

A network diagram featuring several stylized human figures in various shades of brown and orange, connected by white lines on a light blue background. The figures are arranged in a roughly circular pattern, with some connected to multiple others, creating a web-like structure. The background has a subtle gradient and some faint circular patterns.

EN ASTRO!

post ESMO/WCLC update NSCLC oligometastasen

Lizza Hendriks, longarts, Maastricht UMC+
Roermond, 19 november 2018

Disclosure

(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	BMS, Roche, Boehringer Ingelheim, AstraZeneca
<ul style="list-style-type: none">• Sponsoring of onderzoeksgeld• Honorarium of andere (financiële) vergoeding• Aandeelhouder• Andere relatie, namelijk reiskostenvergoeding• Andere relatie, namelijk: PI farma studie	Roche, BI (instituut) adviesraad BMS (instituut/zelf), BI (instituut); interviews Roche (instituut); webinar Quadia Nvt Roche, BMS (zelf) AstraZeneca



Leerdoelen

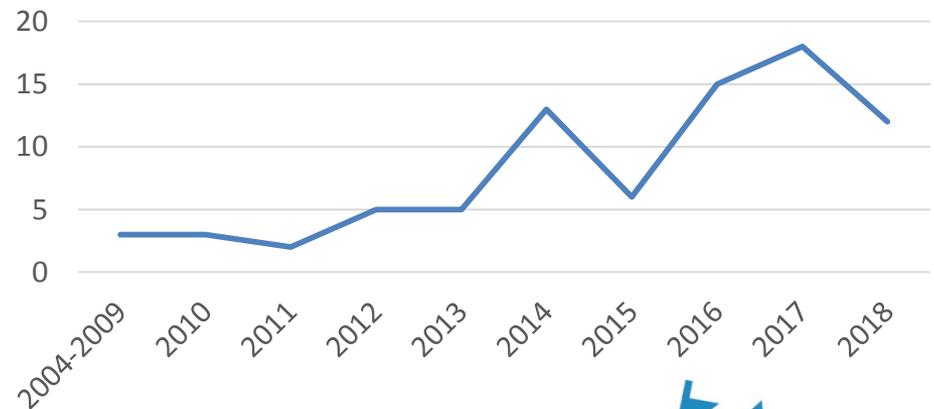
- Relevantie en concept oligometastasen
- Focus **synchrone** oligometastasen
 - Definitie
 - Stadiering
- Nut van toevoegen lokaal ablatieve behandeling
- Conclusie

Introductie concept : 1995!

Hellmann en Weichselbaum: intermediaire staat metastatisch potentieel, deze patiënten kunnen mogelijk baat hebben bij lokaal ablatieve therapie

Door betere stadiering en minder invasieve ablatieve therapie: recent steeds meer belangstelling!

aantal publicaties / year
"oligometastases and NSCLC" op
pubmed



Oligometastasen zijn “hot”!



ASTRO 2018

Meeting Coverage > ASTRO

Aggressive RT, Surgery Doubles OS in NSCLC With Limited Mets

— If new drug produced such a response it would make "millions," said expert

JCO 2018



J Clin Oncol. 2018 Sep 27;JCO1800847. doi: 10.1200/JCO.18.00847. [Epub ahead of print]

The 46th David A. Karnofsky Memorial Award Lecture: Oligometastasis-From Conception to Treatment.

Weichselbaum RR¹.

Clinicaltrials.gov

16 Studies found for: **oligometastatic OR oligometastases OR oligo** | Recruiting, Not yet recruiting Studies | NSCLC

Also searched for **Nonsmall cell lung cancer**. [See Search Details](#)

Maar wat zijn oligometastasen eigenlijk?

oligo- ~~olig~~ This combining form is pronounced ol'igo, not oli'go.

1. A few, a little; too little, too few.

2. In chemistry, used in contrast to "poly-" in describing polymers; for example, oligosaccharide.

[G. *oligos*, few]

SYNCHROON

vs

METACHROON

Baseline / geïnduceerd

Oligoprogressie
Oligorecurrence

oligopersistent?



Synchroon: onduidelijkheid....

ESMO 2018 definitie

Treatment of oligometastatic disease

- Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and local consolidative therapy (high-dose RT or surgery) [III, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [II, B], and inclusion in clinical trials is preferred
- Although operative risk is low and long-term survival may be achieved, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not been established yet

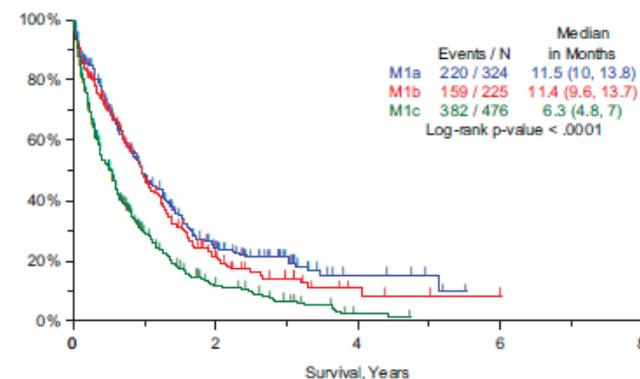
TNM8

TABLE 3. Prognostic Impact of Single and Multiple Metastatic Lesions in a Single C

Proposed Category	Variable	n/N (%)
M1a	M1a	324/1025 (32)
M1b	M1b, single organ/lesion	225/1025 (22)
M1c	M1b, single organ/multiple lesions	229/1025 (22)
	M1b, multiple organs	247/1025 (24)

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

Proposed 8th Edition M Categories
EDC Data Only



Synchroon: de onduidelijkheid gaat door

Author, year, phase trial	Nr of NSCLC patients included	Max nr of metastatic sites	Max nr of organs with metastases	Primary/LN counted
De Ruyscher single arm	40 All histologies	5	5	No

EENDUIDIGE DEFINITIE NODIG!

Phase II randomized	All histologies	first line systemic tx: 3		
Iyengar Phase II randomized	29 Non-EGFR/ALK	6 including primary Max 3 in liver/lung	5	Yes
Bauml Single arm phase II	45 All histologies	4	4	No



EORTC lung cancer group neemt WCLC oligometastasen definitie sessie over!



