8th Annual BM meeting Marseille

Combined Treatments for CNS Metastases

Response Assessment in CNS Metastases: new Challenges in the area of Combination

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Response Assessment in BMs
& *Combined* Treatments

- **Background**
- **Definitions**
- **2015: i-RANO BM**
- **Persisting Issues**
- **Perspectives**

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- Targeted-drugs (Tg.D), *Immunotherapies* (IT)
  - Anti-ALK,-EGFR, -BRAF/MEK, *Checkpoint Inhibitors*
- Better *Extra-CNS* control: + '*long survivors*' > *1Yr*
- *More direct deaths from BMs*

➔ **Melanoma: ~ 40% of *Direct* Deaths from BMs**

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Background

Progress in *Local* TTs: RS / SRT

- Whole-brain RT ➔ **RS** / **SRT** ➔ ***up to 10 BMs***
- **RS / SRT = Local Control** (LC) **> 85% at 1 Yr**
- ***Exclusive WB / SRT don't increase Survival !***
- RS/ SRT *Toxicity*: **Radionecrosis** ~ 20% at 2 Yrs

➔ ***Clinical Benefit: Systemic TTs + RS/SRT ?***

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Background

Tg D / ITs + RS/SRT = 3 (+1) situations

- **1st line:** rapidly '*progressing' / symptomatic* BM's

  In parallel to IT initiation, *due to* long lasting action (x 4 C.)

- **Dissociated** resp: New/Progress. BM / *Extra-CNS OK*

- **Palliative**: Progress. Intra & Extra-CNS + Neurol signs

  → ***1st line Asymptomatic pts: Frontline SRT + IT***

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Questions:

Definition of 'Response & Progression'

- **Combined** # ***Concurrent*** # **Simultaneous**
- **Response Assessment**: MR Imaging + *Patient !*
- Local control / **Intra-CNS Control (PFS)**
- **Progressive Disease** / '*Pseudoprogression*'

→ **Definition of '*Clinical Benefit*'**

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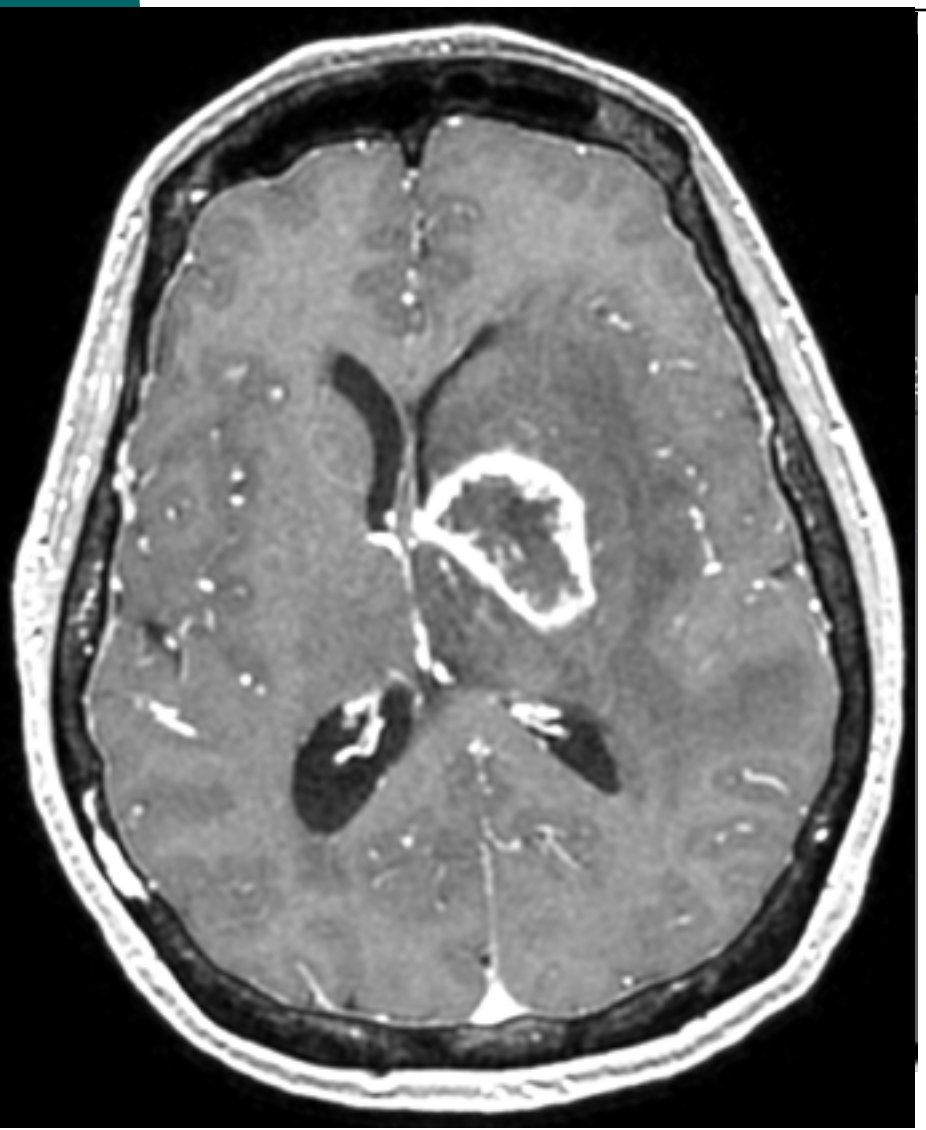
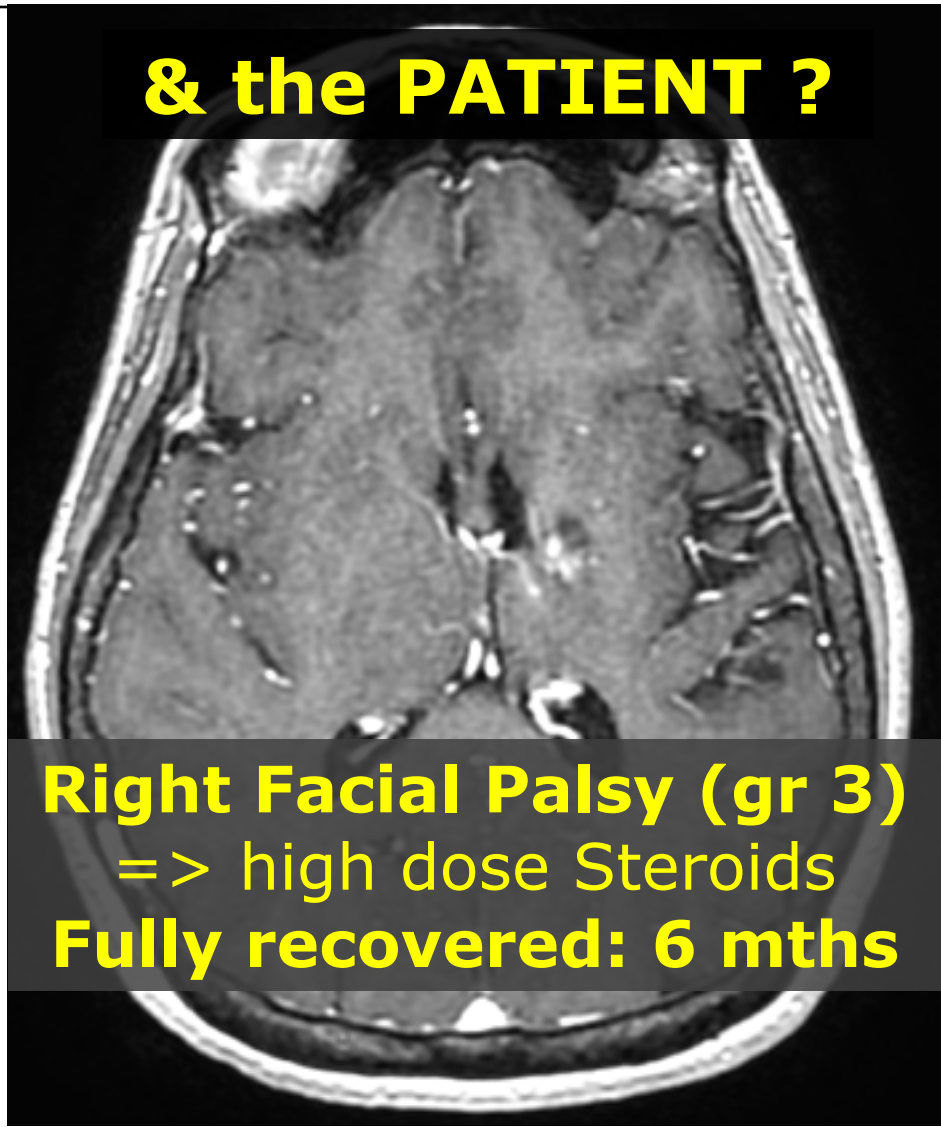
***9 months* after**

