Strategic approach

-Sequence of use of TKI and chemotherapy

-Intercalating EFGR TKI and Chemotherapy

-Definition of progression under TKI

JY Douillard

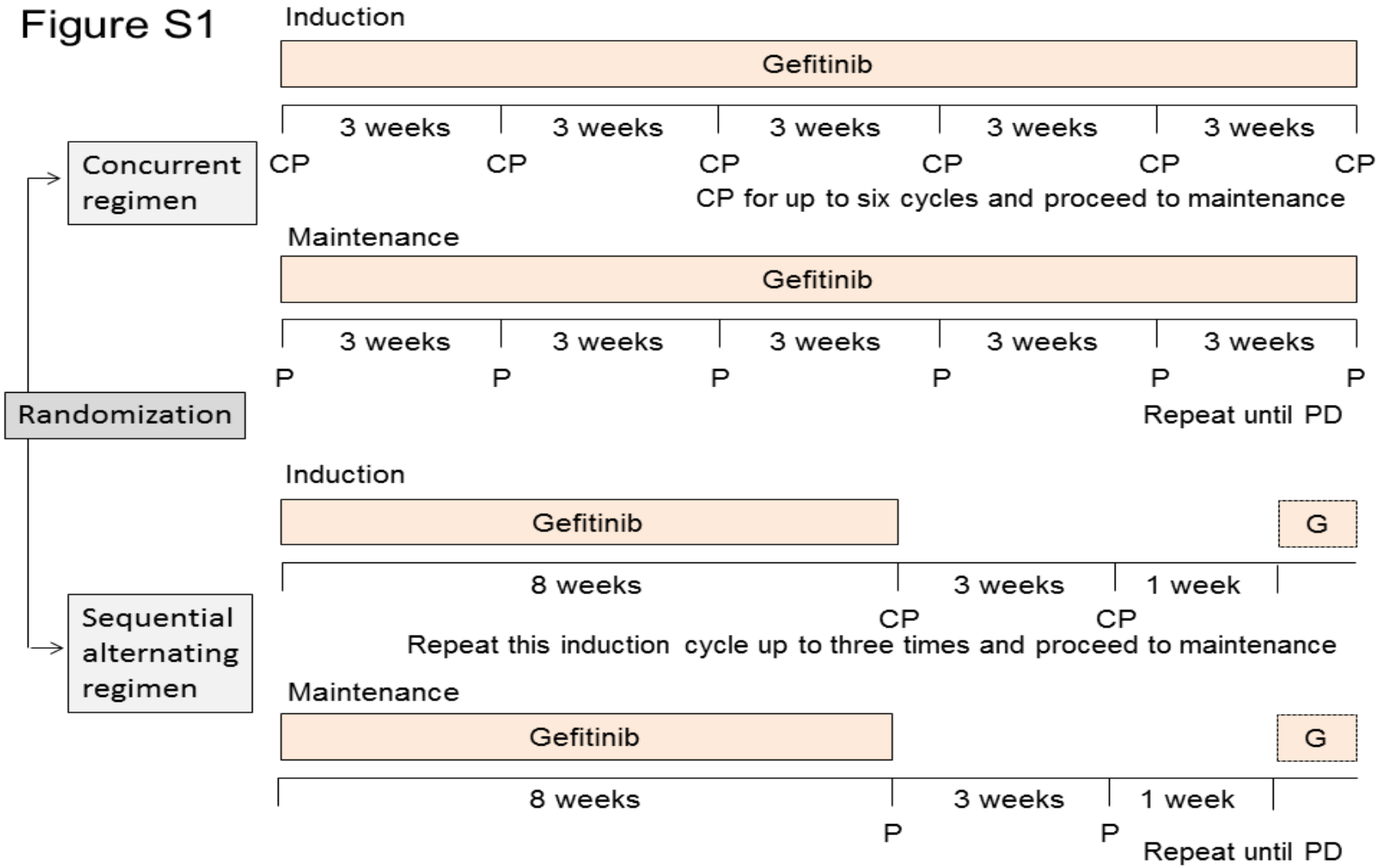
original article

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv063

Randomized phase II study of concurrent versus sequential alternating gefitinib and chemotherapy in previously untreated non-small cell lung cancer with sensitive *EGFR* mutations: NEJ005/TCOG0902

S. Sugawara[1], S. Oizumi[2*], K. Minato[3], T. Harada[4], A. Inoue[5], Y. Fujita[6], M. Maemondo[7], H. Yoshizawa[8], K. Ito[9], A. Gemma[10], M. Nishitsuji[11], M. Harada[12], H. Isobe[13], I. Kinoshita[14], S. Morita[15], K. Kobayashi[16], K. Hagiwara[17], M. Kurihara[18] & T. Nukiwa[19] on behalf of North East Japan Study Group and Tokyo Cooperative Oncology Group

NEJ005/TCOG0902/ Trial design



Sugarawa et al Annals of Oncology 00: 1–7, doi:10.1093/annonc/mdv063

NEJ005/TCOG0902/ Trial design: ORR
Randomized phase II EGFR m+ n=80

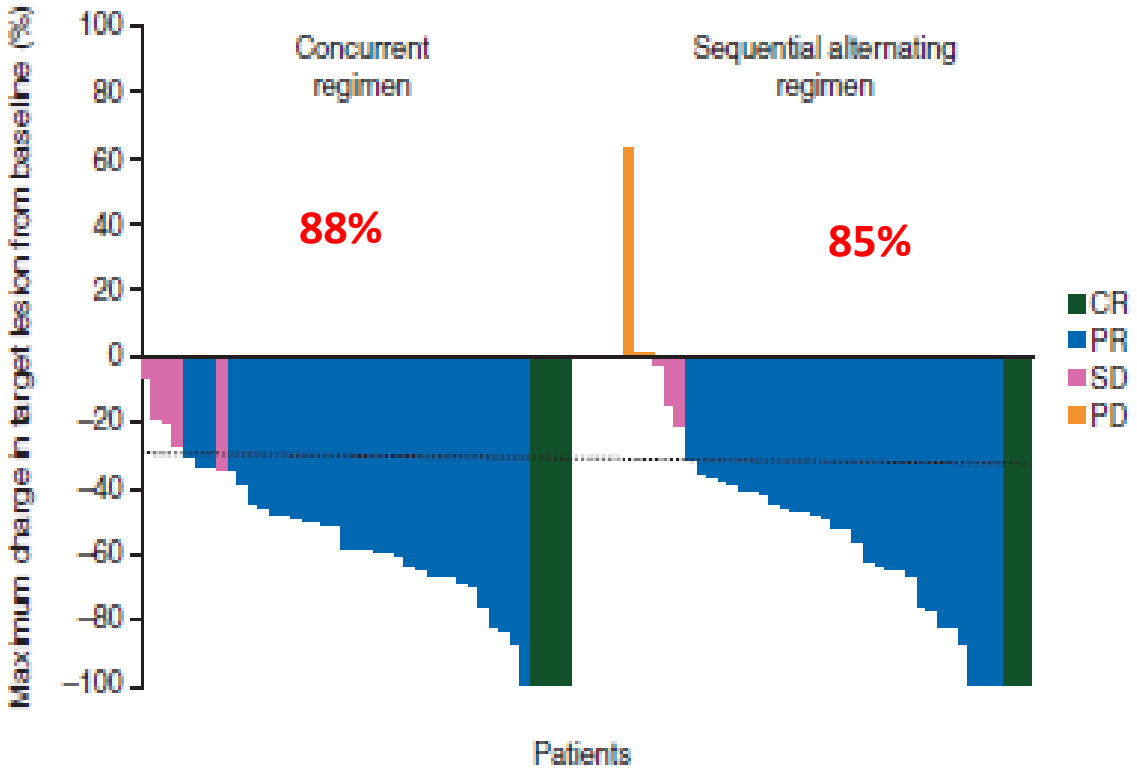
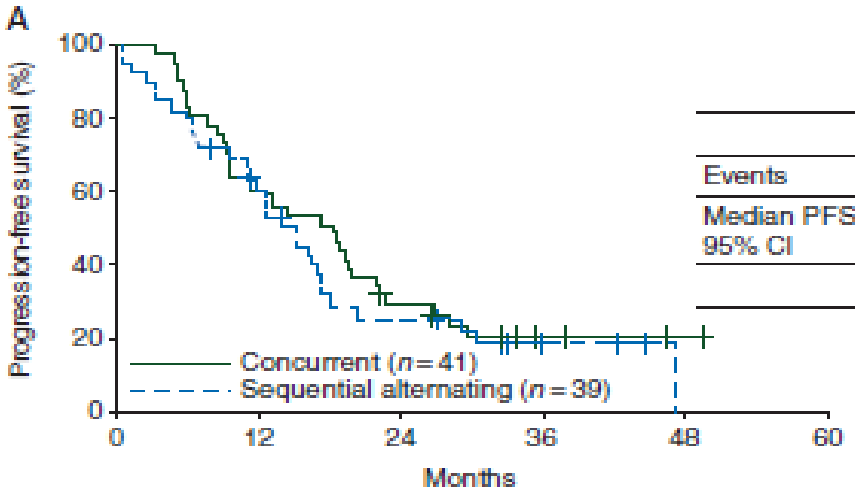


