University of Colorado Cancer Center
University of Colorado Hospital
University of Colorado Health Sciences Center

History, Major Findings and Lessons from LCMC

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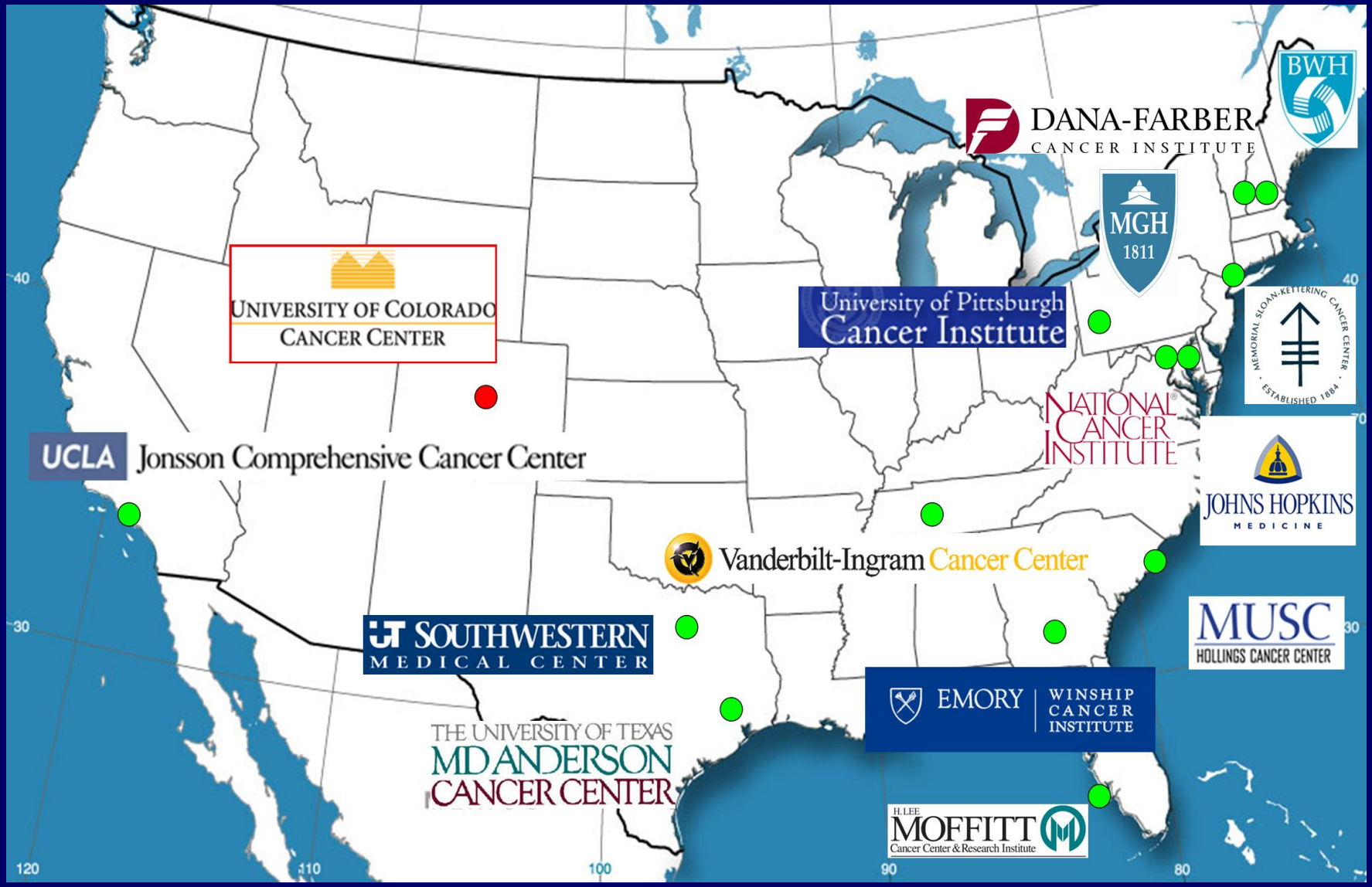
Disclosures

Advisory Committee	Genentech BioOncology, Lilly
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Celgene Corporation, EMD Serono Inc, Genentech BioOncology, Lilly, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc

