MADRID 2014 ESMO congress

The evolving role of systemic therapies in NSCLC:

Targeting tumor addiction

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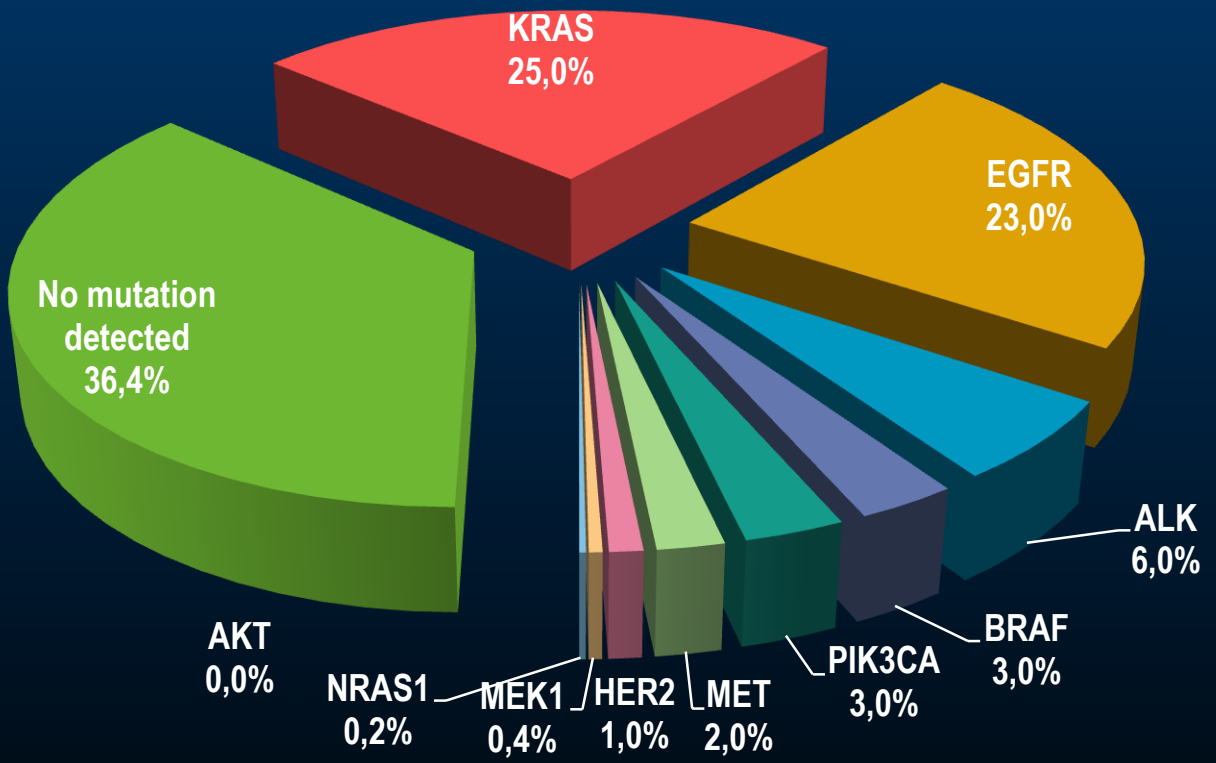
Disclosure slide

Compensated lectures/advisory role:

- Pfizer
- Eli Lilly
- Boehringer-Ingelheim
- Clovis
- Novartis

Lung Cancer Mutation Consortium

Analysis of Lung Adenocarcinomas



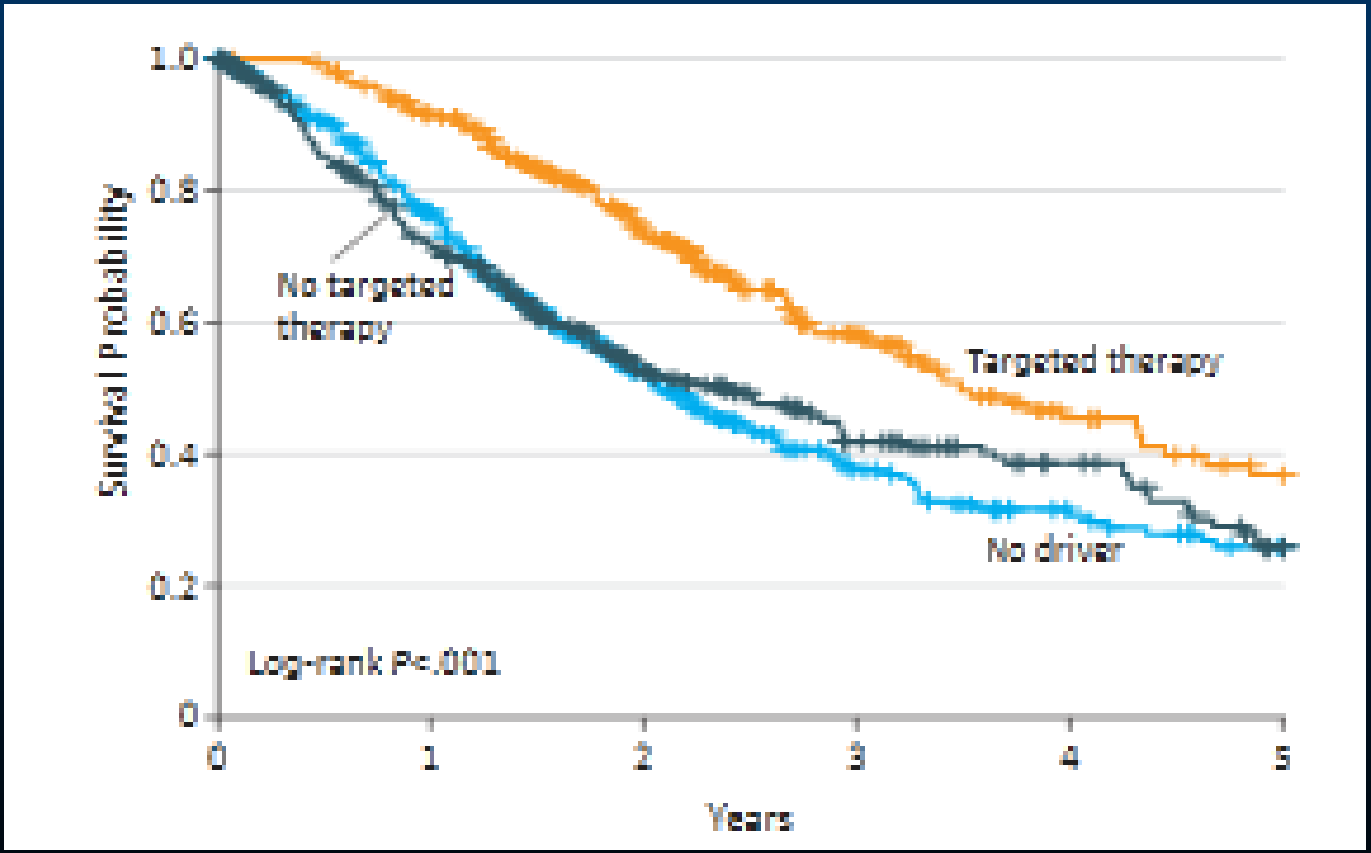
Driver mutations found in 60% (252/422) of tumours completely tested

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homologue; NRAS, neuroblastoma RAS viral oncogene homologue; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit.

Johnson BE, et al. *J Thoracic Oncol*. 2011;6(Supplement 2):abstract O16.01; Kris MG, et al. *J Clin Oncol*. 2011;29(Suppl):abstract CRA7506.

Lung Cancer Mutation Consortium

Survival of patients with targetable alterations vs. others



Kris M. et al., JAMA 2014

„Oncogene-addicted" vs. „non-addicted" NSCLC

„Oncogene-addicted" NSCLC:

- Fulfill preclinical criteria of oncogene addiction
- Long-term responses in the clinical trials
- Targeted therapies prefarably used in the first-line setting
- Monotherapy more common than combination therapies w/cytotoxics

„Non-oncogene addicted" NSCLC:

- No proof of single abnormality driving tumor proliferation
- Targeted therapies much less effective, usually targeting mechanisms of progression, used in the second/third-line setting and in combination w/cytotoxics

„Oncogene-addicted" NSCLC

Type of molecular alteration

Driver mutations:

- EGFR
- HER2
- KRAS
- NRAS
- BRAF
- MEK1
- DDR2 (?)
- PIK3CA (?)

Genomic rearrangements:

- ALK
- ROS1
- RET
- NTRK1
- MYB-NFIB
- CRTC1-MAML2

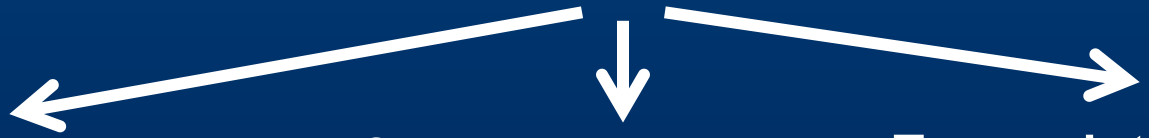
Amplifications and high copy numbers:

- MET
- EGFR (?)
- FGFR1 (?)
- MYC (?)

cAMP, cyclic adenosine monophophate; CRTC1, cAMP response element binding protein-regulated transcription coactivator 1; DDR2, discoidin domain-containing receptor 2; FGFR1, fibroblast growth factor receptor 1; NFIB, nuclear factor 1 B-type; MAML2, mastermind-like protein 2.

„Oncogene-addicted" NSCLC

Role of molecular target



Growth factor receptors:

- EGFR
- HER2
- ALK
- ROS1
- NTRK1
- RET
- MET
- FGFR1
- DDR2

Cytoplasmic proteins:

