1st Line management of EGFR/ALK NSCLC

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Pretreatment Characteristics and Sensitivity to EGFR TKIs – Phase II Trials 2003-4

Predictive	Not Predictive
Never Smoking	EGFR positivity (IHC)
AdenoCa, esp with BAC features	PS
Female Gender	Time since last chemo
Asian Ethnicity	Number or type of prior regimens

1.Fukuoka M, Yano S, Giaccone G et al. *J Clin Oncol.* 2003;21:2237–2246.
2.Kris MG, Natale RB, Herbst RS, et al. *JAMA.* 2003; 290:2149-2158.
3.Pérez-Soler et al. *J Clin Oncol* 2004 22 (16): 3238

The NEW ENGLAND JOURNAL *of* MEDICINE

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib.

Thomas J. Lynch, DW Bell, R Sordella, S Gurubhagavatula, RA Okimoto, BW Brannigan, PL Harris, Sara M. Haserlat, JG Supko, FG Haluska, DN Louis, DC Christiani, J Settleman, and DA Haber

20 May 2004; Vol. 350:2129-2139

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy.

J. Guillermo Paez, Pasi A. Jänne, JC Lee, S Tracy, H Greulich, S Gabriel, P Herman, FJ Kaye, N Lindeman, TJ Boggon, K Naoki, H Sasaki, Y Fujii, Michael J. Eck, William R. Sellers, BE Johnson, and M Meyerson

4 June 2004; Vol. 304:1497-1500

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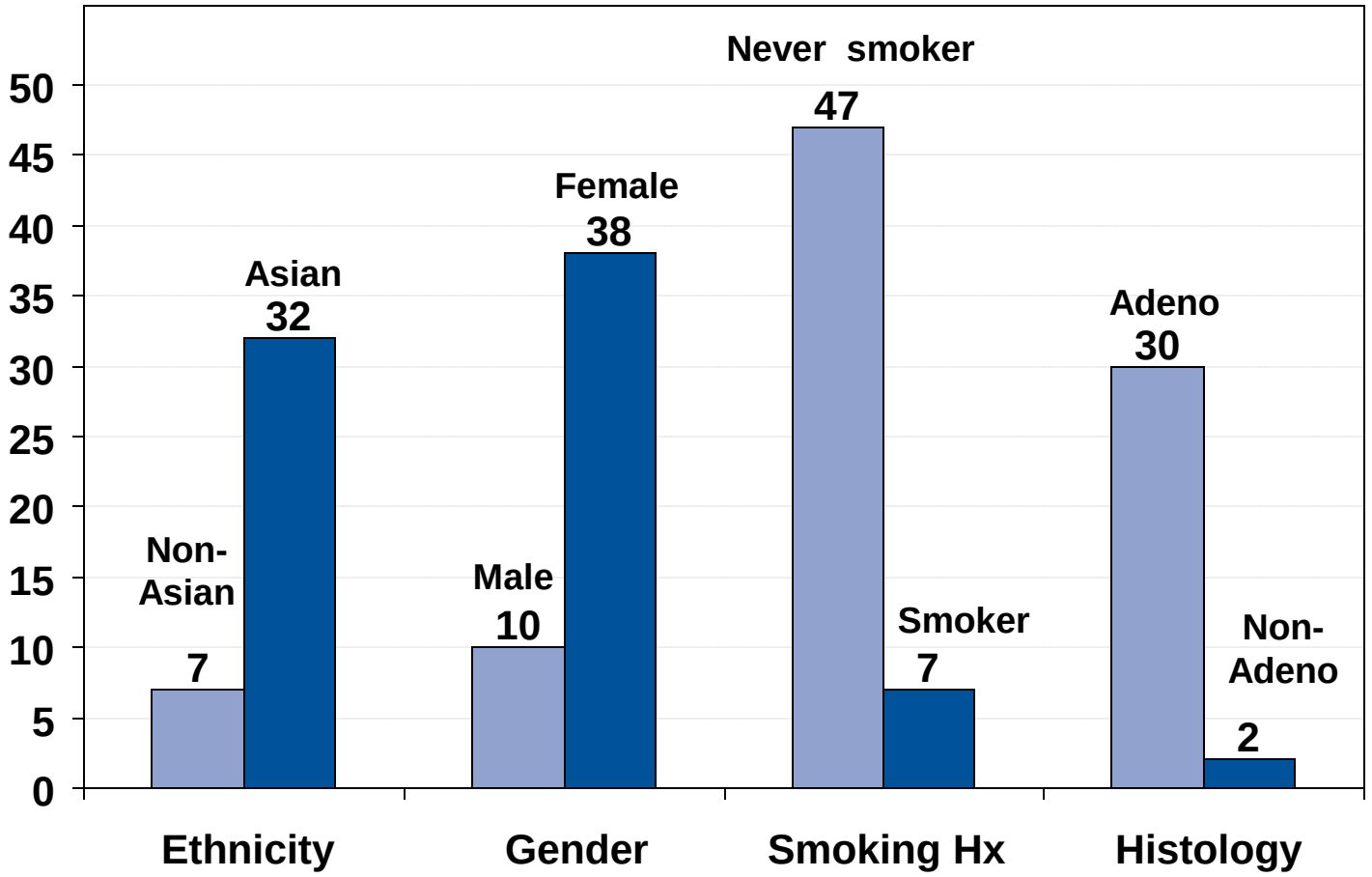
Incidence of *EGFR* Mutations According to Phenotype (N=2880)

(Mitsudomi et al. *Cancer Science* 2007)



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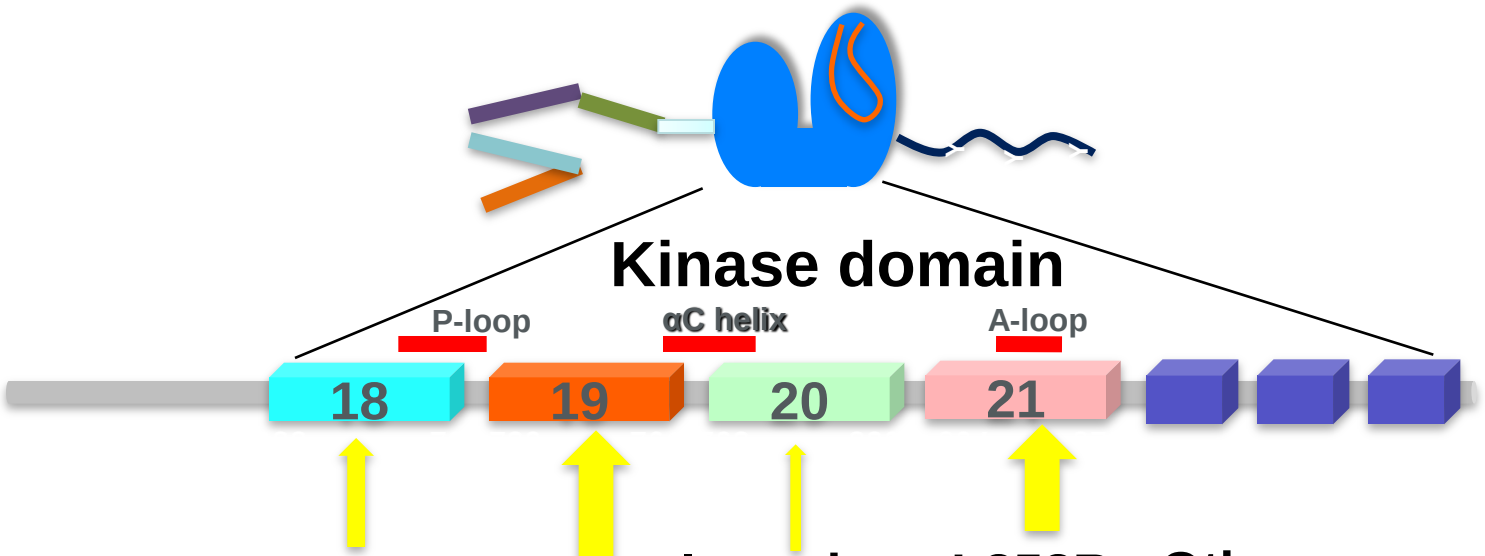
EGFR Mutation: Distribution and Incidence



	G719	Deletion	Insertion	L858R	Others
Incidence (N = 569)	3.2%	48.2%*	3.7%**	42.7%*	2.2%

*Activating mutations with increased EGFR-TKI sensitivity.
**Resistance mutations

Mitsudomi T et al. *Cancer Sci*. 2007;98:1817-1824.

