UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Trattamenti locali nel NSCLC metastatico

Integrazione con i trattamenti sistemici

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DICHIARAZIONE

Relatore: Massimo Di Maio

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
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- Partecipazione ad Advisory Board: **Eli Lilly Italia, Boehringer ingelheim**
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- Altro: **NIENTE DA DICHIARARE**

Tradizionalmente…

…per un paziente con **NSCLC metastatico**, l'oncologo medico sa di poter contare sul **trattamento locale**, allo scopo di migliorare la **qualità di vita** e ridurre i **sintomi**, per:

- Metastasi cerebrali
- Emottisi
- Dolore
- Compressione delle vie aeree…

Hoegler D.
Radiotherapy for palliation of symptoms in incurable cancer.
Curr Probl Cancer 1997; 21(3):129-83.

UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Linee guida

NEOPLASIE DEL POLMONE

Edizione 2014

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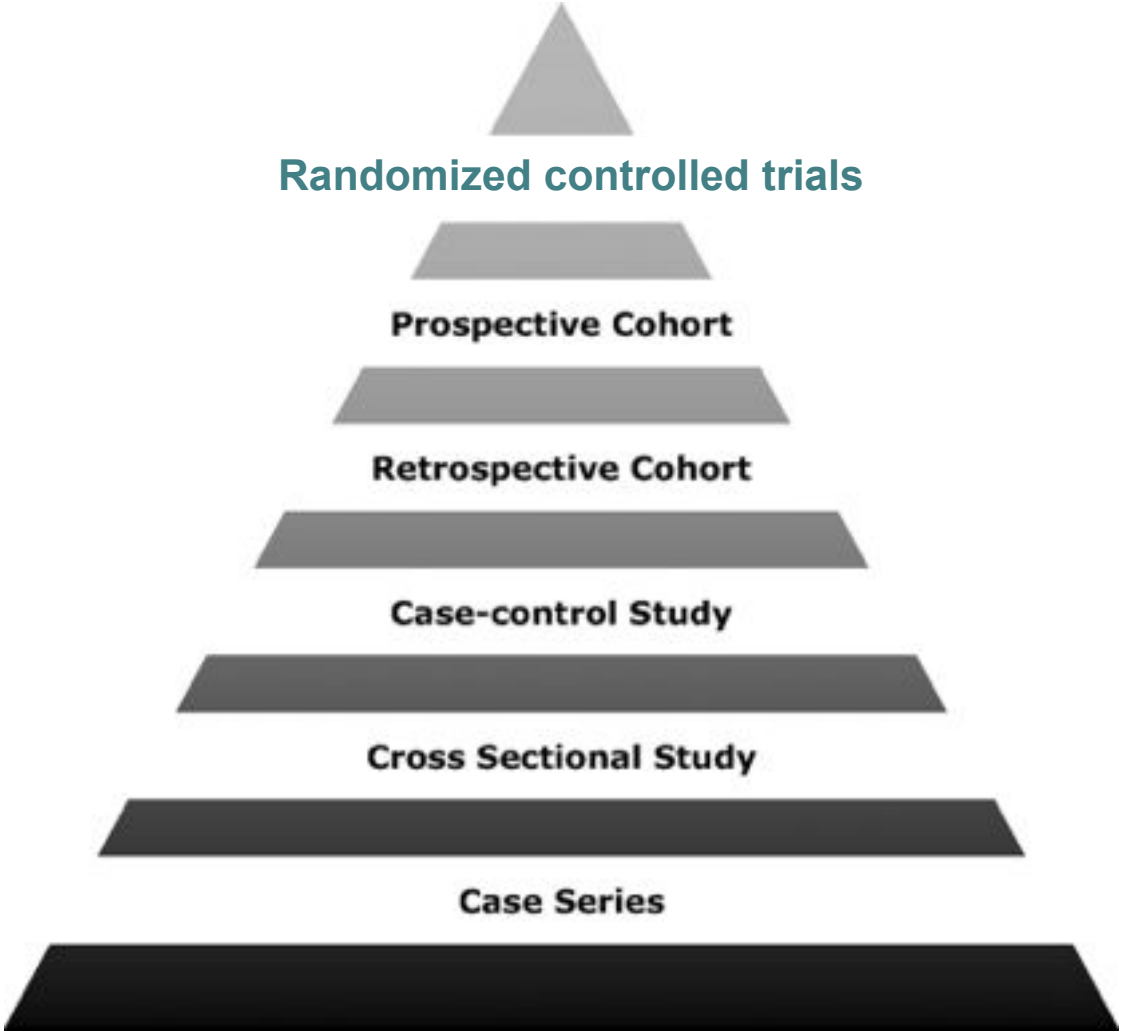
7. NSCLC – Trattamento della malattia avanzata

In sintesi quindi:

- Nei pazienti che presentino mutazioni attivanti di *EGFR*, gli inibitori di TKI attualmente autorizzati e rimborsati per l'impiego nella pratica clinica (gefitinib ed erlotinib) possono essere considerati il trattamento di prima linea.
- In assenza di mutazione attivante di *EGFR*, o nei pazienti in cui lo stato mutazionale di *EGFR* non sia noto, i regimi a due farmaci contenenti cisplatino per 4-6 cicli costituiscono la terapia di scelta nella prima linea.
- Nei pazienti con NSCLC avanzato ad istologia diversa dalla squamosa, la combinazione cisplatino-pemetrexed o l'impiego di bevacizumab in associazione alla chemioterapia nei pazienti eleggibili possono essere valutati come opzioni terapeutiche di prima scelta.
- La terapia di mantenimento è un'opzione terapeutica da discutere con il paziente, tenendo comunque presente che, a maggio 2014, l'unico farmaco rimborsato in Italia per tale indicazione è il pemetrexed dopo combinazione di cisplatino e pemetrexed.
- La terapia radiante svolge un ruolo di pura palliazione, peraltro estremamente importante nel controllo delle metastasi cerebrali, delle sindromi mediastiniche da ostruzione della cava superiore, nelle metastasi ossee e in particolare nelle compressioni midollari da metastasi vertebrali.

Evidence based medicine: la piramide dell'evidenza



Ho P M et al. Circulation 2008;118:1675-1684

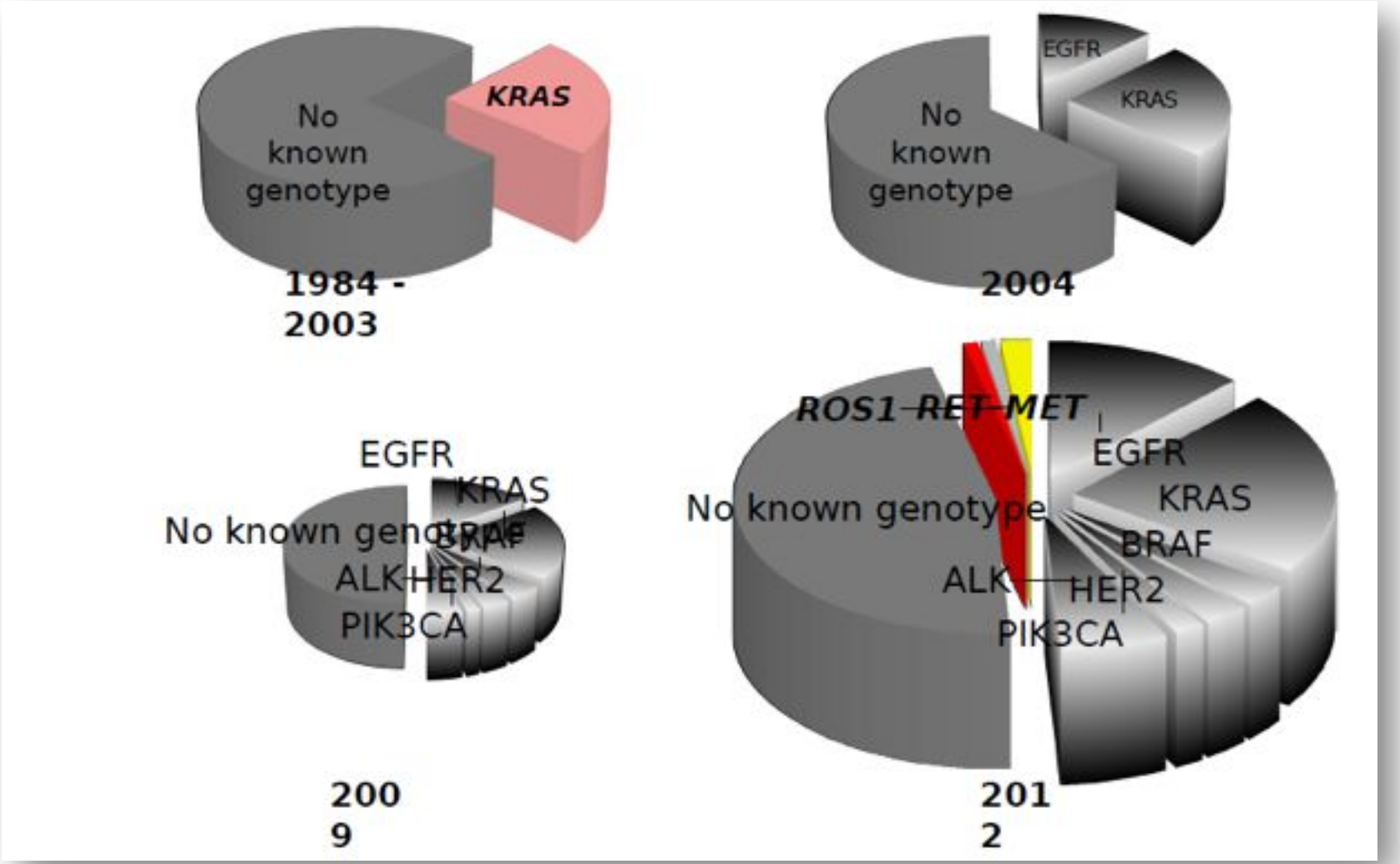
Whether local therapy in the setting of metastatic cancer can affect overall survival is a matter of debate in oncologic practice.

Jabbour SK

Are We Expanding Oligometastatic NSCLC Using Advanced Radiotherapeutic Modalities?