MA25 - Oligometastasis: Defining, Treating, and Evaluating

13:30 - 15:00 | 9/26/2018 | Location: Room 203 BD

Type: Mini Oral Abstract Session | Track: Oligometastatic NSCLC

Moderators: Joanna M Laba, Zishan Allibhai



MA25.01 - EORTC Lung Cancer Group Survey to Define Synchronous Oligometastatic Disease in NSCLC

13:30 - 13:35 | Presenting Author(s): Lizza Hendriks | Author(s): Antonin Levy, Thierry Berghmans, Corinne Faivre-Finn, Matteo Giaj Levra, Niccolo Giaj-Levra, Baktiar Hasan, Nicolas Girard, Laurent Greillier, Sylvie Lantuejoul, John G Edwards, Mary O'brien, Martin Reck, Benjamin Besse, Silvia Novello, Anne-Marie C. Dingemans



MA25.03 - Defining Oligometastatic Non-Small Cell Lung Cancer (NSCLC): An Evolving Multidisciplinary Expert Opinion

13:35 - 13:40 | Presenting Author(s): Lizza Hendriks | Author(s): Christophe A. Dooms, Thierry Berghmans, Silvia Novello, Antonin Levy, Dirk De Ruysscher, Baktiar Hasan, Matteo Giaj Levra, Niccolo Giaj-Levra, Benjamin Besse, Johan F. Vansteenkiste, Anne-Marie C. Dingemans



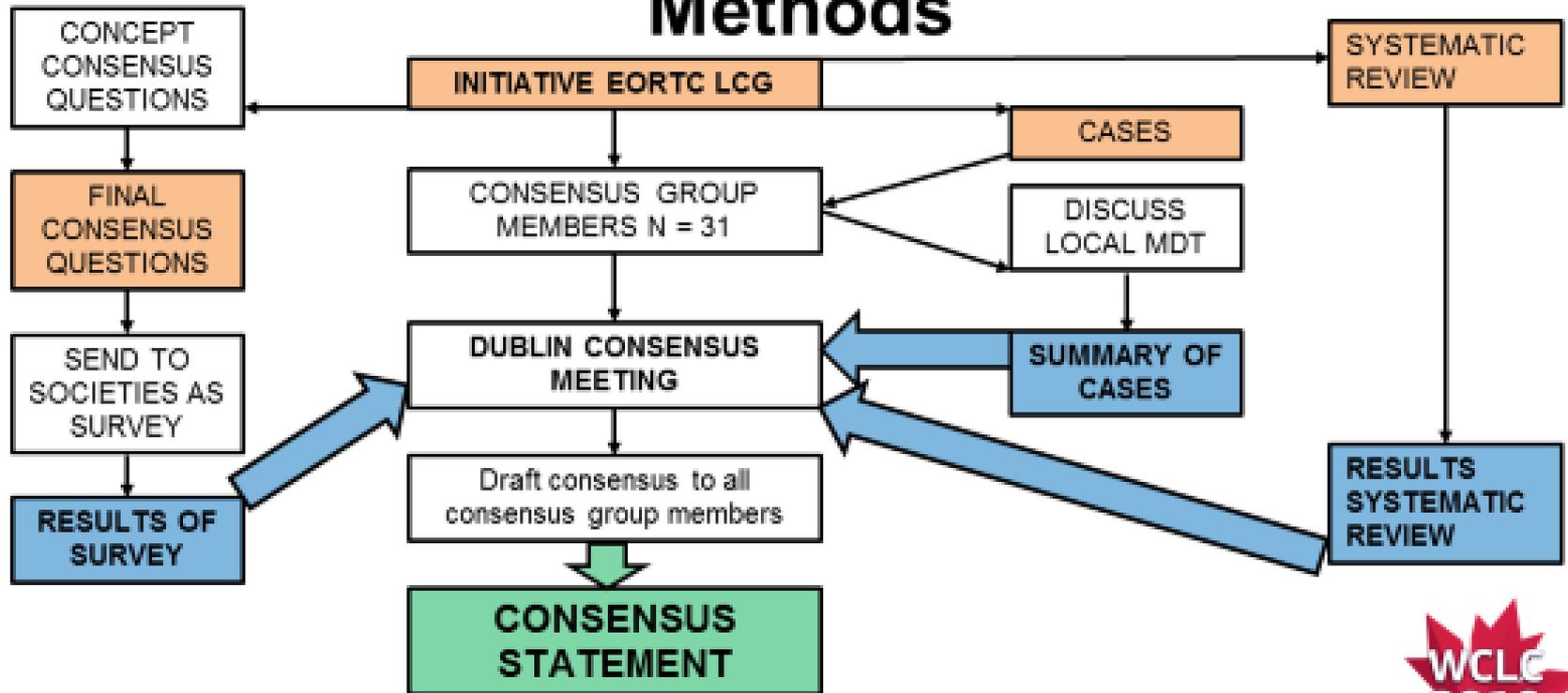
MA25.02 - Searching for a Definition of Synchronous Oligometastatic (sOMD)-NSCLC: A Consensus from Thoracic Oncology Experts

13:40 - 13:45 | Presenting Author(s): Anne-Marie C. Dingemans | Author(s): Lizza Hendriks, Thierry Berghmans, Antonin Levy, Baktiar Hasan, Corinne Faivre-Finn, Matteo Giaj Levra, Niccolo Giaj-Levra, Nicolas Girard, Laurent Greillier, Sylvie Lantuejoul, John G Edwards, Mary O'brien, Martin Reck, Egbert F Smit, Paul Emile Van Schil, Pieter E. Postmus, Sara Ramella, Yolande Lievens, Mina Gaga, Nir Peled, Giorgio Vittorio Scagliotti, Suresh Senan, Luis Paz-Ares, Matthias Guckenberger, Fiona McDonald, Simon Ekman, Tanja Cufer, Hester Gietema, Maurizio Infante, Rafal Dziadziuszko, Benjamin Besse, Silvia Novello





Methods



Voorstel definitie synchrone oligo- metastasen NSCLC

- Definition relevant for patients for whom a radical treatment is technically feasible with acceptable toxicity, taking into account all sites, that may modify the course of the disease, leading to a long-term disease control
- No consensus on maximum nr of metastases
 - Max nr metastases depends on possibility to radically treat all sites with acceptable toxicity, based on review max 5 mets in 3 organs proposed. Diffuse serosal mets and bone marrow mets excluded
- Mediastinal lymph node is considered local disease but should be taken into account in determining whether radical local treatment is possible (and involvement is poor prognostic factor)



Voorkeur uitkomstmaat in contrast met veel (lopende) studies!