- KRAS
- BRAF
- PIK3CA
- MEK1

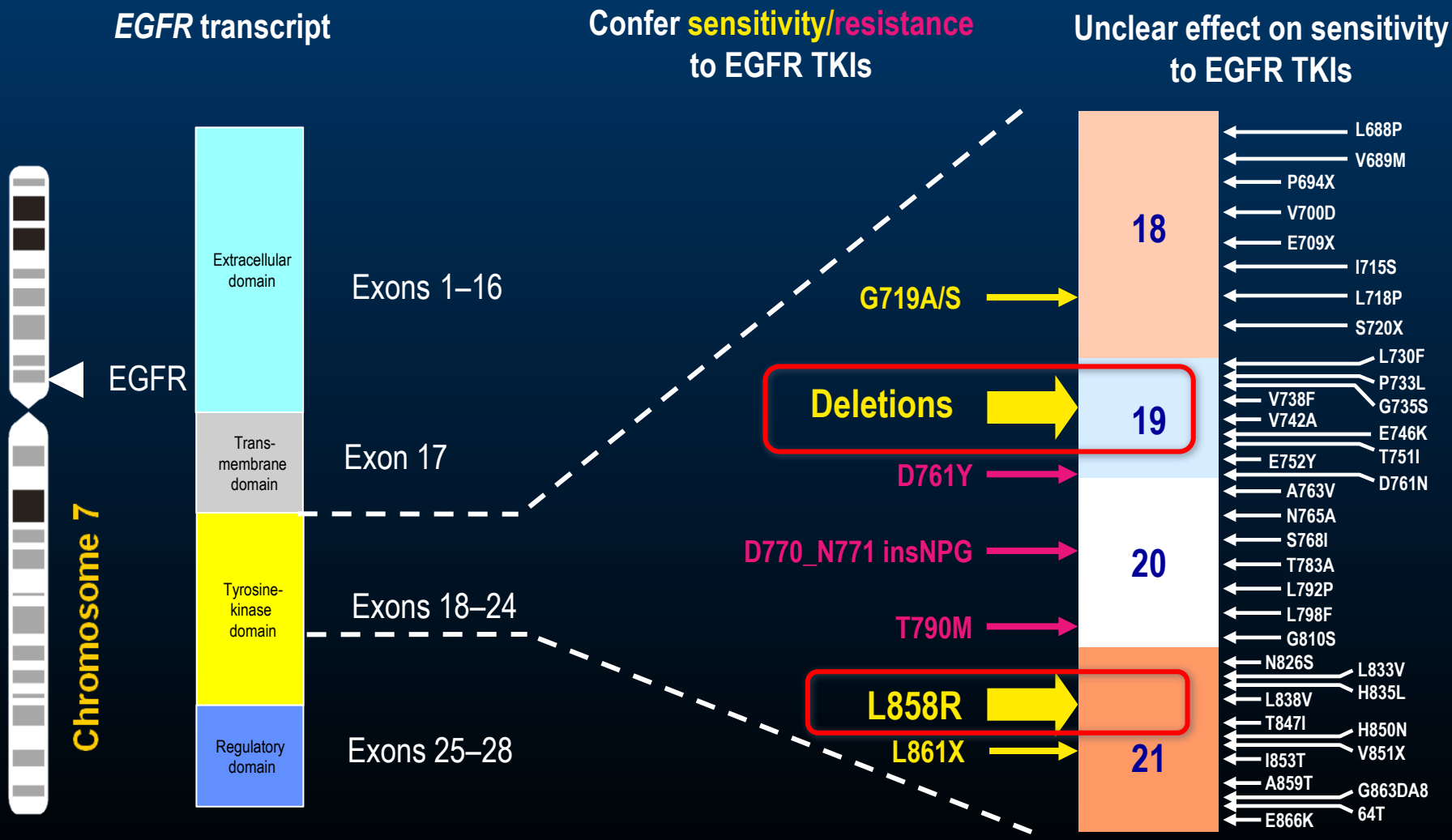
Transcription factors:

- MYB-NFIB
- CRTC1-MAML2

Quick Overview of Targetable „Oncogene Addiction" Pathways in NSCLC

Oncogene addiction: EGFR (10-15%)

Common and Rare EGFR Mutations



Riely GJ, et al. *Clin Cancer Res*. 2006;12(24):7232-7241.

Oncogene Addiction: EGFR

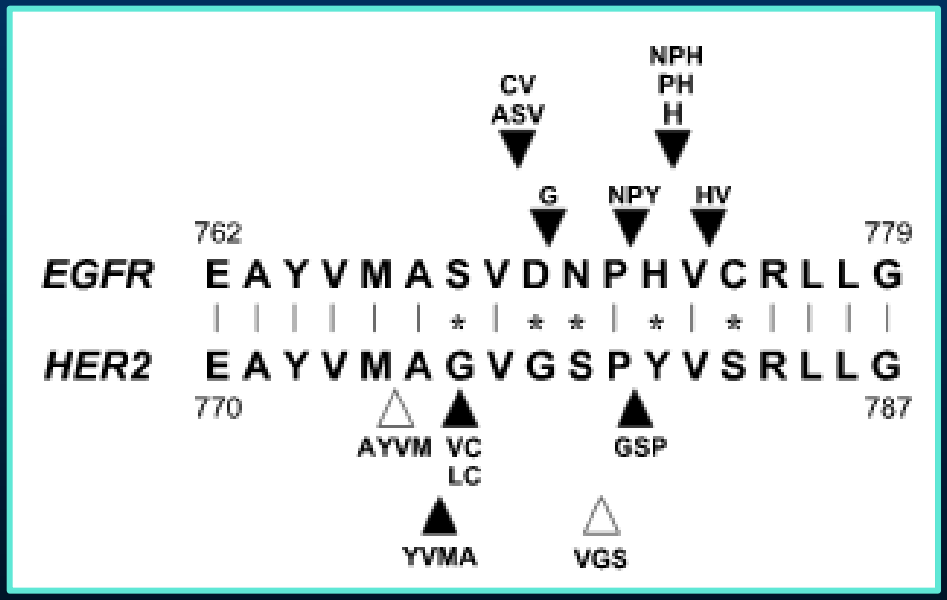
First-line Trials of EGFR TKI vs Chemotherapy

Trial	EGFR TKI	Comparator	N	EGFR mut(+)	RR, %	PFS, months	OS, months
IPASS[1,2]	Gefitinib	Carboplatin/ paclitaxel	1217	261	71 vs 47 *P*=0.0001	9.5 vs 6.3 HR 0.48 (0.36-0.64)	21.6-21.9 HR 1.0 (0.76-1.33)
First-SIGNAL[3]	Gefitinib	Gemcitabine/ cisplatin	309	42	85 vs 38 *P*=0.002	8.0 vs 6.3 HR 0.54 (0.27-1.10)	27.2 vs 25.6 HR 1.04 (0.50-2.18)
NEJ 002[4]	Gefitinib	Carboplatin/ paclitaxel	224	224	74 vs 31 *P*<0.001	10.4 vs 5.5 HR 0.36 (0.25-0.51)	30.5 vs 23.6
WJTOG 3405[5]	Gefitinib	Cisplatin/ docetaxel	172	172	62 vs 32 *P*<0.0001	9.2 vs 6.3 HR 0.5 (0.34-0.71)	30.9 vs NR HR 1.64 (0.75-3.6)
OPTIMAL[6]	Erlotinib	Gemcitabine/ carboplatin	154	154	83 vs 36 *P*<0.0001	13.1 vs 4.6 HR 0.16 (0.10-0.26)	Not mature
EURTAC[7]	Erlotinib	Chemotherapy	173	173	58 vs 15	9.7 vs 5.2 HR 0.37 (0.25-0.54)	19.3 vs 19.5 HR 1.04 (0.6-1.68)
LUX-Lung 3[8]	Afatinib	Cisplatin/ pemetrexed	345	345	56 vs 23 *P*<0.0001	11.1 vs 6.9 HR 0.58 (0.43-0.78)	Not mature

EURTAC, European Randomized Trial of Tarceva versus Chemotherapy; HR, hazard ratio; IPASS, Iressa Pan-Asian Study; mut(+), mutation-positive; NEJ, North East Japan; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate; WJTOG, West Japan Thoracic Oncology Group.

[1]Mok T, et al. *N Engl J Med.* 2009;361(10):947–957; [2]Fukuoka M, et al. *J Clin Oncol.* 2011; 29(21):2866–2874; [3]Han JY et al. *J Clin Oncol.* 2012;30(10):1122–1128; [4]Maemondo M, et al. *N Engl J Med.* 2010;362(25):2380–2388; [5]Mitsudomi T, et al. *Lancet Oncol.* 2010;11(2):121–128; [6]Zhou C, et al. *Lancet Oncol.* 2011;12(8):735–742; [7]Rosell R et al. *Lancet Oncol.* 2012;13(3):239–246; [8]Sequist JC, et al. *J Clin Oncol.* 2013;31(27):3327-3334.

Oncogene Addiction: *HER2* Mutations (2-3%)

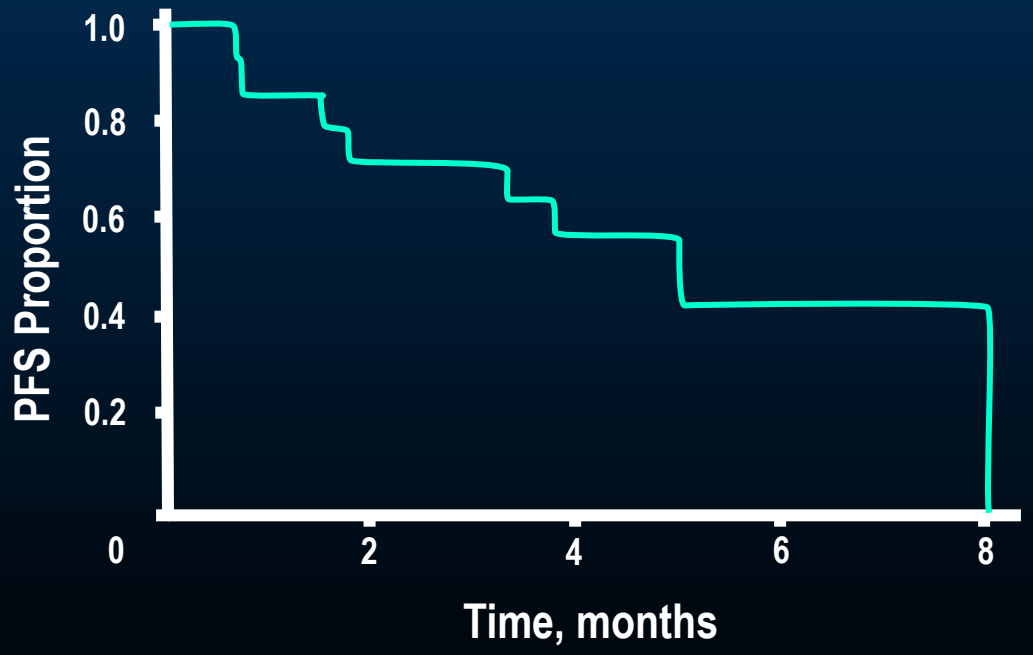


Insertions/duplications of 3 – 12 bp in exon 20
~2,8% lung adenocarcinomas

Shigematsu H, et al. *Cancer Res*. 2005;65(5):1642-1646.

Oncogene Addiction: *HER2* Mutations (2-3%)

- Trastuzumab +/- chemotherapy (taxanes or vinorelbine)
- Afatinib
- Lapatinib (low efficacy)

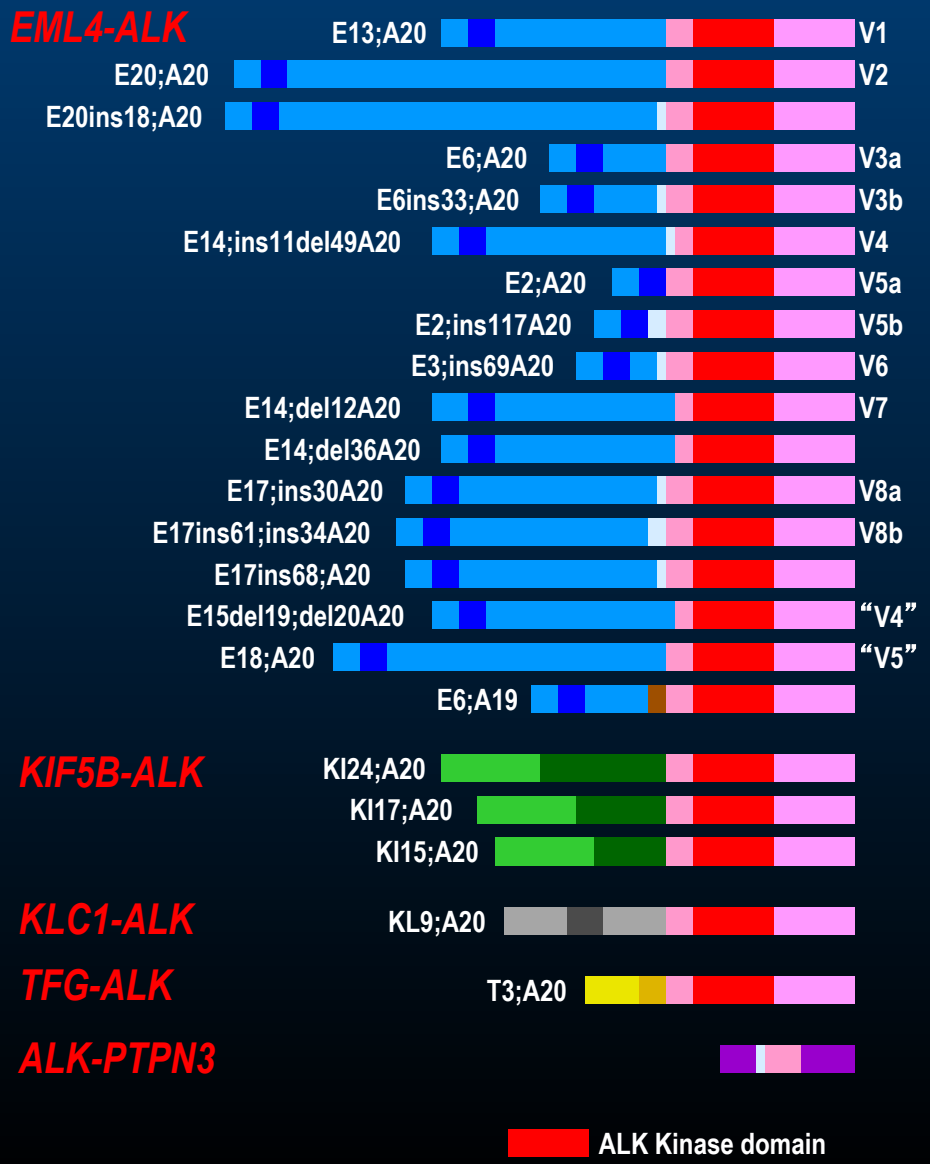


PFS, progression-free survival.