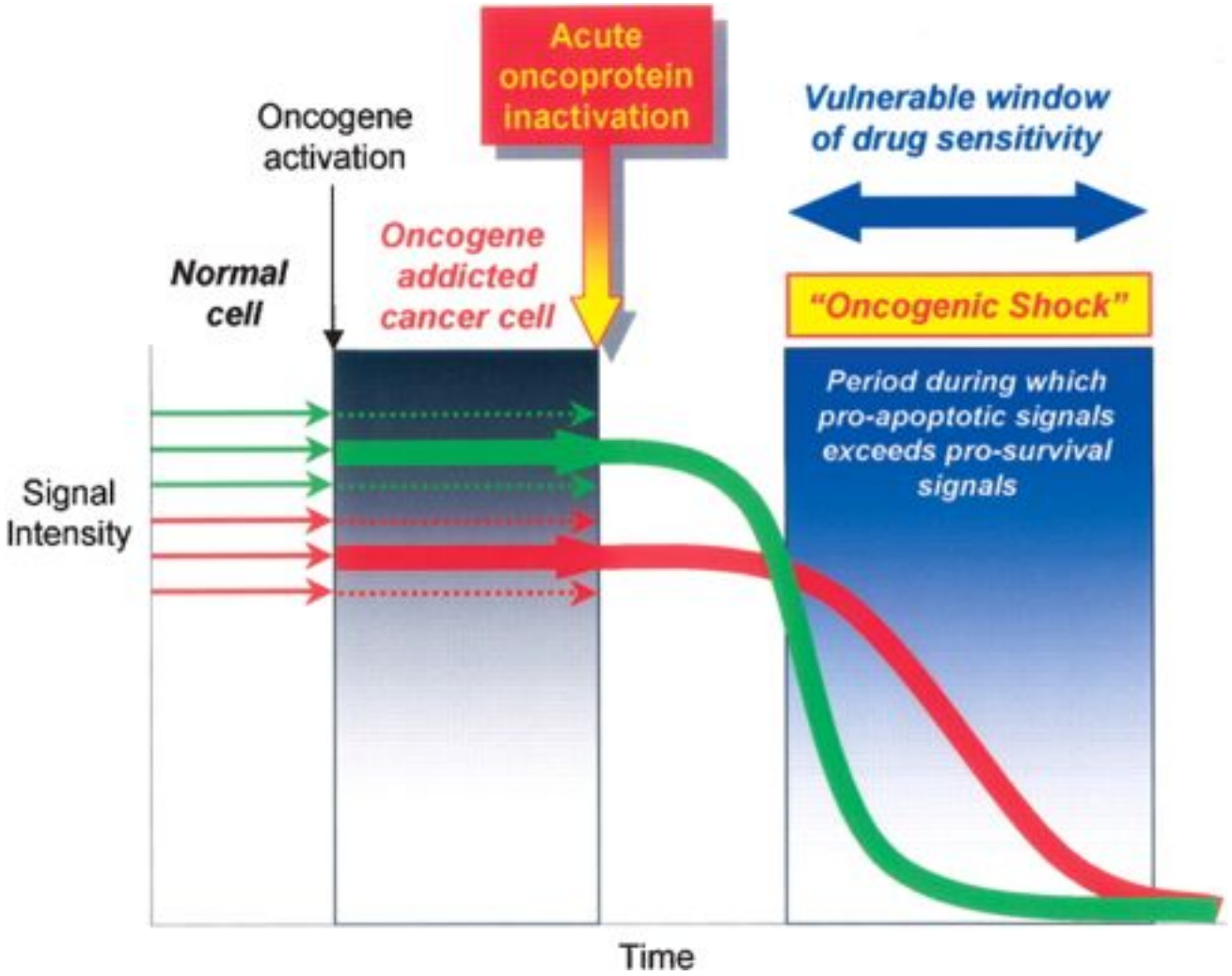
J Clin Oncol 2014 [Epub ahead of print October 27]

Non tutti i NSCLC sono uguali…



Matthew Meyerson. What can we learn from lung cancer sequencing? Sidney, WCLC 2013

Relationship between oncogene addiction and oncogenic shock



Sharma SV, Settleman J. Genes Dev. 2007;21:3214-3231

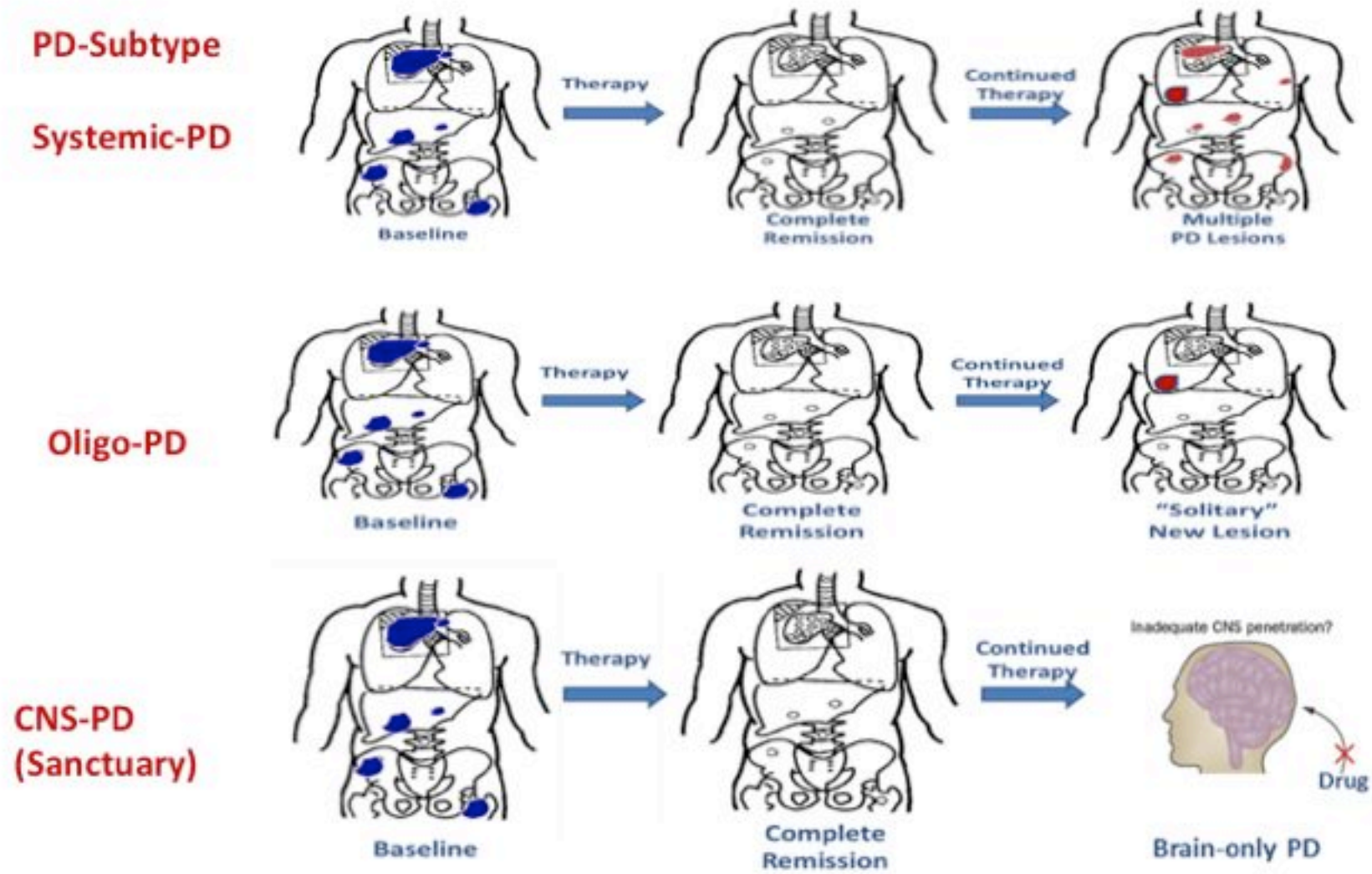
Approach to the management of *EGFR* mutant NSCLC with progression on first-line EGFR TKI

There is not one uniform approach to treating resistance

Sacher, Jänne & Oxnard Cancer 2014

Pasi Janne, ESMO 2014

Not all Patients with Acquired Resistance to Targeted TKIs are Created Equal: Three PD Subtypes



Gandara D. - Educational ASCO 2013

Potential strategies at the time of clinical progression for oncogene addicted NSCLC

- Switch to chemotherapy
- Add chemotherapy
- Continue EGFR or ALK TKIs beyond progression
  - *Local therapies*
- Different targeted therapy based on specific resistance mechanism