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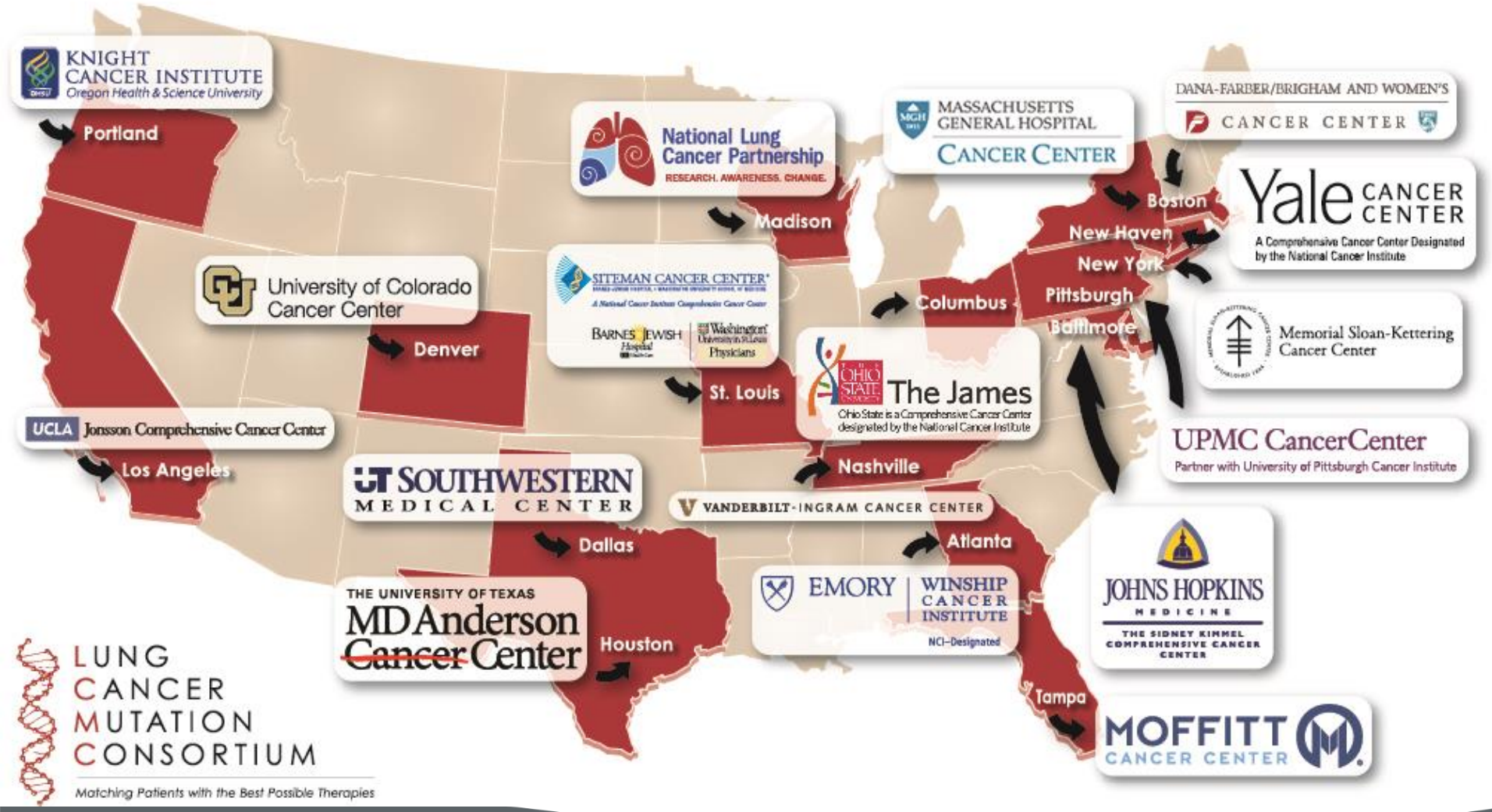
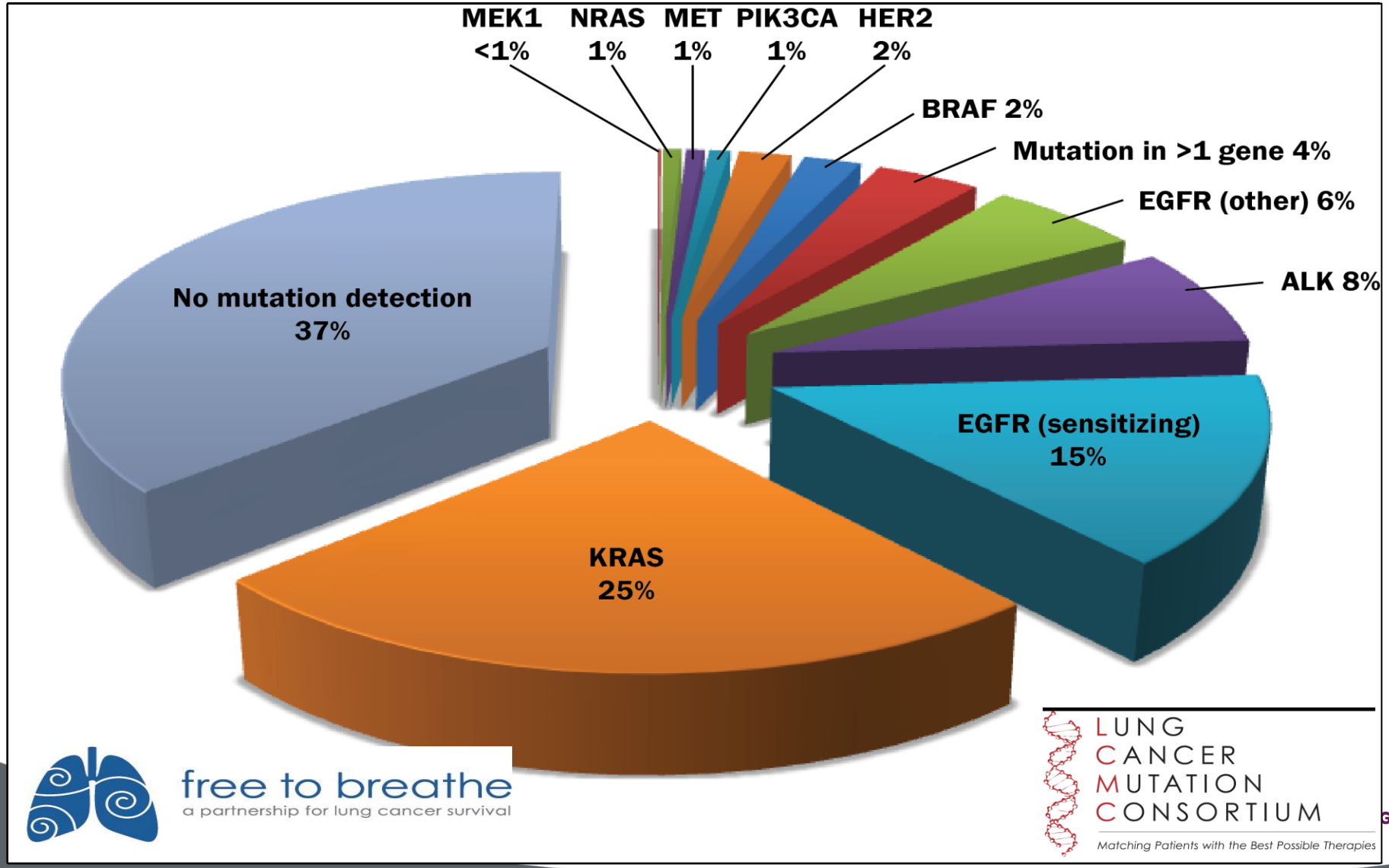
Lung Cancer Mutation Consortium Sites