RS + Pembro *Conco*

***30 mths* after RS …**

Treatment **R**elated **I**maging **C**hange





& the PATIENT ?

Right Facial Palsy (gr 3)

=> high dose Steroids

Fully recovered: 6 mths

Questions (2)

***Confounding* factors** in retrospective studies

- **BM**: *Histo-molecular* profile, Size / Volume
- **Drug**: Tg D / ImmunoTT / Class ? Dosage ?
- **Timing**: SRS *'within' 6 mth*, *4 wks* … / Drug
- **Previous** Tts: WB or SRS / No / Steroids ?

➔ **Duration of** MRI / Clinical **follow-up !**

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MR Imaging Acquisition & Process

A US & European joint Effort for *Standardization*

Neuro-Oncology 17(9), 1188–1198, 2015
doi:10.1093/neuonc/nov095
Advance Access date 6 August 2015

2015

Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Benjamin M. Ellingson, Martin Bendszus, Jerrold Boxerman, Daniel Barboriak, Bradley J. Erickson, Marion Smits, Sarah J. Nelson, Elizabeth Gerstner, Brian Alexander, Gregory Goldmacher, Wolfgang Wick, Michael Vogelbaum, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Whitney B. Pope, Dewen Yang, Caroline Chung, Michael V. Knopp, Soonme Cha, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

Implemented in real life ?