- RECIST 1.1

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other local ablative therapy, are usually not considered measurable lesions unless there has been demonstrated progression. Study protocols should detail the criteria under which such lesions would be

Table 2 – Time point response for non-target disease only.

Non-target lesions	Target lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

OS preferred outcome measure

Patients in both groups were followed for adverse events and progression (with imaging) every 6 weeks (plus or minus 2 weeks) after randomisation for the first year, and then at the physician's discretion thereafter. Acceptable follow-up tests included systemic imaging with either CT or PET-CT, and brain imaging (MRI or CT) if the patient had intracranial metastases. Progression was defined according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1¹⁰ and assessed by the treating physician and confirmed by an investigator of the study (principal investigator, coprincipal investigator, or site principal investigator). Disease progression was subcategorised as



from L.B. Marks

Slide courtesy prof Dingemans Eisenhauer, EJC 2009, Gomez, lancet oncology 2017; Levy, WCLC 2018



Voorstel stadiering oligometastasen

Mandatory: ^{18}F FDG-PET-CT, brain imaging (MRI)

Advised:

In case of a solitary liver metastasis: dedicated liver MRI

For a solitary pleural metastasis: thoracoscopy and biopsies of ipsilateral pleural sites

Mediastinal staging:

Minimum: ^{18}F FDG-PET scan, pathological confirmation recommended

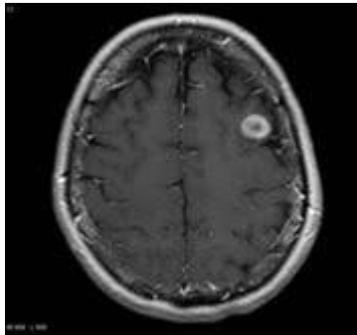
if this influences treatment strategy

Single metastatic location:

Pathology proof required, unless the multidisciplinary team decides that the risk outweighs the benefit

Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group

Nandita M. deSouza ^{a,*}, Yan Liu ^b, Arturo Chiti ^c, Daniela Oprea-Lager ^d,
Géraldine Gebhart ^e, Bernard E. Van Beers ^{f,g}, Ken Herrmann ^h,
Frederic E. Lecouvet ⁱ



Conventional staging imaging per routine practice

^{18}F -FDG-PET/CT at diagnosis

^{18}F -MRI Brain if above positive or patients with neurological symptoms

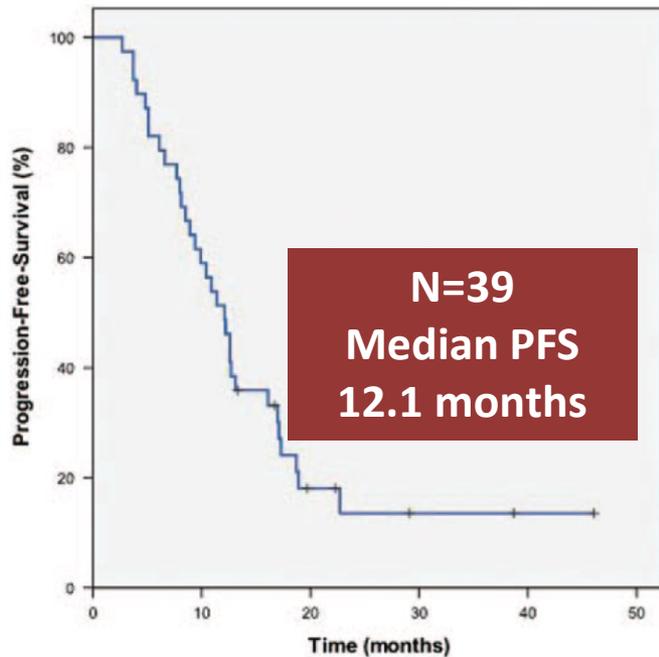
^{18}F -FDG-PET/CT in presence of suspicious lesion on surveillance imaging

WB-MRI if available

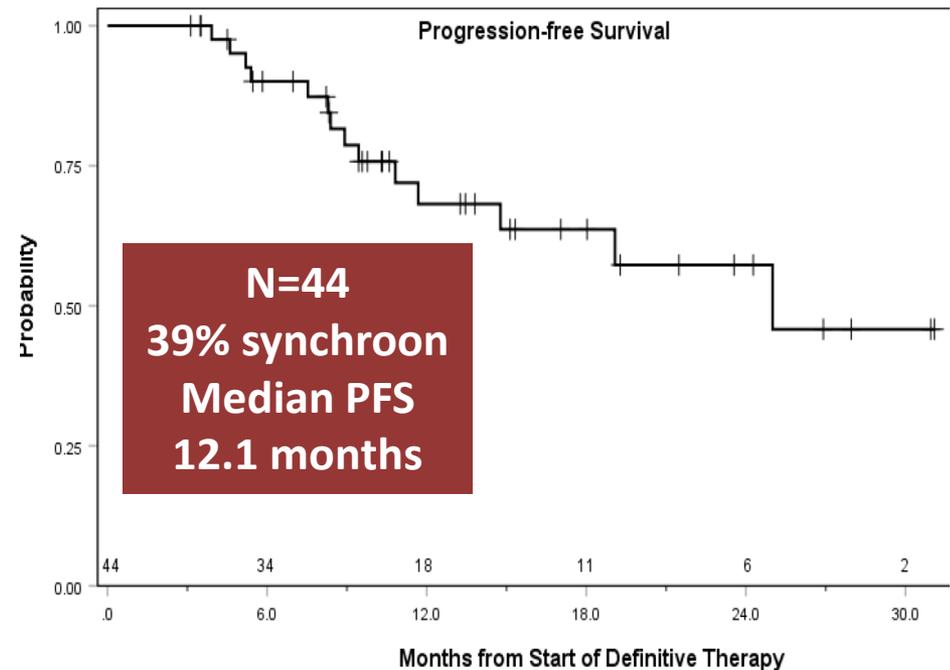
PET/MRI if available



Welke data waren er VOOR WCLC / ESMO?