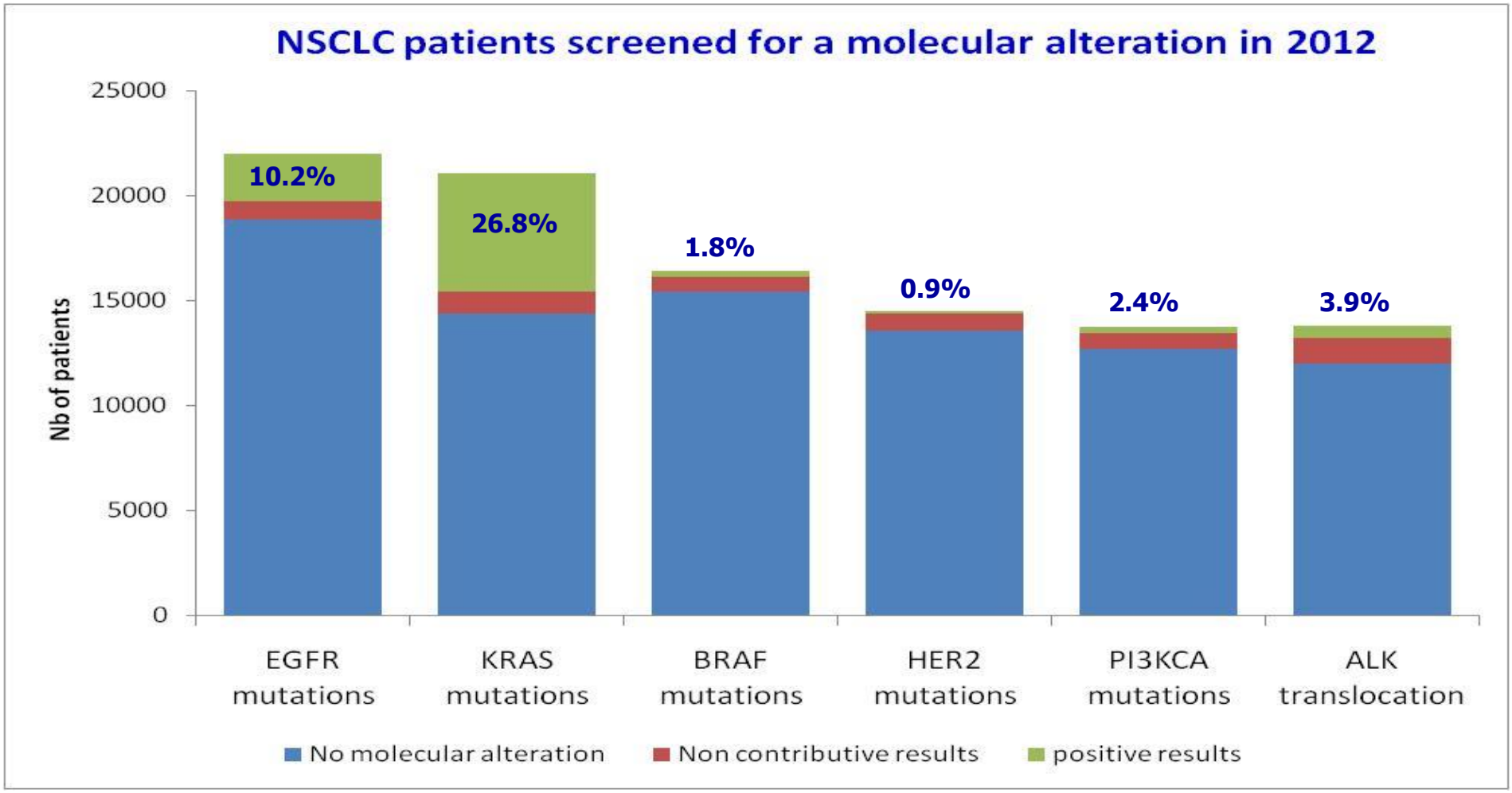
LCMC: Frequency of Oncogenic Drivers
733 Specimens with All 10 Drivers Assayed



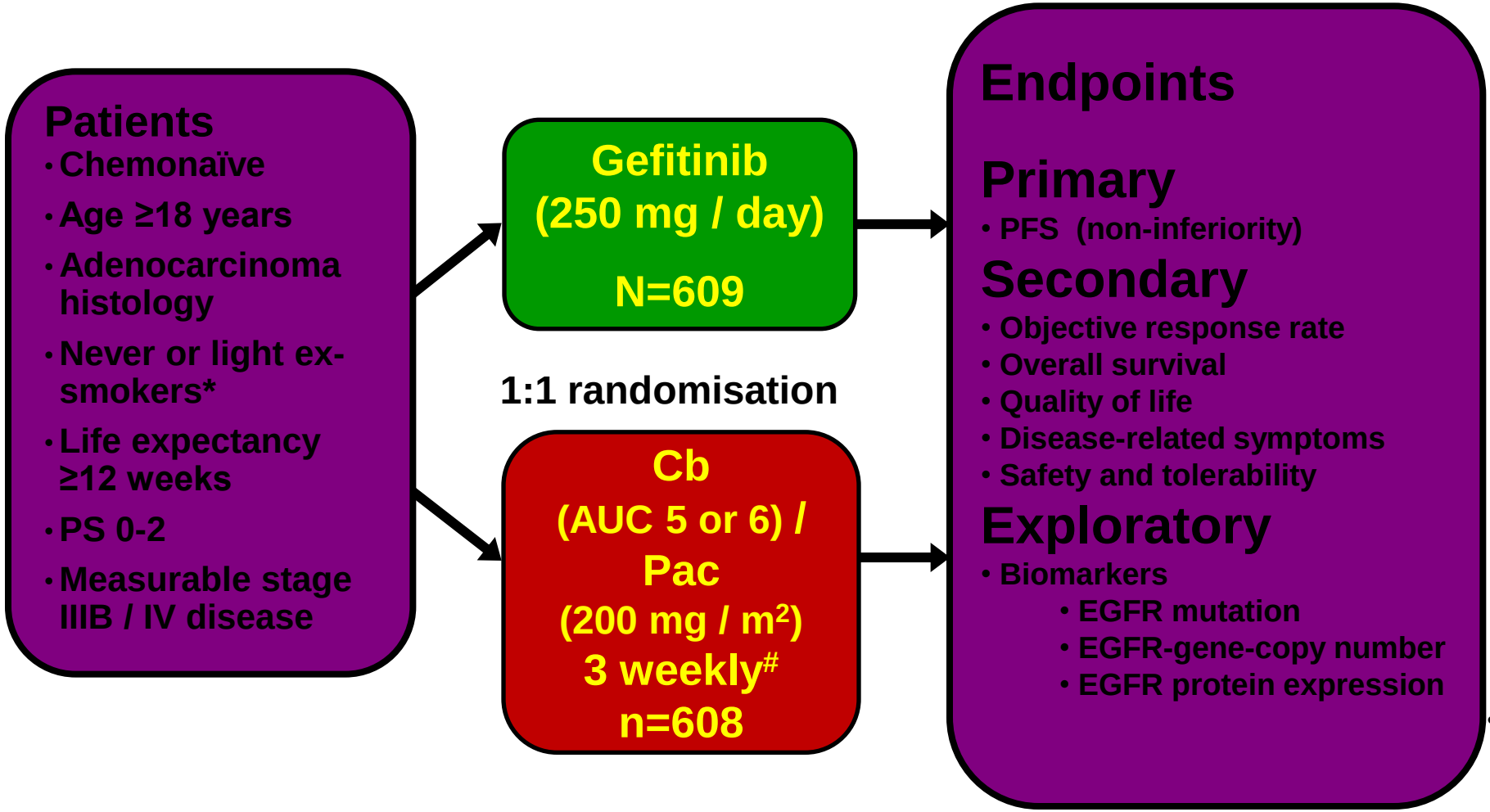
free to breathe
a partnership for lung cancer survival

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

The French Experience (2012)



IPASS Study design



*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

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Mok et al, N Engl J Med, 2009

IPASS Study design

Patients
- Chemor
- Age ≥18
- Adenoc histolog
- Never o smoker
- Life exp ≥12 wee
- PS 0-2
- Measur IIIB / IV

Homogeneous Population

100% Asian
100% Adenocarcinoma
79% Female
94% Never Smokers

3 weekly#
n=608

Endpoints

ate

toms

- EGFR-gene-copy number
- EGFR protein expression

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

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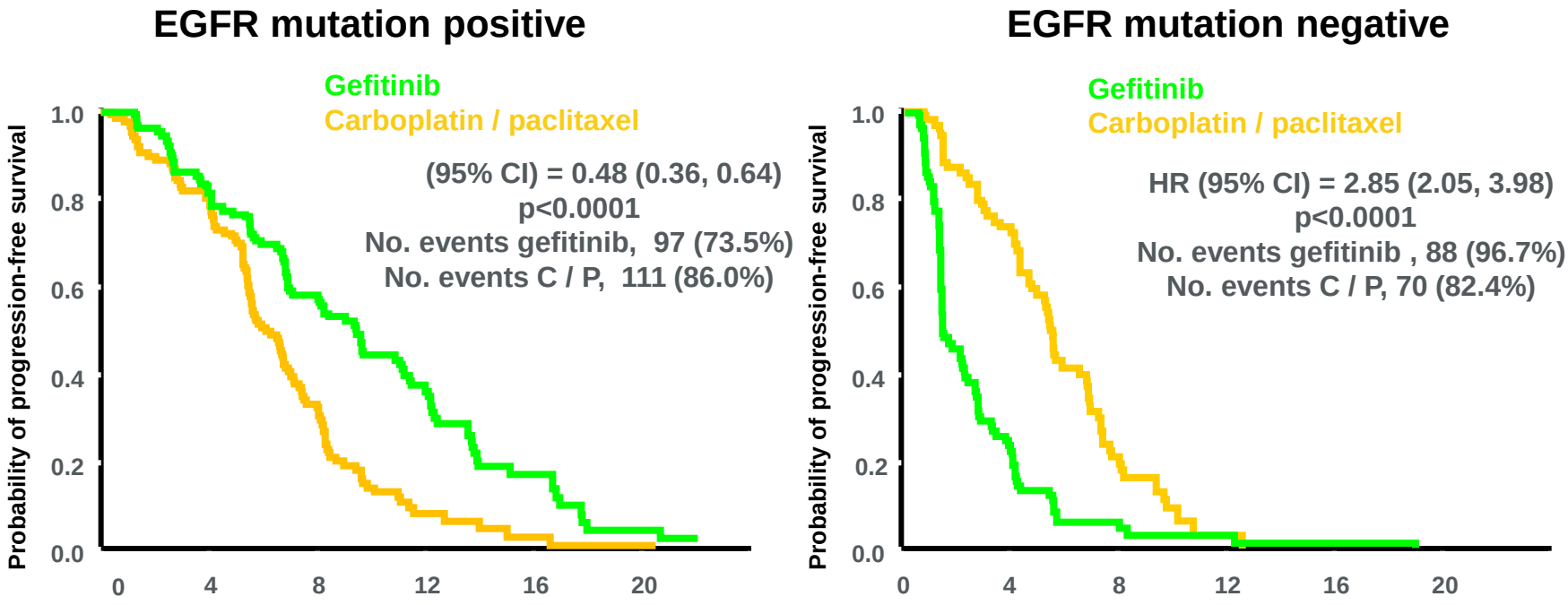
Mok et al, N Engl J Med, 2009