Lung Cancer Mutation Consortium I



Lung Cancer Mutation Consortium I

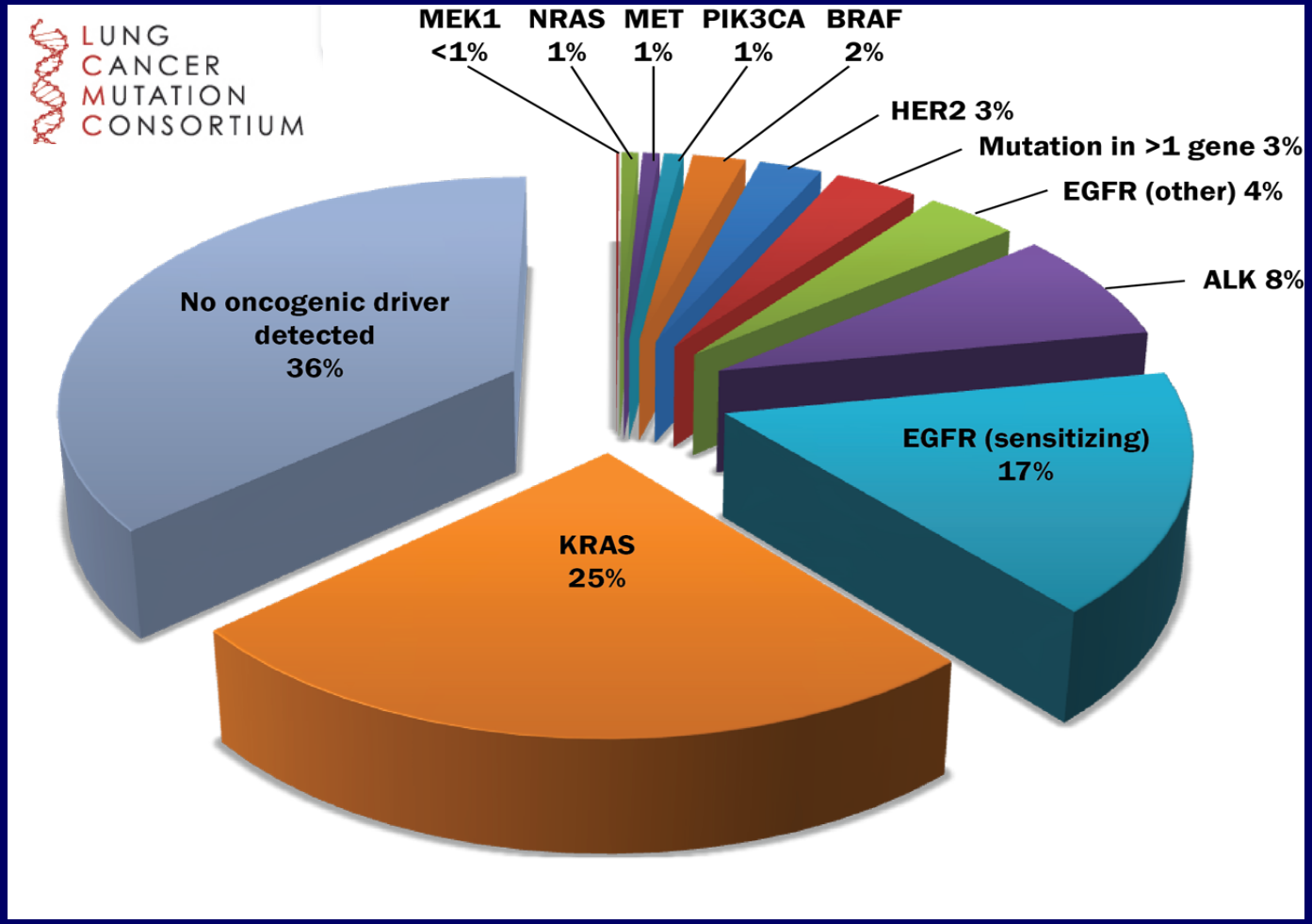
- **Goals: Run a panel of molecular tests on consecutive patients with advanced lung adenocarcinoma and then put as many patients with molecular drivers on molecular therapy to determine the value of the testing and treatment.**

LCMC protocols linked to specific molecular lesions detected

Target	Agent	LCMC Lead
MEK1	GSK1120212 Trametinib	P Jänne
BRAF (V600E)	GSK2118434 Dabrafenib	B Johnson
BRAF (not V600E)	GSK1120212	P Jänne
HER2	Dacomitinib	M Kris
PIK3CA	BKM120	J Engelman
EGFR	Erlotinib + OSI 906 Erlotinib + MM 121	C Rudin L Sequist
KRAS *NRAS*	Tivantinib + Erlotinib Trametinib	J Schiller, P Jänne G Blumenschein
MET Amplification	Crizotinib	R Camidge
ALK	Crizotinib	R Camidge
ROS	Crizotinib	R Camidge

