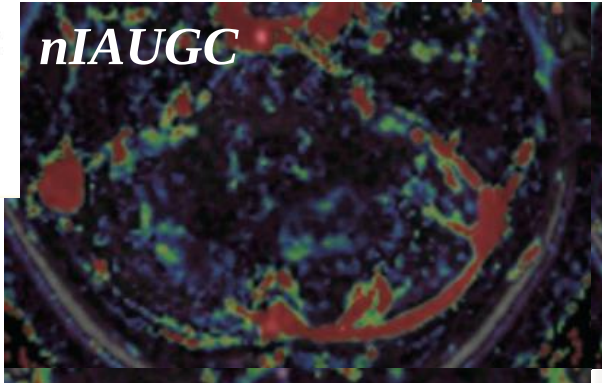
Review Article

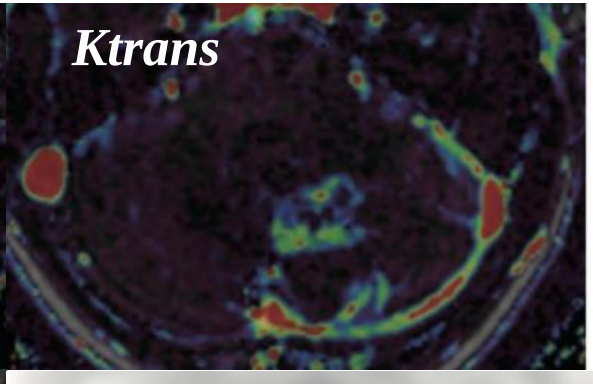
Defining the endpoints: how to measure the efficacy of drugs that are active against central nervous system metastases

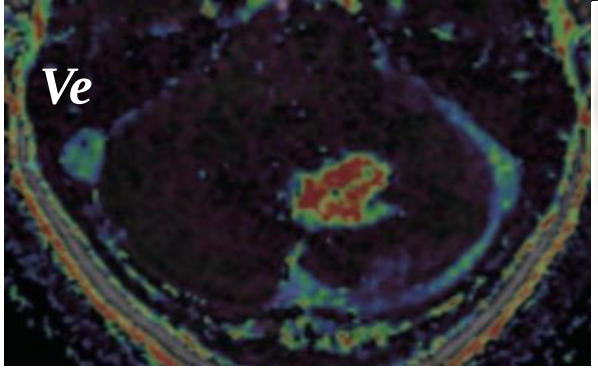
Alessandra Fabi[1], Antonello Vidiri[2]