Progression-Free Survival in EGFR Mutation Positive and Negative Patients (n=437)

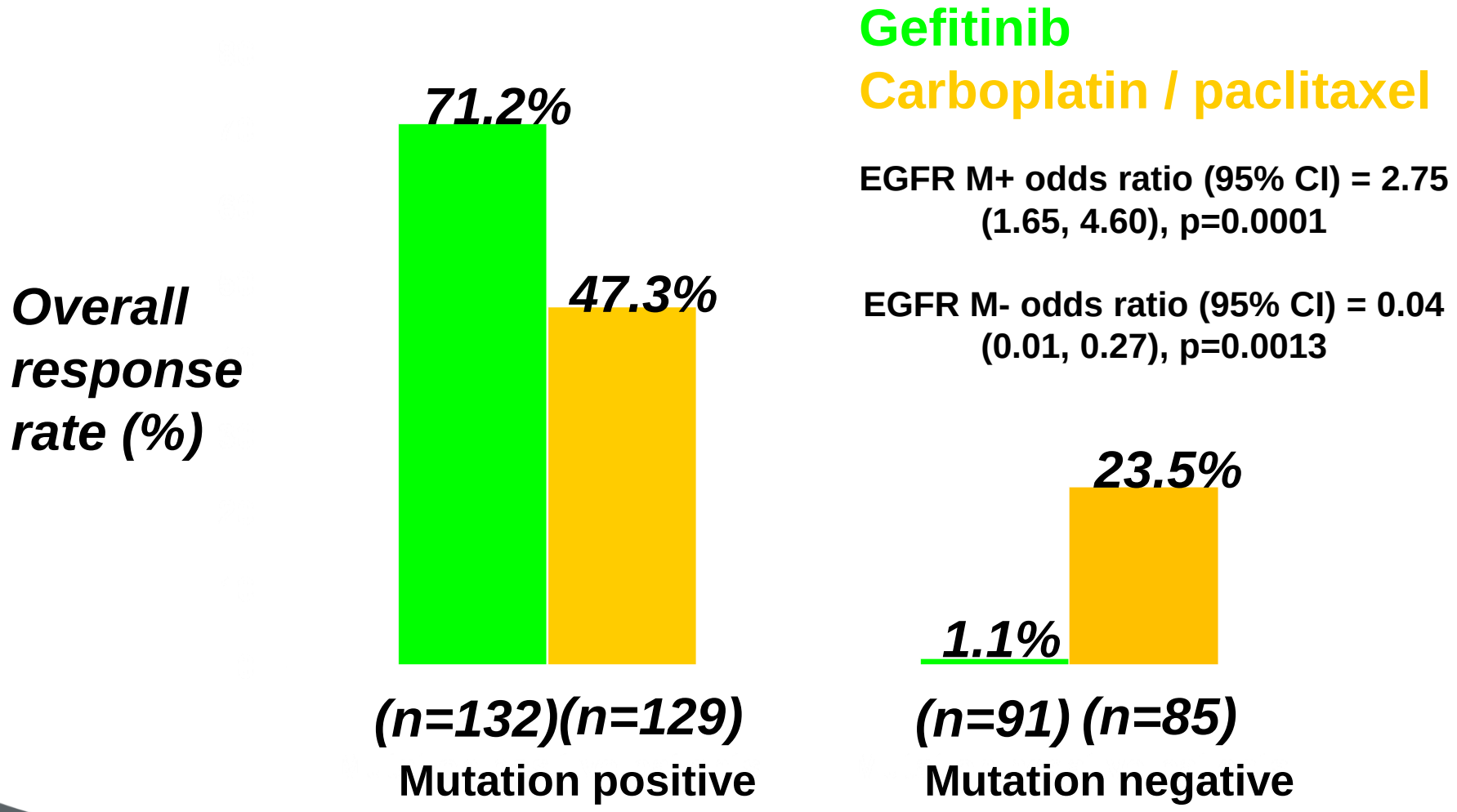


Treatment by subgroup interaction test, p<0.0001

EGFR mutation rate – 60%

Mok et al, N Engl J Med, 2009

Objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Mok et al, N Engl J Med, 2009

Studies Using EGFR TKIs as Front-Line Treatment

Trial	TKI	Chemo	Type of mutations N = EGFR mut +	No. Patients	Median PFS (months) Response Rate (%)	HR
IPASS (Asia)	gefitinib	carbo/ taxol	T29 (V1) 266	261	9.5 vs 6.3 (inv) 71.2% vs 47.3%	0.48 (0.36-0.64) P<0.01
NEJSG (Japan)	gefitinib	carbo/ taxol	Del19/L858R (94%)	230	10.8 vs 5.4 (ind)	0.30 (0.22-0.41) P<0.001
WJOG (Japan)	gefitinib	cis/doc	Del19/L858R	177	9.2 vs 6.3 (inv)	0.49 (0.34-0.71) p<0.0001
EURTAC (Spain, France, Italy)	erlotinib	cis/doc gem/cis carbo/ doc carbo/gem	Del19/L858R 135	173	9.7 vs 5.2 (inv) 10.4 vs 5.2 (label)	Inv: 0.42 (0.27-0.64) p<0.0001 Ind: 0.37 (0.25-0.54) p=0.0001
OPTIMAL (China)	erlotinib	carbo /gem	Del19/L858R 154	165	13.1 vs 4.6 (inv) 83% vs 36%	0.16 (0.1-0.26) p<0.0001
LUX-Lung 3	afatinib	pem/cis	T29 (V2) 308 (L858R/Del 19)	345 (ITT) 308 (common M+)	11.1 vs 6.9 (ind) 56% vs 23%	Ind: 0.58 (0.43-0.78) p=0.0004
					13.6 vs 6.0 (ind)	Ind: 0.47 (0.34-0.65) p=0.0001
LUX-Lung 6	Afatinib	gem/cis	324 (L858R/del 19)	364	11.0 vs. 5.6 (ind) 67% vs. 23%	Ind: 0.28 (0.20-0.39) P<0.0001