Table 1. Minimum standard 1.5 T & 3 T MRI protocol

	3D T1w Pre[b]	Ax 2D FLAIR[j]	Ax 2D DWI		Ax 2D T2w[h,i]	3D T1w Post[b]
Sequence	IR-GRE[e,f]	TSE[c]	SS-EPI[g]		TSE[c]	IR-GRE[e,f]
Plane	Sagittal/axial	Axial	Axial		Axial	Sagittal/axial
Mode	3D	2D	2D		2D	3D
TR [ms]	2100[m]	>6000	>5000		>2500	2100[m]
TE [ms]	Min	100–140	Min		80–120	Min
TI [ms]	1100[n]	2000–2500[k]				1100[n]
Flip angle	10°–15°	90°/≥160°	90°/180°		90°/≥160°	10°–15°
Frequency	≥172	≥256	≥128		≥256	≥172
Phase	≥172	≥256	≥128		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm[l]	≤4 mm[l]		≤4 mm[l]	≤1.5 mm
Gap/spacing	0	0	0		0	0
Diffusion options[p]			b = 0, 500, 1000 s/mm^2 ≥3 directions			
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan time (approx) [benchmarked on 3 T Skyra]	5–10 min [5:49 for 1 mm isotropic]	4–8 min [3:22 for 2D FLAIR]	2–4 min [1:22 for 3 direction DWI and 3 b-values]		4–8 min [5:10 for dual echo]	5–10 min [5:49 for 1 mm isotropic]

Contrast Injection[a]

RANO-BM (1)

2015

Lancet Oncology 2015; 16: e270–78

'Target' lesion = 'Measurable' in 1 size = 5 mm +

Definitions

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≤1·5 mm apart with 0 mm skip). Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline. Measurement of a tumour around a cyst or surgical cavity is a particularly difficult challenge. Generally, such lesions should be considered non-measurable unless there is a nodular

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Panel 1: Response assessment of target and non-target lesions

RANO-BM *(2)*

Target lesions

Complete response

Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

Partial response

At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease

At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.

Stable disease

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

(i) RANO-BM (3)

Lancet Oncology 2015; 16: e270–78

Non-target lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

Complete response

Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

Non-complete response or non-progressive disease

Persistence of one or more non-target CNS lesion or lesions.

Progressive disease

Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

i- RANO

Lancet Oncol 2015; 16: e534–42

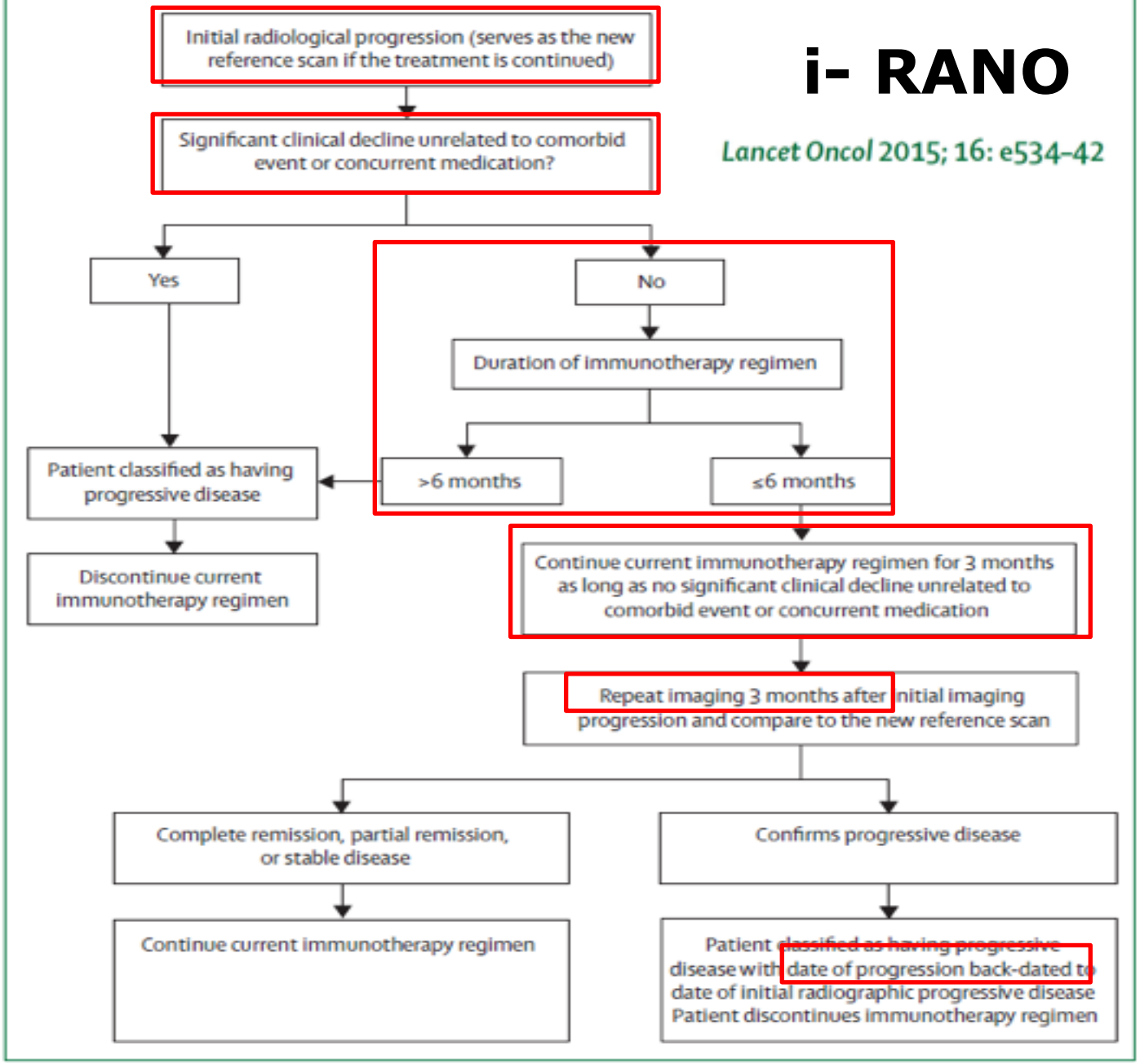

Figure 3: **iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy**
iRANO=immunotherapy Response Assessment in Neuro-Oncology.