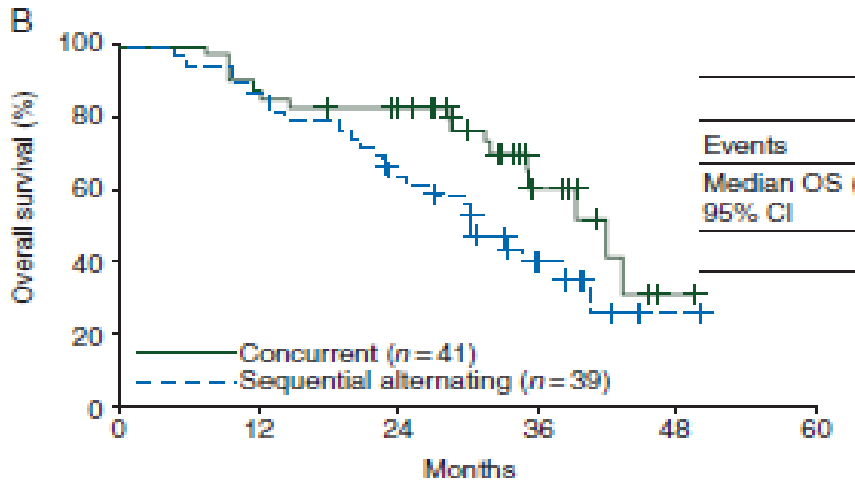
Figure 3. Response to the concurrent and the sequential alternating regimens. In this waterfall plot, the bars indicate the largest percentage change in target lesions from baseline. The dashed line indicates a 30% reduction from baseline.

Sugarawa et al Annals of Oncology 00: 1–7, doi:10.1093/annonc/mdv063

NEJ005/TCOG0902/ Trial design: PFS and OS



	Concurrent	Sequential
Events	32 (78.0%)	31 (79.5%)
Median PFS (months)	18.3	15.3
95% CI	9.7–21.9	11.3–17.4
	$P = 0.20$, HR 0.80	



	Concurrent	Sequential
Events	16 (39.0%)	24 (61.5%)
Median OS (months)	41.9	30.7
95% CI	35.1–NR	23.2–40.5
	$P = 0.042$, HR 0.55	

Figure 2. Kaplan–Meier curve of progression-free survival (PFS; A) and overall survival (OS; B) for all randomly assigned patients.

Sugarawa et al Annals of Oncology 00: 1–7, doi:10.1093/annonc/mdv063

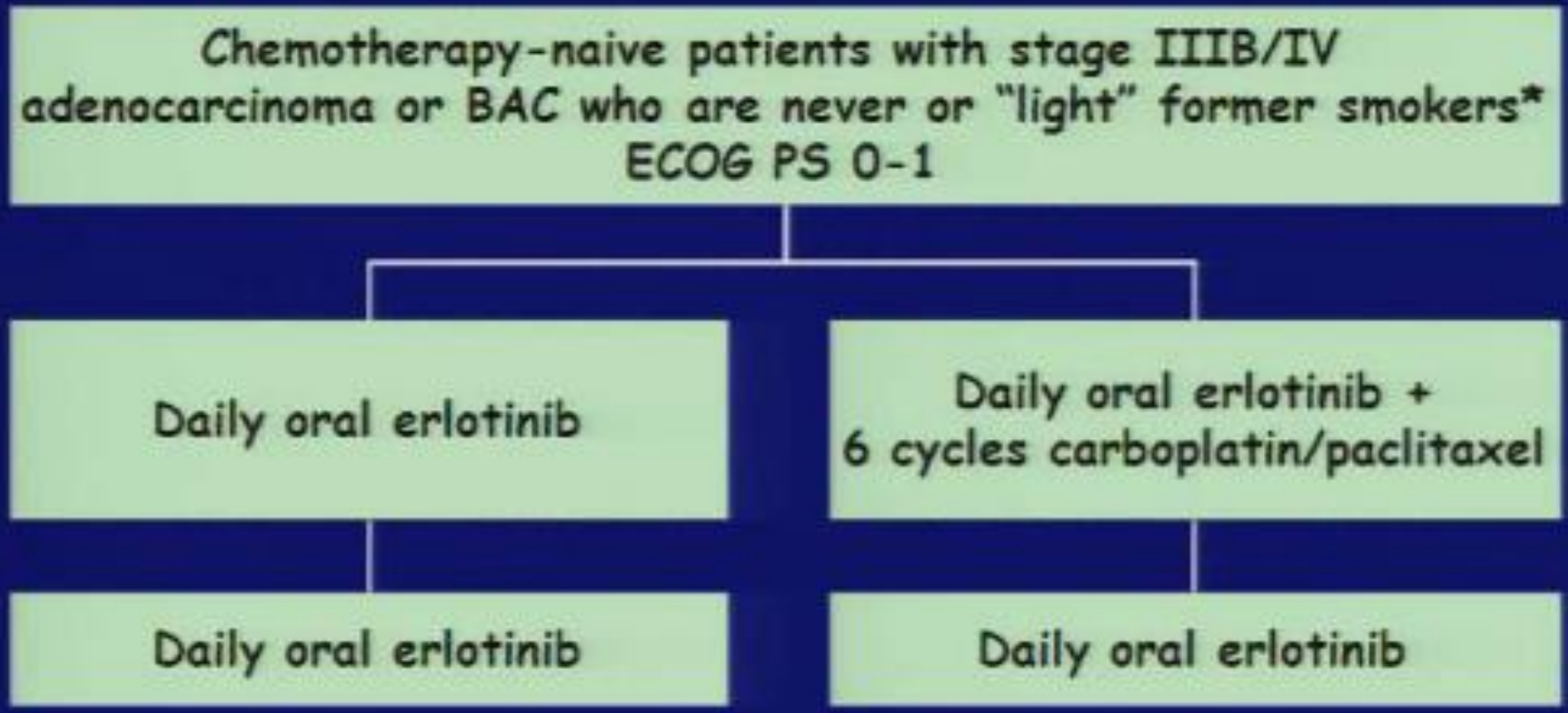
How to improve efficacy of EGFR TKI in First line treatment of mutant? Combination with chemotherapy

- NEJ005/TCOG0902 shows an advantage to concurrent CT/TKI over sequential-alternating regimen

- The next trial should be:

  - **Control arm: TKI 1st line until progression followed by 2nd line CT**
  - **Experimental arm: Concurrent TKI/CT**