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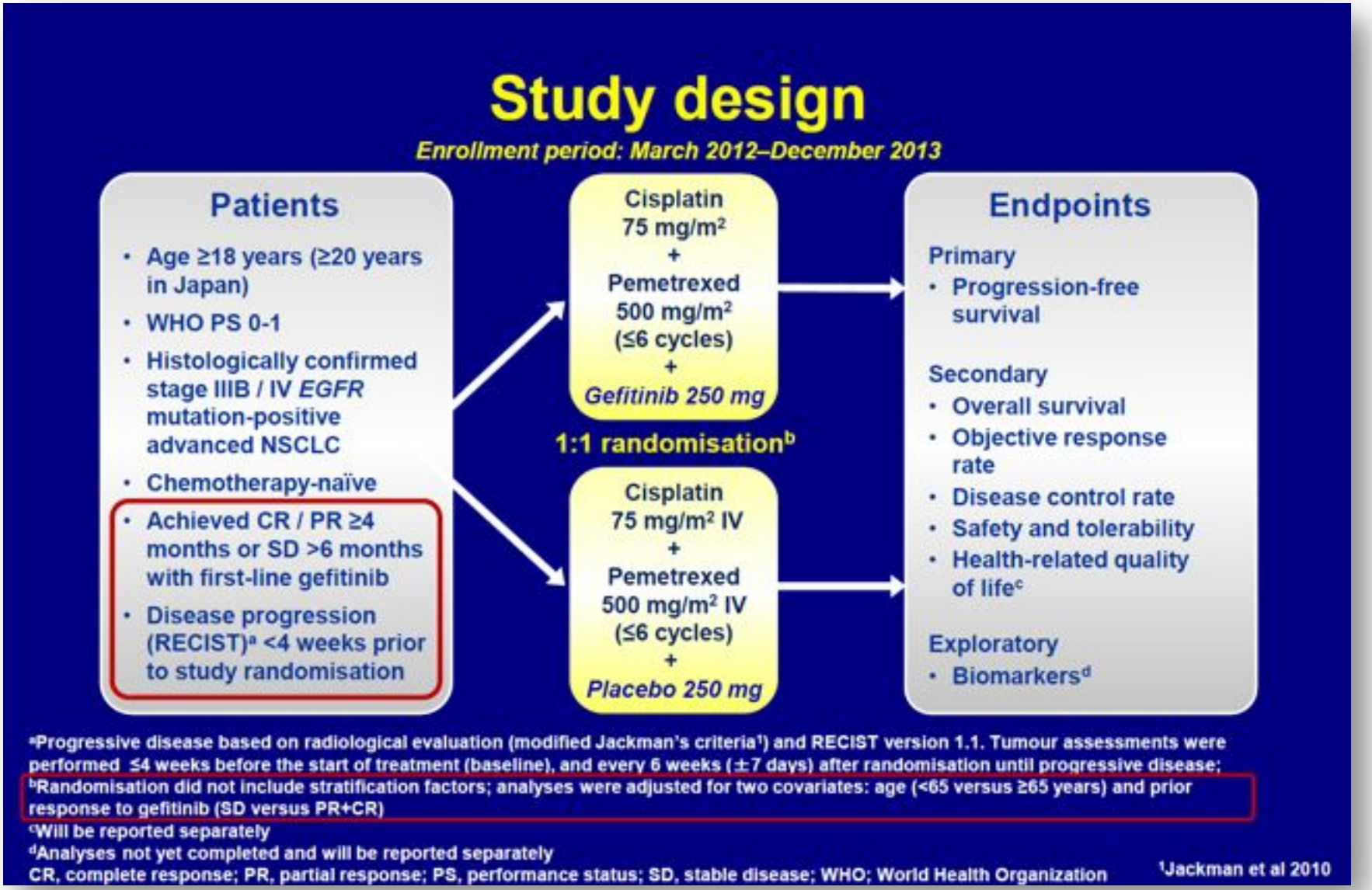
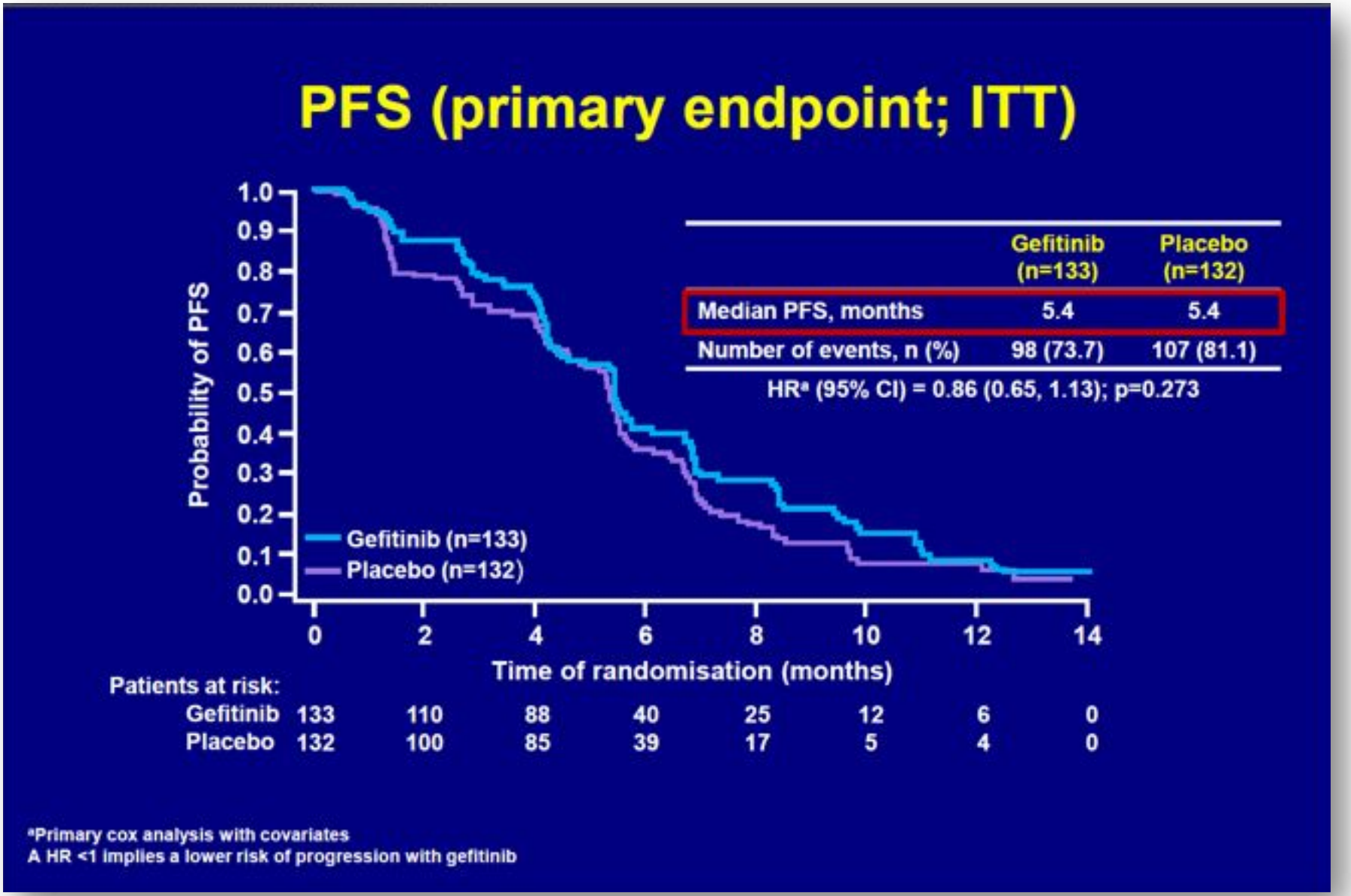
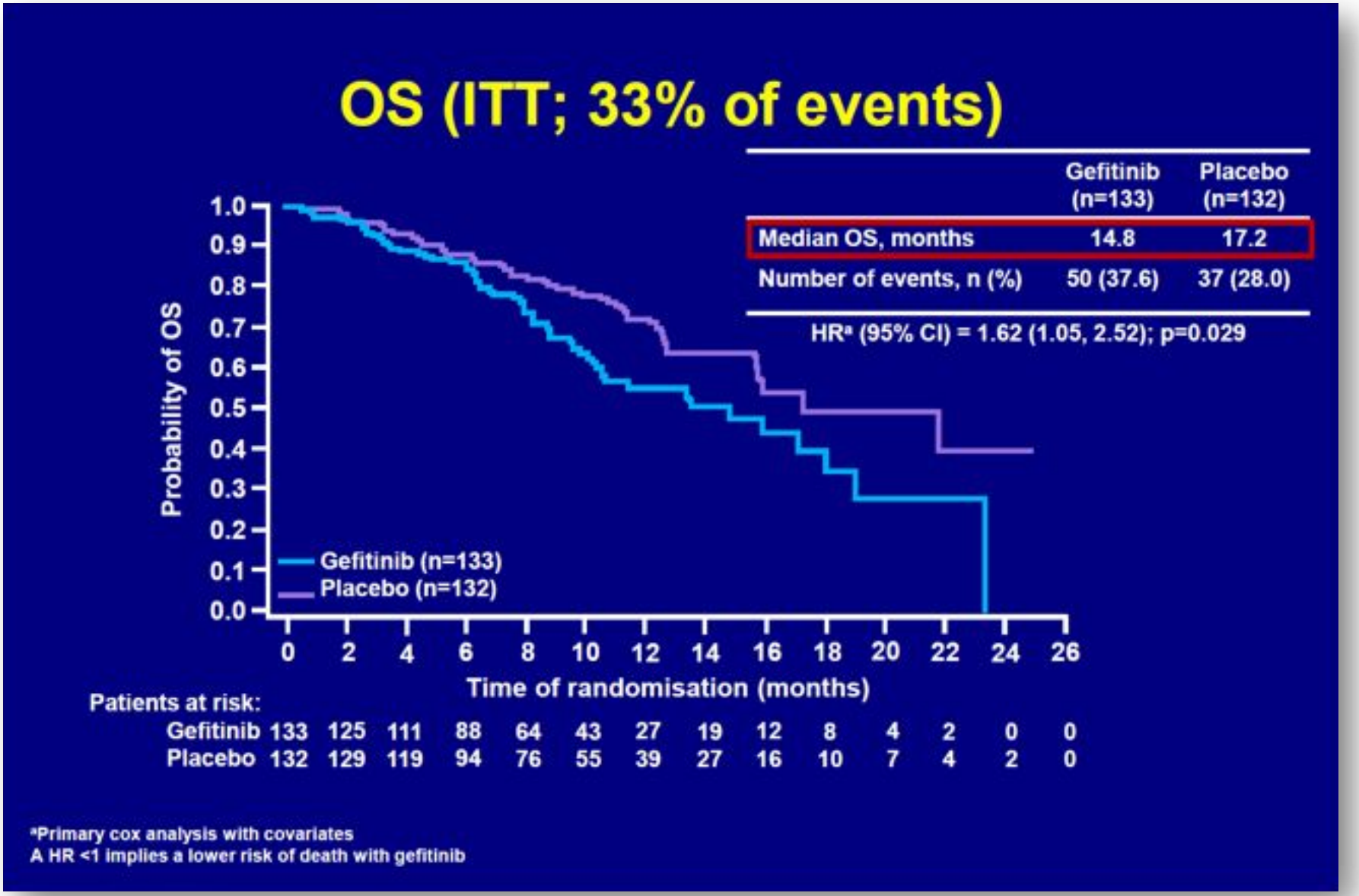
IMPRESS



Toni Mok, ESMO 2014 (abstract LBA2_PR)



Toni Mok, ESMO 2014 (abstract LBA2_PR)



Toni Mok, ESMO 2014 (abstract LBA2_PR)

Potential strategies at the time of clinical progression for oncogene addicted NSCLC

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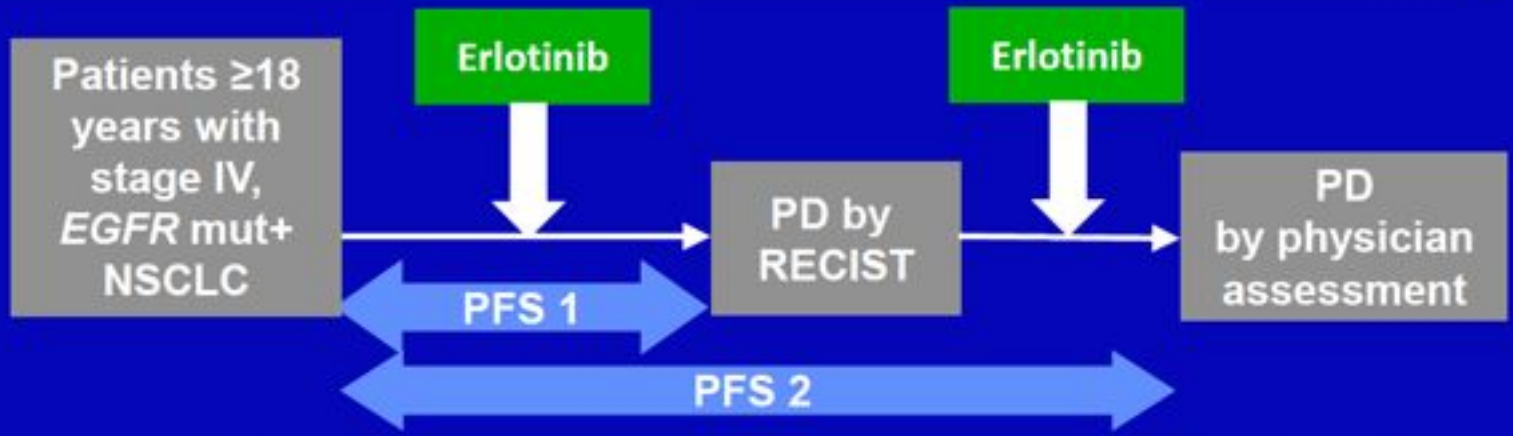
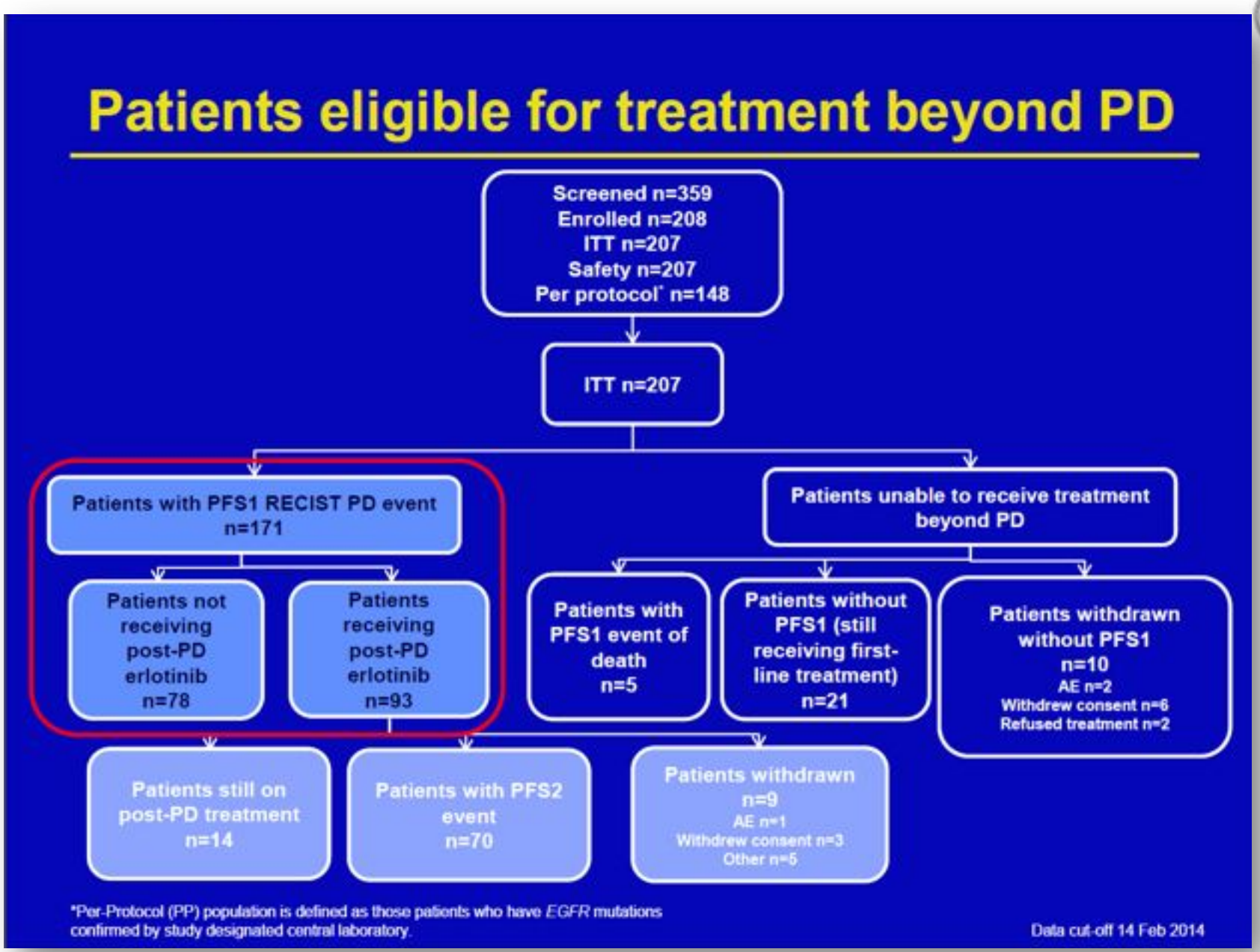
ASPIRATION
Study design