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RANO – BM for CNS

RECIST 1.1 for *Non* CNS

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Response
Complete response, partial response, or stable disease	Complete response, partial response, or stable disease	Log as CNS and non-CNS complete response, partial response, or stable diseases
Complete response, partial response, or stable disease	Progressive disease	Log as CNS complete response, partial response, or stable disease; log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as CNS progressive disease; log as non-CNS complete response, partial response, or stable disease
Progressive disease	Progressive disease	Log as both CNS and non-CNS progressive disease

Table 3: CNS and non-CNS response assessment

CNS (RANO-BM)	Non-CNS (RECIST 1·1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a progression-free survival event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a progression-free survival event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a progression-free survival event	Log as both CNS and non-CNS progressive disease

Table 4: Bi-compartmental progression-free survival

Persisting Issues
'Non (i) RANO' parameters

- **Previous lines** of Systemic / Local TTS ?
- Place for **RANO** criteria **for *Targeted drugs*** ?
- **RS**: 1 x 20 Gy # **SRT**: 5 x 6 Gy ➔ *# mechanisms*
- BM MR ***Dynamics*** *before / after* Combination
  - *Clinical benefit #* if 'rapidly' / 'slowly' growing BM
- **Radionecrosis** / Real Progression ?
  - Role of *Perfusion MR* techniques: standardization !

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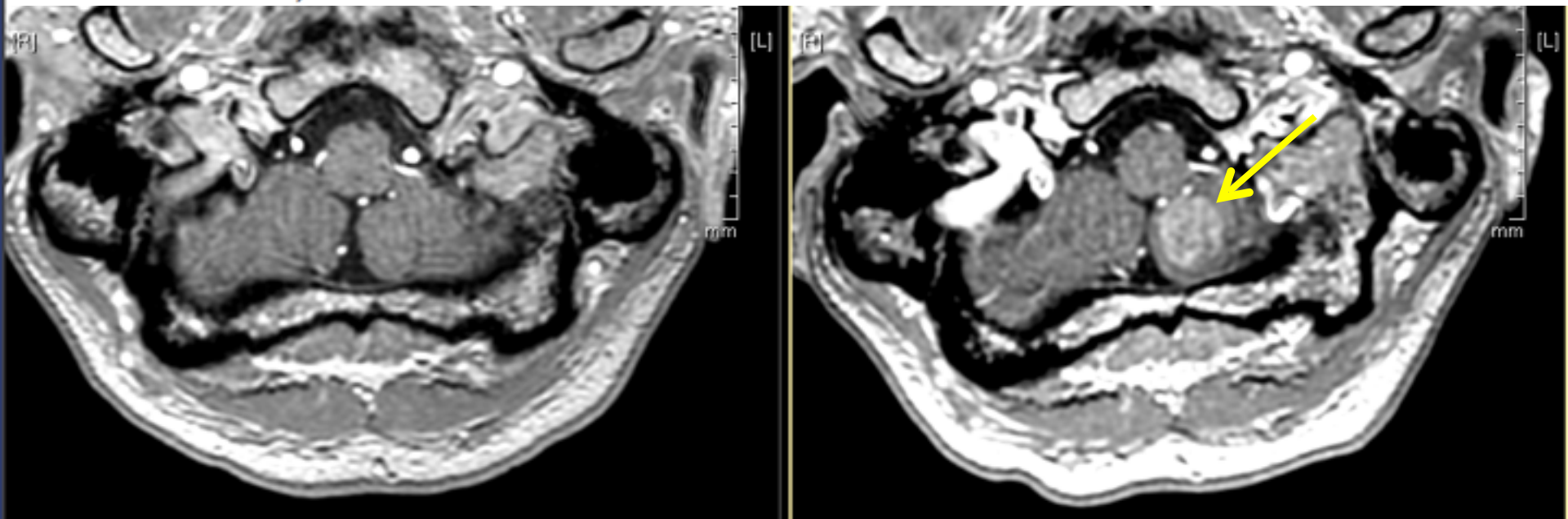
A Rapidly evolving BM: in a 3 weeks interval

Primary endpoint: *early local control* !

Neuro-Oncology 17(8), 1148–1156, 2015
doi:10.1093/neuonc/nou364
Advance Access date 2 February 2015

Dynamic susceptibility contrast MRI measures of relative cerebral blood volume as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 multicenter trial

Kathleen M. Schmainda, Zheng Zhang, Melissa Prah, Bradley S. Snyder, Mark R. Gilbert, A. Gregory Sorensen, Daniel P. Barboriak, and Jerrold L. Boxerman



Persisting Issues (2)
'Early evaluations': + *or* **- ?**

- 'Early' evaluation/ SRS: 6 Weeks / 3 Mths ?
- 'Early' response: *'favorable' in Renal Cell K* …
- 'Early' response in *Melanoma*: *Unfavorable* ??

➔ *Median Follow-up:* < or > 6 Mths ?