CALGB 30406 Randomized Phase II Study: Trial Design



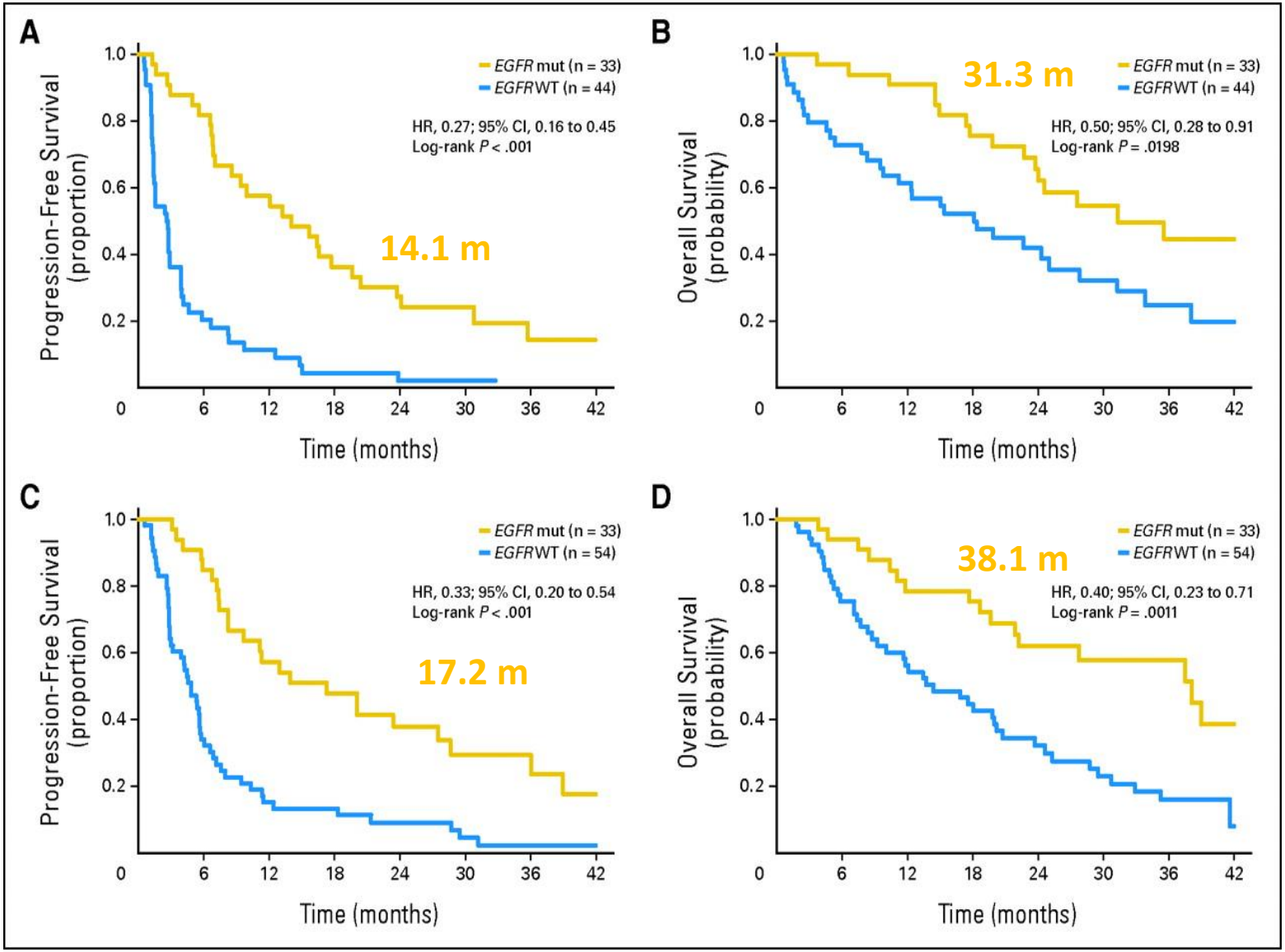
Response evaluation every 2 cycles (6 weeks). Therapy could continue until disease progression or toxicity

* never smoker: ≤ 100 cigarettes/lifetime; "light" former smoker: quit ≥ 1 year ago and ≤ 10 pack years

CALGB 30406: PFS and OS in EGFR mutant.