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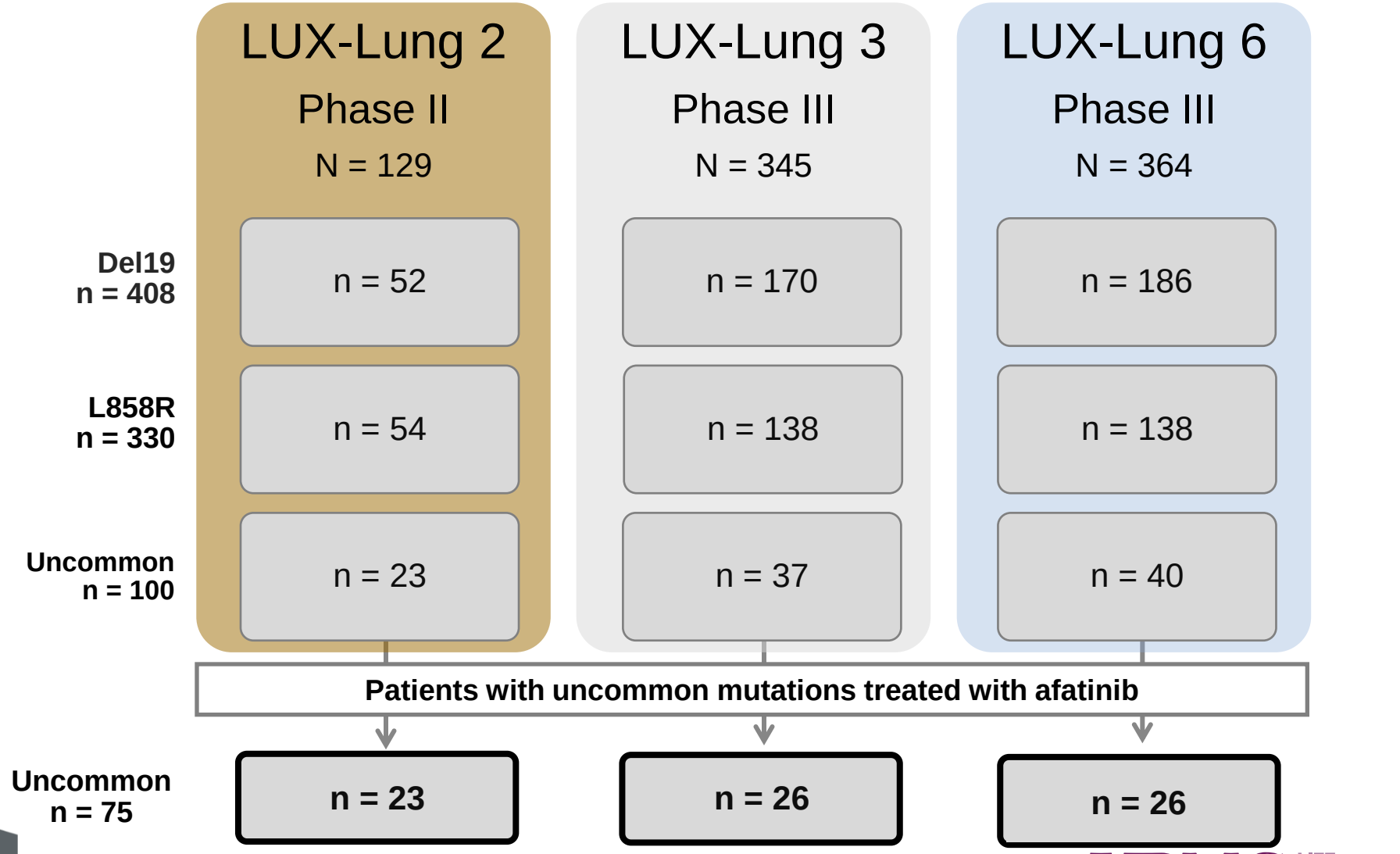
Uncommon EGFR mutations: LUX-Lung trials



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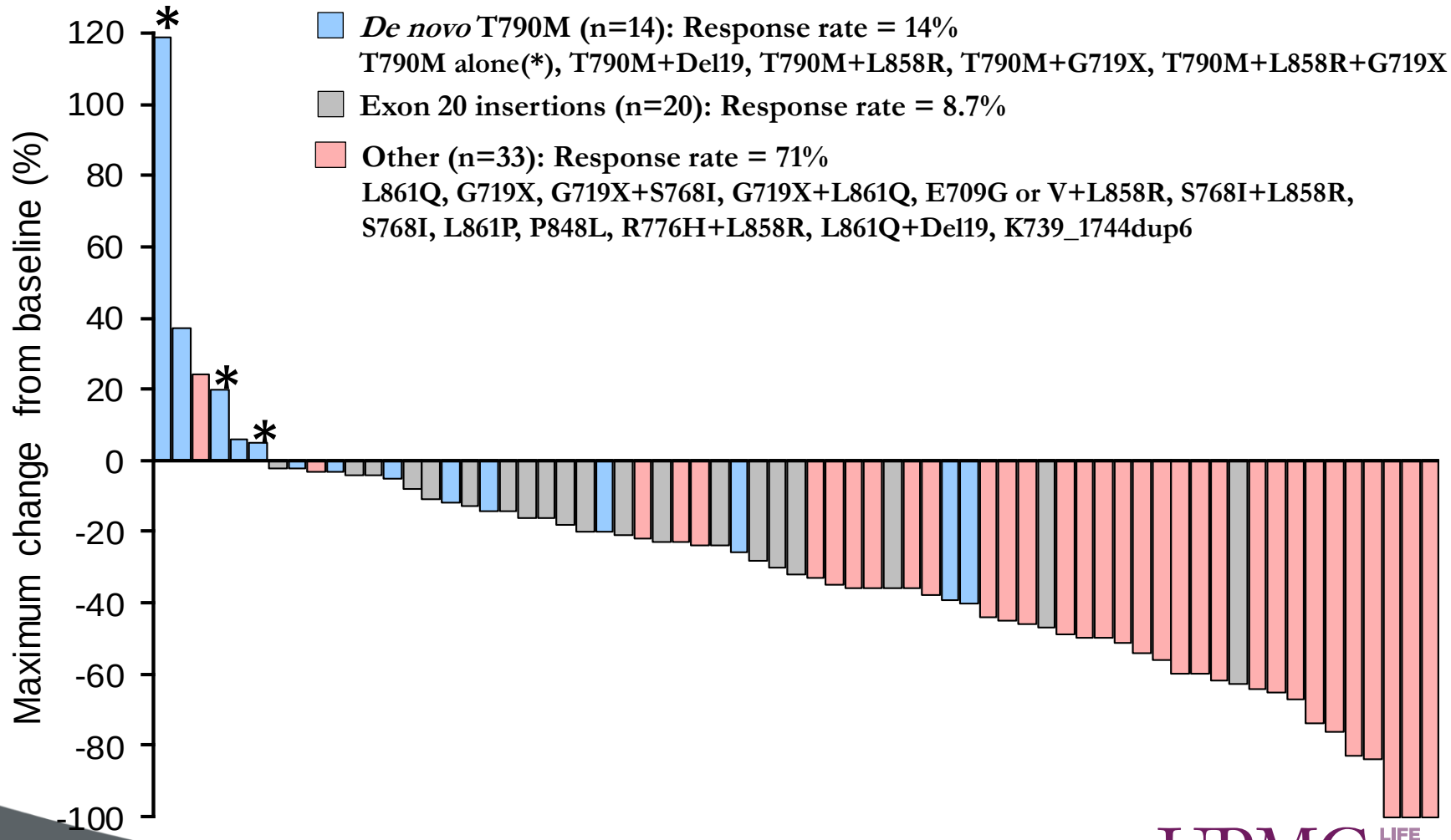
Subgroups of patients with uncommon mutations

Categories	*De novo* T790M	Exon 20 insertions	Other (exon 18, 19, 20, 21)
n=	14	23	38
Mutations (n)	T790M alone (3) T790M+Del19 (3) T790M+L858R (6) T790M+G719X (1) T790M+L858R+G719X (1)	n/a	L861Q alone (12) G719X alone (8) G719X+S768I (5) G719X+L861Q (3) E709G or V+L858R (2) S768I+L858R (2) S768I alone (1) L861P alone (1) P848L alone (1) R776H+L858R (1) L861Q+Del19 (1) K739_1744dup6 (1)

Tumour shrinkage in patients with uncommon mutations



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†8 patients were not included due to insufficient data

Progression-free survival and overall survival in patients

	De novo T790M n=14	Exon 20 insertions n=23	Other n=38
Median PFS, months (range)	2.9 (0.3−13.8)	2.7 (0.4-11.9)	10.7 (0.0+-35.8+)
Median OS, months (range)	14.9 (1.5-30.5)	9.4 (0.4-32.2+)	18.6 (0.0+-51.3+)

T790M + L858R, n=6

Patient	PFS	OS
1	0.8	8.7
2	2.6	24.9
3	6.7	13.2
4	8.3	30.5
5	9.6*	24.4*
6	11.0	20.8
Median	**7.5**	**22.9**

T790M + Del19, n=3

Patient	PFS	OS
1	0.3	8.1
2	1.2	7.5
3	3.0	24.6
Median	**1.2**	**8.1**

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+Patient data censored; NE = not