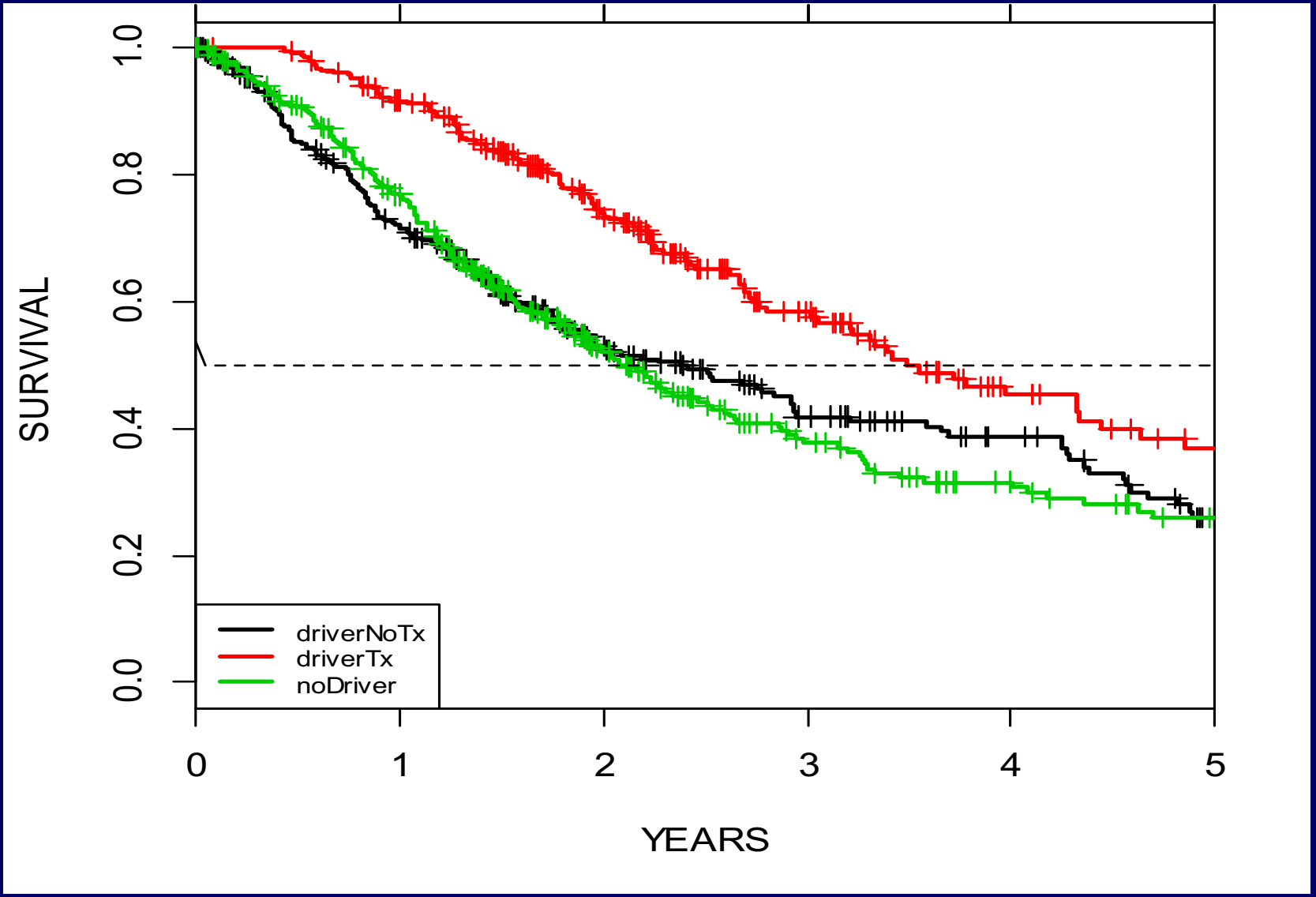
Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006.

Lung Cancer Mutation Consortium I: Survival by Group



Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006

Lung Cancer Mutation Consortium I: Conclusions

- It is possible and valuable to run a panel of molecular tests on consecutive patients with advanced lung adenocarcinoma and then treat with molecular therapy which provides high response rates and longer survival compared to conventional cytotoxic therapy.
- These data helped in the formation of guidelines for routine molecular testing for EGFR and ALK.
- However, the panel was limited and more than one platform was required for testing.