Arm A: Erlotinib

Arm B: Erlotinib+PC

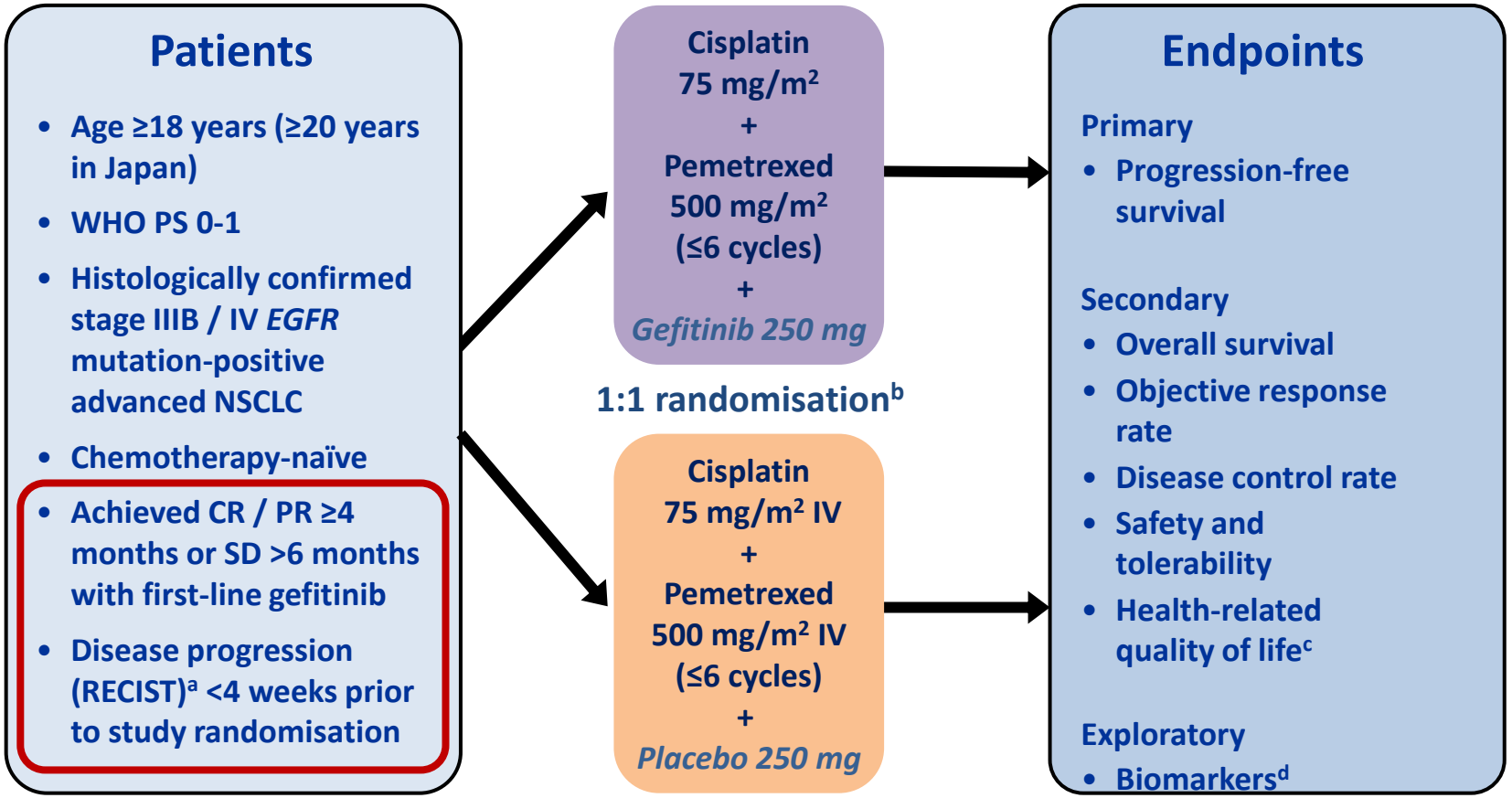


Jänne P A et al. JCO 2012;30:2063-2069

JOURNAL OF CLINICAL ONCOLOGY

IMPRESS: Study design

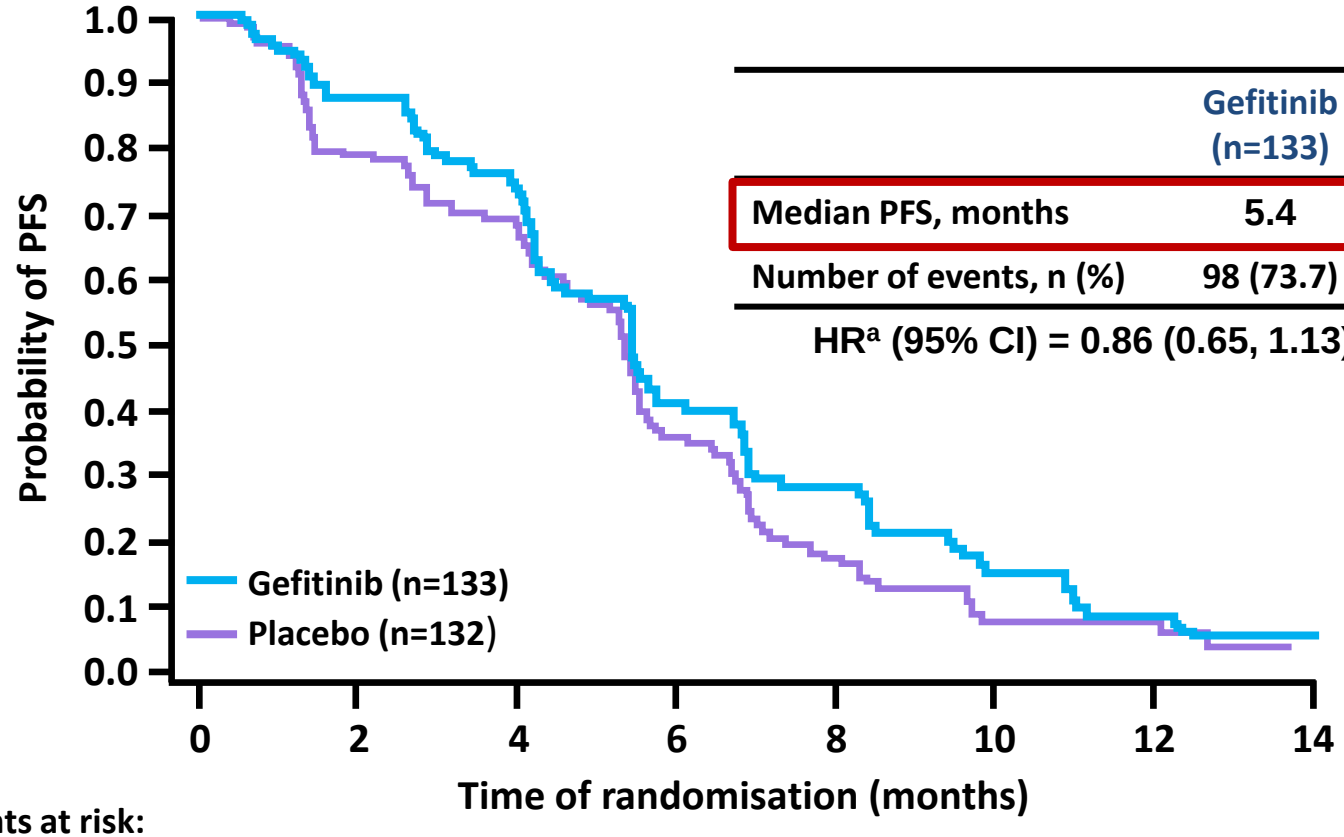
Enrollment period: March 2012–December 2013



[a]Progressive disease based on radiological evaluation Tumour assessments were performed ≤4 weeks before the start of treatment (baseline), and every 6 weeks (±7 days) after randomisation until progressive disease;
[b]Randomisation did not include stratification factors; analyses were adjusted for two covariates: age (<65 versus ≥65 years) and prior response to gefitinib (SD versus PR+CR)
[c]Will be reported separately
[d]Analyses not

Courtesy of T Mok ESMO 2014 LBA2-PR

PFS (primary endpoint; ITT)



	Gefitinib (n=133)	Placebo (n=132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

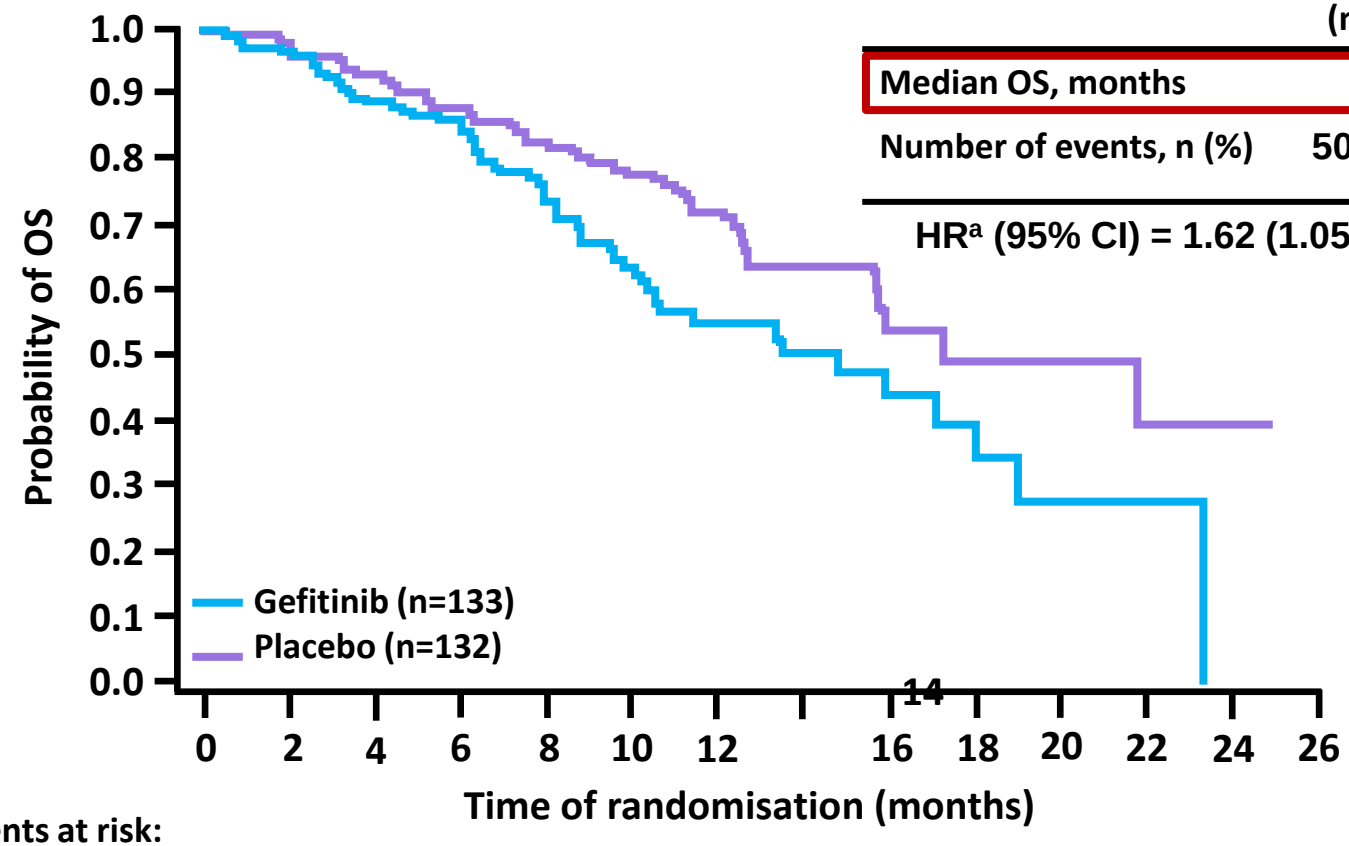
HR[a] (95% CI) = 0.86 (0.65, 1.13); p=0.273