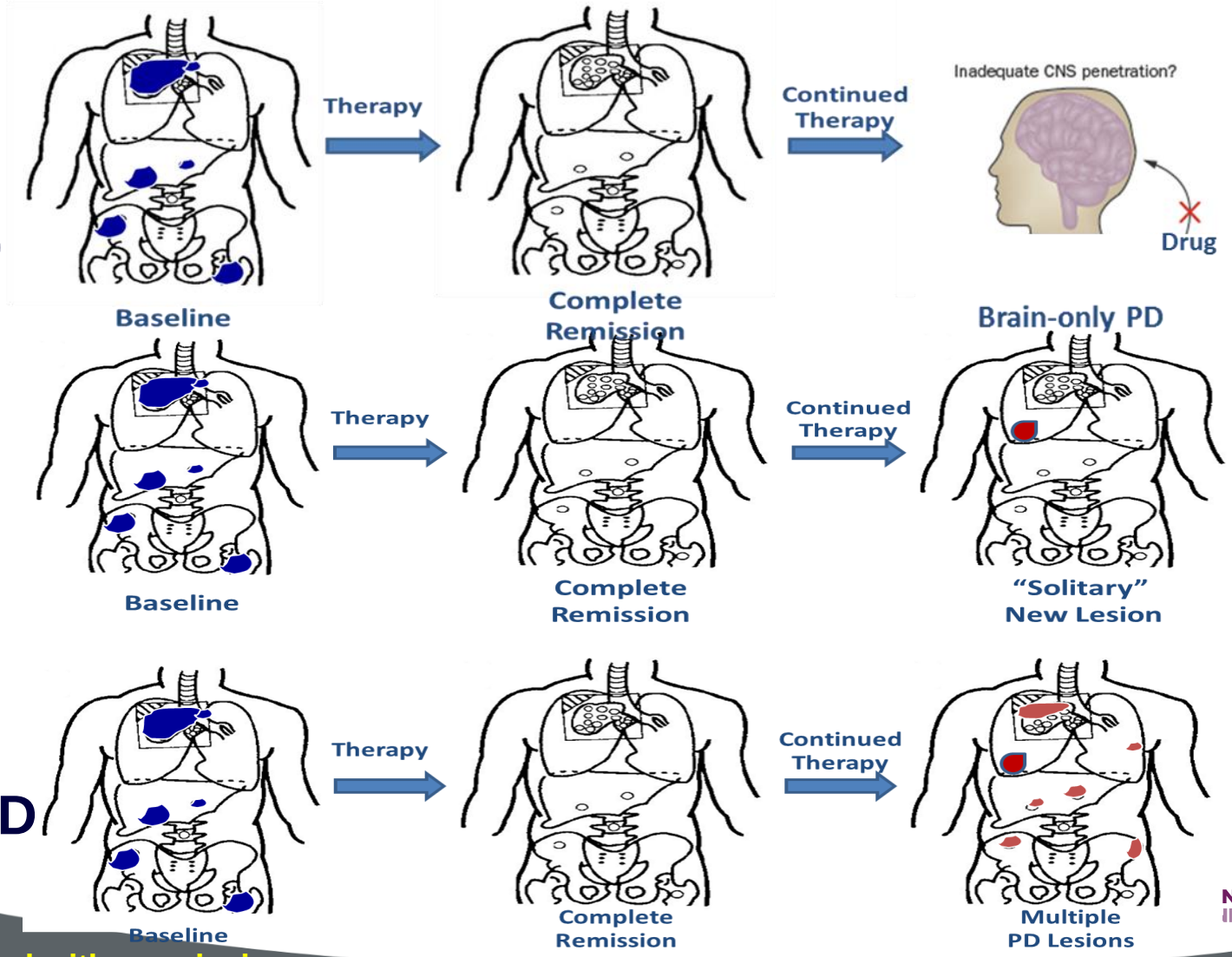
EGFR TKIs Vs Platinum Doublets in EGFR Mutant NSCLC

- Eight of 8 trials have shown in predominantly exon 19/21 EGFR mutations
  - Improved PFS
  - Improved ORR
  - Better toxicity profile

- Uncommon mutations – some may be sensitive but not all

- Zero of 8 trials have shown a survival benefit
  - Cross-over effect (but 100% of patients do not cross-over)
  - Development of resistance

At Least 3 Clinical Subtypes of Acquired Resistance to Targeted TKIs



Gandara, CLC 2013; used with permission

What are Treatment Options?

- Continue 1st-generation TKI
- Local Rx given to limited site of progression while continuing TKI
- Chemotherapy (either single agent or combination) added to 1st-generation TKI or alone
- Novel therapies:
  - Cetuximab/afatinib
  - CO-1686 Trial
  - AZD9291 Trial
  - Anti-PD-1 or Anti-PD-L1 Trial

Chemo added to TKI

- **Few studies have looked at the effectiveness of chemotherapy after TKI in EGFR-mutant cancers**

Study	Regimen	N	RR	Design
Gridelli, JCO, 2012	cis/gem	13	15%	Prospective
Wu, IJC, 2010	various	41	15%	Retrospective
Goldberg, ASCO, 2012	various	28	18%	Retrospective

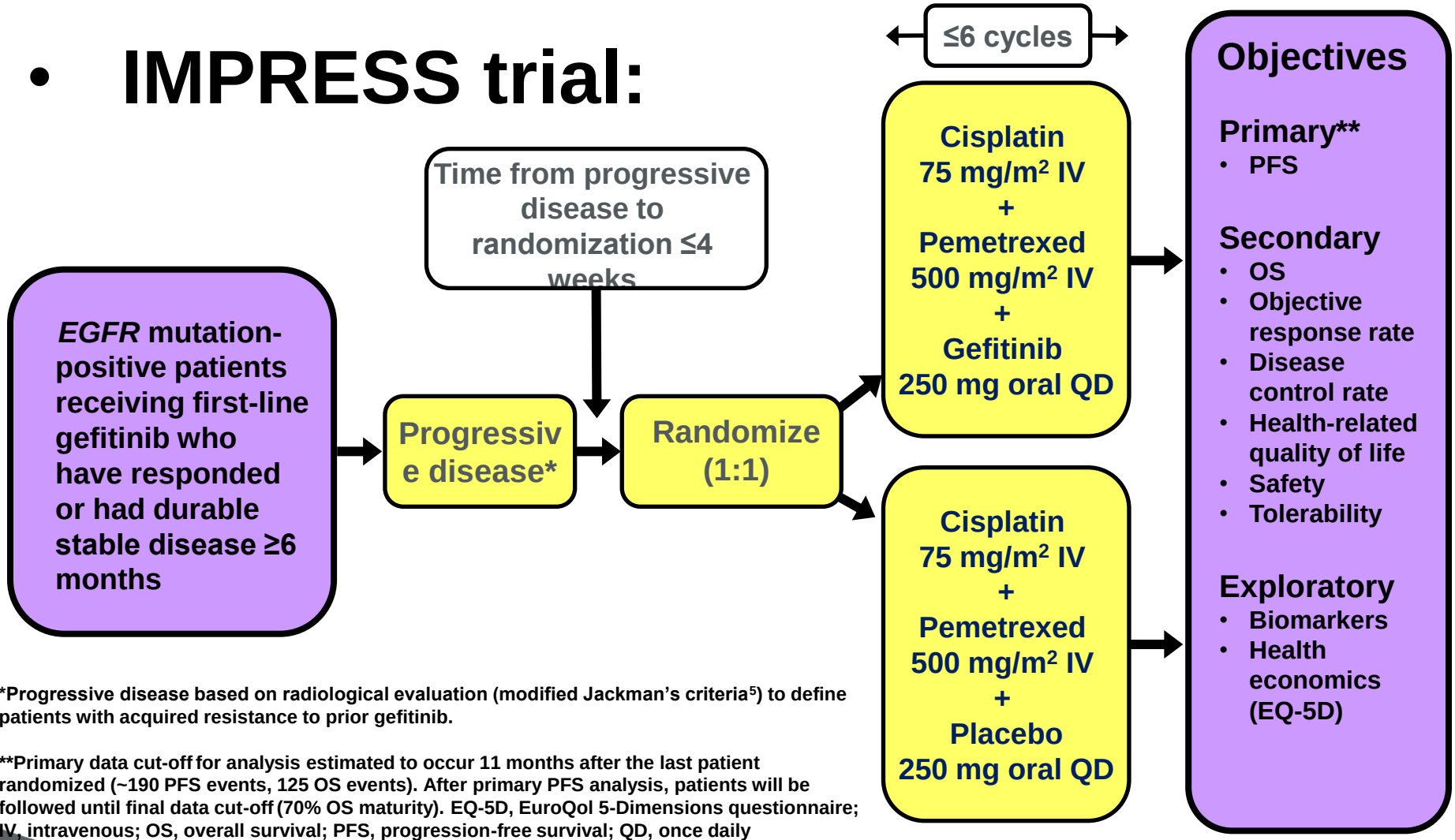
- **Only published prospective study of chemo after acquired resistance used pemetrexed/TKI showed a 7 month PFS**

Study	Regimen	N	RR	Design
Yoshimura, JTO, 2012	Pem/TKI	27	26%	Prospective

Oxnard et al, ASCO, 2013

Chemo added to TKI

- **IMPRESS trial:**



*Progressive disease based on radiological evaluation (modified Jackman's criteria[5]) to define patients with acquired resistance to prior gefitinib.