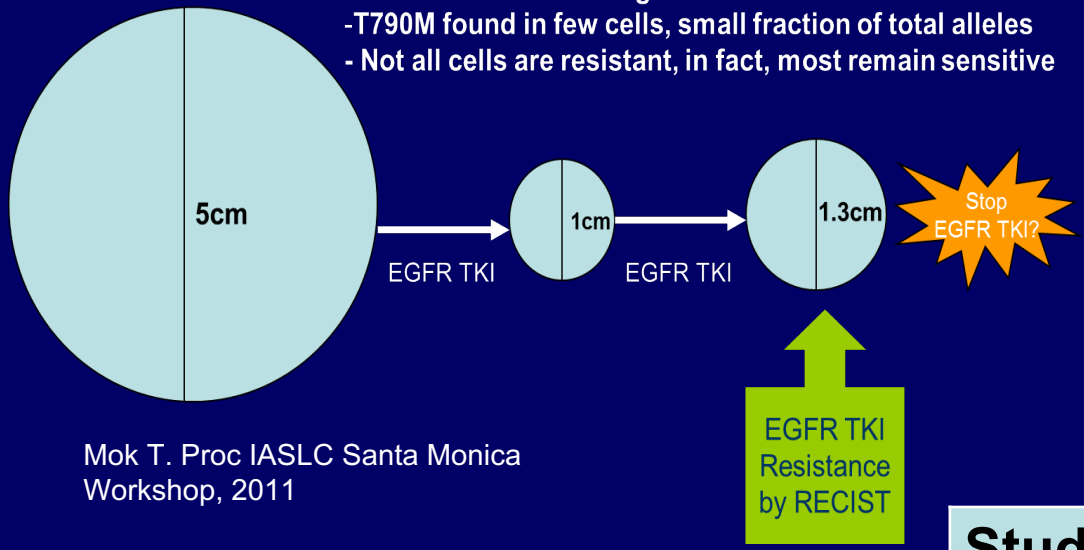
Randomized Studies of First Line EGFR TKI in Patients with EGFR Mutations

Author	Study	Agent	N (EGFRm+)	RR	Median PFS (months)	Median OS (months)
Mok et al.	IPASS	Gef	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Lee et al.	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al.	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al.	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al.	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al.	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al.	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
Wu et al.	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

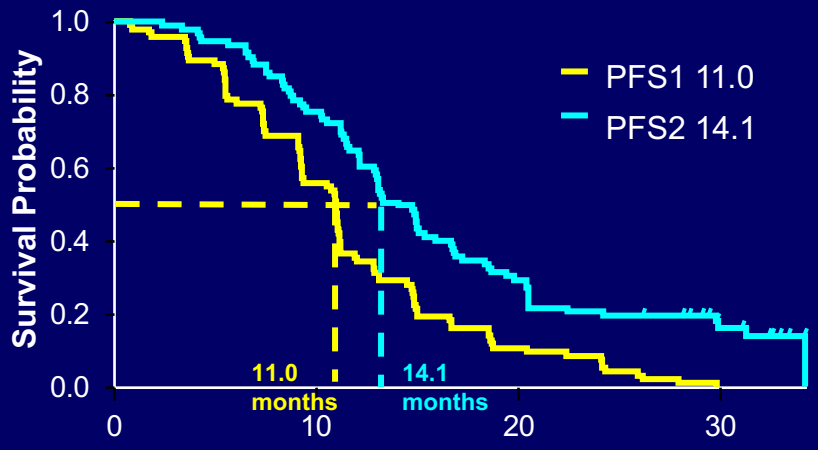
Mok et al. *N Engl J Med*. 2009;361:947-57
Lee et al. WCLC 2009
Mitsudomi et al. *Lancet Oncol*. 2010;11;121-8
Maemondo et al. *N Engl J Med*. 2010;262:2380-88
Zhou et al. ESMO 2010
Rosell et al. ASCO 2011
Yang et al. ASCO 2012, Sequist IASLC 2012
Wu et al. ASCO 2013

Cross-over to an EGFR TKI in the control groups felt to reduce detectability of any possible OS benefit (all mutations)