Patients at risk:

Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

Courtesy of T Mok ESMO 2014 LBA2-PR

OS (ITT; 33% of events)



	Gefitinib (n=133)	Placebo (n=132)
Median OS, months	14.8	17.2
Number of events, n (%)	50 (37.6)	37 (28.0)

HR[a] (95% CI) = 1.62 (1.05, 2.52); p=0.029

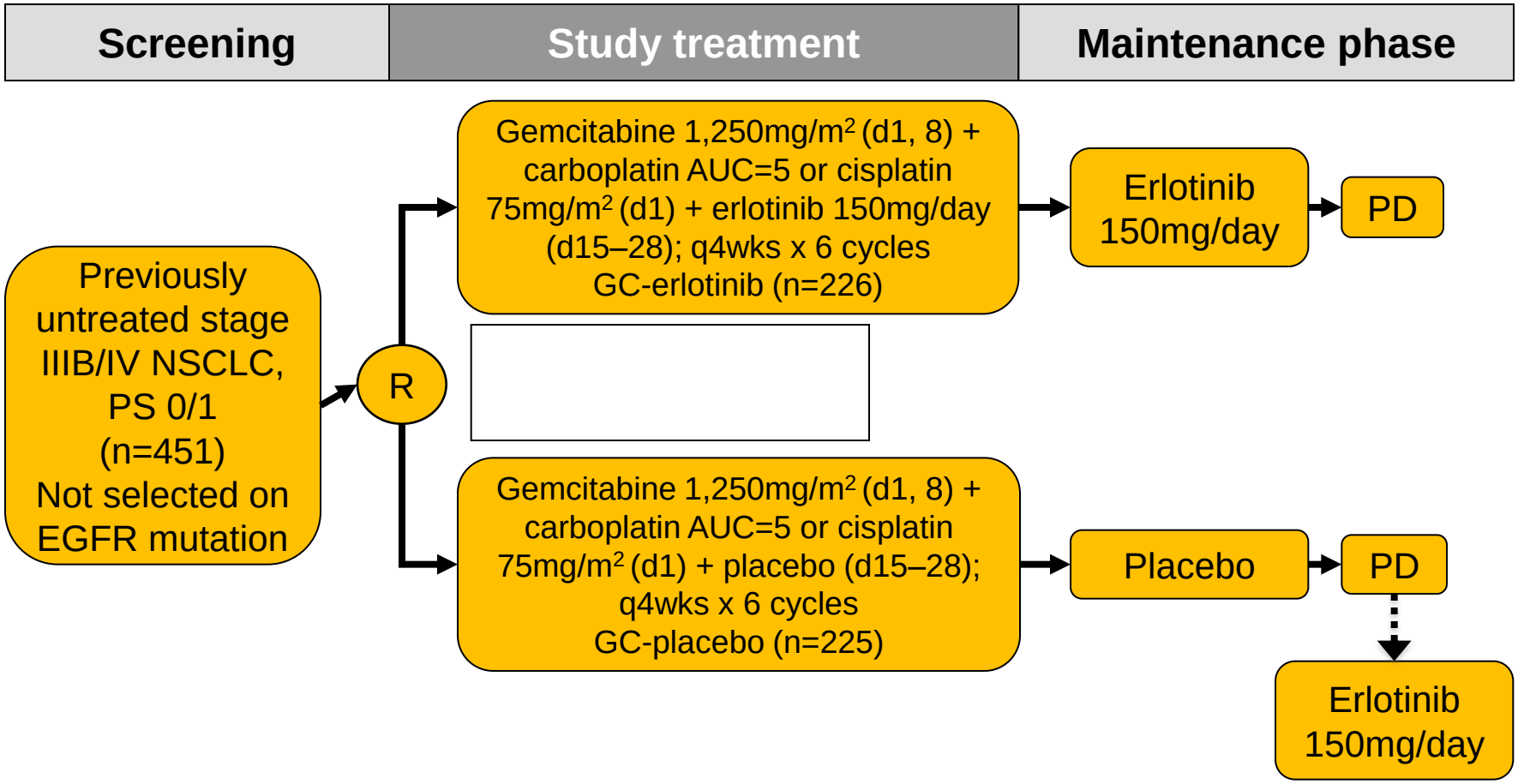
Patients at risk:

Gefitinib	133	125	111	88	64	43	27	19	12	8	4	2	0	0
Placebo	132	129	119	94	76	55	39	27	16	10	7	4	2	0