radionecrosis

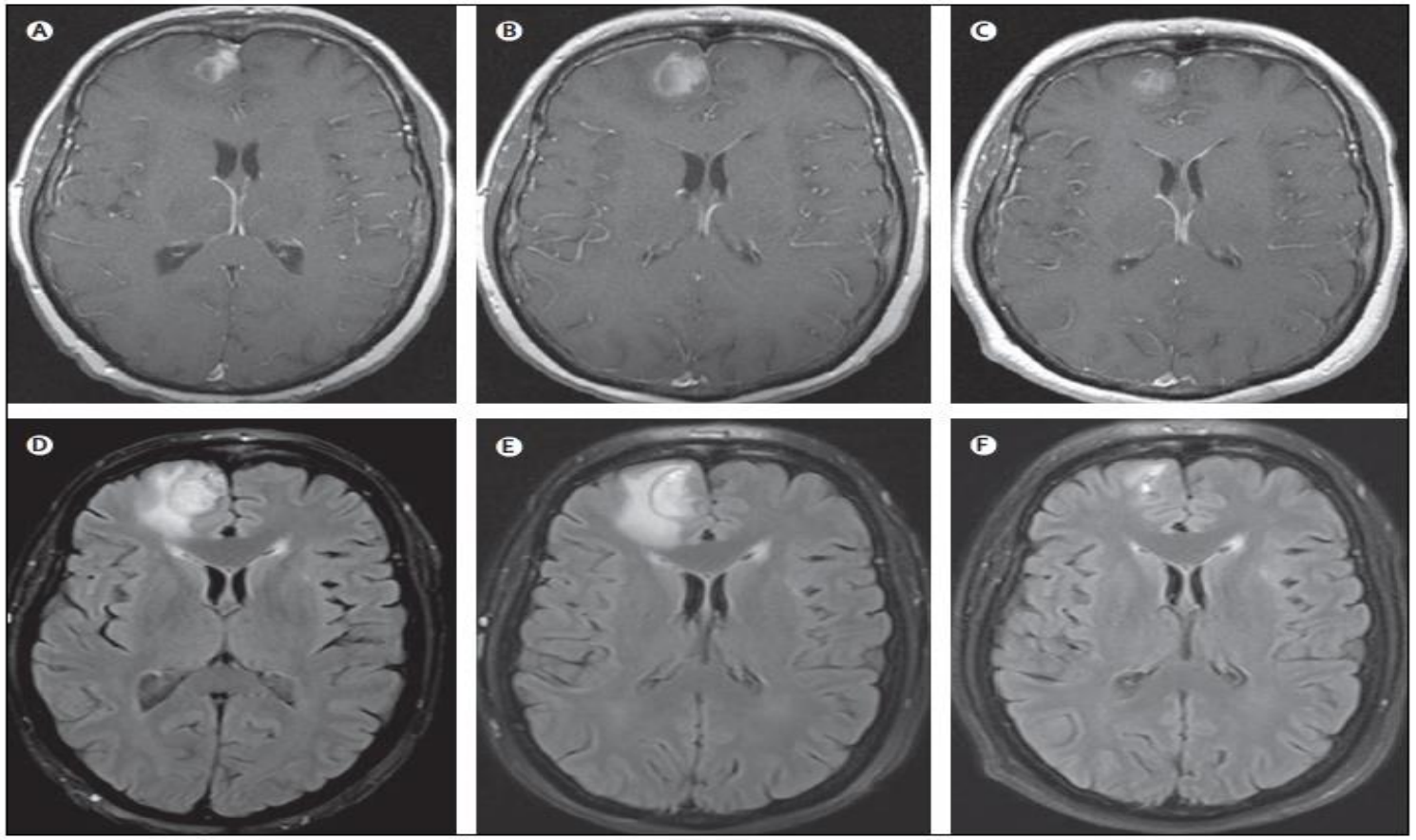
Perfusion MR







Pseudoprogressione in corso di immunoterapia

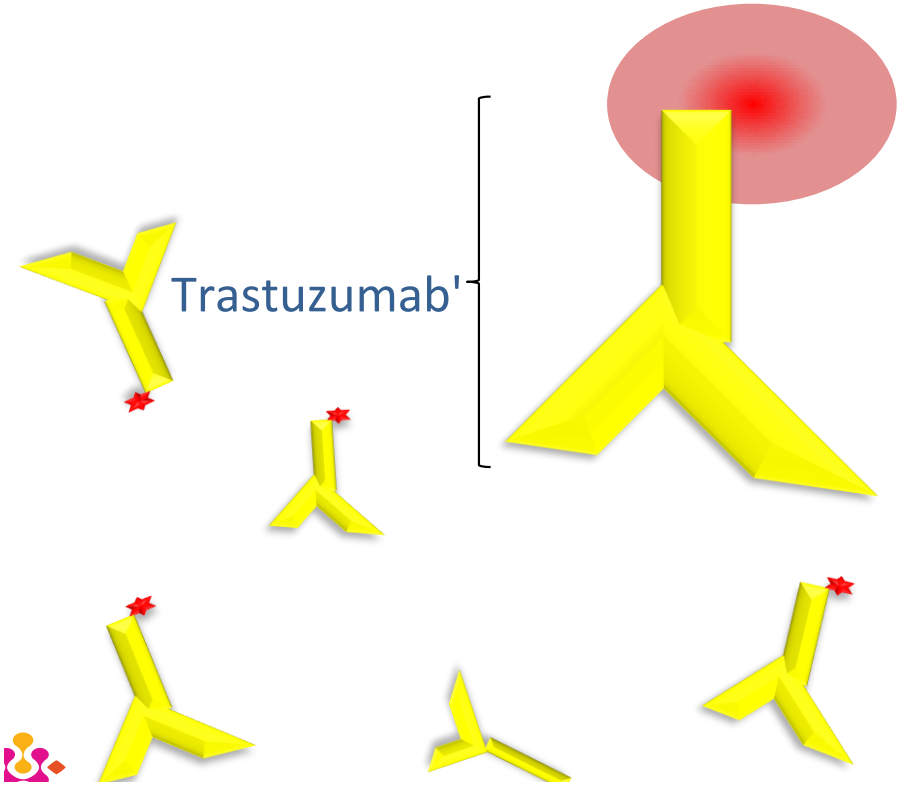


Basaline after 8 weeks after 16 weeks

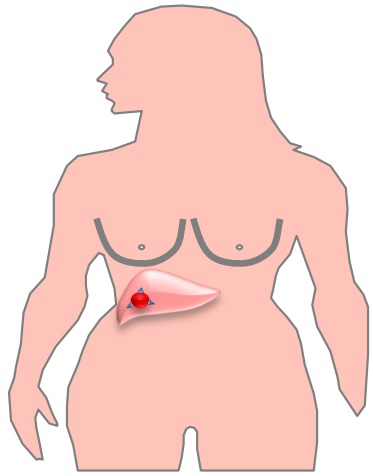
TNBC patients

Biomarkers: Radiomic

HER2!Imaging:!