- Inclusion criteria: patients ≥18 years with confirmed stage IV or recurrent NSCLC with exon 18–21 mutations (except T790M) with measurable disease and ECOG PS 0–2
- Exclusion criteria: T790M mutations, prior chemotherapy, prior treatment with anti-HER agents, uncontrolled systemic conditions, pre-existing lung conditions, warfarin use
- Primary endpoint: PFS1 (time to RECIST PD or death)
- Secondary endpoints:
  - PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD)
  - PFS1 in exon 19 deletion/L858R subsets
  - OS
  - ORR/DCR/BOR
  - safety

BOR = best overall response, ECOG PS = Eastern Cooperative Oncology group performance status, DCR = disease control rate mut+ = mutation positive
ORR = objective response rate OS = overall survival, PFS = progression-free survival

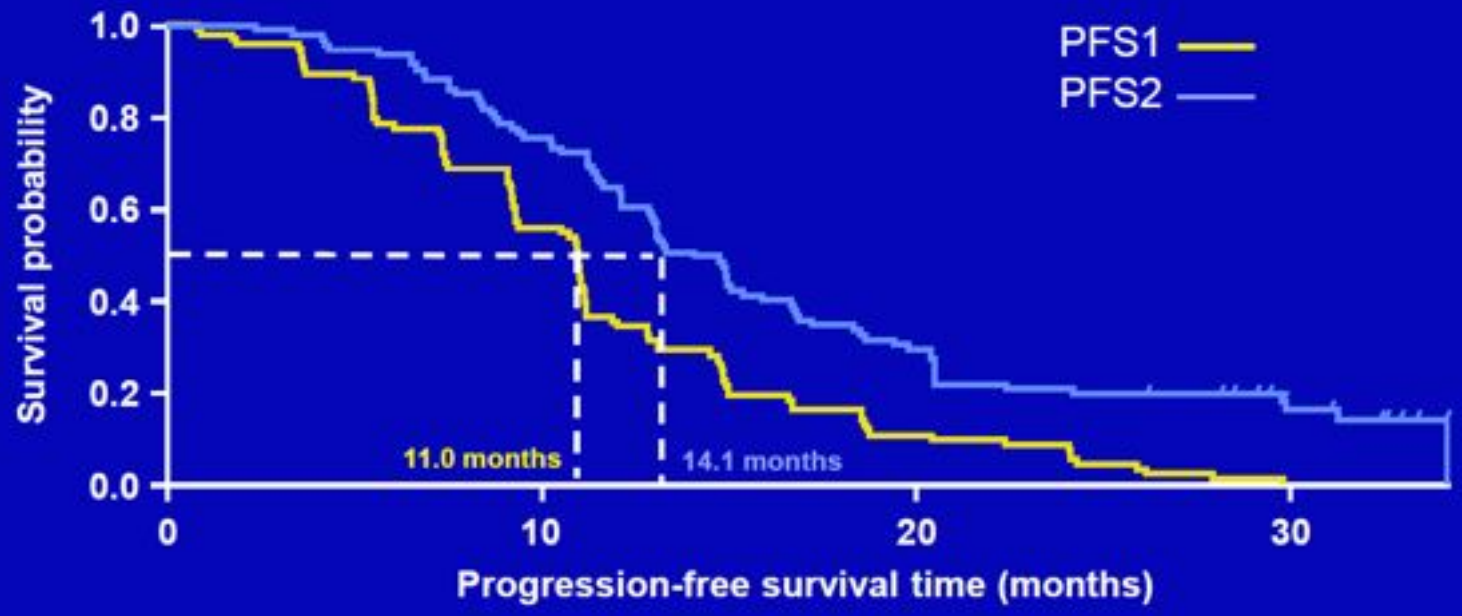
Keunchil Park, ESMO 2014 (Abstract 1223O)



Keunchil Park, ESMO 2014 (Abstract 1223O)

Continuation of erlotinib post-PD extended PFS

- In patients receiving post-PD erlotinib (n=93)
  - PFS1 was 11.0 months
  - the difference between PFS1 and PFS2 was an additional 3.1 months



Keunchil Park, ESMO 2014 (Abstract 1223O)

Local ablative therapy of oligoprogressive disease in oncogene-addicted NSCLC treated with TKI

- Patients with metastatic ALK+ NSCLC treated with crizotinib (n=38) and EGFR-mut NSCLC treated with erlotinib (n=27)

- A subset of patients with either non-leptomeningeal CNS and/or ≤4 sites of extra-CNS progression (**oligoprogressive disease**) suitable for **local ablative therapy** received either **radiation** or **surgery** to these sites and continued on the same TKI.

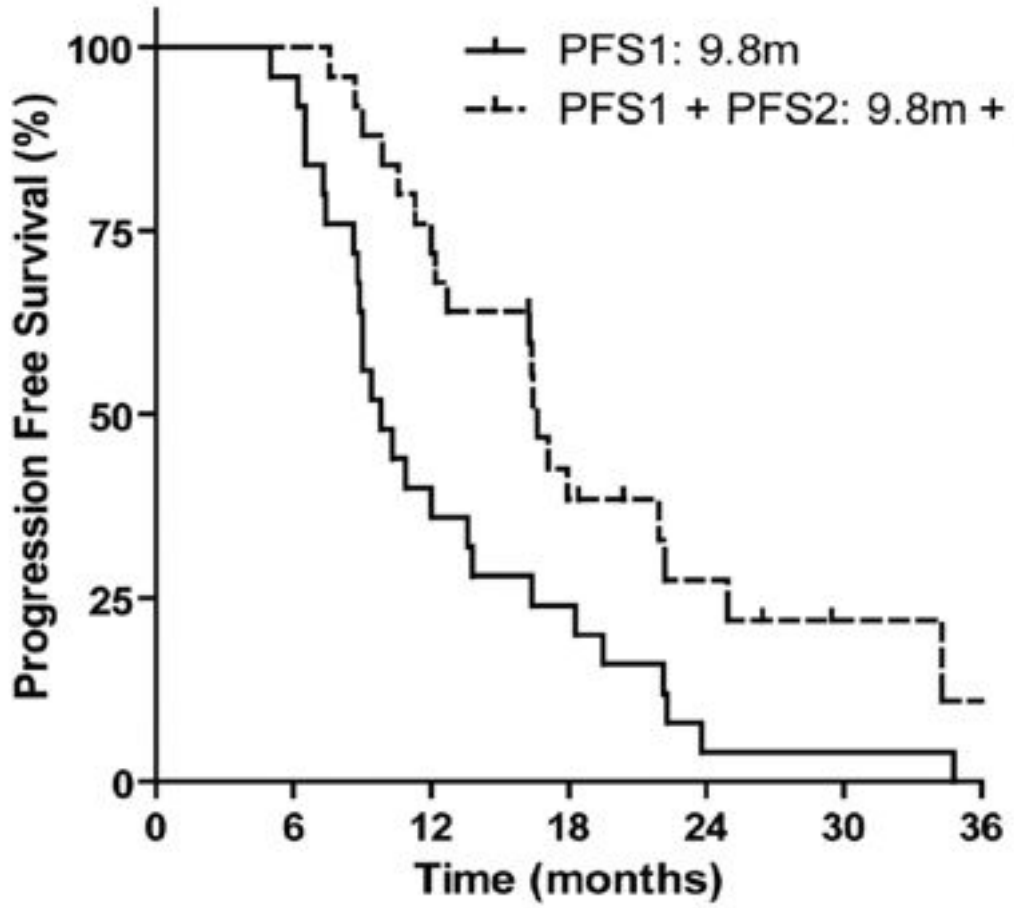
Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.