Post EGFR TKI Recist progression: Continue or Local Therapy



Mok T. Proc IASLC Santa Monica Workshop, 2011

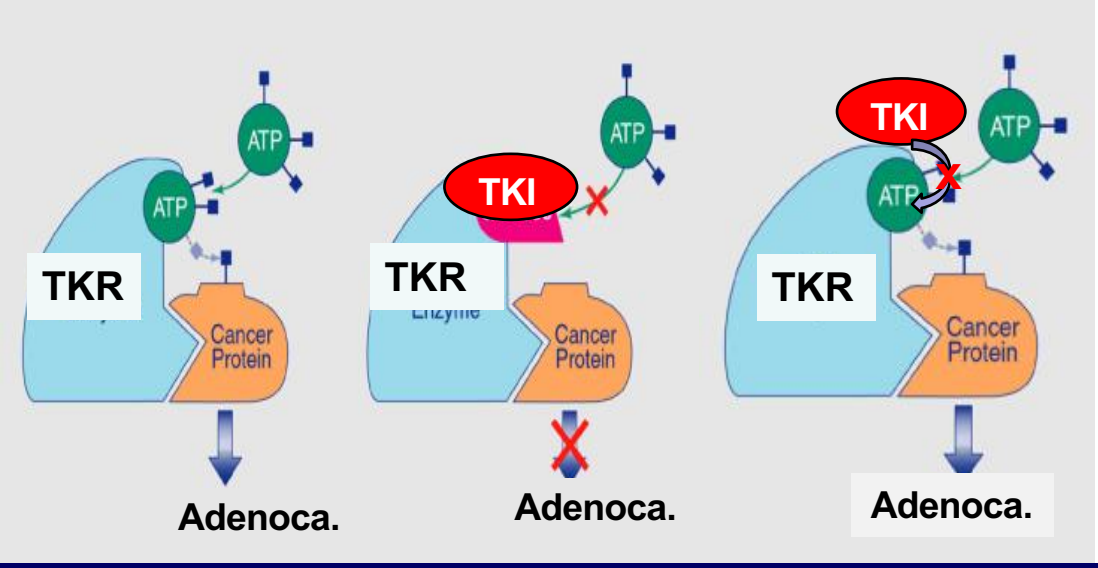


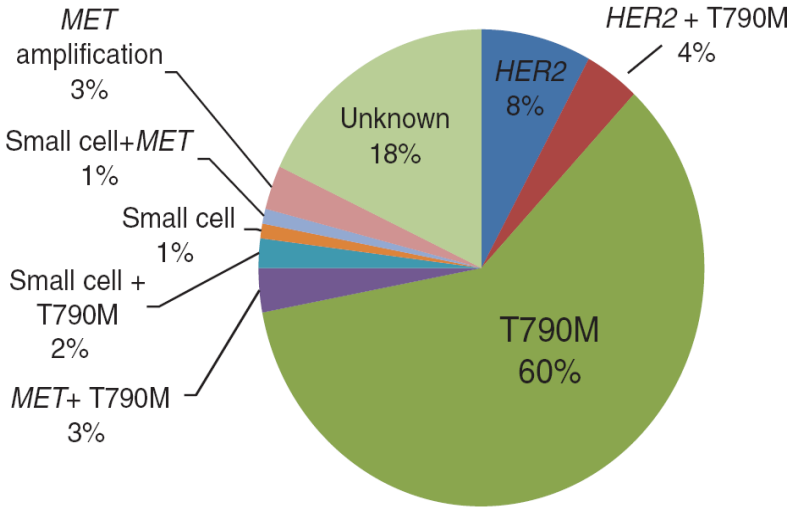
Park et al., ESMO 2014

Study	N pts	PFS1	PFS2
Colorado	25	10	6.2
MSKCC	18	19	10

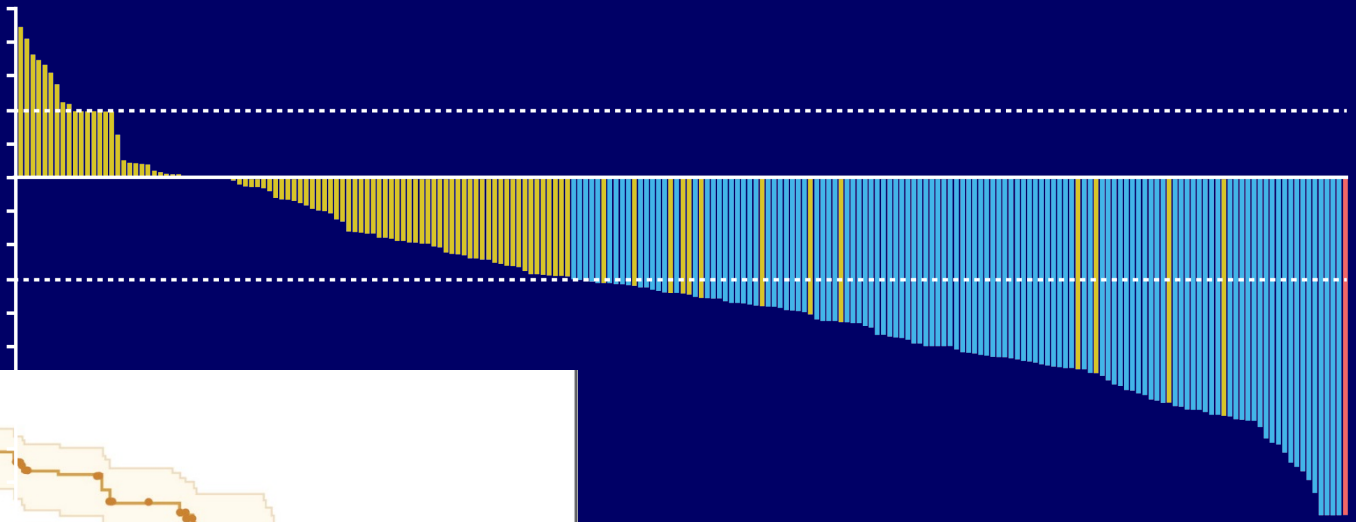
Weickhardt A et al, Proc ASCO 2012 # 7526
Yu A et al, Proc ASCO 2012 # 7527