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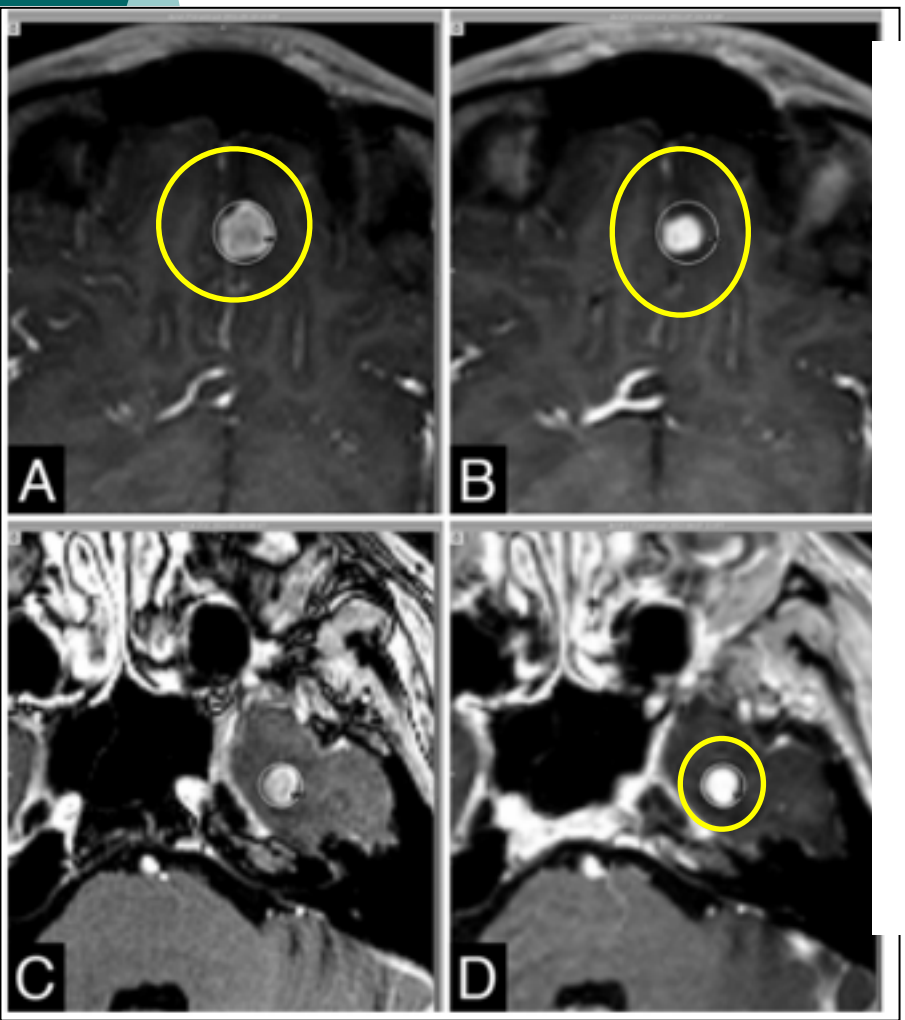
Early imaging radioresponsiveness of melanoma brain metastases as a predictor of patient prognosis

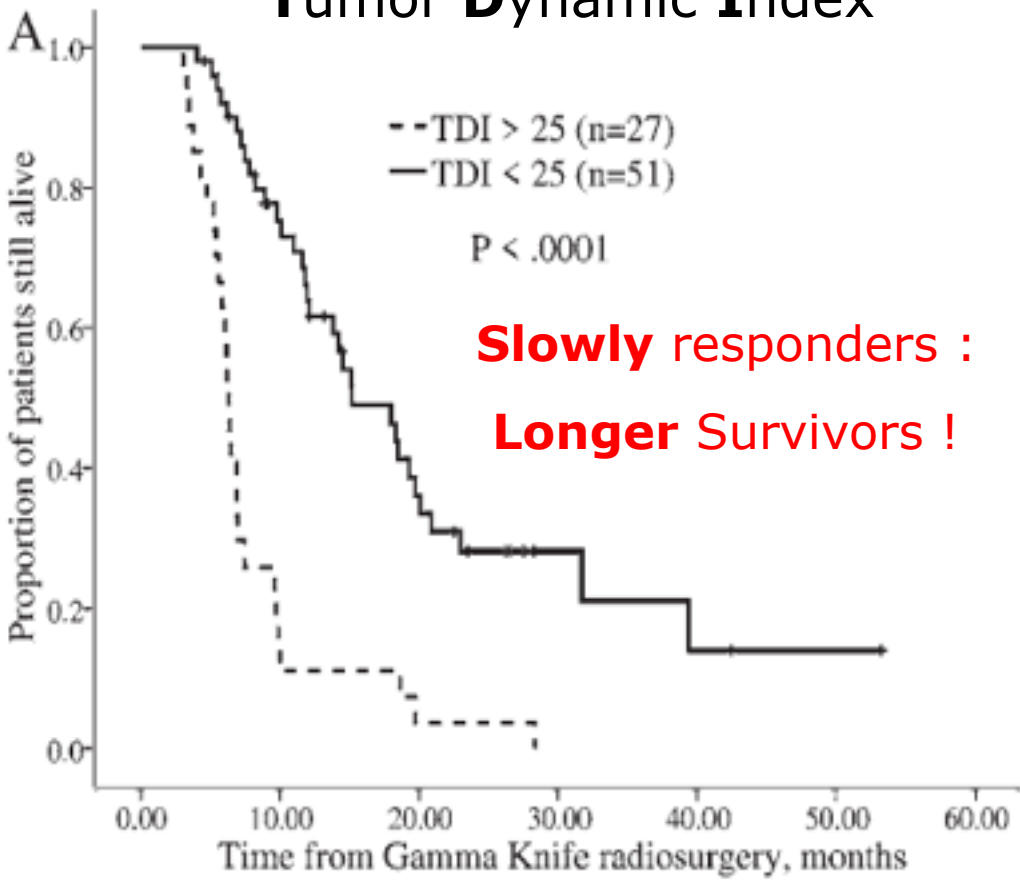
Irina Zubatkina, PhD,[1] and Pavel Ivanov, MD, PhD[1,2]

J Neurosurg August 25, 2017

78 pts – 298 BM



Tumor **D**ynamic **I**ndex



Slowly responders :

Longer Survivors !