Sites of oligoprogression and LAT treatment modality

	No. PTS	SRS	WBRT	SBRT	XRT	Surgery
CNS as site of first progression						
Lesions < 4	6	6		-	-	-
Lesions ≥ 4	7	1	6	-	-	-
eCNS as site of first progression						
Bone	7	-	-	5	2	-
Lung	7	-	-	7	-	-
Lymph node	2	-	-	2	-	-
Adrenal	2	-	-	1	-	1
Liver	1	-	-	1	-	-

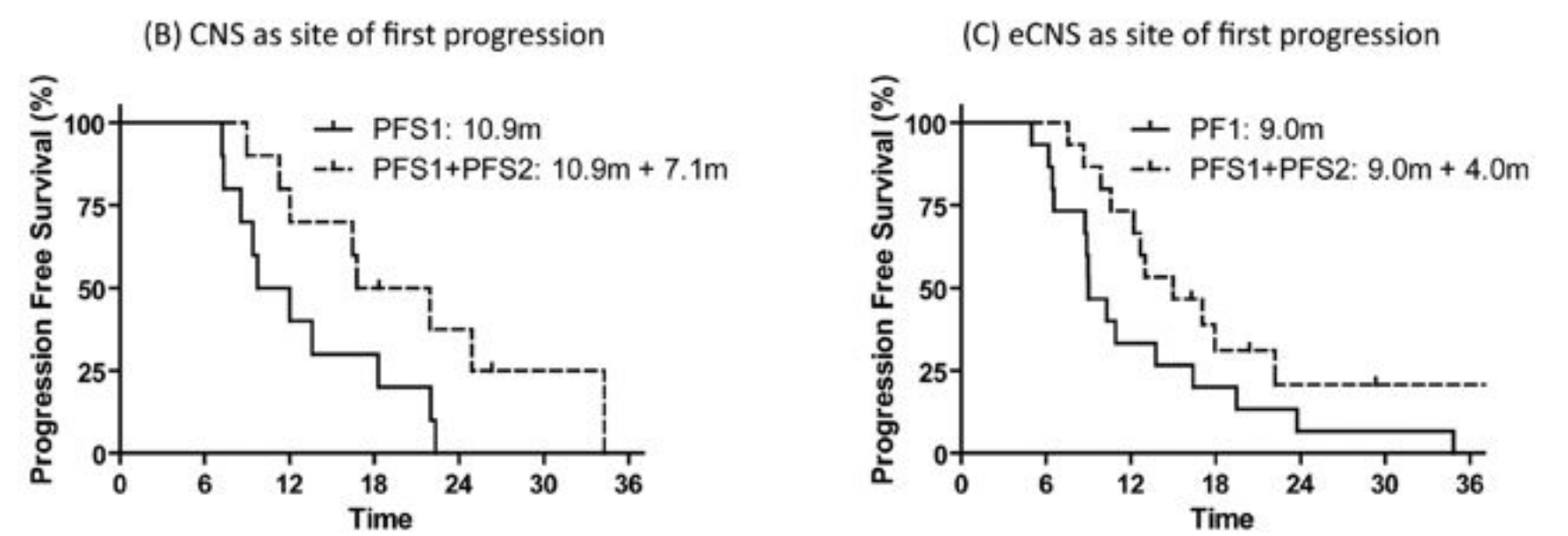
Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.

(A) PFS of all patients treated with LAT and continuation of TKI therapy



N = 25 patients

Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.



N = 10 patients

N = 15 patients
Including 3 patients with simultaneous CNS + eCNS progression

Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.

Based on the practices within this study, suggested criteria for considering local ablative therapy of oligoprogressive disease and treatment with a TKI beyond progression include:
1. *ALK* positive or *EGFR* mutant metastatic NSCLC
2. Relevant TKI (e.g. crizotinib or erlotinib) is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as: **a.** CNS progression without leptomeningeal disease amenable to WBRT, SRS or surgical resection **b.** Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT or surgical resection

Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.

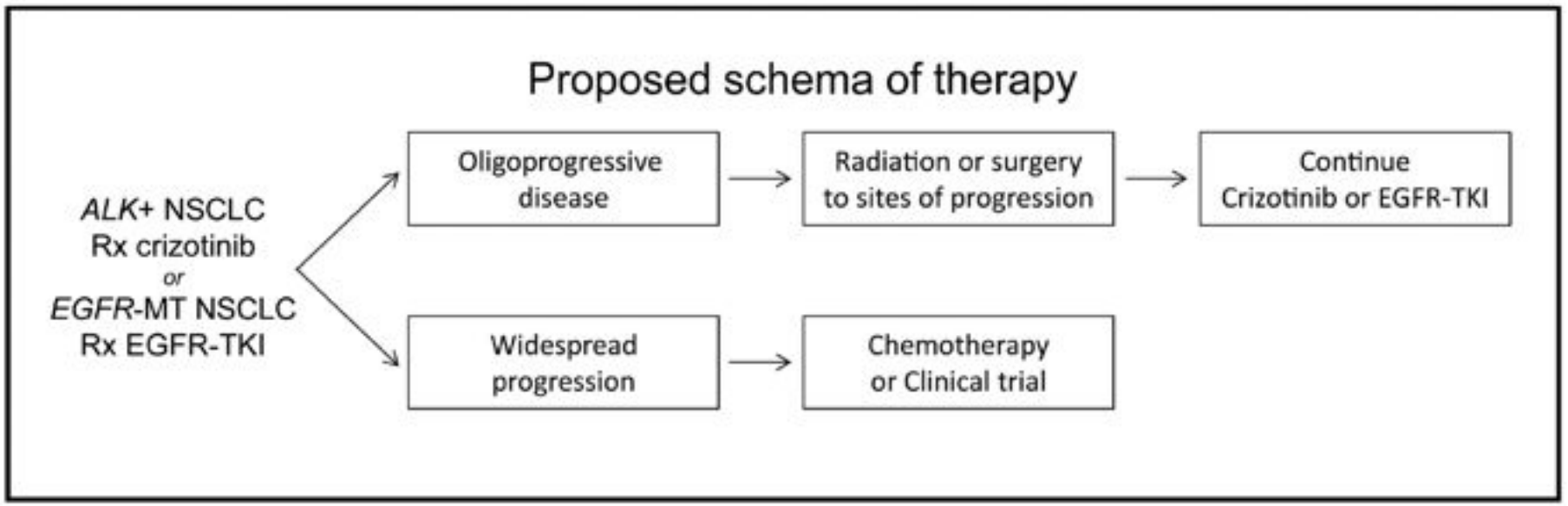


Figure 2.
Proposed schema for incorporating local ablative therapy (LAT) into therapy at time of first progression with *ALK*+ or *EGFR*-MT NSCLC patients treated with TKI therapy.

Weickhardt AJ et al, J Thorac Oncol. 2012 December ; 7(12): 1807–1814.

Stereotactic Radiotherapy for Extra-CNS Oligoprogressive Disease in ALK+ Lung Cancer Patients on Crizotinib

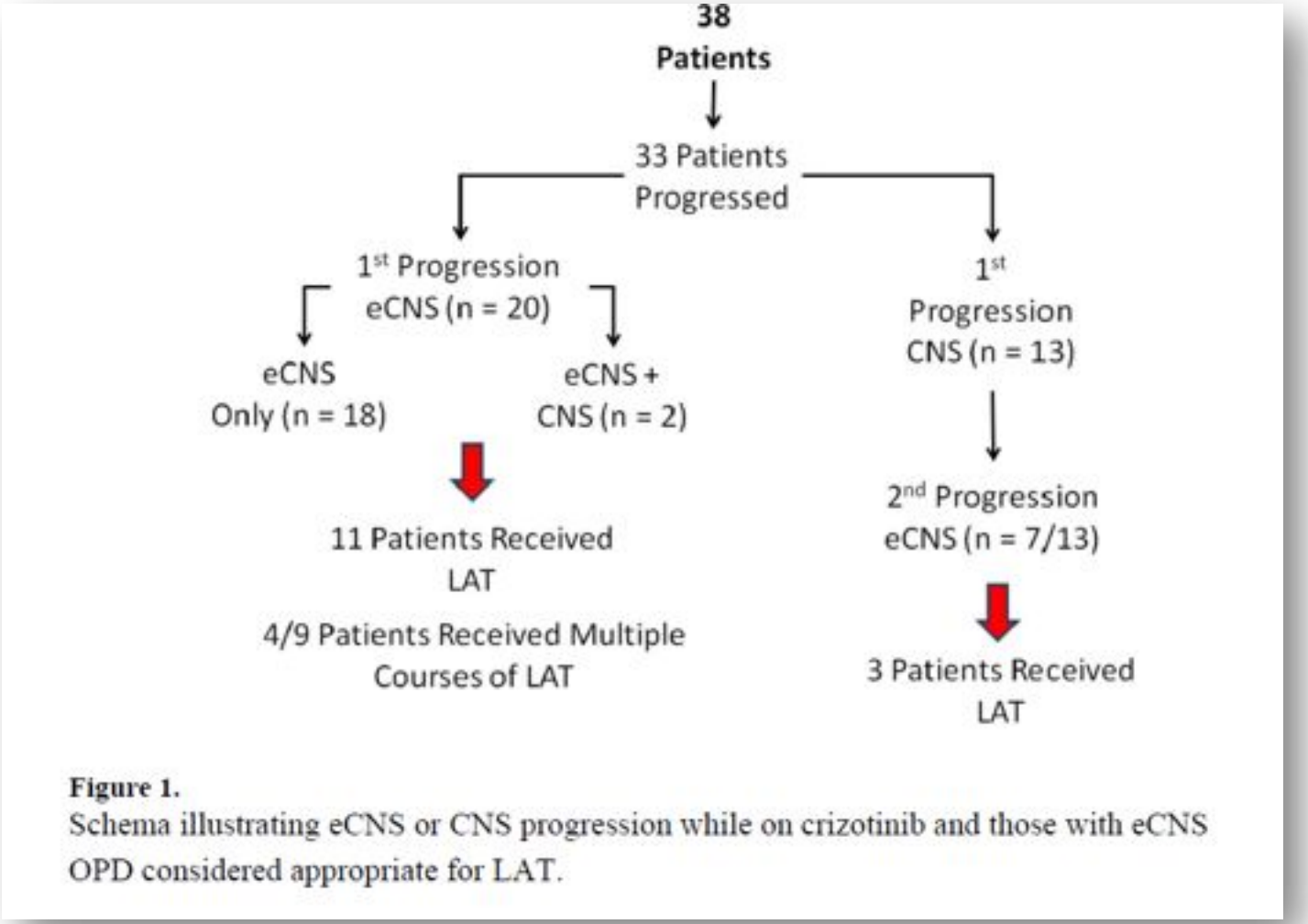


Figure 1.
Schema illustrating eCNS or CNS progression while on crizotinib and those with eCNS OPD considered appropriate for LAT.

Gan GN et al, Int J Radiat Oncol Biol Phys. 2014 March 15; 88(4): 892–898.

Stereotactic Radiotherapy for Extra-CNS Oligoprogressive Disease in ALK+ Lung Cancer Patients on Crizotinib