12 month PFS	51%
2 & 3 year PFS	13.6%
Median OS	13.5 mnd

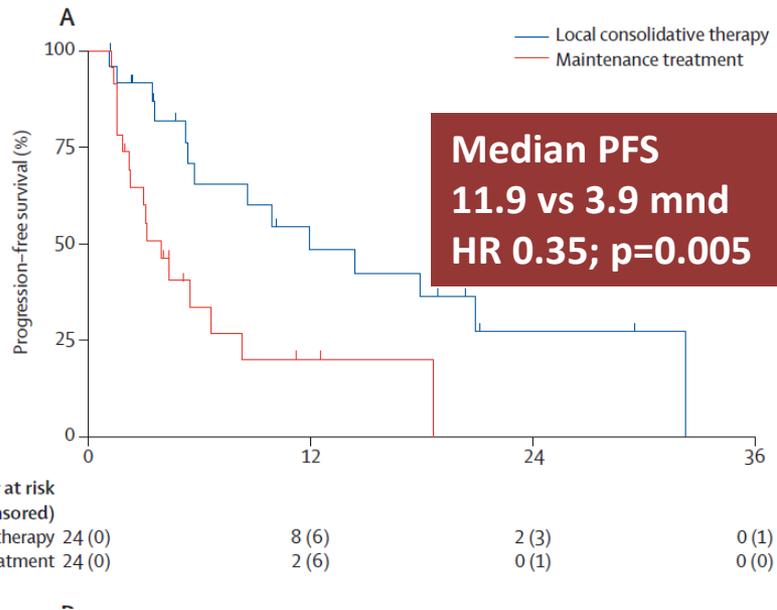


6 month PFS	90 \pm 5%
12 month PFS	68 \pm 8%
18 month PFS	64 \pm 9%



Welke data waren er VOOR WCLC / ESMO?

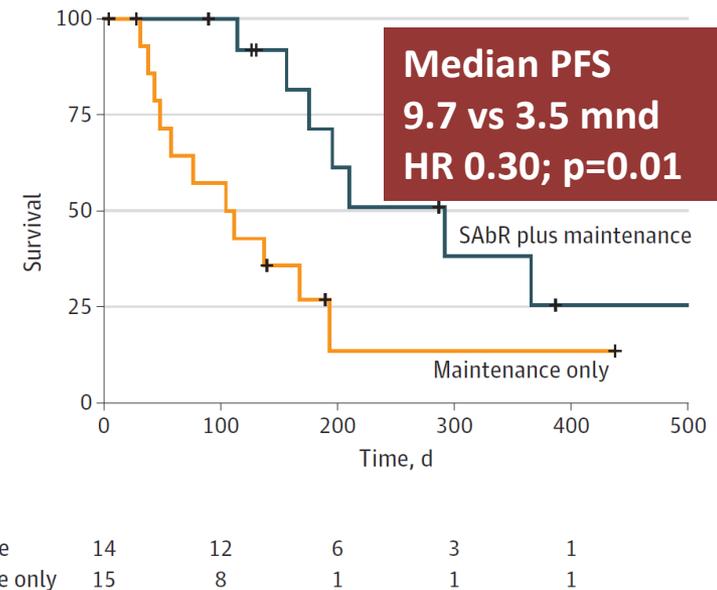
Gomez



**R 1:1 N = 49
8 driver mut+**

vs

Iyengar



**R 1:1 N = 39
0 driver mut+**



WCLC 2018

vs

ESMO 2018

+ MS03 - New Frontiers in Oligometastases
10:30 - 12:00 | 9/24/2018 | Location: Room 203 BD
Type: Mini Symposium | Track: Oligometastatic NSCLC

+ MS06 - Practical Issues in the Management of Oligometastatic NSCLC
13:30 - 15:00 | 9/24/2018 | Location: Room 206 BD
Type: Mini Symposium | Track: Oligometastatic NSCLC

+ OA07 - Oligometastasis: What Should Be the State-Of-The-Art?
15:15 - 16:45 | 9/24/2018 | Location: Room 107
Type: Oral Abstract Session | Track: Oligometastatic NSCLC

+ PC08 - The Great Oligometastatic Debates
13:30 - 15:00 | 9/25/2018 | Location: Room 105
Type: Pro-Con Session | Track: Oligometastatic NSCLC

+ ES06 - Oligometastatic Disease
10:30 - 12:00 | 9/26/2018 | Location: Room 202 BD
Type: Educational Session | Track: Oligometastatic NSCLC

+ MA25 - Oligometastasis: Defining, Treating, and Evaluating
13:30 - 15:00 | 9/26/2018 | Location: Room 203 BD
Type: Mini Oral Abstract Session | Track: Oligometastatic NSCLC



Exclusief 3 EGFR-TKI
studies die (wrsch)
retrospectief zijn



Oncologisch Netwerk
Zuidoost-Nederland





PFS and OS Beyond 5 years of NSCLC Patients with Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450)

Dirk De Ruyscher¹, Rinus Wanders¹, Lizza Hendriks², Angela Van Baardwijk¹, Bart Reymen¹, Ruud Houben¹, Gerben Bootsma³, Cordula Pitz⁴, Anne-Marie C. Dingemans²

¹Maastricht University Medical Centre, Maastricht/Netherlands, ²Maastricht University Medical Center, Maastricht/Netherlands, ³Zuyderland MC, Heerlen/Netherlands, ⁴Laurentius MC, Roermond/Netherlands