**Primary data cut-off for analysis estimated to occur 11 months after the last patient randomized (~190 PFS events, 125 OS events). After primary PFS analysis, patients will be followed until final data cut-off (70% OS maturity). EQ-5D, EuroQol 5-Dimensions questionnaire; IV, intravenous; OS, overall survival; PFS, progression-free survival; QD, once daily

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Chemo added to TKI

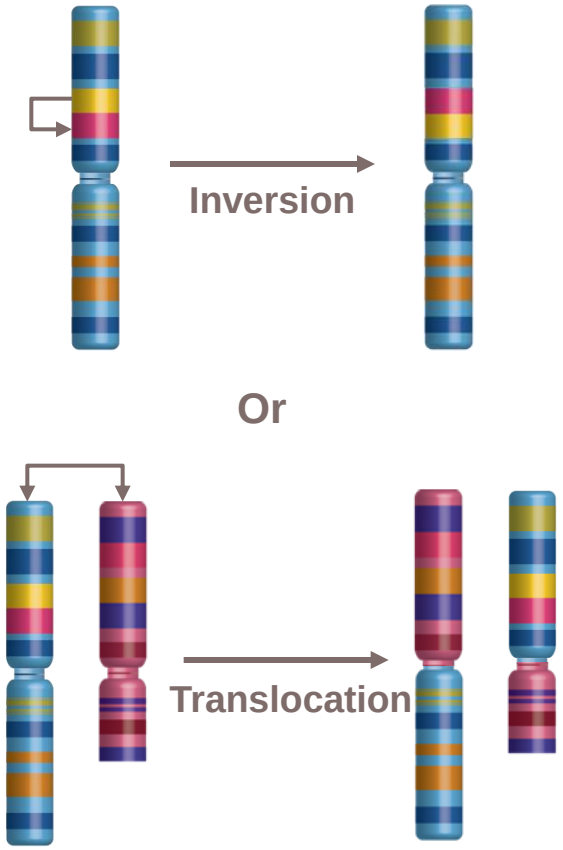
Study	Phase	N	Primary Endpoint	Patients		Treatment arm
STEP (UMIN000006433)	II	60	PFS	Acquired resistance to Gefitinib	→	Gefitinib + S-1
LOGiK1102 (UMIN000006976)	II	80	PFS	Acquired resistance to 2nd line~ EGFR-TKI	→	EGFR-TKI + Singlet chemo Singlet chemo
JMTO LC12-01 (UMIN000007765)	II	60	PFS	≥75 years, Acquired resistance to 1st line Gefitinib	→	Gefitinib + DTX DTX
LOGiK1105 (UMIN000008027)	II	70	PFS	≥70 years, Acquired resistance to 1st line Gefitinib	→	Gefitinib + Singlet chemo Singlet chemo
NEJ017 (UMIN000008364)	II	100	PFS	≥75 years or PS2, Acquired resistance to 1st line EGFR-TKI	→	EGFR-TKI + DTX or PEM DTX or PEM
IMPRESS (NCT01544179)	III	250	PFS	Acquired resistance to 1st line Gefitinib	→	Gefitinib + CDDP/PEM CDDP/ PEM

Clinical Conundrum

- If mutation status unknown and patient needs treatment, the lesson of IPASS is chemo must be given
- What if after starting chemo, the mutation test returns and shows a sensitivity mutation
- Options
  - continue chemotherapy +/- maintenance → EGFR TKI (2nd)
  - stop chemotherapy → EGFR TKI
  - add EGFR TKI to chemotherapy

- No published data on this scenario
- Decision should be made based on disease response and treatment tolerance

ALK Rearrangement in Cancer



ALK-POSITIVE CANCERS:

- **NSCLC – *EML4-ALK, KIF5B- ALK, TFG-ALK* (3-5%)**
- **Anaplastic large cell lymphoma – *NPM-ALK***
- **Inflammatory myo-fibroblastic tumor – *TPM3-ALK, TPM4-ALK***
- **Other solid tumors**

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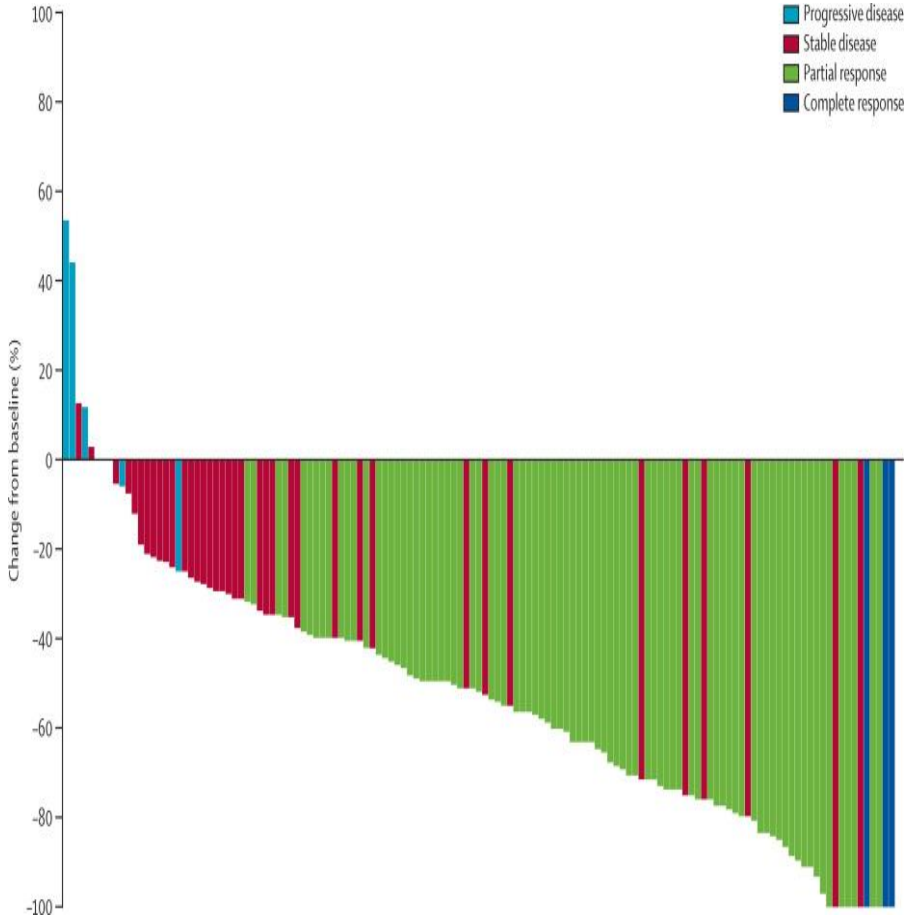
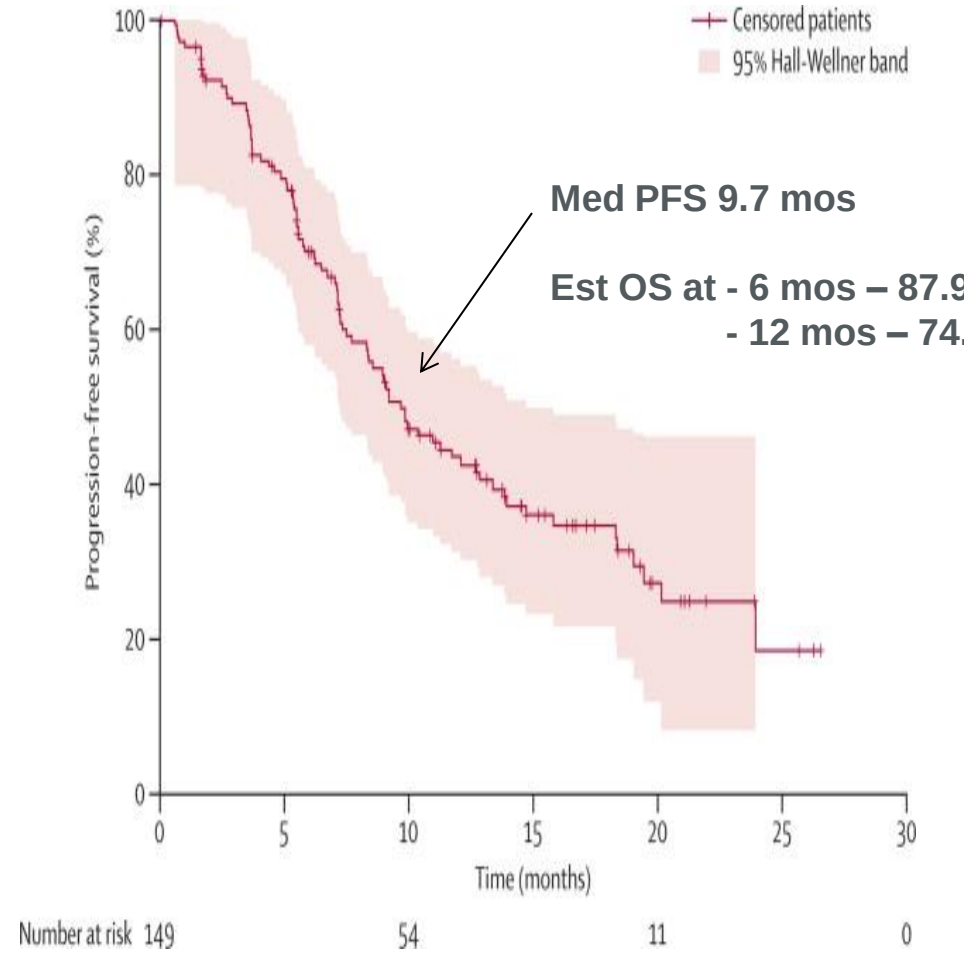
Updated Phase I Results: Crizotinib in ALK+ NSCLC



ORR – 60.8%



Med PFS 9.7 mos

Est OS at - 6 mos – 87.9
- 12 mos – 74.