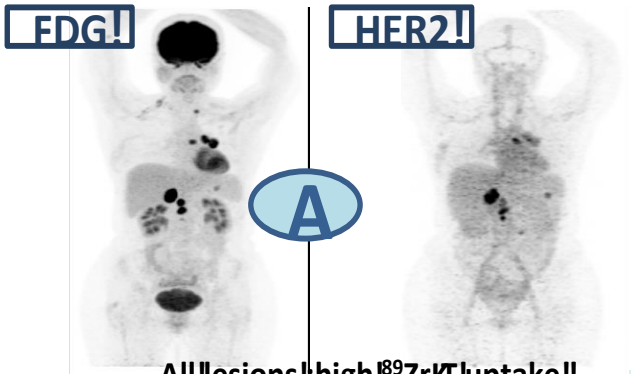
Zirconium^{89}'
Gpositron'emiN ng'isotope'✂'PET'
Gcompa$ble'physical'characteris$c''
'(HalfGife'78.4'h)'
'



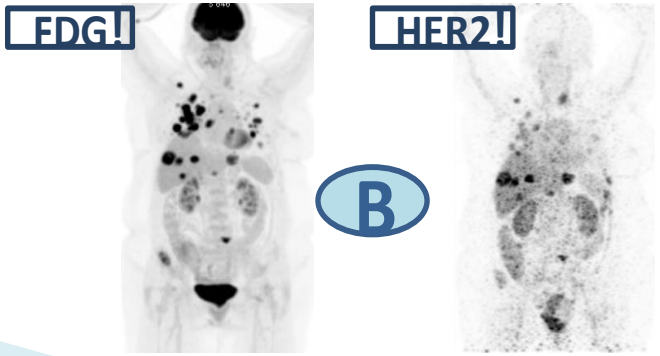
Courtesly by Azambuya

The ZEPHIR Trial: Study Design

Pax erns of ^{89}Zr-trastuzumab PET/CT confronted with FDG-PET/CT



All lesions: high ^{89}Zr-T uptake

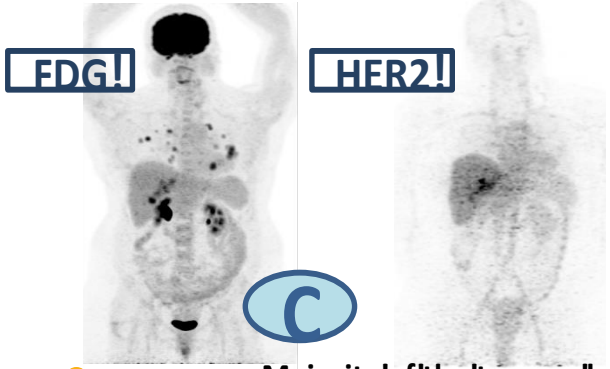


Majority of the tumour load: high ^{89}Zr-T

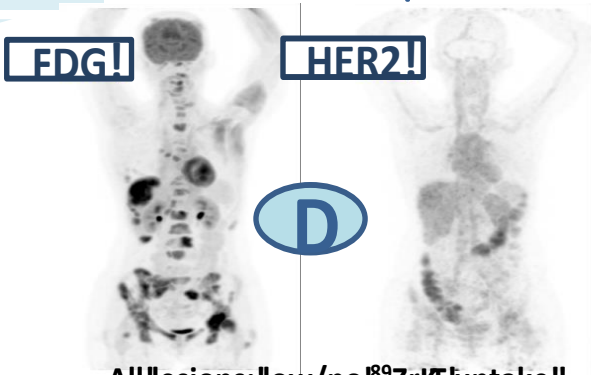
+

HER2 IMAGING METHODOLOGY

−



Majority of the tumour load: low/no ^{89}Zr-T uptake



All lesions: low/no ^{89}Zr-T uptake

Gebhart G et al, Ann Oncol 2016

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Conclusioni

✓**Adeguarsi ai criteri sulla base del tipo della molecola d'uso e della sede di malattia**

✓ **Accordo e alleanza con il radiologo dal "baseline"**

✓ **Identificare l'end point (Risposta vs PFS)**

✓ **Le metastasi cerebrali e immunoterapia : non ancora uno standard sull'imaging**

Grazie