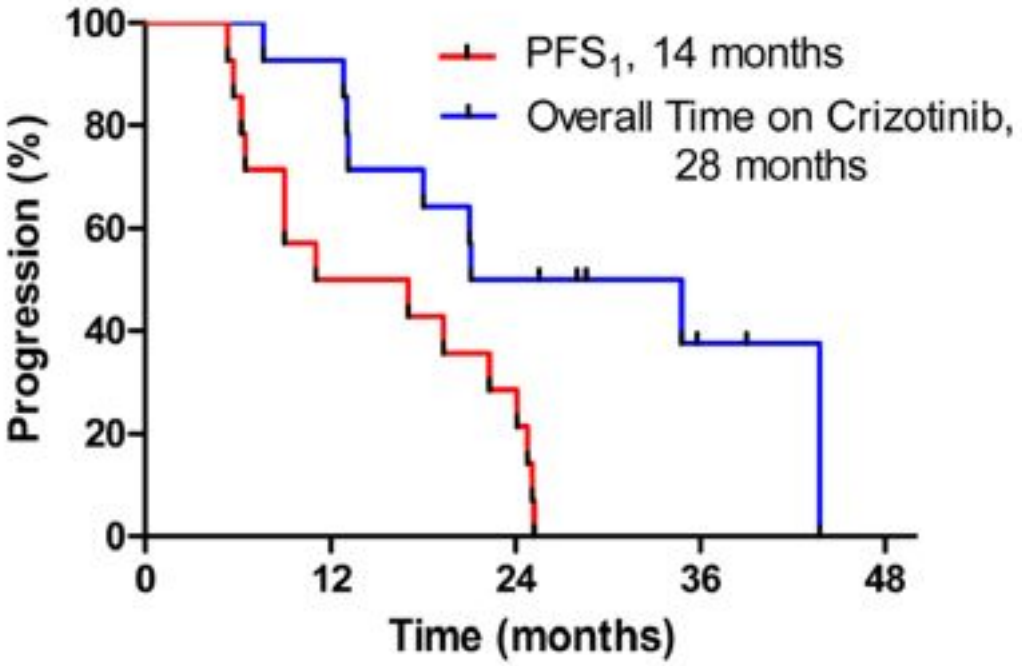
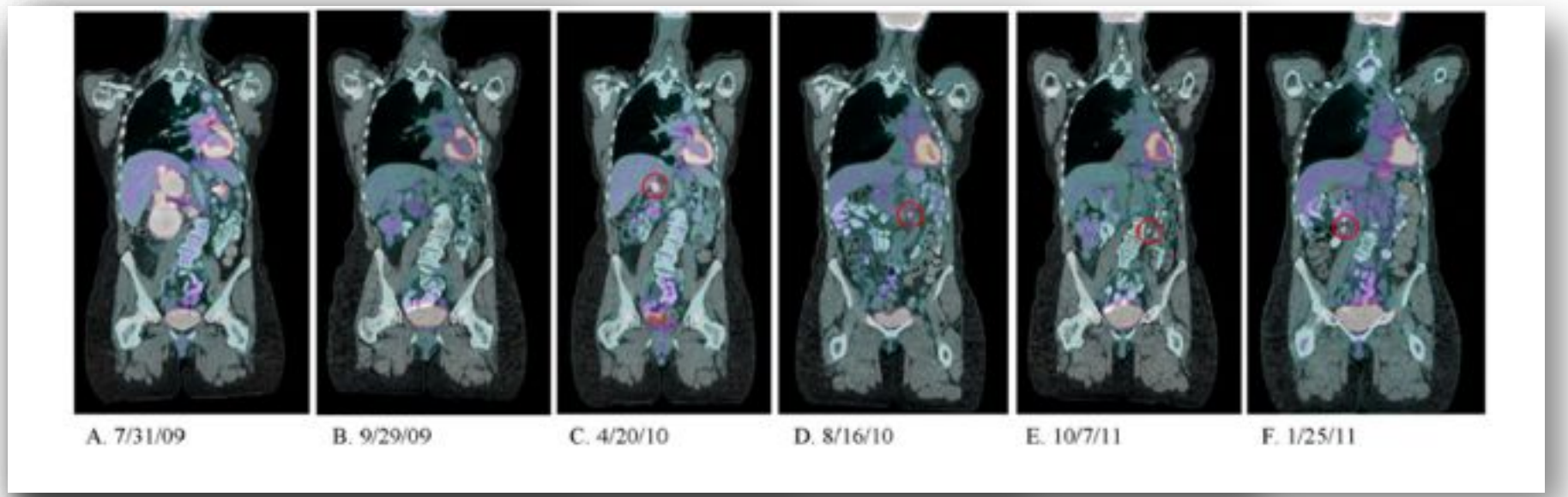


Figure 3.
Evaluating KM median PFS1 and overall time on crizotinib in patients who received eCNS LAT. Time is measured from start of crizotinib to time of first progression or maximum time while on crizotinib.

Gan GN et al, Int J Radiat Oncol Biol Phys. 2014 March 15; 88(4): 892–898.

Stereotactic Radiotherapy for Extra-CNS Oligoprogressive Disease in ALK+ Lung Cancer Patients on Crizotinib



Gan GN et al, Int J Radiat Oncol Biol Phys. 2014 March 15; 88(4): 892–898.

Potential strategies at the time of clinical progression for oncogene addicted NSCLC

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Next Gen EGFR TKIs: Mutant Specific Agents Emerge

IC50 nM	EGFR WT	EGFR Mut	EGFR L858R/ T790M
Erlotinib	449	3.2	2253
HM61713	2225	9	10
CO-1686	4275	7	33
AZD 9291	480	17	15

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Presented By Thomas Lynch at 2014 ASCO Annual Meeting

Preliminary Efficacy Comparison

	RR T790M +	RR T790M -	PFS
Afatanib/Cetux	32%	28%	4.66
HM 61713	29%	12%	4.34*
CO-1686	58%	Inc.	↑
AZD 9291	65%	22%	↑

25

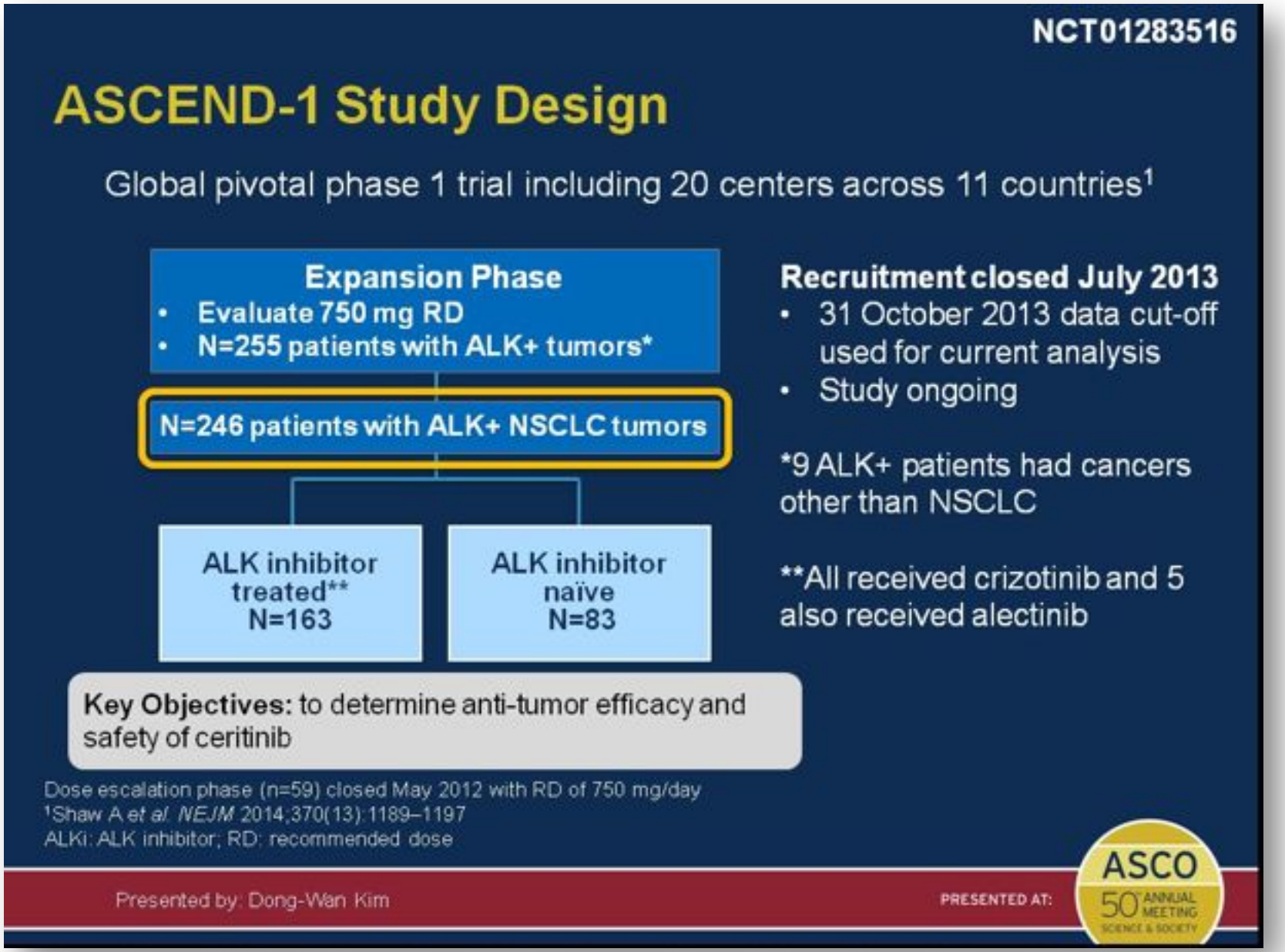
Presented By Thomas Lynch at 2014 ASCO Annual Meeting

Toxicity Comparison

Any Grade (Gr3)	Diarrhea	Rash	ILD/SOB *	Inc BS	QTc
Erlotinib	57%	80%	1%	NR	NR
Afatanib/Cetux	71%	97%	NR	NR	NR
CO-1686	23%	4%	NR	55% (22%)	15% (7%)
AZD 9291 80mg	20%	27%	3%	1%	1%
HM 61713	21%	24%	10%*	0%	3%

26

Presented By Thomas Lynch at 2014 ASCO Annual Meeting



Presented By Dong-Wan Kim at 2014 ASCO Annual Meeting

Overall Response Rate in ALK+ NSCLC Patients Treated with Ceritinib (750 mg daily)

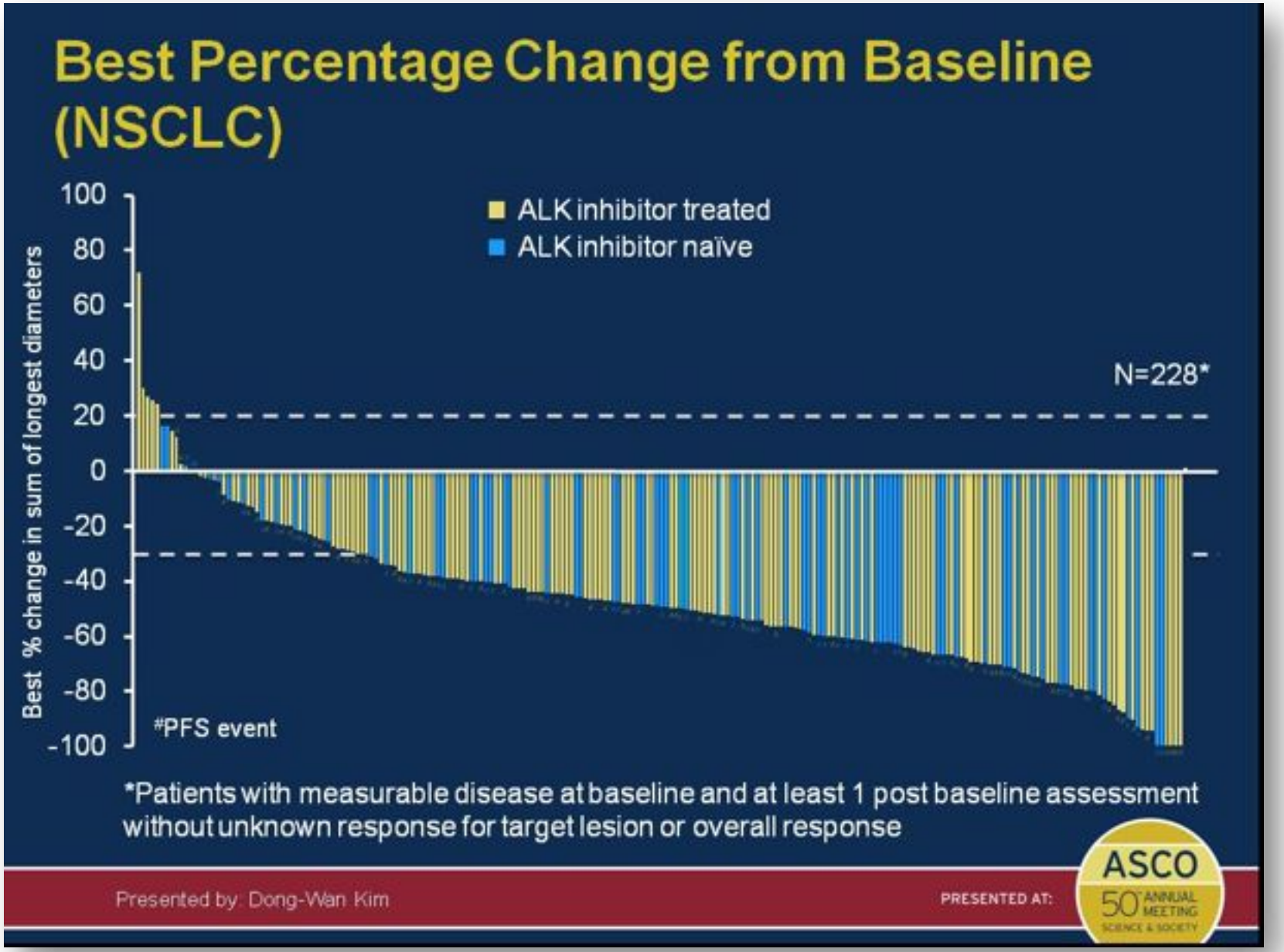
Efficacy Parameter (RECIST 1.0)	ALK inhibitor treated (N=163)	ALK inhibitor naïve (N=83)	All (N=246)
Complete Response (CR), n (%)	2 (1.2)	1 (1.2)	3 (1.2)
Partial response (PR), n (%)	87 (53.4)	54 (65.1)	141 (57.3)
Stable Disease (SD), n (%)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive Disease (PD), n (%)	16 (9.8)	0	16 (6.5)
Unknown*, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Overall Response Rate (ORR), n (%) [95% CI]	89 (54.6) [46.6, 62.4]	55 (66.3) [55.1, 76.3]	144 (58.5) [52.1, 64.8]