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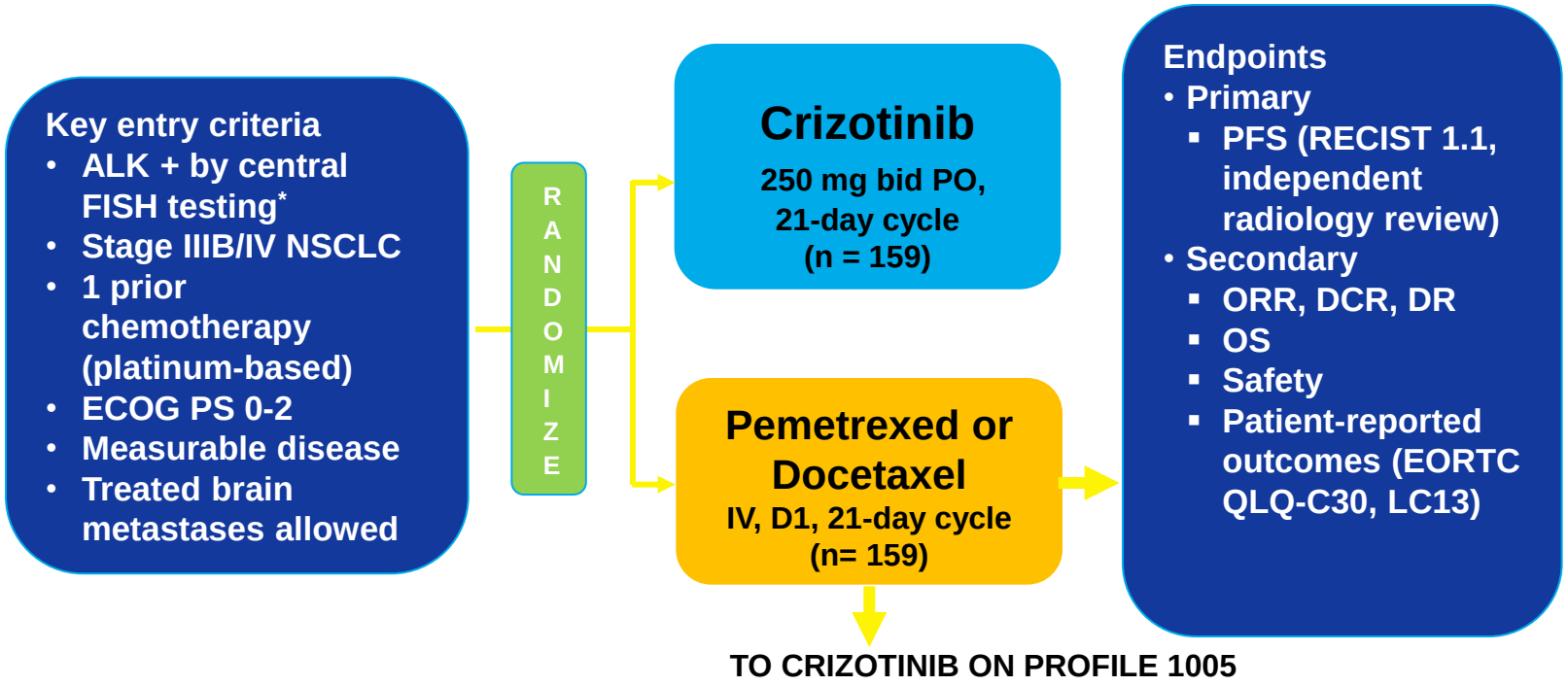
Camidge DR et al Lancet Oncology 13:1011-19, 2012

PROFILE 1007: Crizotinib vs Chemotherapy as Second-Line Therapy in ALK+ NSCLC



- **Primary endpoint: PFS: 7.7 vs 3.0 months (HR 0.49, *P*<0.0001)**
- **Secondary endpoint:**
  - **ORR (65% vs 20%; *P*<0.0001)**
  - **OS, safety and tolerability, and patient-reported outcomes**

Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no).

Shaw AT et al. ESMO 2012. Abstract LBA-1.

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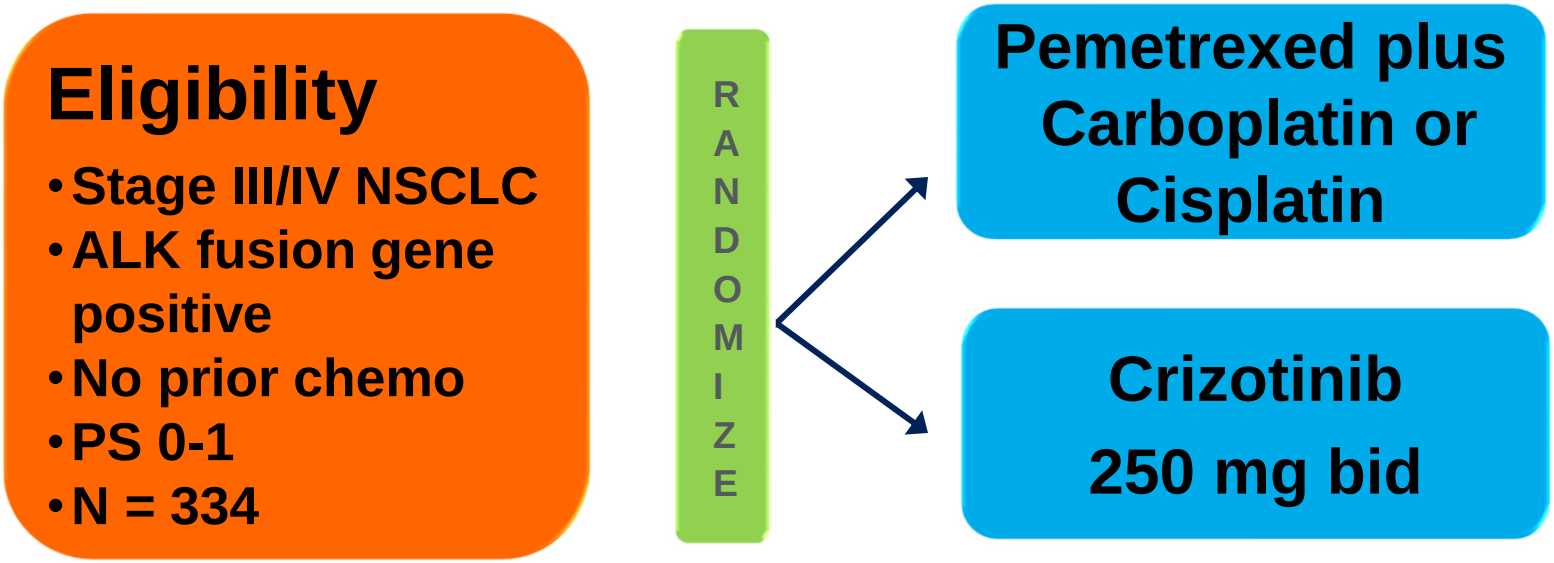
PROFILE 1014: Phase 3 First-Line Trial of Crizotinib vs Platinum/Pemetrexed



- Primary endpoint: PFS
- Secondary endpoint: ORR, OS, safety and tolerability, and patient-reported outcomes

First and Second Generation ALK TKIs in Clinical Development

Name	Company	Status	Comments
Crizotinib	Pfizer	1st and 2nd line registration trials are ongoing. 2nd line trial is >75% accrued	Accelerated approval granted August 26, 2011
LDK378	Novartis	Phase 1 dose escalation	Activity observed at 400 mg. Enrolling in the US and Europe
AF802	Chugai	Phase 1/2 in Japan and starting in US	Activity observed in crizotinib-naïve pts
AP26113	Ariad	Phase 1	Some activity against EGFR T790M. Enrolling in the US
ASP3026	Astellos	Phase 1	Similar to TAE684. Enrolling in Japan
CEP-28122	Cephalon	Preclinical	
NMS-E628	Nerviano	Preclinical	
X276/396	Xcovery	Preclinical	

EGFR and ALK

Two examples in NSCLC where molecularly targeted therapies in molecularly defined patient populations are superior to traditional cytotoxic chemotherapy

Conclusions: 1st Line Management of EGFR/ALK NSCLC

- **EGFR Mutants (exons 19/21)**
  - 1st line EGFR TKIs improve ORR and PFS
  - No difference in OS
  - Toxicity more “favorable” with TKIs vs platinum doublets
- **Uncommon EGFR Mutants**
  - Mix of sensitive/resistant mutations

- **ALK translocation positive**
  - No 1st line data to date but it is common practice to use ALK inhibitors in this setting
  - Crizotinib improves ORR and PFS in the 2nd line setting vs standard 2nd line options with no difference in OS