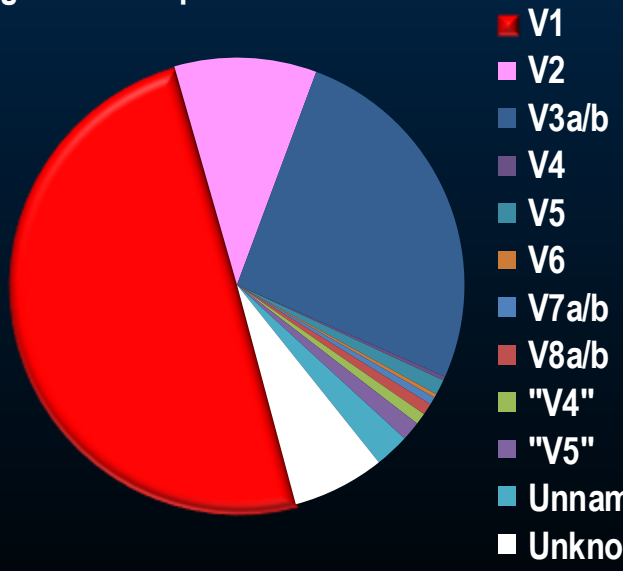
Mazieres J, et al. *J Clin Oncol*. 2013;31(16):1997-2003.

Oncogene Addiction:

ALK Fusion Transcripts (3-5%)



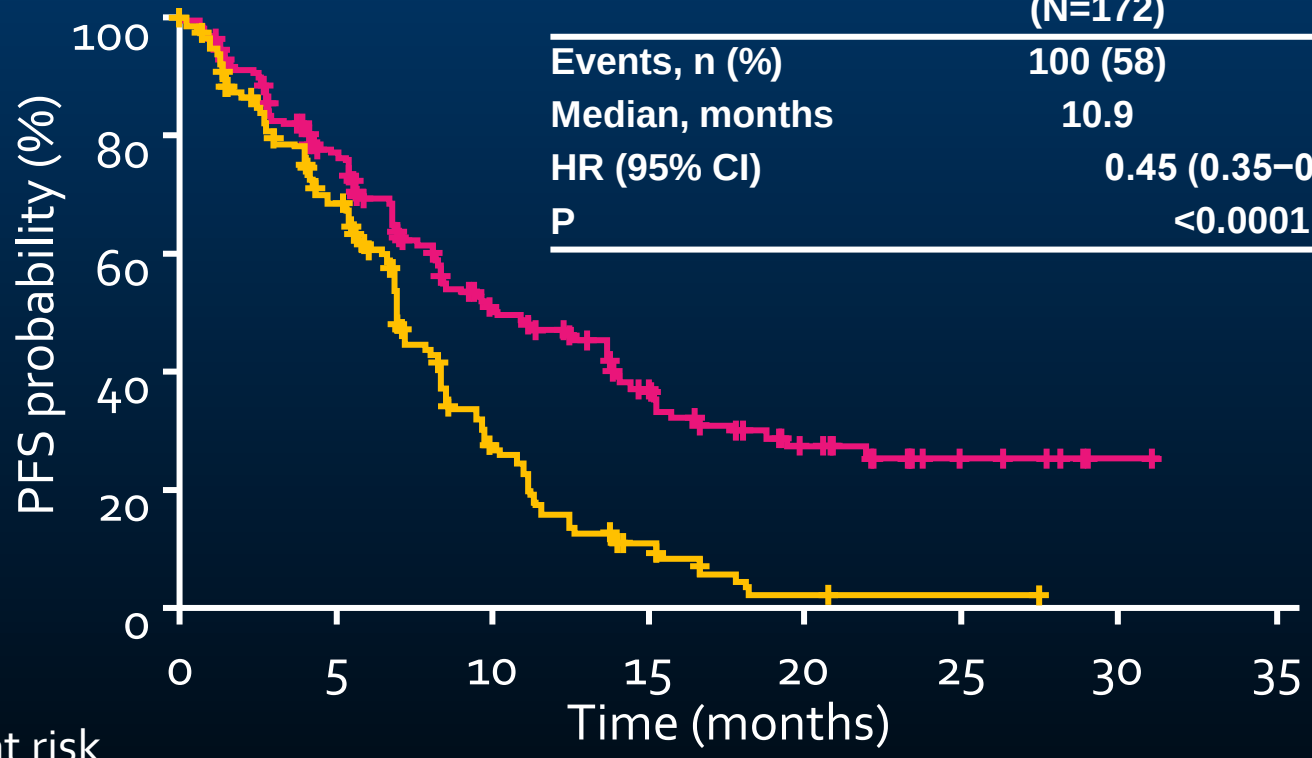
- Several *EML4-ALK* fusion variants have been identified in NSCLC that demonstrate gain-of-function properties
- ALK tyrosine kinase activity is required for transforming activity
- ALK inhibitors promote to tumour shrinkage *in vivo*, and suggests oncogene addiction, and the potential target for therapeutic intervention



V, variant.

Ou SH, et al. *Oncologist*. 2012;17(11):1351-1375.