Significant detrimental effect, increased in the risk of death: +62%

Courtesy of T Mok ESMO 2014 LBA2-PR

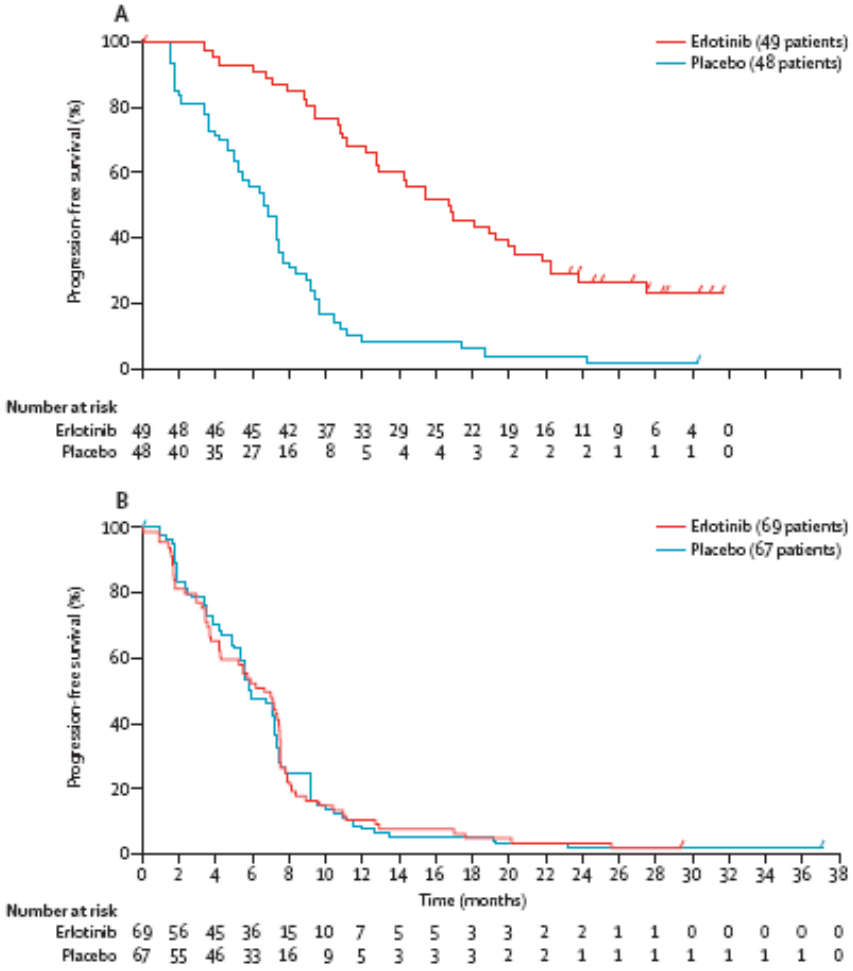
FASTACT-2 study design



IRC = independent review committee

Wu YL et al Lancet Oncology 2013

PFS benefit confined to patients with EGFR mutations



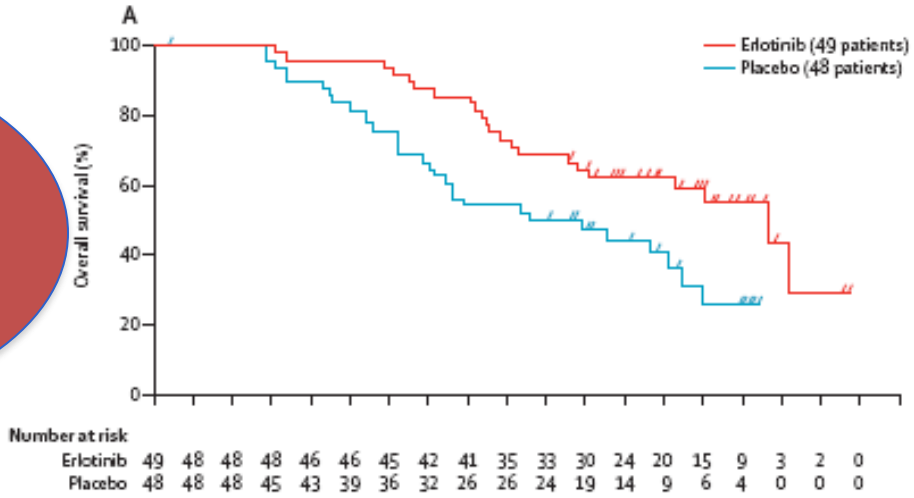
EGFR Mutation

EGFR Wild type

Wu and Mok Lancet Oncology 2013

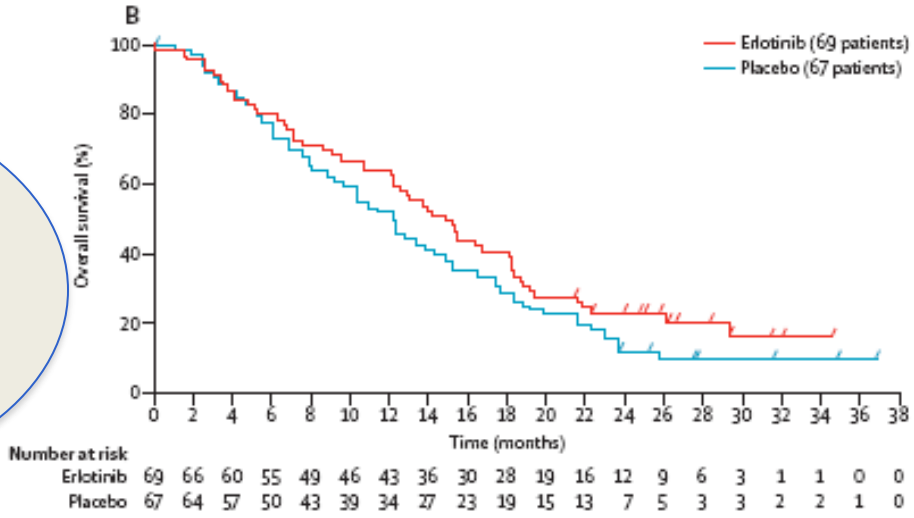
OS benefit confined to patients with EGFR mutations