Automatic Volumetric analysis

Early imaging radioresponsiveness of melanoma brain metastases as a predictor of patient prognosis

Irina Zubatkina, PhD,[1] and Pavel Ivanov, MD, PhD[1,2]

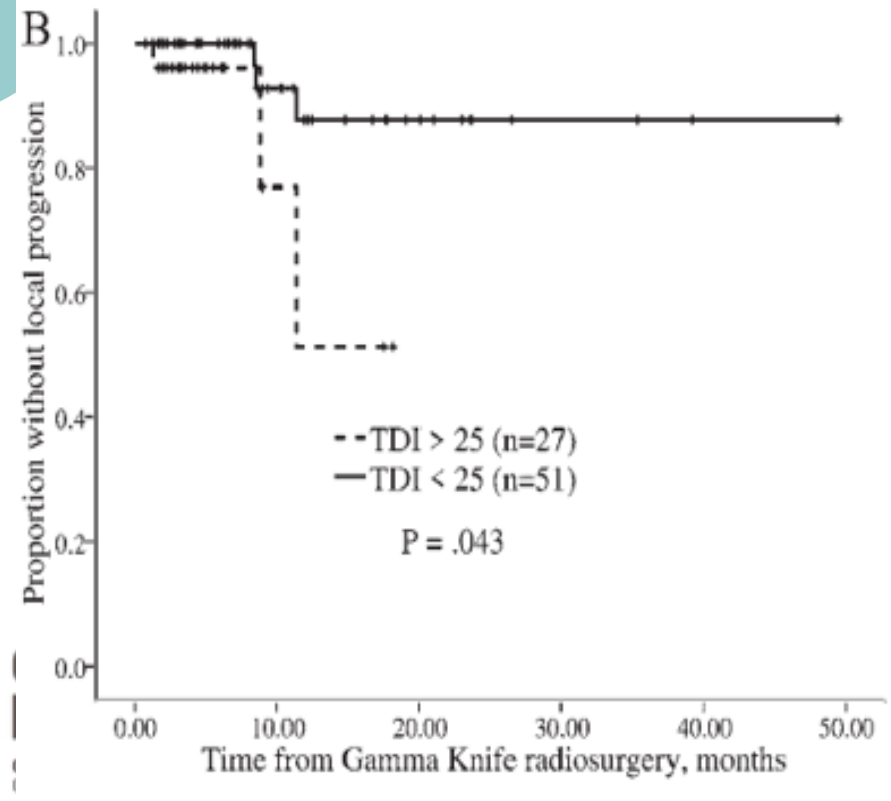
Tumor **D**ynamic **I**ndex

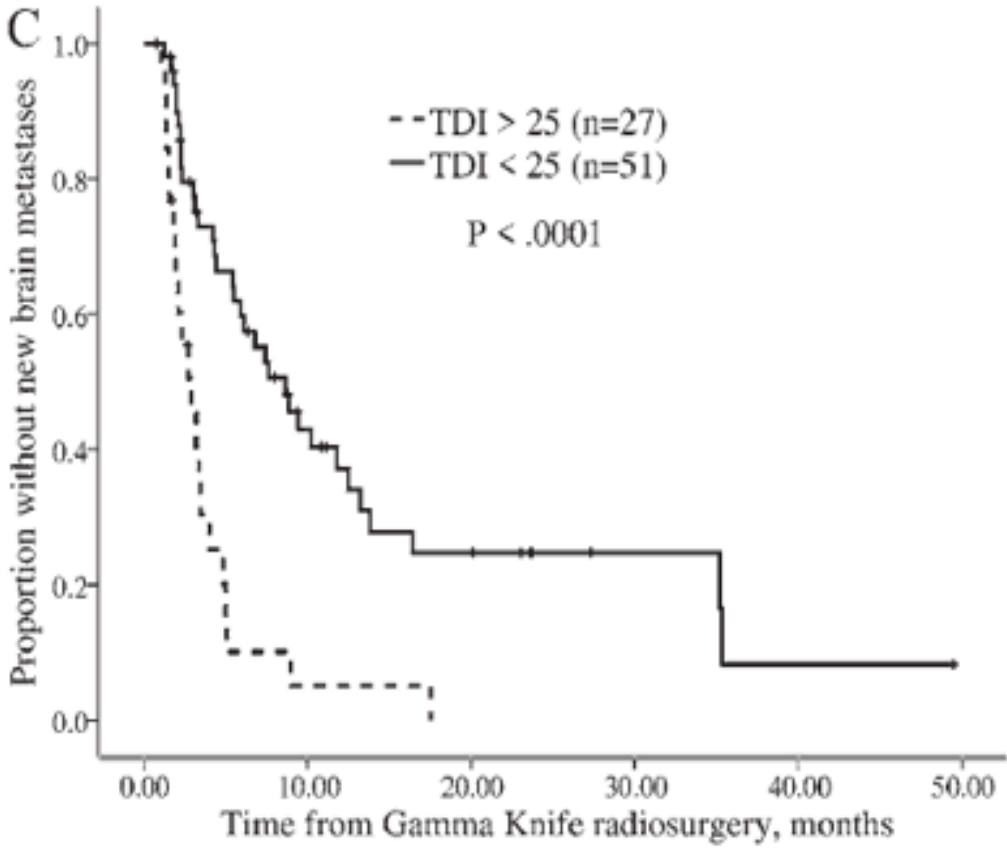
RS exclusively !