*No post-baseline assessment done, or the post-baseline assessment had overall response that was not CR, PR, SD or PD

Presented by: Dong-Wan Kim

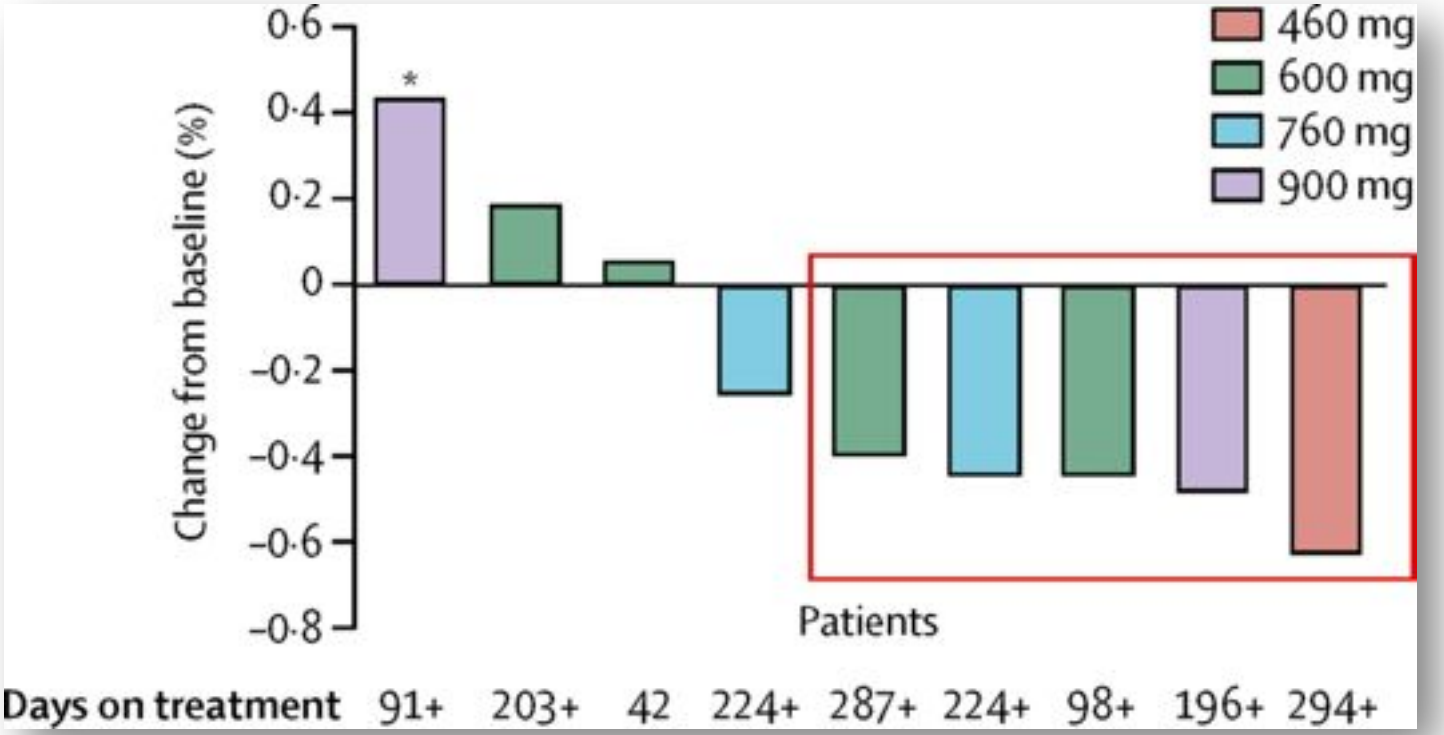
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Dong-Wan Kim at 2014 ASCO Annual Meeting



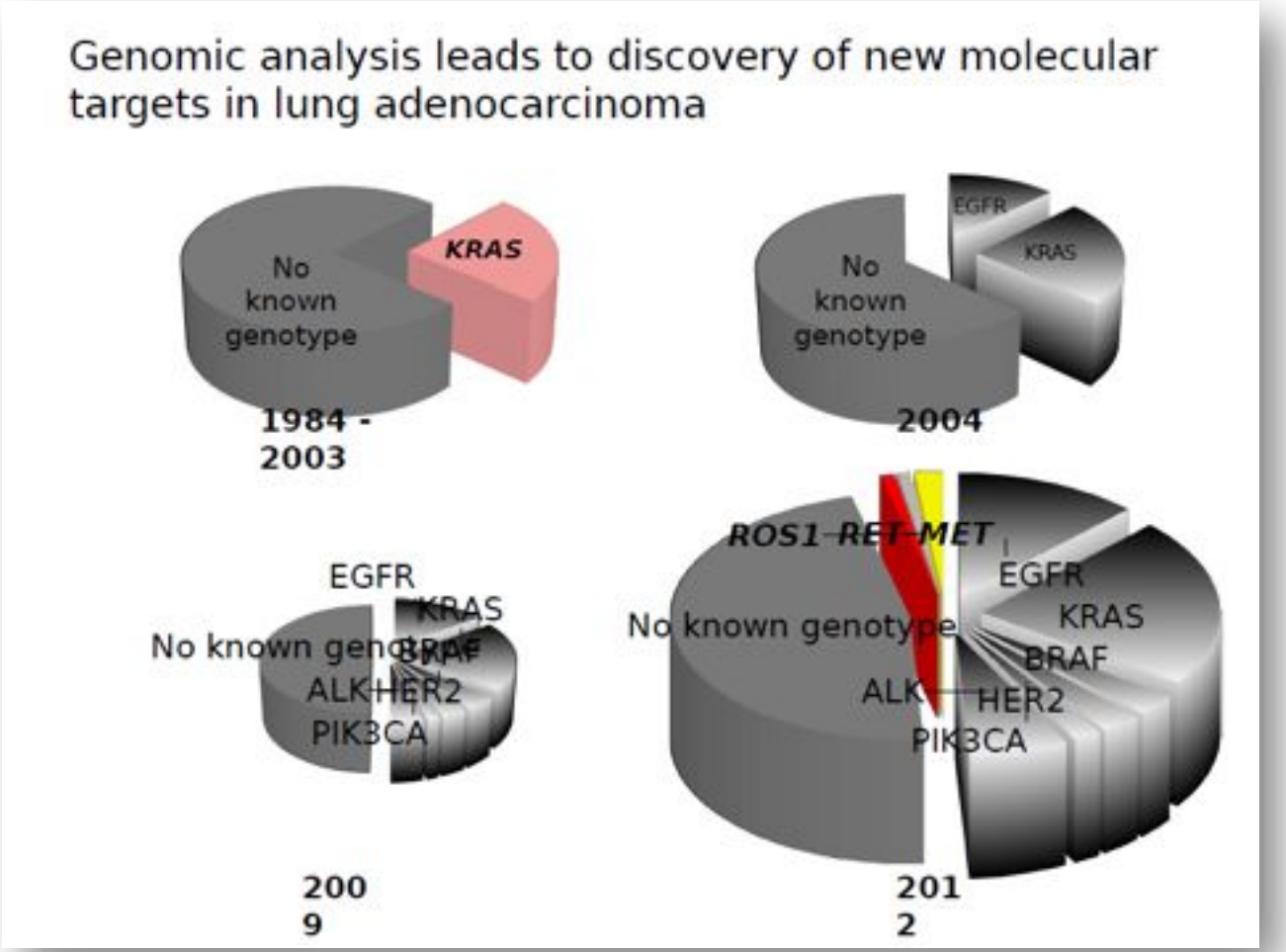
Presented By Dong-Wan Kim at 2014 ASCO Annual Meeting

Activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant *ALK*-rearranged NSCLC



Gadgeel SM, Lancet Oncology 2014; 15(10):1119-1128

…ma i tumori oncogene-addicted trattabili con farmaci target, al momento, sono una minoranza!



Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

Puneeth Iyengar, Brian D. Kavanagh, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, Paul A. Bunn, Hak Choy, and Robert Timmerman

See accompanying article doi: 10.1200/JCO.2014.58.5539

Puneeth Iyengar, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, Hak Choy, Robert Timmerman, University of Texas Southwestern Medical Center, Dallas, TX; Brian D. Kavanagh, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, and Paul A. Bunn, University of Colorado School of Medicine, Aurora, CO.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2014.56.7412

A B S T R A C T

Purpose
Patients with stage IV non–small-cell lung cancer (NSCLC) who progress through first-line therapy have poor progression-free survival (PFS) and overall survival (OS), most commonly failing in original sites of gross disease. Cytoreduction with stereotactic body radiation therapy (SBRT) may help systemic agents delay relapse.

Patients and Methods
Patients in our single arm phase II study had stage IV NSCLC with no more than six sites of extracranial disease who failed early systemic chemotherapy and were able to receive SBRT and concurrent erlotinib until disease progression. After erlotinib commencement, SBRT with equipotent fractionation was delivered to all sites of disease. PFS, OS, and other end points were evaluated.

Results
Twenty-four patients (13 men and 11 women) with a median age of 67 years (range, 56-86 years) were enrolled with median follow-up of 11.6 months. All patients had progressed through platinum-based chemotherapy. A total of 52 sites were treated with 16 of 24 patients receiving SBRT to more than one site. Lung parenchyma was most often irradiated. Median PFS was 14.7 months, and median OS was 20.4 months. Most patients progressed in new distant sites with only three of 47 measurable lesions recurring within the SBRT field. Two grade 3 toxicities were radiation related. Zero of 13 patients tested were positive for an *EGFR* mutation.