PROFILE 1014 Results: First-line crizotinib vs. PEM/CIS or PEM/CARBO

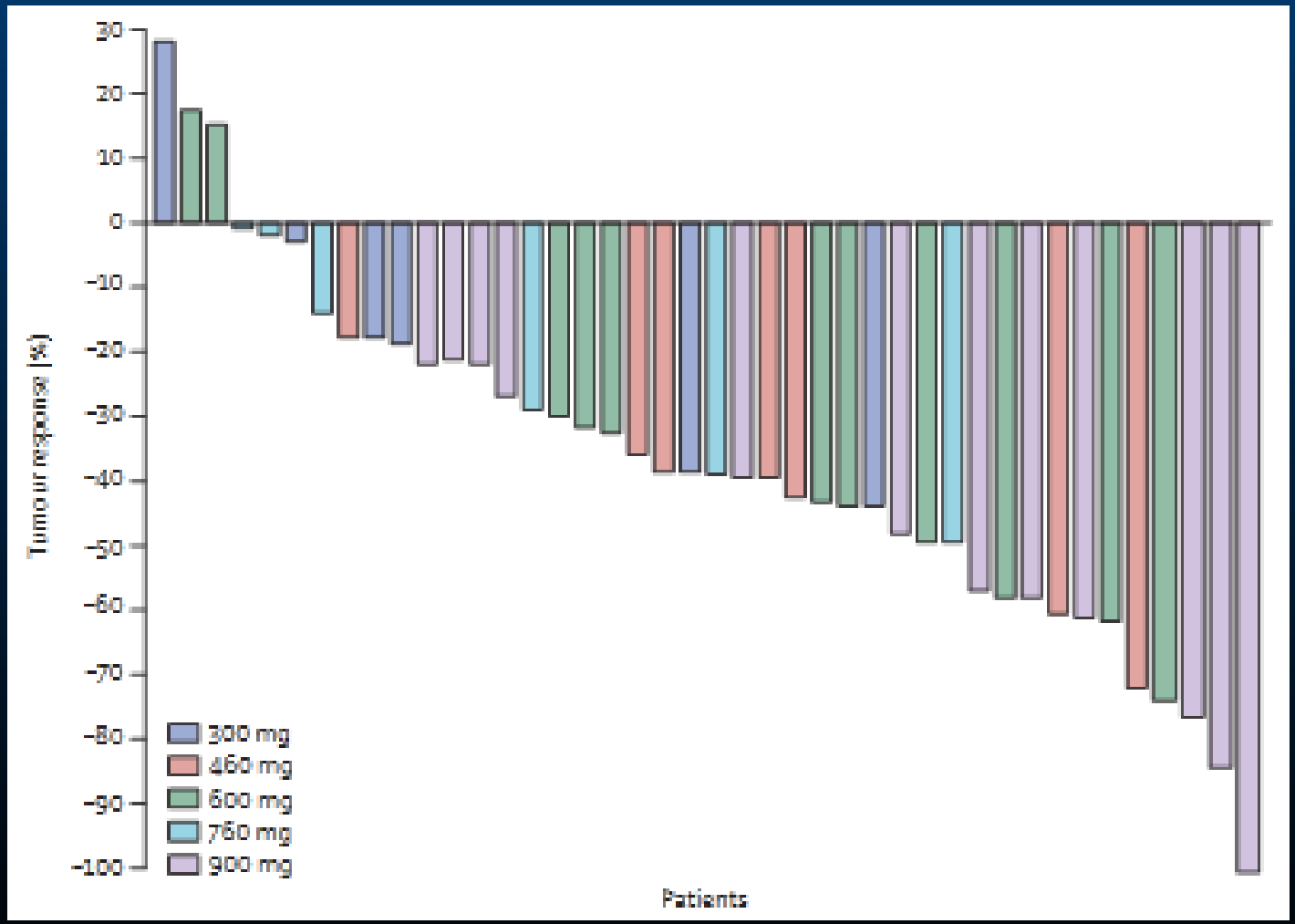


	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	
P	<0.0001	

No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

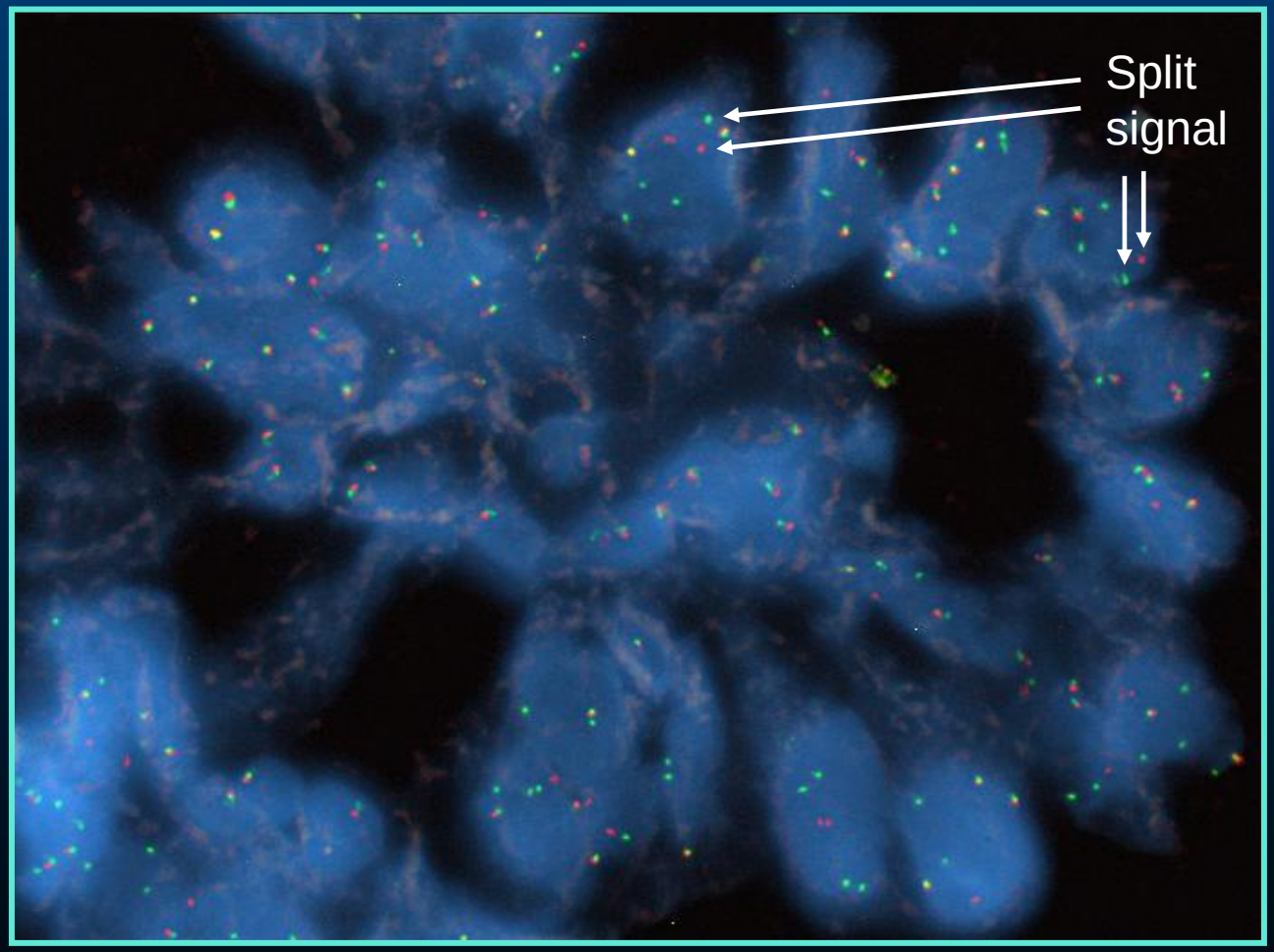
Mok et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8002)

Alectinib in crizotinib-pretreated ALK+ NSCLC patients; phase 1 data



Gadgeel S. et al. Lancet Oncol; 15: 1119

Oncogene Addiction: ROS1 (1-2%)

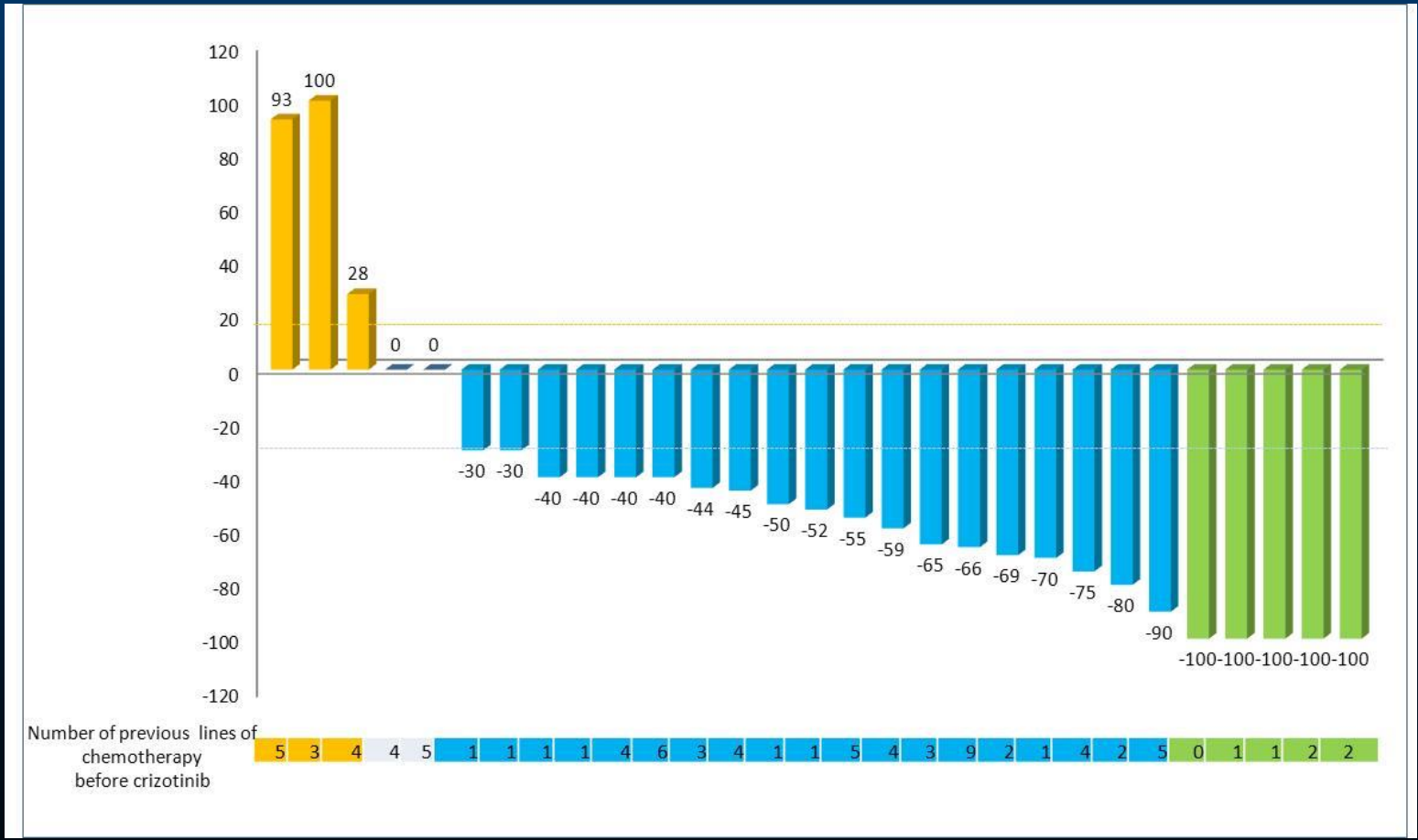


ROS1 rearrangement in a tumour from a 38-year-old patient with advanced lung adenocarcinoma

Dziadziuszko R, unpublished data.

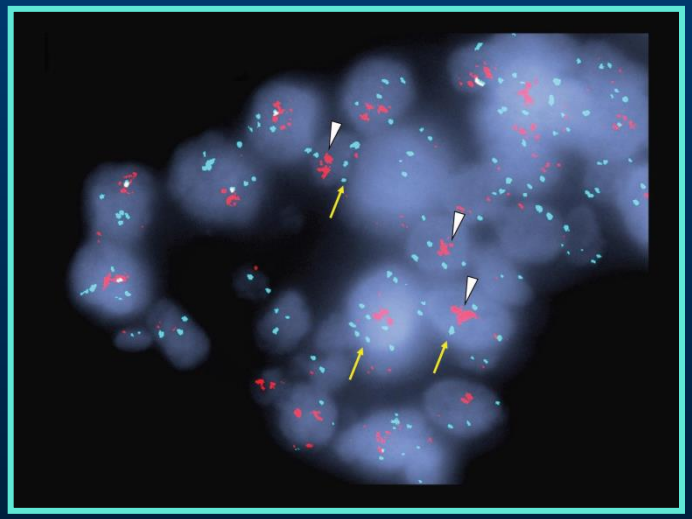
Oncogene Addiction: ROS1 (1-2%)

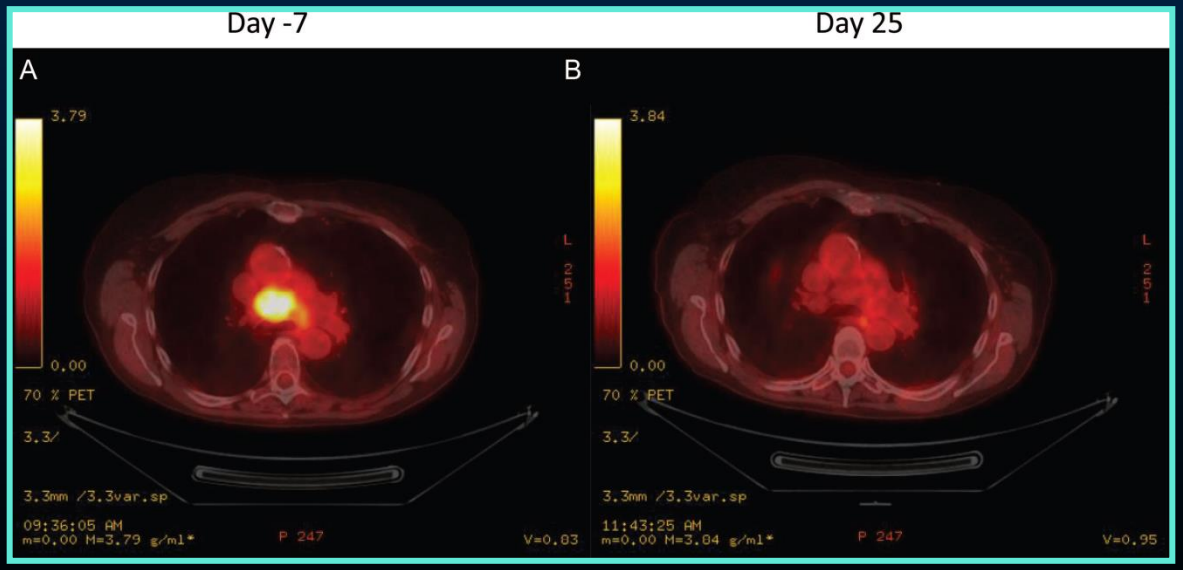
European cohort of ROS1+ patients treated with crizotinib



Mazieres J et al., data presented at ESMO 2014 Congress.