Not Combined with IT

Slow responders:

Less DISTANT Failures…

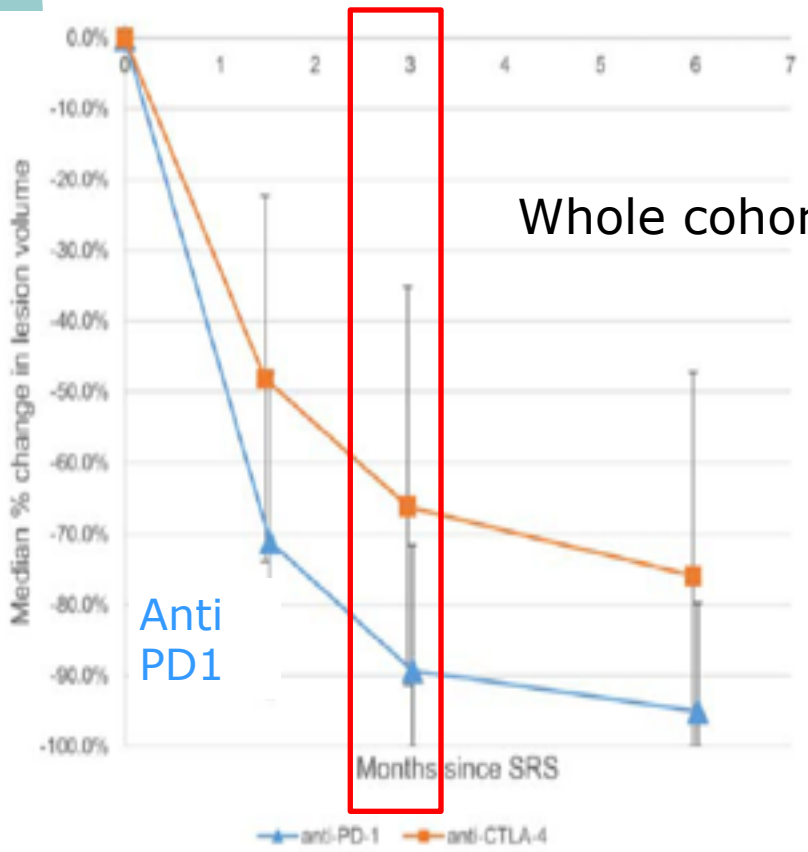




Timing and Type of Immune Checkpoint Therapy Affect the Early Radiographic Response of Melanoma Brain Metastases to Stereotactic Radiosurgery

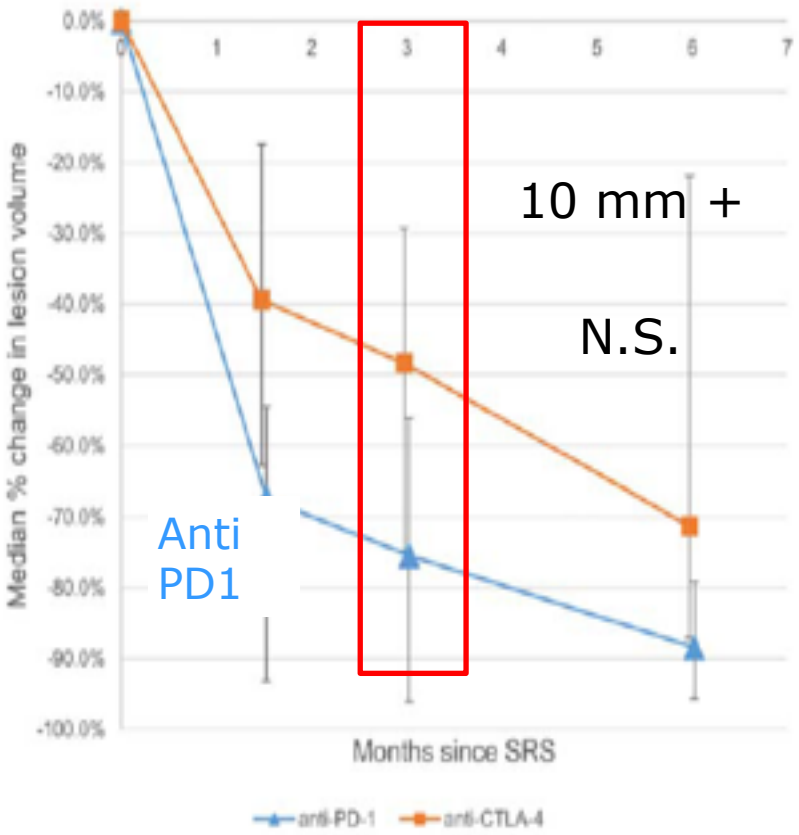
Jack M. Qian, BS[1]; James B. Yu, MD[1]; Harriet M. Kluger, MD[2]; and Veronica L. S. Chiang, MD[1,3]

Endpoint: ***% change in lesion volume*** *at 1.5 / 3 mths*



(A)