Dirk De Ruyscher, Maastricht clinic, The Netherlands

N = 39, < 5 mets
PET & CT/MRI brein+
Primaire eindpunt: OS na
2 en 3 jaar



Patiënt karakteristieken & geupdate OS en PFS

51% lokaal stad IIIB
44% hersenmeta's
87% solitaire metastase
> 90% chemoRT

<u>Time</u>	<u>Overall Survival (n=39)</u>	<u>Progression-Free Survival (PFS)</u>
Median	13.5 months	12.1 months
1 year	56.4 %	51.3 %
2 year	23.3 %	13.6 %
3 year	12.8 %	12.8 %
4 year	10.3 %	7.7 %
5 year	7.7 %	7.7 %
6 year	5.1 %	2.5 %



Phase II Study of Pembrolizumab for Oligometastatic Non-Small Cell Lung Cancer (NSCLC) Following Completion of Locally Ablative Therapy (LAT)

Joshua Bauml, MD; Rosemarie Mick, MS; Christine Ciunci, MD, MSCE; Charu Aggarwal, MD, MPH; Christiana Davis, MD; Tracey Evans, MD; Charuhas Deshpande, MD; Linda Miller, RN; Pooja Patel; Evan Alley, MD, PhD; Christina Knepley, CRNP; Faith Mutale, CRNP; Roger B. Cohen, MD; Corey J. Langer, MD



N = 45, < 5 mets

31% synchronon

**Primaire eindpunt: PFS &
tox**

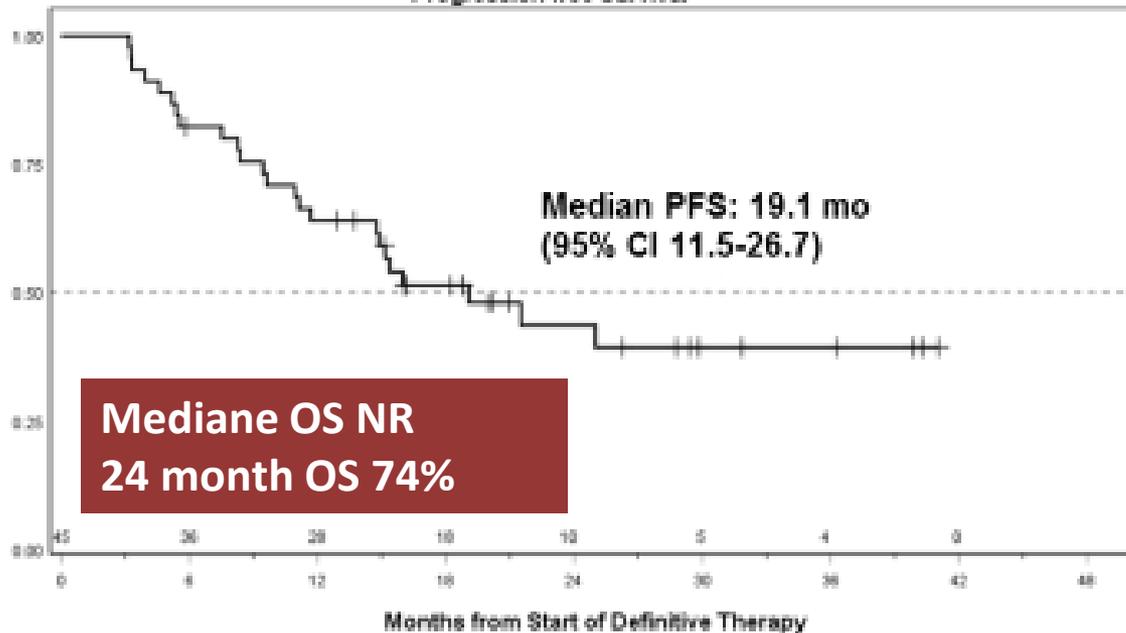


Resultaten

58.5% N0/1, 47% PD-L1 NEG
36% hersenmets
62% 1 metastase

3x gr ≥ 3 pneumonitis
2x gr 3 colitis
1x gr 3 bijnierinsuff

Progression-free Survival



	PFS1 (Definitive Rx)	PFS2 (Enrollment)
12 mo	64 _± 7.2%	63.7 _± 7.3%
18 mo	51.3 _± 7.7%	49.9 _± 7.9%
24 mo	43.6 _± 8.3%	42.1 _± 8.4%

Compare median PFS 19.1 mos (SE=3.9)
to historical control (6.6 mos)
One sided p value= 0.00066



ASTRO 2018: OS data Gomez trial

Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

Daniel R. Gomez, MD, Chad Tang, MD, Jianjun Zhang, MD, PhD, George R. Blumenschein Jr, MD, Mike Hernandez, MS, J. Jack Lee, PhD, Rong Ye, MS, David A. Palma, MD, PhD, Alexander V. Louie, MD, PhD, D. Ross Camidge, MD, PhD, Robert C. Doebele, MD, PhD, Ferdinandos Skoulidis, MD, Laurie E. Gaspar, MD, James W. Welsh, M.D., Don L. Gibbons, MD, PhD, Jose A. Karam, MD, Brian D. Kavanagh, MD, Anne S. Tsao, MD, Boris Sepesi, MD, Stephen G. Swisher, MD,* John V. Heymach, MD, PhD*

*Dr. Swisher and Dr. Heymach contributed equally to this project.