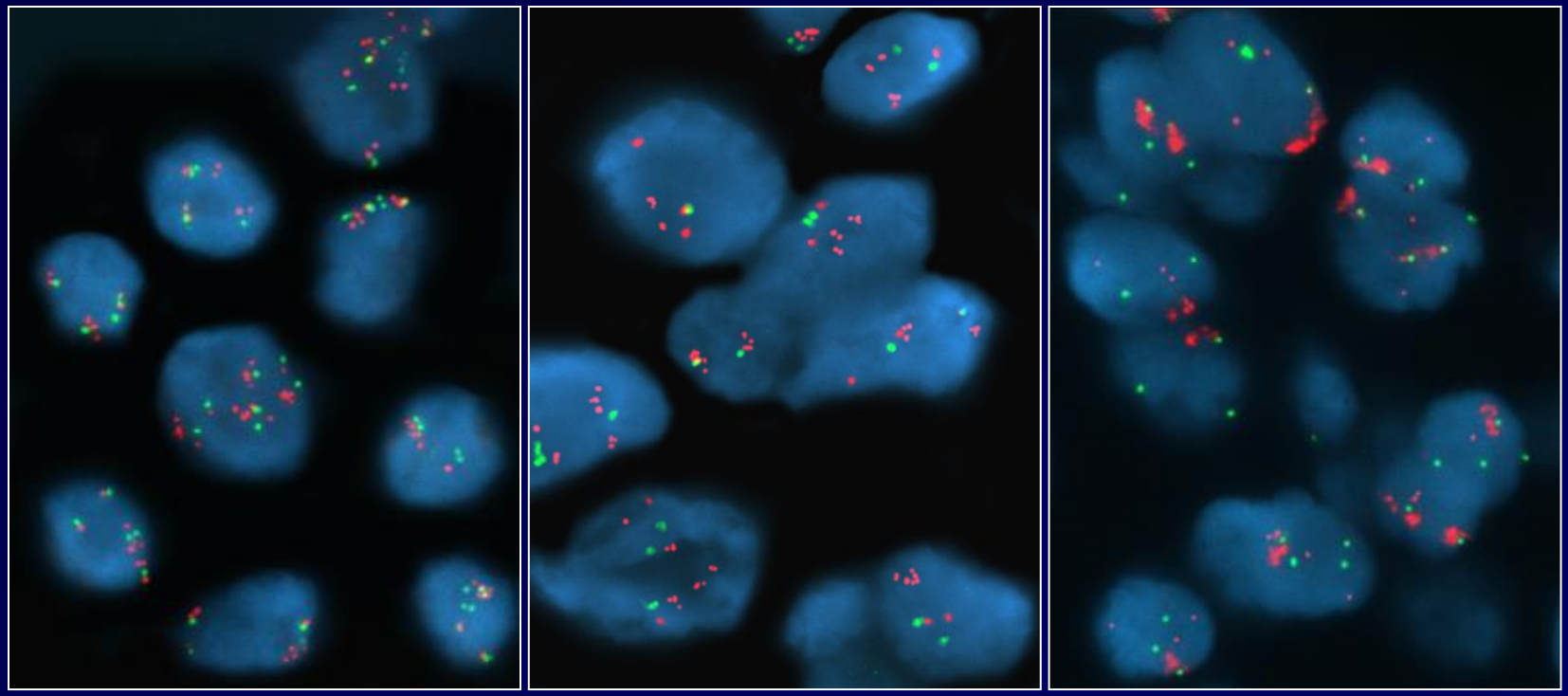
Oncogene Addiction: *MET* Amplification (2-4%)





Ou SH, et al. *J Thoracic Oncol*. 2011;6(5):942-946.

ASCO 2014 #8001: *MET* amplification cohorts determined by FISH



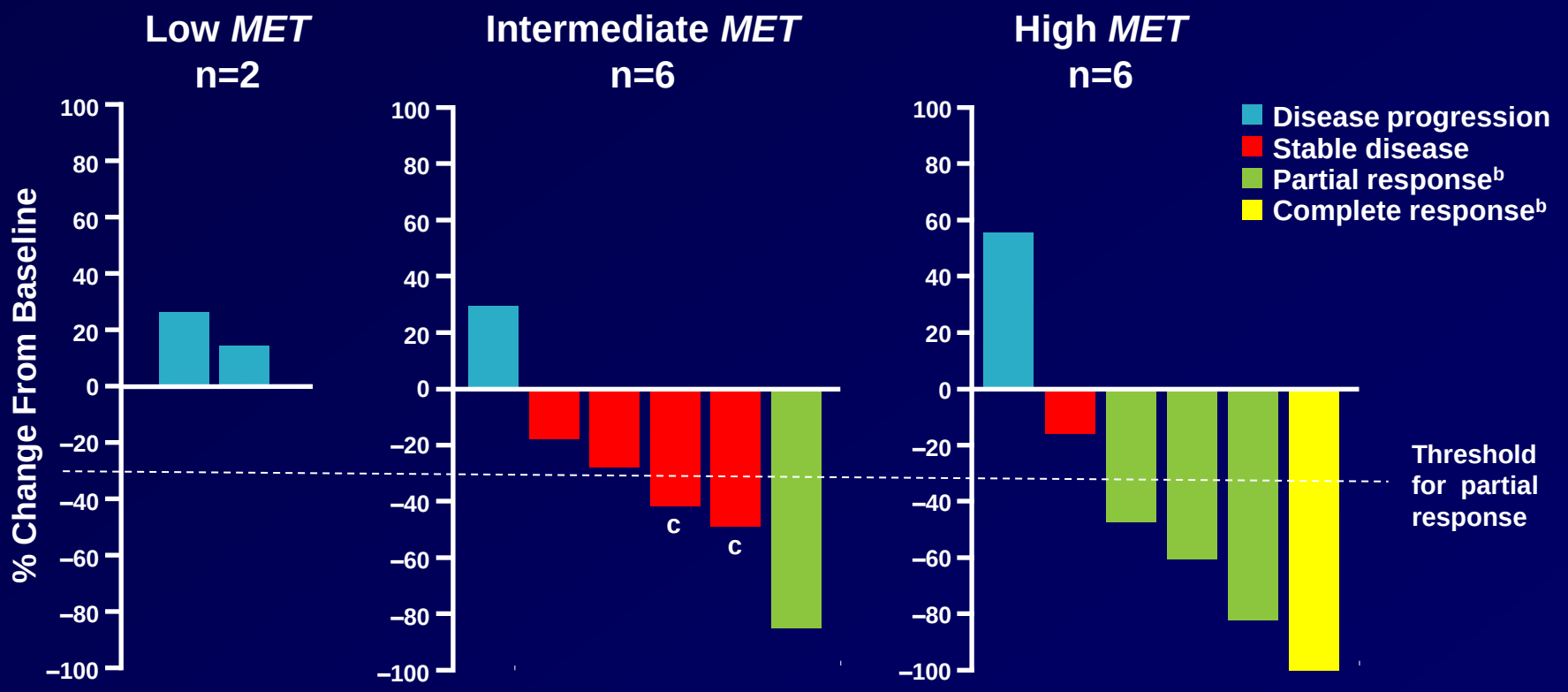
Low *MET* level	Intermediate *MET* level	High *MET* level
MET/CEP7 ratio ≥1.8–≤2.2	*MET/CEP7* ratio >2.2–<5.0	*MET/CEP7* ratio ≥5
Mean MET cell: 9.0	Mean MET cell: 7.0	Mean MET cell: 15.7
Mean CEP 7 cell: 4.7	Mean CEP 7 cell: 2.1	Mean CEP 7 cell: 2.8
Ratio: 1.9	Ratio: 3.3	Ratio: 5.6

Varella-Garcia L, University of Colorado

Camidge et al., ASCO2014 #8001.

ASCO 2014 #8001: Tumor Shrinkage Seen in Intermediate and High *MET* Cohorts

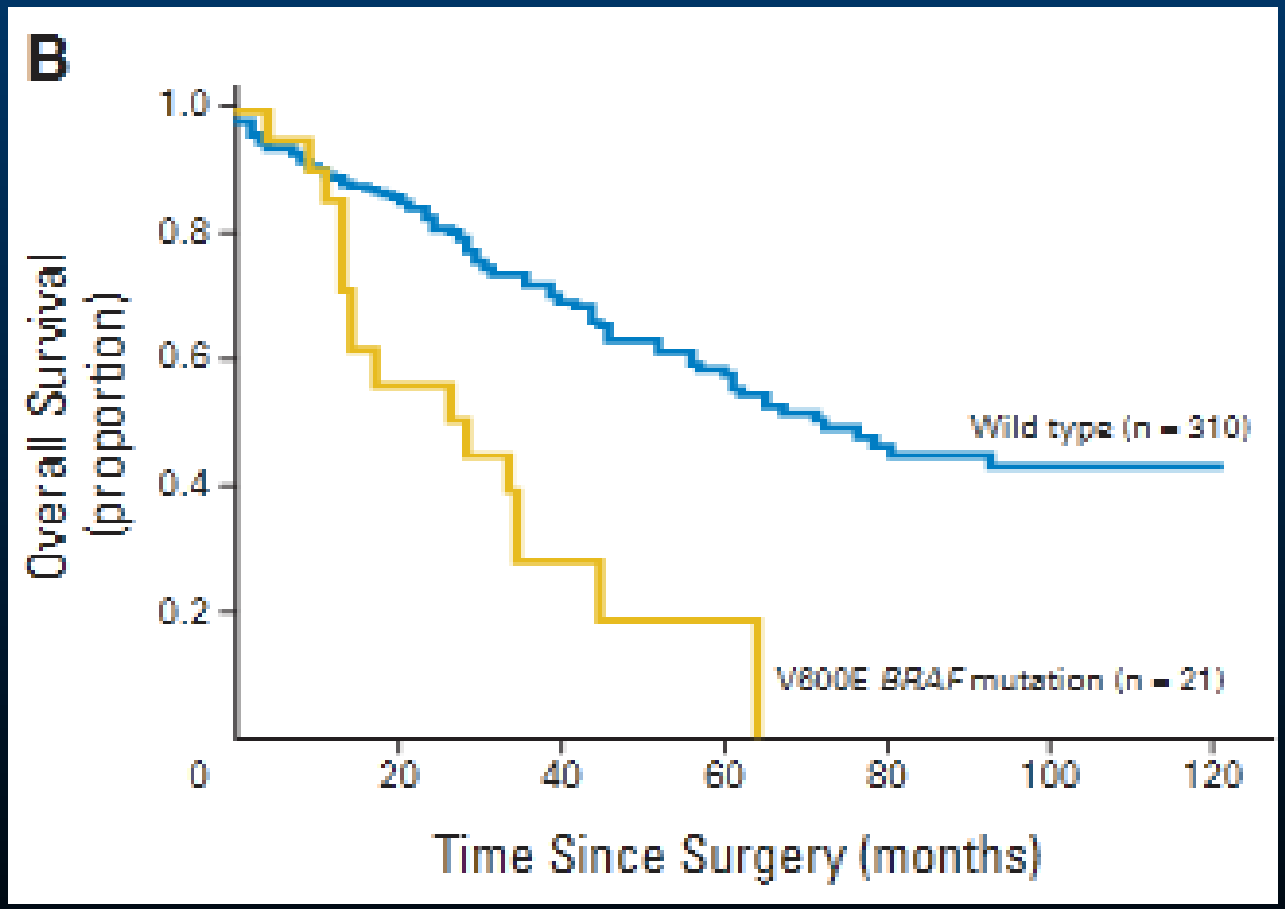
Best percent change from baseline in target tumor lesions[a] by patient



[a]Confirmed objective responses.
[b]Based on investigator assessment.
[c]Two patients in the intermediate *MET* group had an unconfirmed PR that was not confirmed in a second assessment.

Camidge et al., ASCO2014 #8001.