Time (months)	1.5	3	6
P value	<.0001	<.0001	.0004



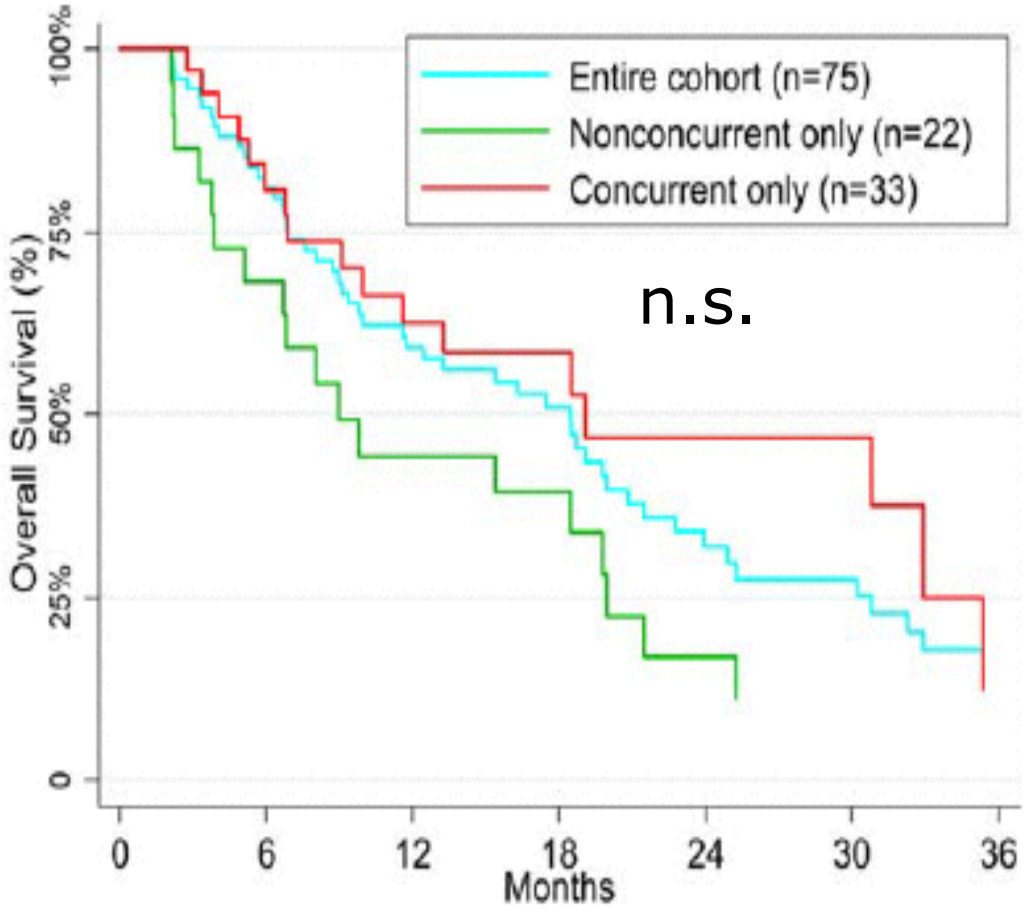
(B)

Time (months)	1.5	3	6
P value	<.0001	.008	.0154

Timing and Type of Immune Checkpoint Therapy Affect the Early Radiographic Response of Melanoma Brain Metastases to Stereotactic Radiosurgery

Jack M. Qian, BS[1]; James B. Yu, MD[1]; Harriet M. Kluger, MD[2]; and Veronica L. S. Chiang, MD[1,3]

Survival



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Proposals

i-RANO / RECIST 'in the pocket' + MTD Staffs

- **Volumetrics:** Automatic Delineation (easy, stand.)
- **Combined**: 6 Months # **Concurrent**: 1 Month
- **Integrating:** Drug + RT scheme + Timing
- **New Endpoints:** Tumor Dynamic Index ? Radiomics ?
- **Prospective *Registration Cohorts*** for Most pts
- **Prospective *Randomized Trials*** for Sugbroups
  - EORTC BTG proposal: Tg D or IT +/- SRS in NSCLC

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Perspectives

Response Assessment: **moving** from …

- Anatomical / Perfusion MRI => **Radiomics ?**
- SRS 1 fraction => **SRT: 3 fractions**
- Combined => **Concurrent** TTs (window of x days)
- 6-Mths => **9 – 12 Mths** endpoints
- Local Control => **Intra-CNS Control**
- RANO => **Patient**: NANO/ Pt Reported Outcome

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Still a Long way …

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Response Assessment in Neuro-Oncology Clinical Trials

Patrick Y. Wen, Susan M. Chang, Martin J. Van den Bent, Michael A. Vogelbaum, David R. Macdonald, and Eudocia Q. Lee

Author affiliations and support information (if applicable) appear at the end of this article.

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0732-183X/17/3521w-2439w/$20.00

A B S T R A C T

Development of novel therapies for CNS tumors requires reliable assessment of response and progression. This requirement has been particularly challenging in neuro-oncology for which contrast enhancement serves as an imperfect surrogate for tumor volume and is influenced by agents that affect vascular permeability, such as antiangiogenic therapies. In addition, most tumors have a nonenhancing component that can be difficult to accurately quantify. To improve the response assessment in neuro-oncology and to standardize the criteria that are used for different CNS tumors, the Response Assessment in Neuro-Oncology (RANO) working group was established. This multidisciplinary international working group consists of neuro-oncologists, medical oncologists, neuroradiologists, neurosurgeons, radiation oncologists, neuropsychologists, and experts in clinical outcomes assessments, working in collaboration with government and industry to enhance the interpretation of clinical trials. The RANO working group was originally created to update response criteria for high- and low-grade gliomas and to address such issues as pseudoresponse and non-enhancing tumor progression from antiangiogenic therapies, and pseudoprogression from radio-chemotherapy. RANO has expanded to include working groups that are focused on other tumors, including brain metastases, leptomeningeal metastases, spine tumors, pediatric brain tumors, and meningiomas, as well as other clinical trial end points, such as clinical outcomes assessments,