ASTRO Clinical Trials Session

October 21, 2018

2018 ANNUAL MEETING | HENRY B. GONZALEZ CONVENTION CENTER | SAN ANTONIO

  #ASTRO18



Oncologisch Netwerk
Zuidoost-Nederland



Design Gomez trial

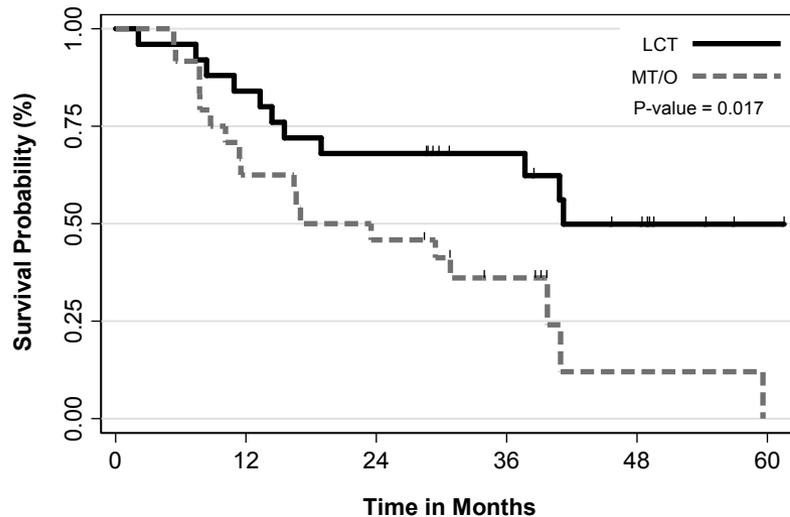
**Crossover allowed
at time of
progression**

P
S
N

Secondary Endpoints: Overall survival, safety/toxicity, time to appearance of new lesions

Balanced randomization. 1) Number of metastases (0-1 vs. 2-5), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

OS data Gomez trial



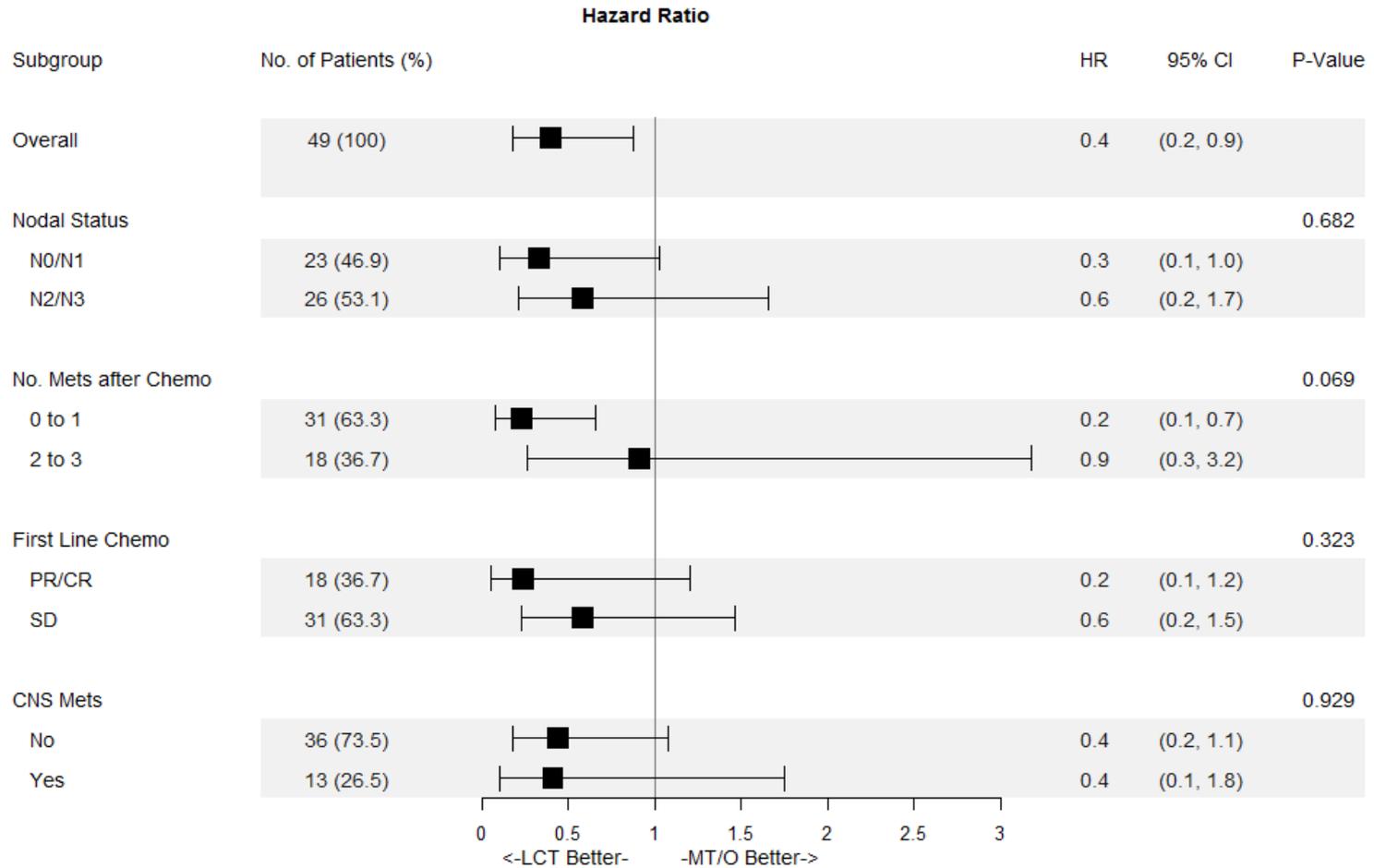
**Median 17.0 months [95%
CI 10.1–39.8] vs. 41.2
months LCT [95% CI 18.9–
not reached]
HR 0.40;p=0.017**

Number at risk

LCT:	25	21	17	12	7	1
MT/O:	24	15	11	6	1	0

**Ttv PD: 32% in LCT arm nogmaals LCT en
42% in observatie arm**

Gomez subgroup analyses



Samenvatting Gomez 2016 & ASTRO 2018

Oligometastatische NSCLC patienten NA inductie 1e lijn, hebben met LAT, tov follow-up:

- Betere PFS en OS
- Trend tot langere tijd tot verschijnen nieuwe laesies
- > 50% komt niet meer in aanmerking voor LAT bij progressie

Toxiciteit acceptabel met LAT

Meeste baat bij LAT:

- 0-1 metastasen NA inductie 1e lijn
- N0/N1 disease

Maar...