Oncogene Addiction: *BRAF* Mutation (1-3%)



Marchietti A. et al., J Clin Oncol 2011

ASCO 2013 #8009: Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation–positive NSCLC patients

Key patient inclusion criteria
- NSCLC
- BRAF V600E mutation
- ≥1 line prior treatment

(n=53)

→ Stage 1 Dabrafenib 150 mg bid (n=20) → Stage 2 Dabrafenib 150 mg bid (n=20)

Primary endpoint

ORR (investigator assessed) = 40%

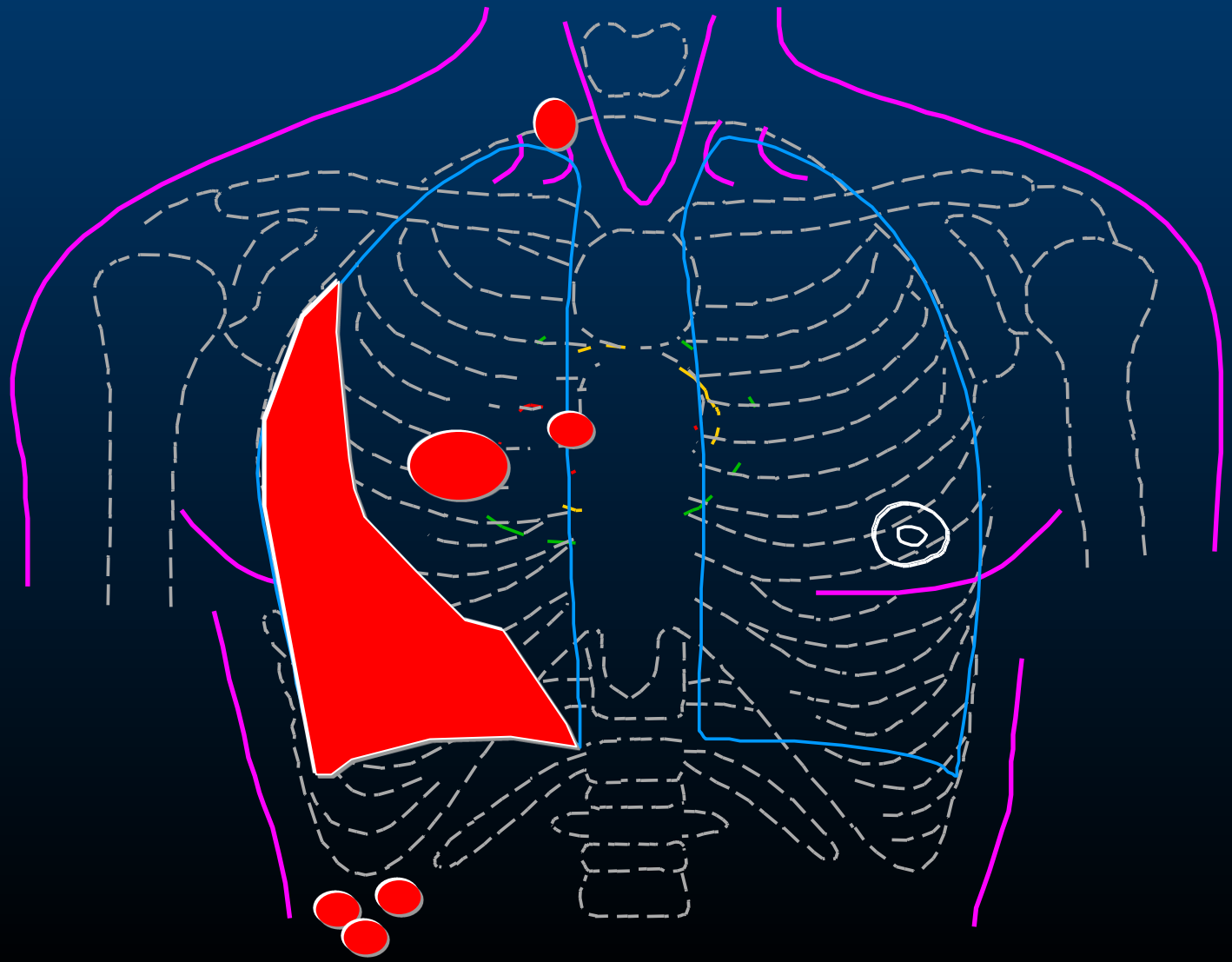
Planchard et al. J Clin Oncol 31, 2013 (suppl; abstr 8009)

What have we learned about oncogene-addicted NSCLC over the last decade?

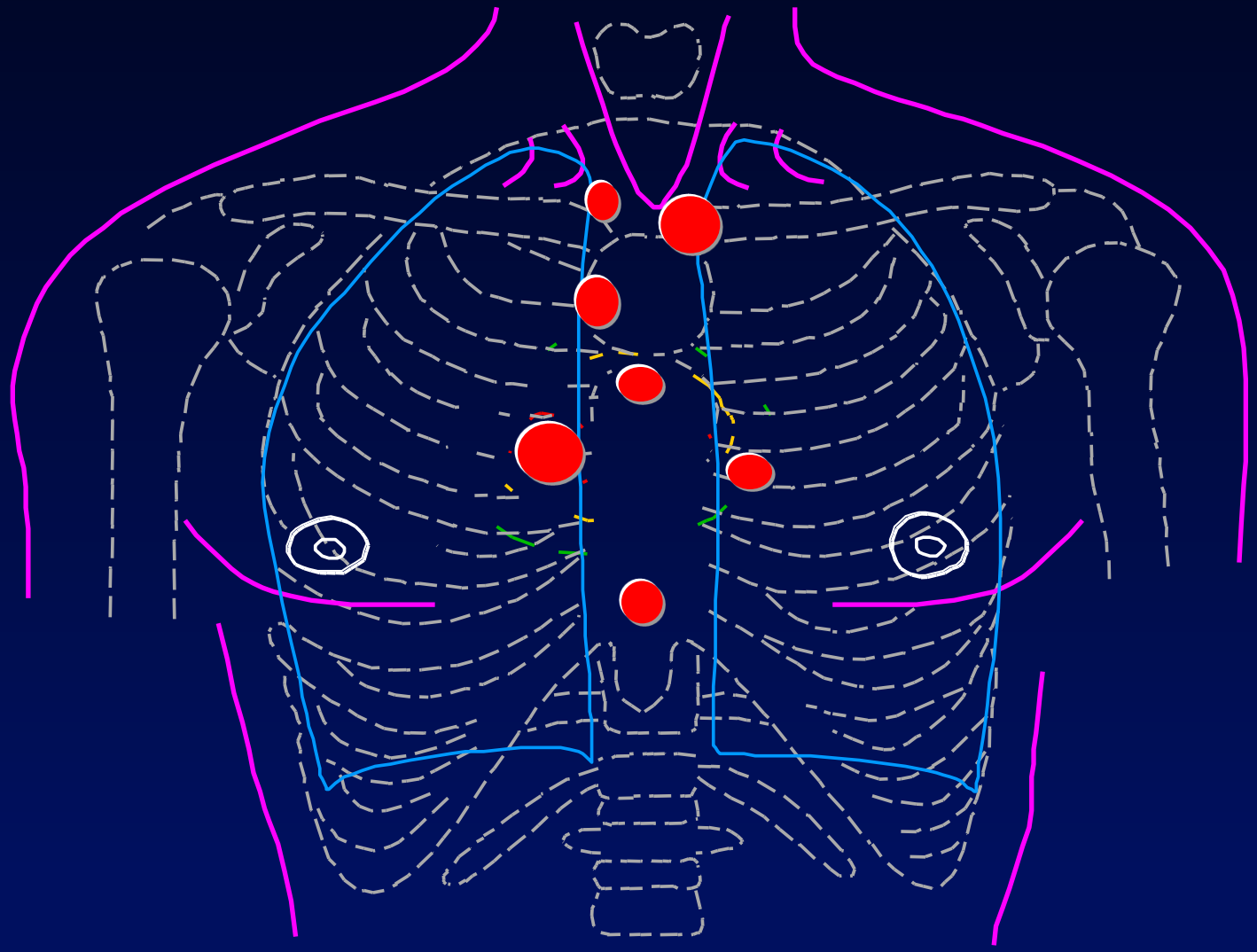
Lessons learned

1. Quick and reliable multiplex molecular testing is essential for proper identification of molecular aberrations to guide treatment decissions.
2. Each molecularly defined cohort is related to different presentation, prognosis, sensitivity to chemotherapy / radiation and targeted agents.
3. There is wide geographical variation in proportion of patients with driving molecular abnormality.

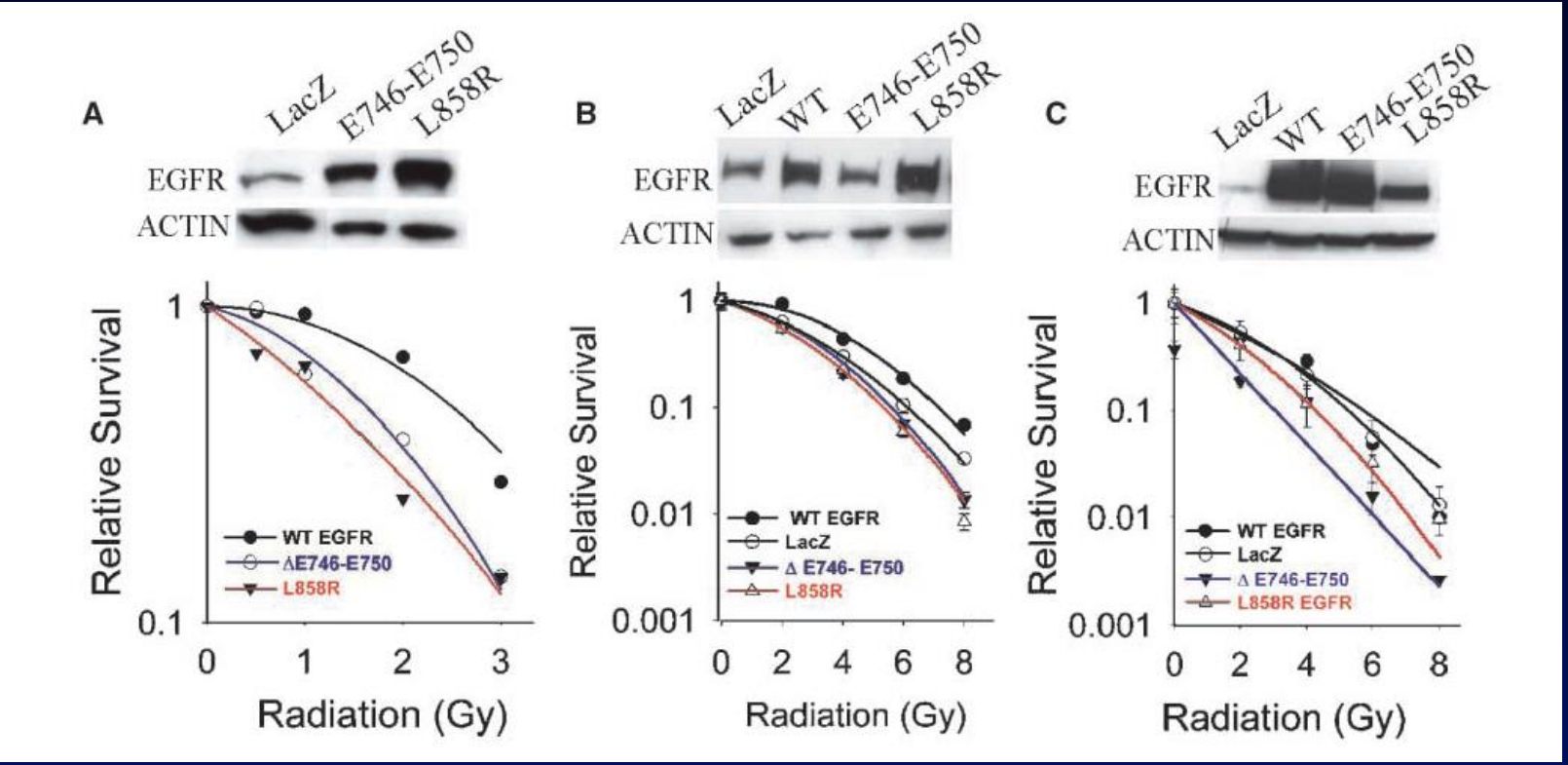
Patient 1+2+3 (35 y.o., 38 y.o., 42 y.o.)
ALK+ initial presentations