Conclusion
Use of SBRT with erlotinib for unselected patients with stage IV NSCLC as a second- or subsequent line therapy resulted in dramatic changes in patterns of failure, was well tolerated, and resulted in high PFS and OS, substantially greater than historical values for patients who only received systemic agents.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology

Table 1. Baseline Characteristics of Patients Treated on Protocol

Characeristic	No.	%
Sex		
Female	11	46
Male	13	54
Age, years		
Median	66.9	
Standard deviation	7.6	
Range	56-86	
Previously treated brain metastases		
No	22	92
Yes	2	8
Follow-up, months		
Mean	16.8	
Standard deviation	14.5	
Range	3.4-60.3	
Study site		
University of Colorado	6	25
UT Southwestern Medical Center	18	75
Survival, last follow-up		
Alive	11	46
Dead	13	54
No. of previous systemic therapy regimens		
1	15	63
2	7	29
3	2	8
Race		
White, Hispanic	23	96
African American	1	4

Iyengar P et al
J Clin Oncol 2014 [Epub ahead of print October 27]

Table 2. SBRT Treatment Patterns

Treatment Pattern	No.	%
SBRT sites treated per patient		
1	8	33
2	8	33
3	5	21
4	2	9
5	1	4
SBRT courses to specific sites		
18	Lungs (35% of 52 sites treated)	
13	Mediastinum/hilum (25)	
7	Adrenals (13)	
6	Bone/spine/chest wall (13)	
4	Liver/paracaval (8)	
3	Nonmediastinal lymph nodes (5)	
1	Kidney (1)	
Lesions treated with specific SBRT fractionation schemas		
21	3 fx to 27-33 Gy (40)	
21	5 fx to 35-40 Gy (40)	
10	1 fx to 19-20 Gy (20)	

Abbreviations: fx, fractions; SBRT, stereotactic body radiation therapy.

Iyengar P et al
J Clin Oncol 2014 [Epub ahead of print October 27]

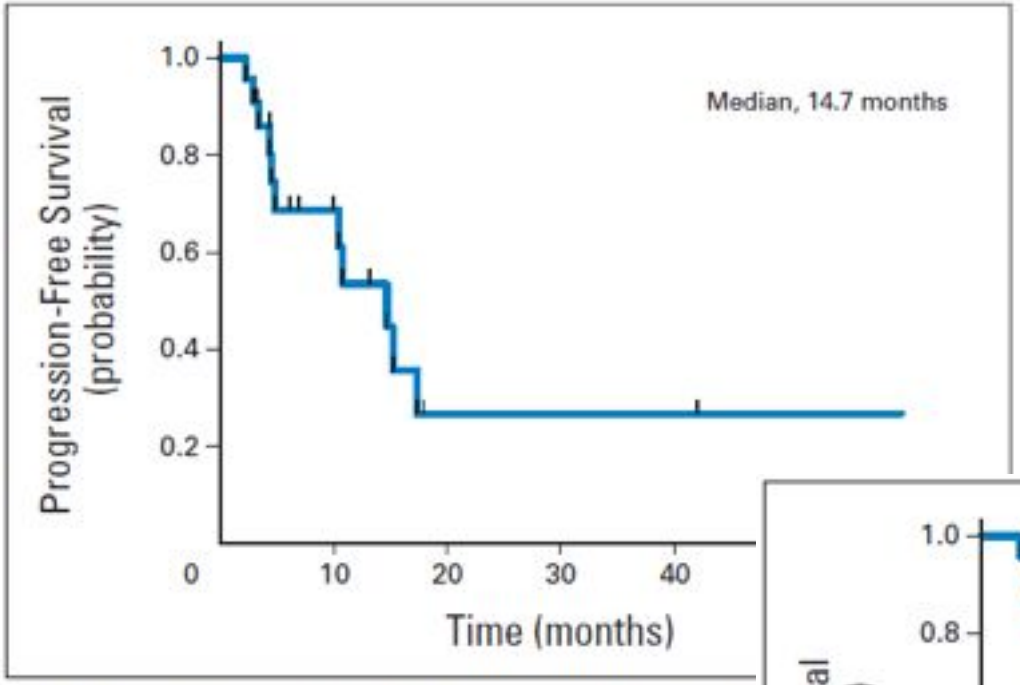

Fig 1. Kaplan-Meier analysis of progression-free survival (F
24 patients enrolled on the study.

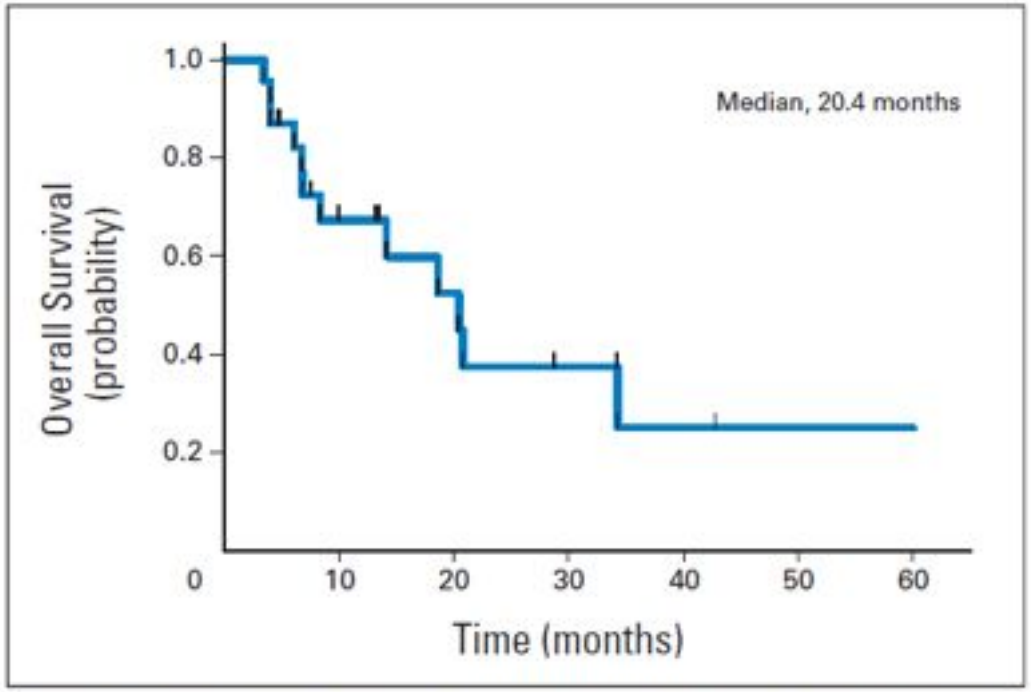

Fig 2. Kaplan-Meier analysis of overall survival (OS) in months for all 24 patients enrolled on the study.

Iyengar P et al
J Clin Oncol 2014 [Epub ahead of print October 27]

[…]

Our study enriched for patients with limited metastatic disease amenable to SBRT, introducing some advantage when comparing our outcomes with those of second-line or maintenance studies with all comers of stage IV NSCLC.

[...]

?

Iyengar P et al
J Clin Oncol 2014 [Epub ahead of print October 27]

[…]
Patients with limited metastases may have biology that allows them to have longer survival independent of the success of local or systemic therapies.
However, with studies suggesting that 53% of patients that advanced NSCLC would have SBRT-treatable metastases after first-line therapy, a significant proportion of patients could potentially benefit.
[…]

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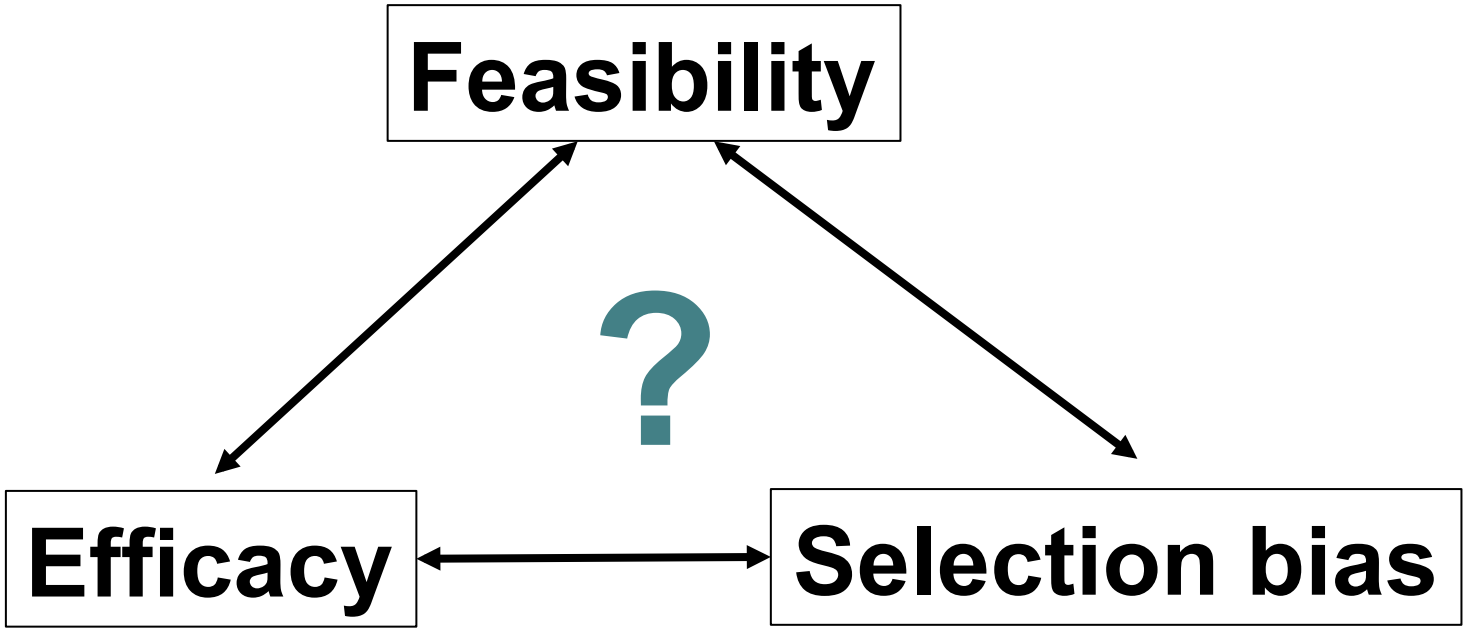
In the absence of randomized trials…



Additional support from ongoing and future randomized clinical trials will be necessary to prospectively evaluate aggressive local therapy to the primary tumor and limited metastatic foci after and with systemic treatments.

It is hoped that the advent of targeted agents can allow for longer patient survivals and thereby improve the ability of local therapy to further bolster outcomes for our patients.

Jabbour SK

Are We Expanding Oligometastatic NSCLC Using Advanced Radiotherapeutic Modalities?

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Trattamenti locali nel NSCLC metastatico

Integrazione con i trattamenti sistemici

- I trattamenti locali hanno un chiaro ruolo nel NSCLC metastatico, per il miglioramento della **qualità di vita** e il **controllo dei sintomi.**
- Negli ultimi anni, l'impiego di trattamenti locali è stato proposto nei **pazienti con NSCLC *oncogene-addicted*, in oligo-progressione**, con risultati giudicati promettenti.
- Per questi pazienti, peraltro, lo scenario terapeutico è in **rapida evoluzione**.

UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Grazie per l'attenzione!

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