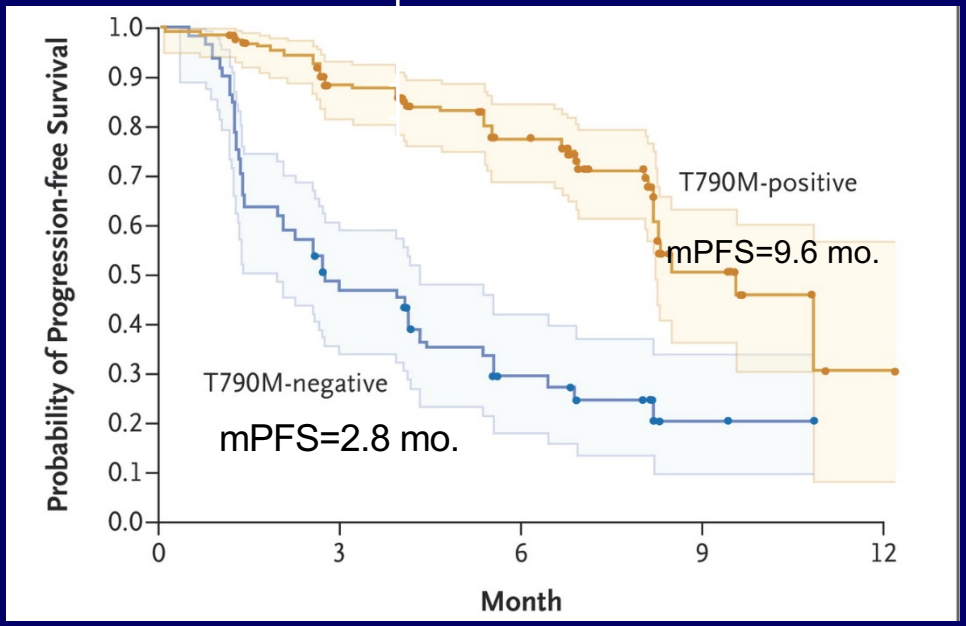
Tyrosine Kinase Inhibitor Resistance





AZD9291 (Osimertinib): Response and PFS by *EGFR* T790M Status.





	20 mg	40 mg	80 mg	160 mg	240 mg
N (205)	20	57	61	55	12
ORR	55%	44%	54%	58%	67%

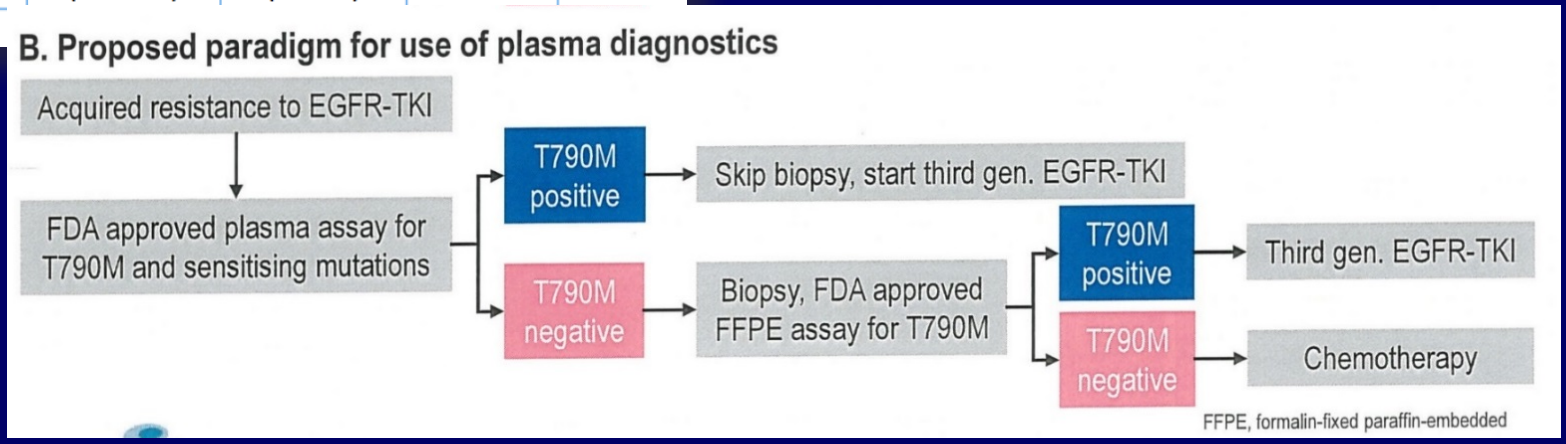
Yang JC, et al, JTO 10 (9 suppl 2)S319,2015
Mitsudomi T, et al JTO 10 (9 suppl 2)S320,2015