Trial voortijdig gestopt, subgroup analyses moeilijk

Fase II

Heterogeniteit behandeling maintenance arm

Weinig driver mutatie patienten, trial geïnitieerd voor immunotherapie “hot” werd

Hoe patienten te selecteren die meeste baat hebben?

Inclusie bias?

Zou u deze patiënten includeren?



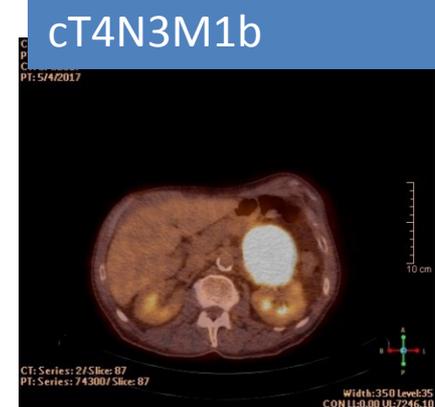
cT3N0M1b



cT4N0M1b



cT4N3M1b



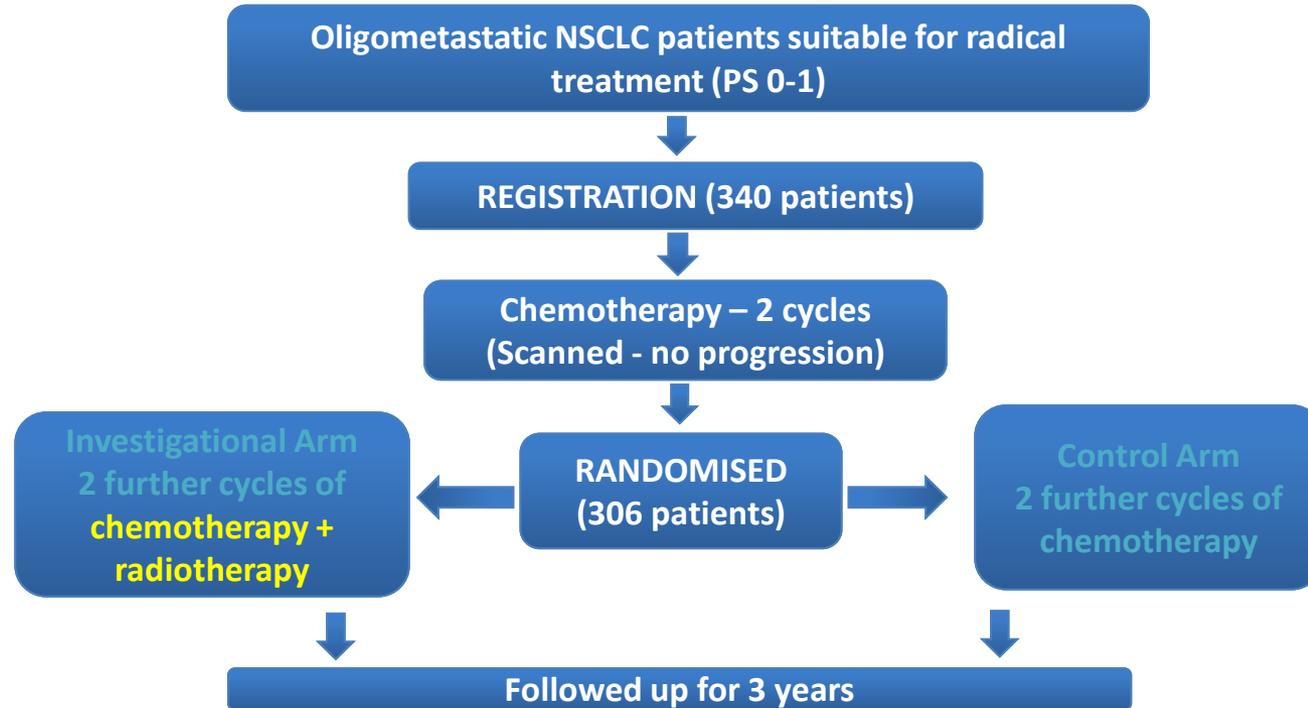
Wat komt er aan?



Oncologisch Netwerk
Zuidoost-Nederland



Stereotactic Ablative Radiotherapy for Oligometastatic Non-small cell lung cancer
SARON: Trial design



Cancer Research UK & UCL Cancer Trials Centre

Saron: stratification & main outcome measures

- Hospital site (randomising)
- Adenocarcinoma versus non-adenocarcinoma
- N-stage disease (N0/1 vs N2/3)
- Number of metastases involved (1 vs 2 or 3)
- Brain metastases (present vs absent)