Patient 4 (42 y.o.)
- ALK+ initial presentation



Exon 19 or 21 Mutant *EGFR* cell lines have markedly increased radiation sensitivity

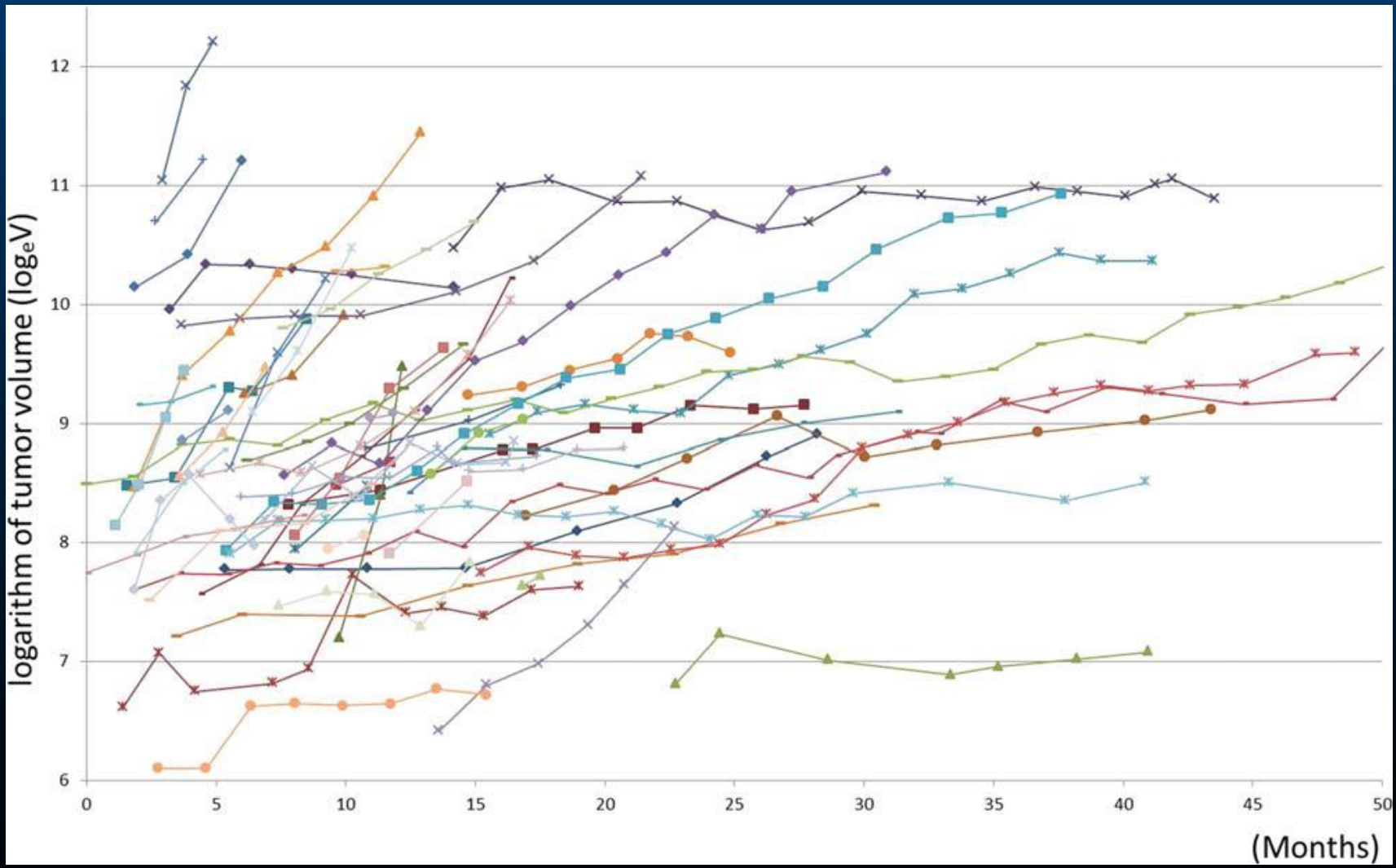


Das AK et al., Cancer Res 2006

Lessons learned

4. Different types of progression: CNS only („pharmacodynamic"), oligometastatic, wide-spread systemic.
5. Treatment beyond progression may provide additional benefit
6. Upon resistence, tumors are often still dependent on the target

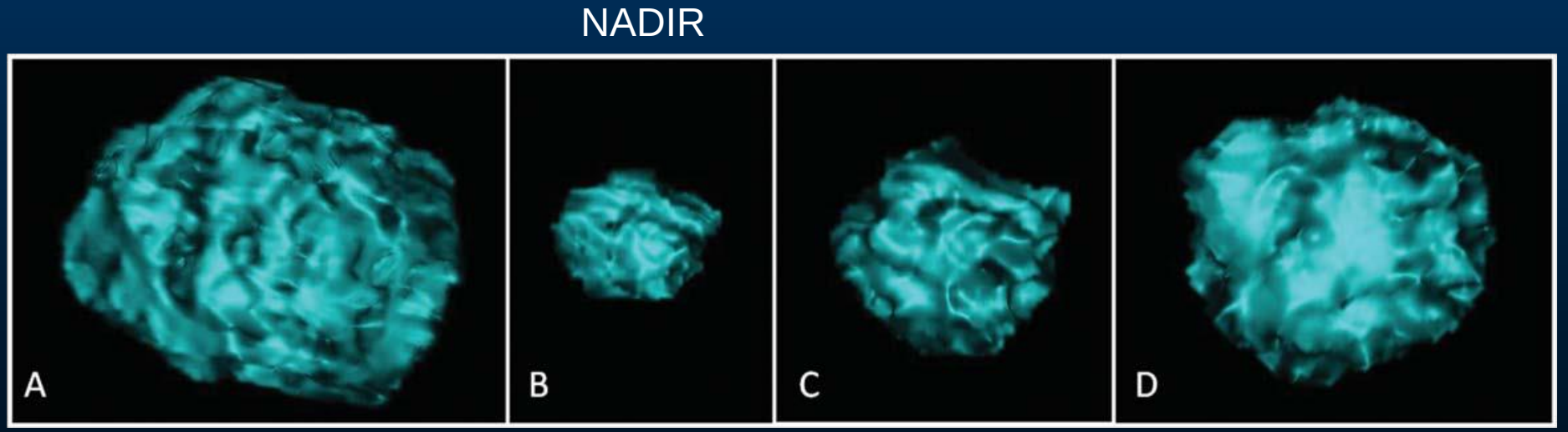
What is the evidence to use EGFR TKIs beyond progression? When to stop?



Nishino M et al. Cancer 2013;119:3761-3768

What is the evidence to use EGFR TKIs beyond progression? When to stop?

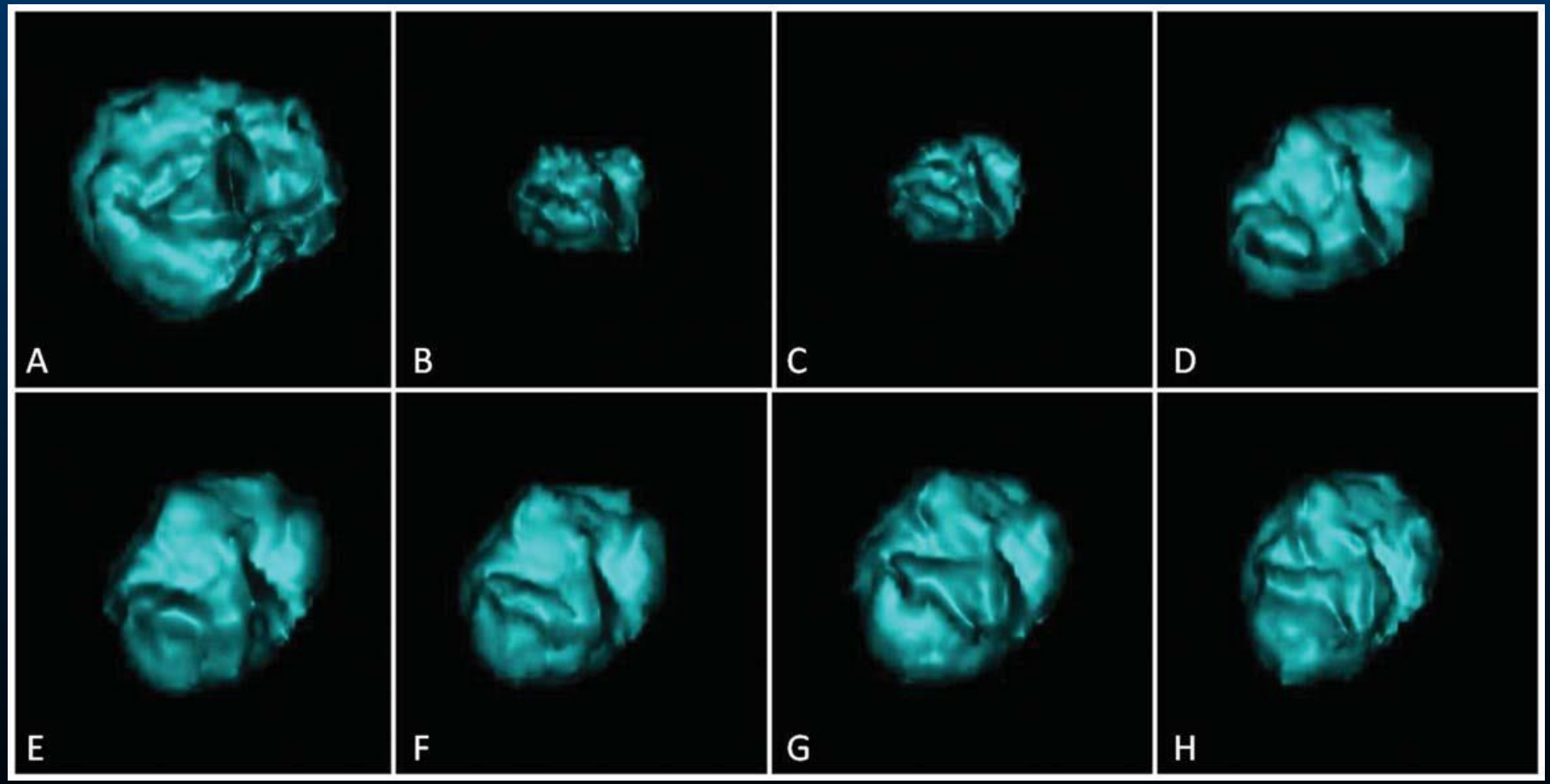
Example of rapidly growing target nodule



Nishino M et al. Cancer 2013;119:3761-3768

What is the evidence to use EGFR TKIs beyond progression? When to stop?