Plasma T790M for 3rd generation EGFR TKI activity

Objective response rate for 188 evaluable patients with both central T790M tissue test result and plasma T790M result

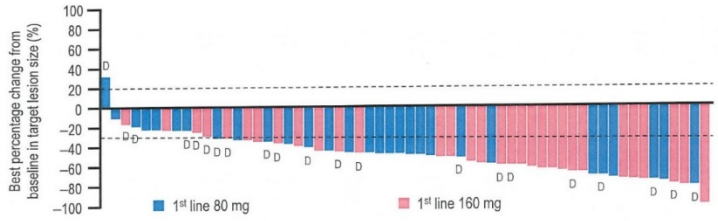
		Plasma T790M		
		+	-	
Tissue T790M	+	55% (72/130)	43% (13/30)	53% (85/160)
	–	35% (6/17)	27% (3/11)	32% (9/28)
		53% (78/147)	39% (16/41)	

Goldman et al. AACR 2015
Sequist et al. ASCO 2015



Osimertinib results in 1st line

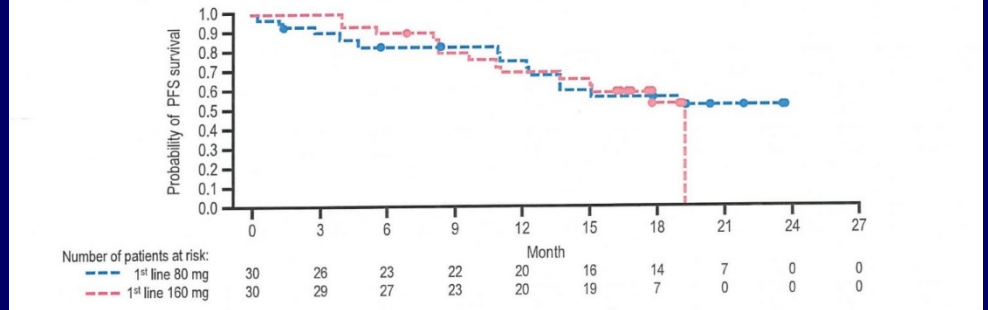
Tumour response to osimertinib in EGFRm first-line cohorts (investigator assessed)



	80 mg n=30	160 mg n=30	Total N=60
Confirmed ORR	67% (95% CI 47, 83)	87% (95% CI 69, 96)	77% (95% CI 64, 87)
Disease control rate*	93% (95% CI 78, 99)	100% (95% CI 88, 100)	98% (95% CI 89, 100)
Best objective response			
Complete response	0	2	2
Partial response	20	24	44
Stable disease ≥6 weeks	8	4	12
Progressive disease	2	0	2

Confirmed ORR=77%
Disease control rate=98%

PFS in osimertinib EGFRm first-line cohorts (investigator assessed)



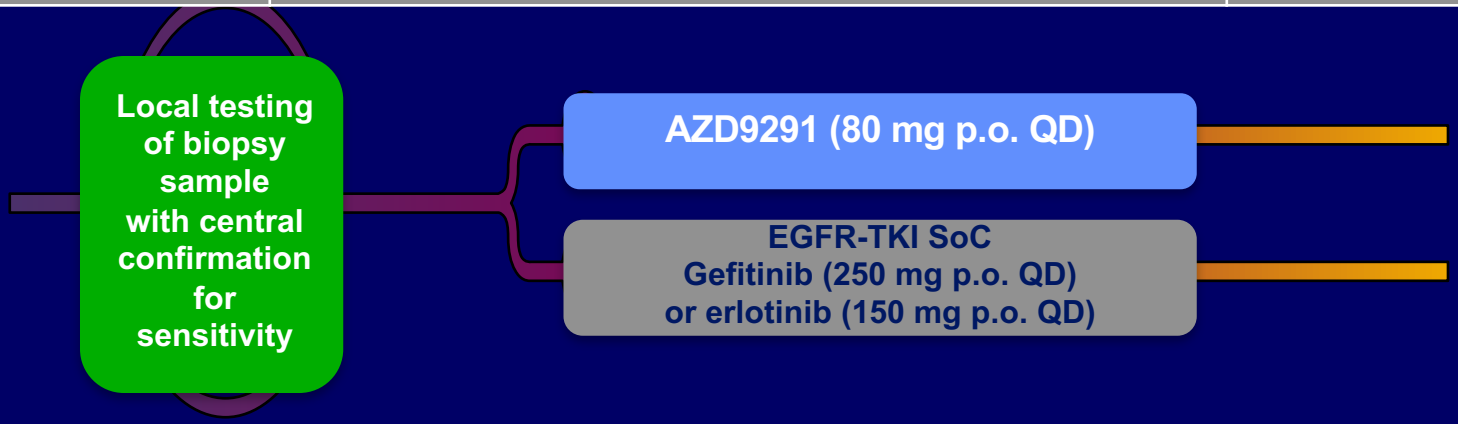
	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