85% of control arm received TKI as second line therapy



EGFR Mutation

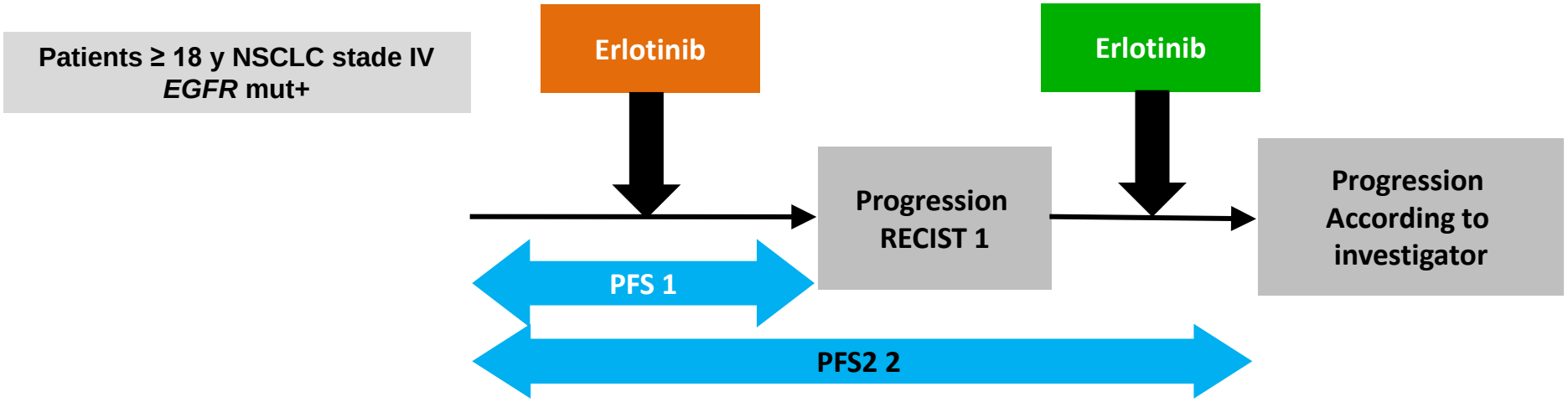
FASTACT 3:
Need to use TKI as control



EGFR Wild type

Wu and Mok Lancet Oncology 2013

ASPIRATION : Continuing EGFR TKI after RECIST progression

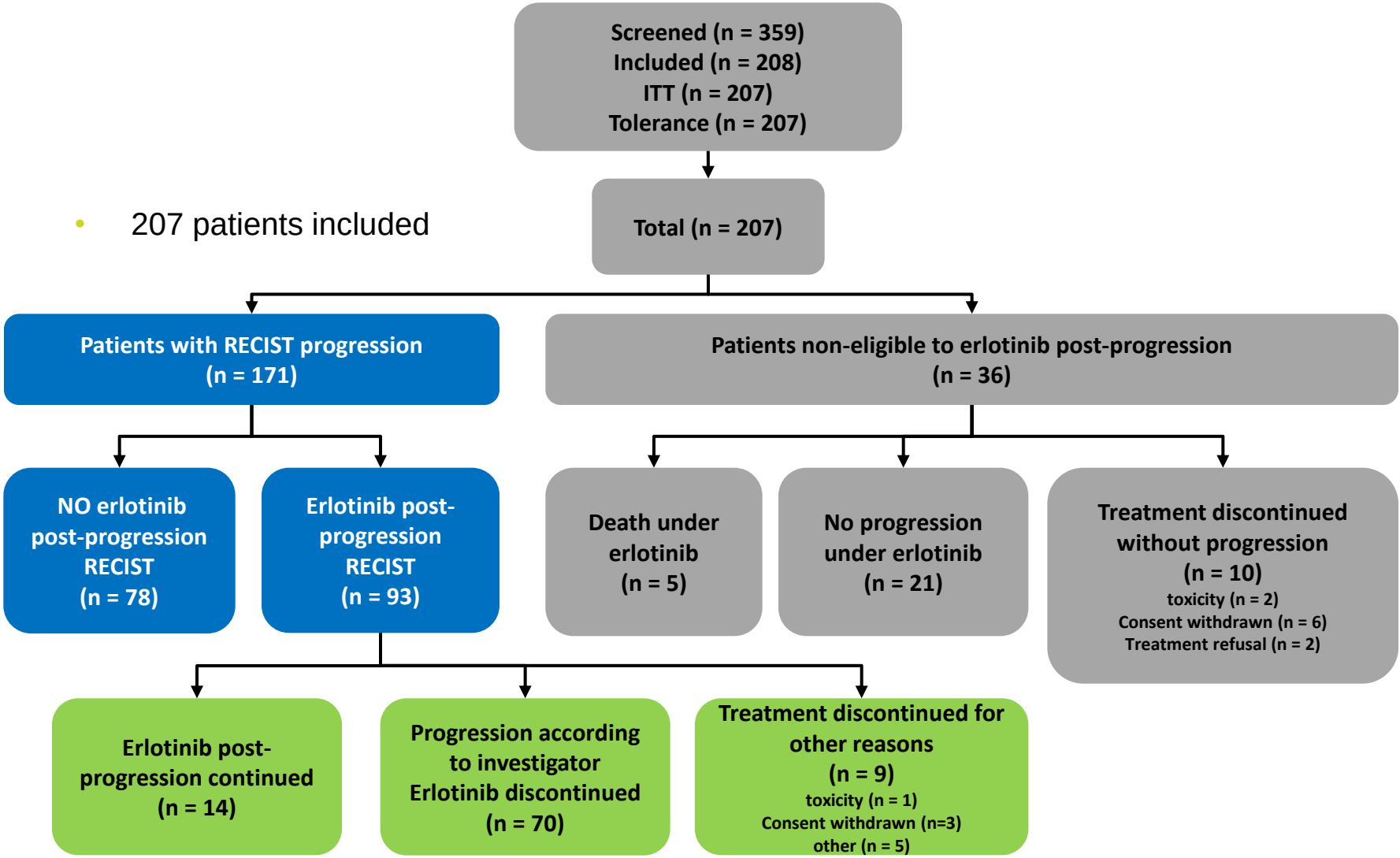


- Phase II open trial in Asia
- Inclusion criteria: patients ≥ 18 ans with NSCLC stage IV with EGFR mutation exons 18-21 (except T790M), ECOG PS 0-2
- Exclusion criteria: mutation T790M, previous treatment with chemotherapy or EGFR TKI , co-morbidities , treatment with warfarin
- Primary Endpoint : PFS1 (according to RECIST or death)
- Secondary endpoints :
  - PFSP2 (time to erlotinib discontinuation due to progression defined by investigator)
  - OS/ ORR/ DCR/ tolerance

Adapted from Park K et al. ESMO 2014 Abstract 12230

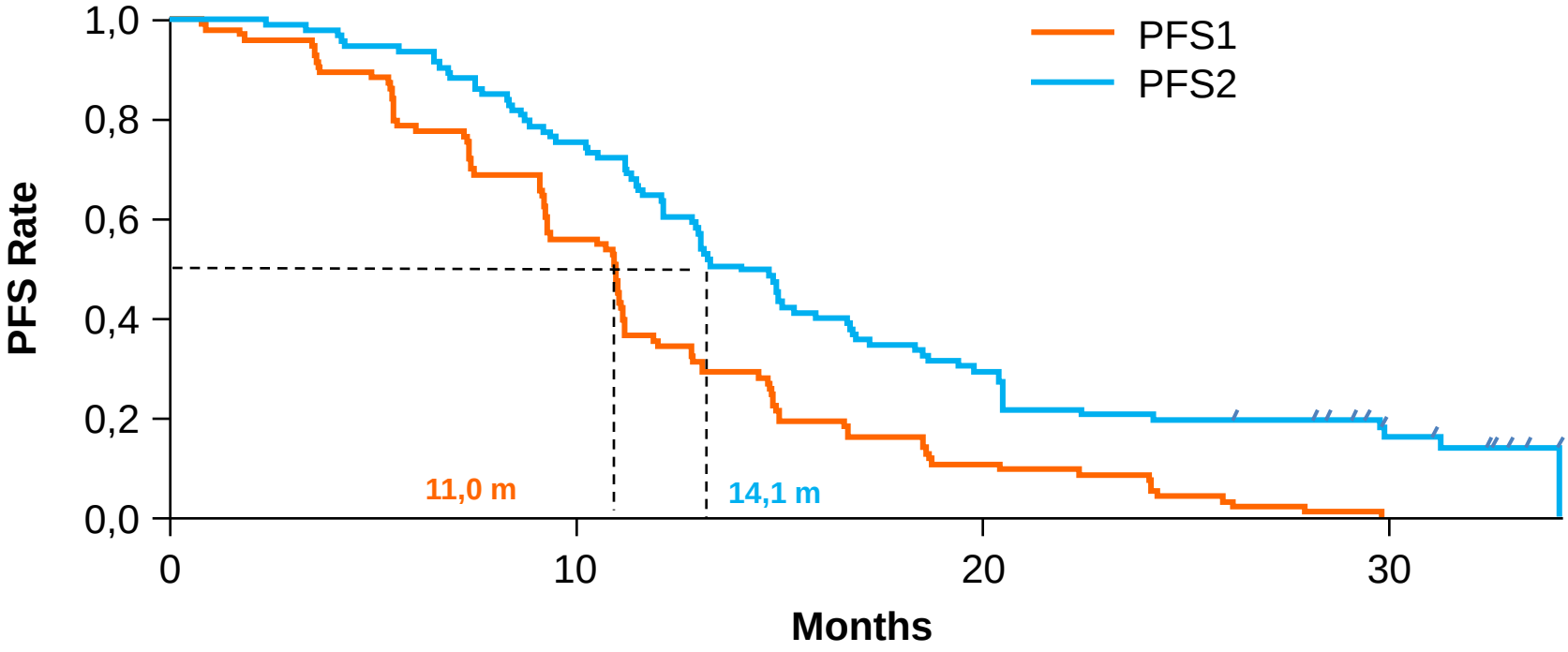
ASPIRATION : Continuing EGFR TKI after RECIST progression

- 207 patients included



ASPIRATION : Continuing EGFR TKI after RECIST progression

- Survival benefit without progression with Erlotinib post- RECIST progression (93 patients): 3,1 months
- Tolerance profile was similar