Example of slowly growing target nodule



$\log_e V = 0.09 mm^3/month$

Nishino M et al. Cancer 2013;119:3761-3768

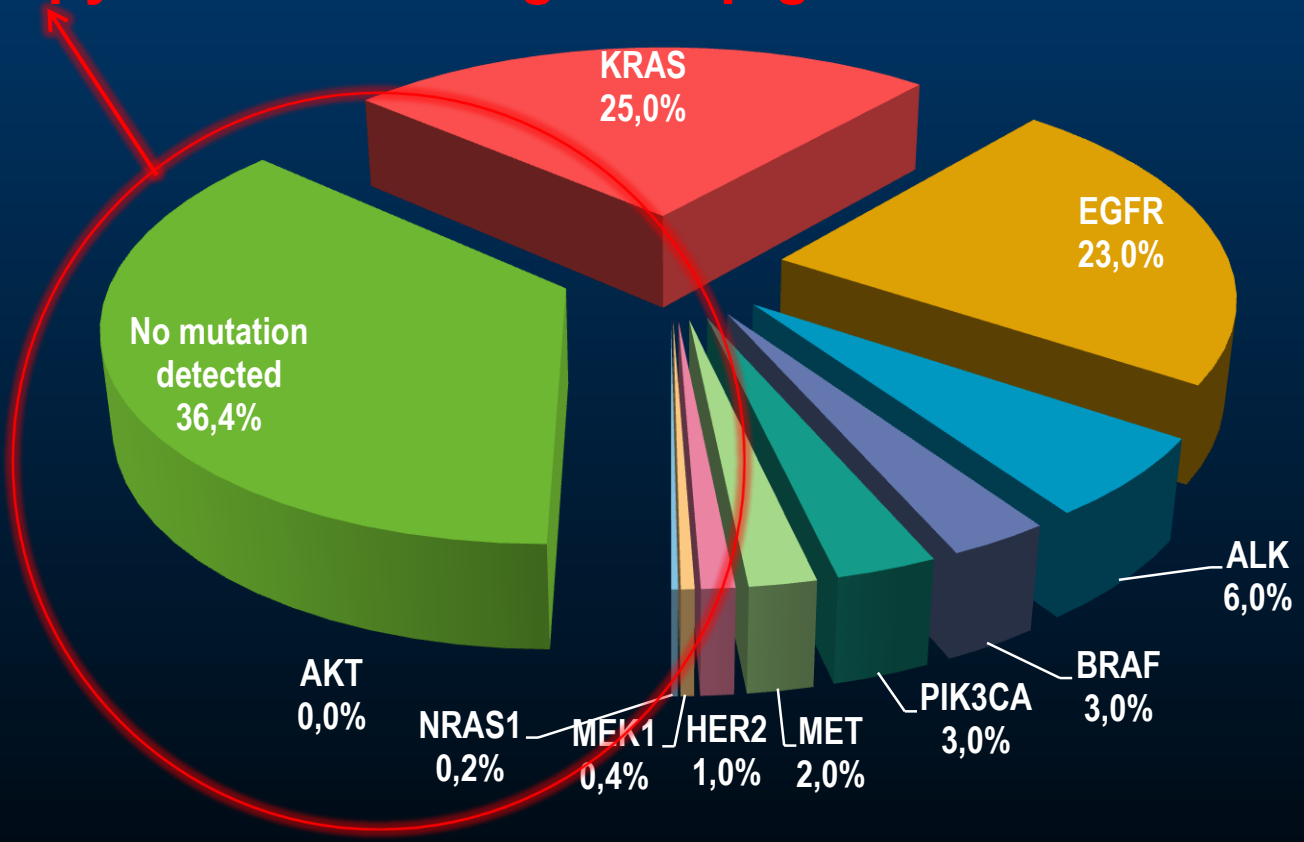
What is the evidence to use EGFR TKIs beyond progression? When to stop?

- Current limited data suggest that treatment beyond progression may offer additional benefit to selected asymptomatic patients
- RECIST progression criteria not very useful; other criteria are being defined ($log_eV>0.15mm^3$/month)
- Treatment should be stopped and switched to chemotherapy upon symptomatic progression, rapid tumor growth, decline of performance status

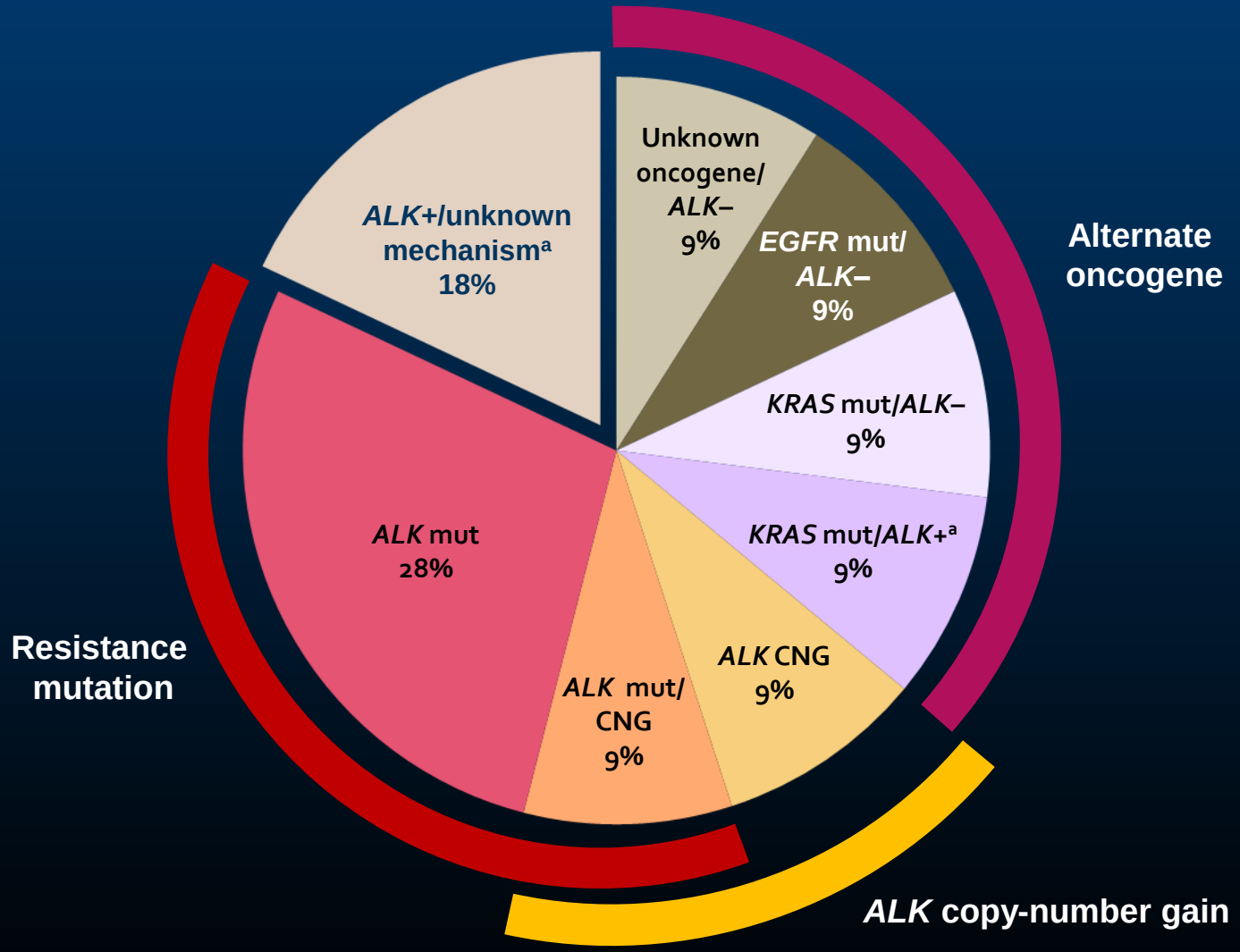
Questions for the future

Questions for the future:

Other oncogenes? Tumor supressor genes?
Gene copy number changes? Epigenetic?



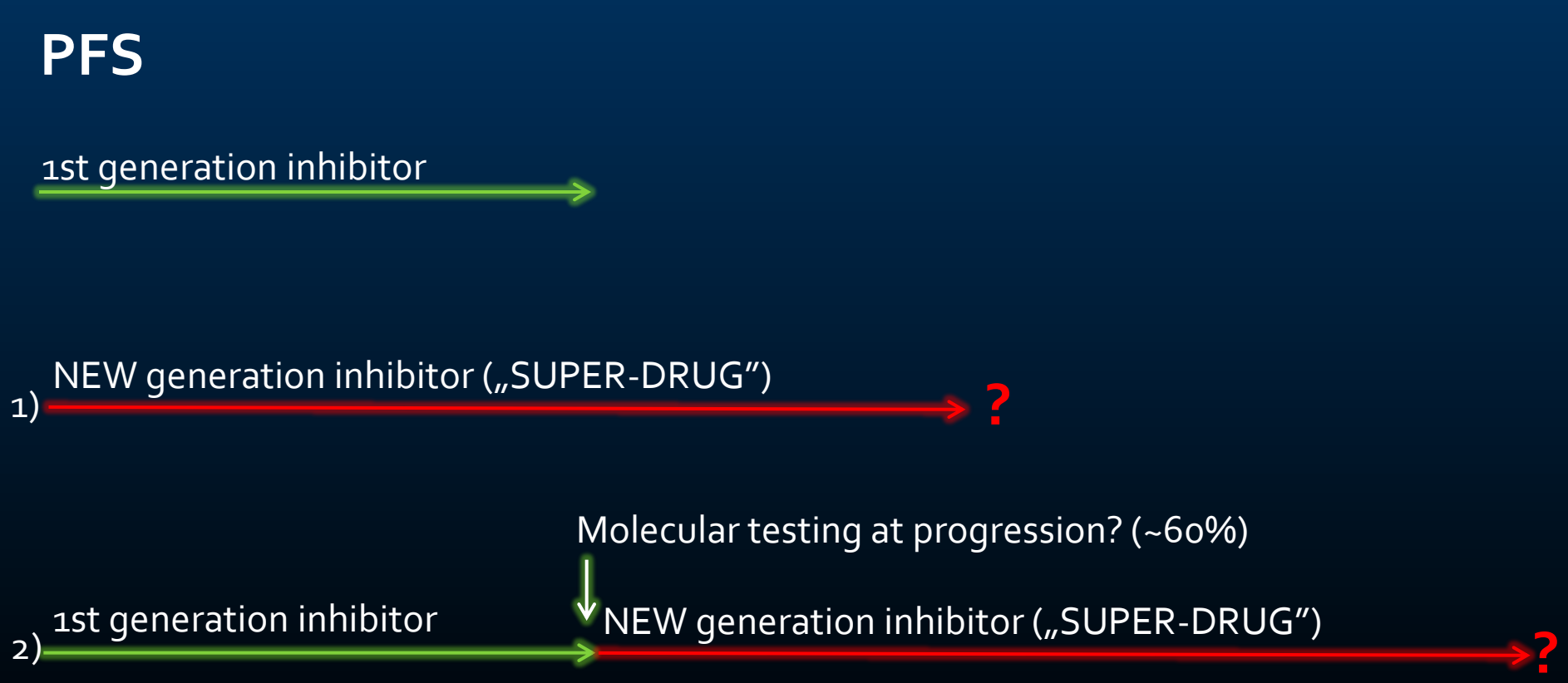
Questions for the future:
Resistance mechanisms (example: crizotinib)



CNG, copy-number gain; mut, mutation
[a]One patient had intrinsic resistance within this category

Doebele RC, et al. *Clin Cancer Res* 2012;18:1472–1482

Questions for the future: Optimal place of a „super-drug”?



Take-home messages

- Identification of oncogene-addicted NSCLC subsets becomes essential part of routine practice with clear impact on patient's outcomes
- Understanding the mechanisms of resistance is a key to further success
- Place of novel „super-drug" inhibibitors needs to be properly tested in view of sequencing issues
- Second biopsies and liquid biopsies will become part of routine care in the next decade