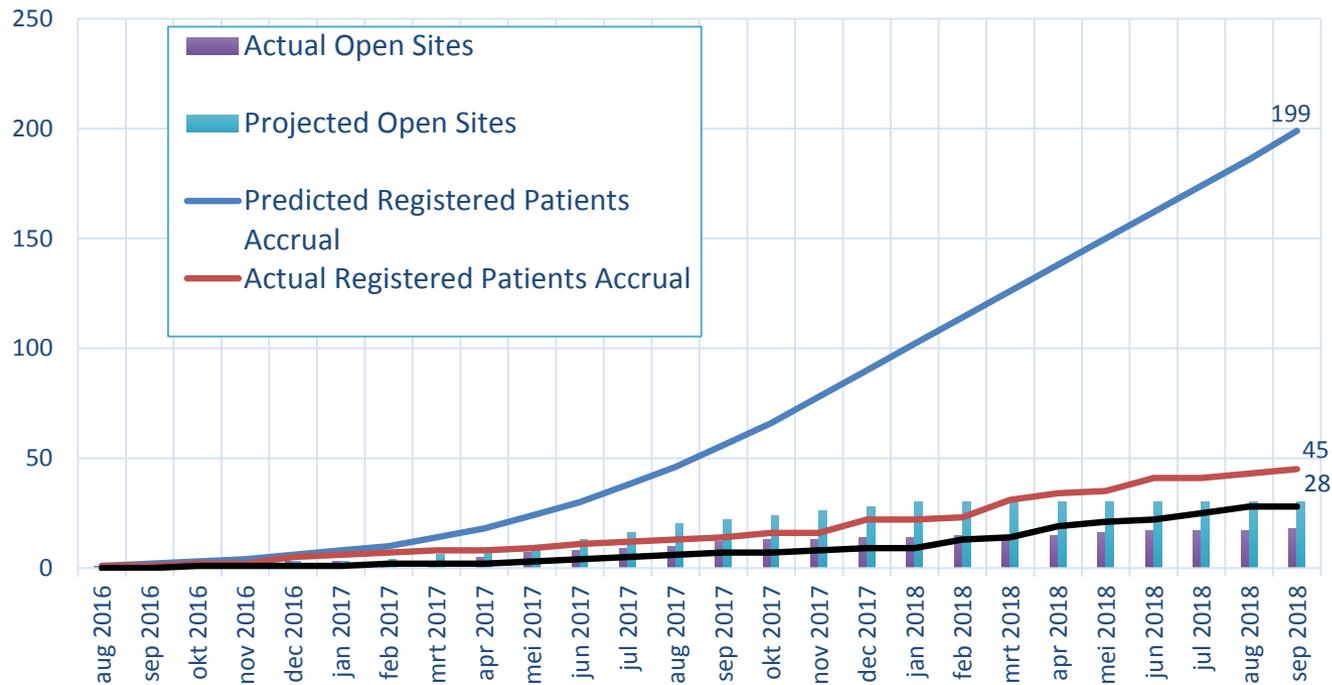
Sub-Studies

- Feasibility Assessment (N=50)
 - Recruitment rate
 - Logistical practicalities
 - Contamination (patients who seek SABR/SRS outside of the trial)
- Thoracic SABR Safety (N=20)
 - Grade 3-5 Radiation Induced Pneumonitis
 - Other grade 3-5 RT adverse events

Status SARON trial

18 sites open
45 patients recruited
(28 randomised;
4 pending)

Predicted and Actual Accrual and No. of sites opened (as of 20/09/2018)



Discussie:
IO
toevoegen?

EORTC-RP-1822 OligoCare

- A **pragmatic observational cohort study** to evaluate radical radiotherapy for **oligo-metastatic cancer** patients
- Objectives
 - Identifying patient, tumor, diagnostic and treatment characteristics influencing safety and efficacy
 - Evaluating patterns-of-care and patterns-of-outcome
- First primary diseases: lung, breast, prostate and colorectal cancer
- Study coordinators:
 - Matthias Guckenberger, University Hospital of Zurich
 - Piet Ost, University Hospital Ghent

OligoCare – selection criteria

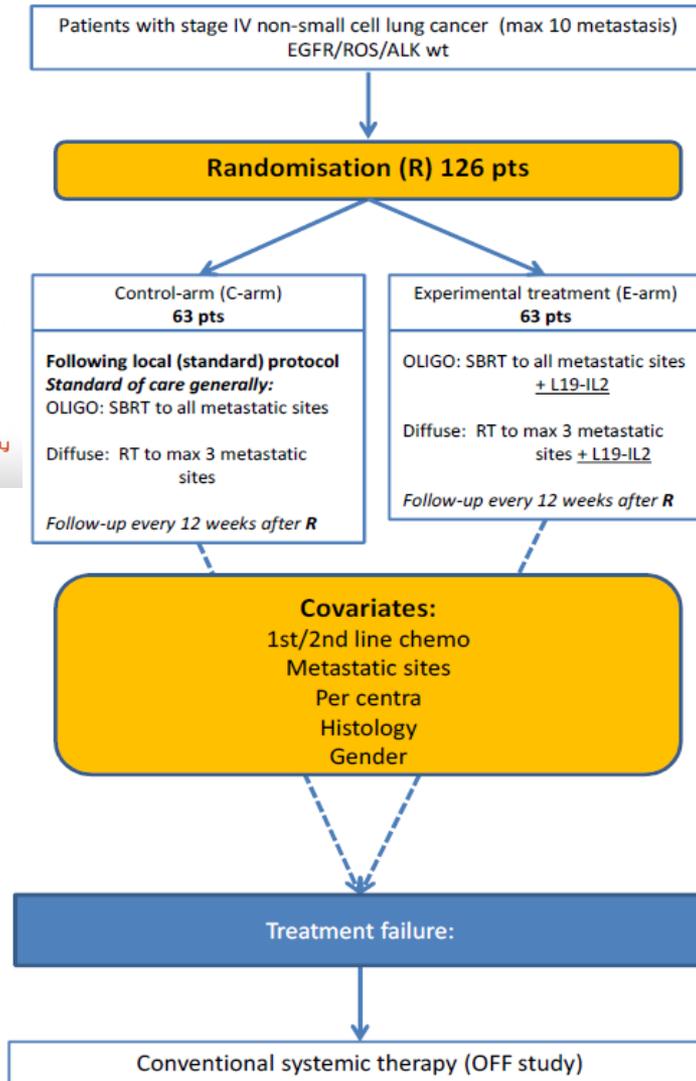
- Oligometastatic disease can be diagnosed synchronously or metachronously

No upper limit of metastases

- All cancer lesions are treated with radical intent
- No restrictions with respect to prior surgical, locally ablative, radiotherapy and systemic treatments performed
- Radical radiotherapy must be a component of treatment



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733008



Outcome analysis

Primary endpoint
 Progression free survival (PFS)

Secondary endpoints

- Overall survival
- QoL
- Abscopal response
- Subgroup analyse
- Associative biomarker studies:
 - EDB expression
 - Immune monitoring
 - Radiomics
 - Hypoxia status
 - Non-synonymous mutational burden
 - Stool collection
 - Research Biopsy

ongoing clinical trials: WE NEED LONG TERM OUTCOME DATA

- Duidelijke definitie oligometastasen nodig
 - Voorstel EORTC definitie hanteren
- Cave N2-N3 ziekte
- Stadiering++ (PET / MRI brein)
- Eindpunt PFS “soft”
- ASTRO: fase II studies ook pos voor OS
- Betere patiënten selectie nodig, rol immunotx in multi-modaliteitstherapie? Biomarker?