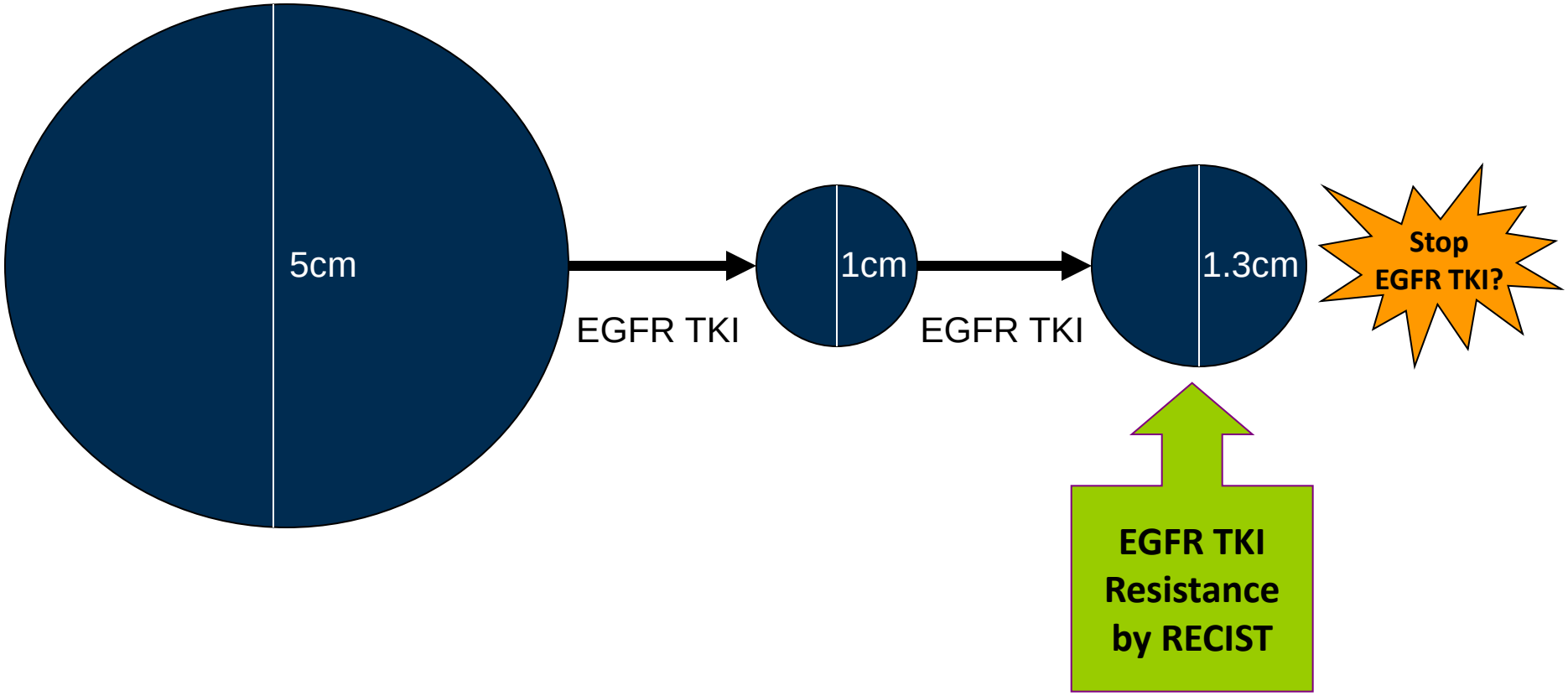
Park K et al. ESMO 2014 Abstract 12230

Progression under EGFR TKI treatment

– Post progression strategies after failing 1st line TKI

➢ **How to define progression under TKI?**

RECIST Criteria



Acquired resistance to EGFR-TKIs

Jackman Criteria

1. Previously received treatment with a **single-agent EGFR TKI**.

2. Either of the following:
   - A. A tumor that harbors an **EGFR mutation** known to be associated with drug sensitivity (ie, G719X, exon 19 deletion, L858R, L861Q)
   - **B. Objective clinical benefit** from treatment with an EGFR TKI as defined by either:
     - a. Documented partial or complete response (RECIST or WHO), or
     - b. Significant and durable (**≥6 months**) clinical benefit (stable disease as defined by RECIST or WHO)

3. **Systemic progression** of disease (RECIST or WHO) while on continuous treatment with gefitinib or erlotinib within the last **30 days**.

4. **No intervening systemic therapy** between cessation of gefitinib or erlotinib and initiation of new therapy.

Jackman D, J Clin Oncol 2010; 28: 357-360

NSCLC treatment algorithm

Expert interview summary

July/August 2011

Experts interviewed

- **Jean-Yves Douillard, Chair**

- Wilfried Eberhardt
- Tony Mok
- Egbert Smit
- Ralf Stahel (+ Solange Peters)
- Francesco Grossi
- Giorgio Scagliotti
- Luis Paz-Ares
- Johan Vansteenkiste
- Nicholas Thatcher

Second-line options at progression

1. **Slow progression – how is it defined and treated?**
   - Asymptomatic
   - CT evidence of minor progression
   - No altered PS

Keep TKI until symptoms

Second-line options at progression

2. Stable in lung but other metastases (eg bone or brain)

Keep TKI and use local radiation

Do you ever consider changing to a different TKI?

No, except for clinical trials

– most would not change to a different TKI

-2nd generation TKI have been disappointing after progression on 1st generation TKI

How does performance status affect the choice of 2nd-line chemotherapy?

- **PS ≥ 2 may favour 2nd-line choice towards a single-agent,**
- **PS 0-1 platinum doublet preferred**

Second-line options at progression

3. Rapid progression

- Symptoms
- Altered PS
- Clinical progression
- CT scan/radiologic progression

Switch to chemotherapy without delay

- **Risk of a “Flare effect”**

Disease Flare at TKI discontinuation

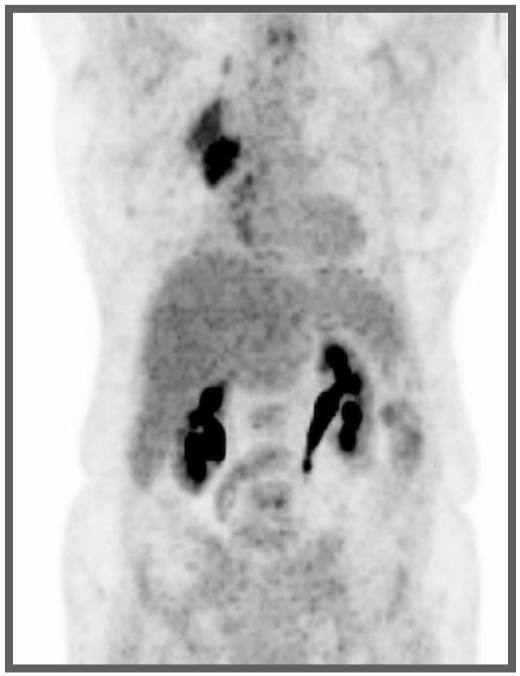
- Disease flare definition:
  - Accelerated disease progression (symptoms, declining PS)
  - Hospitalization for disease progression
  - Death

- Characteristics associated with disease Flare:
  - Shorter PFS on TKI
  - Pleural and CNS metastasis
  - No clear correlation with resistance mechanism

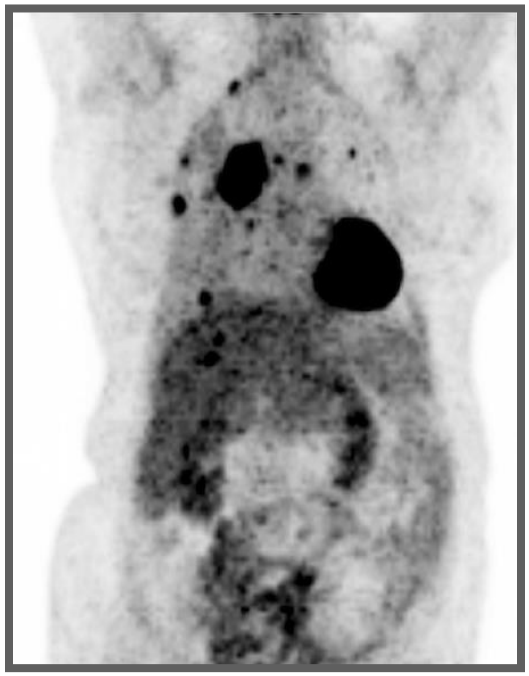
- Recommendations to avoid flare
  - Keep TKI until 2nd line is delivered
  - The usual wash-out period of 3-4 weeks to be avoided
  - Disease Flare occurs in a median of 8 days after TKI discontinuation

Chaft J. et al Clin Can Res 2011 17 6298

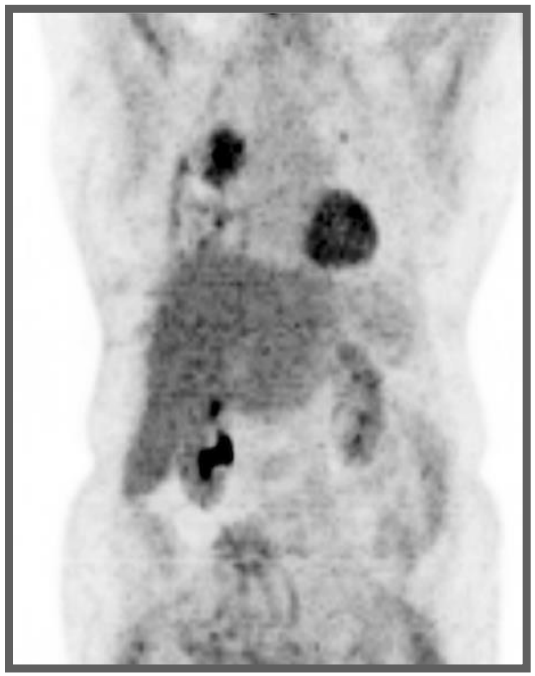
Flare effect illustration



Day 0
Last day on TKI



Day 21
Off TKI



Day 42
Resume TKI

When should platinum be incorporated?

- **At symptomatic progression in fit patients.**
- **If fit, they should receive a second-line doublet**