Median PFS=19.3 mo

Ramalingam S, et al ELCC, 2016

FLAURA: 1st Line 3rd Gen. EGFR TKI vs Soc TKI

FLAURA		Status
Phase III study	Sample size 650 treatment-naïve patients with EGFR-sensitising mutation-positive (EGFRm) NSCLC, who are eligible for first-line treatment with EGFR-TKI will be randomised 1:1 to AZD9291 vs. gefitinib or erlotinib	Ongoing Recruiting



Sequence	PFS
1st Generation to 3rd Generation to CT	10+10=20 mo to CT
3rd Generation to CT	20 mo to CT

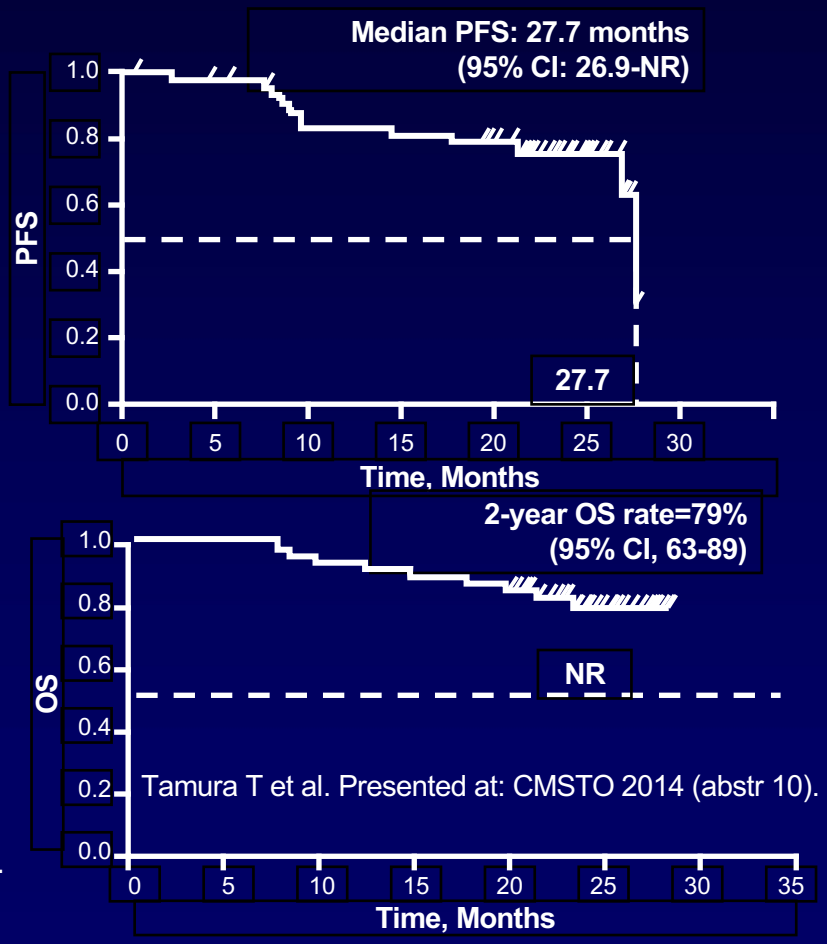
Next Generation ALK Inhibitors

In Crizotinib Resistance

	Status	ORR	PFS, mo	DR, mo	CNS RR
Ceritinib[1] (LDK378)	Approved	55% (N = 163)	6.9	7.4	Yes (50%)
Alectinib[2] (CH5424802)	Approved	50% (N = 122)	8.9	11.2	Yes (57%)
Brigatinib[3] (AP26113)	Phase II	71% (N = 70)	13.4	9.3	Yes (53%)
PF-06463922[4]	Phase I/II	44% (N = 34)	NR	NR	Yes (36%)

1. Kim D-W, et al. *J Clin Oncol* 2014;32(5S): Abstract 8003; 2. Ou S-H, et al. *J Clin Oncol* 2015;33(Suppl): Abstract 8008;
3. Camidge DR, et al. *J Clin Oncol* 2015;33(Suppl): Abstract 8062; 4. Shaw AT, et al. *J Clin Oncol.* 2015;33(Suppl): Abstract 8018.

1st Line



ALK kinase domain mutations – drug efficacy

	1st gen	2nd gen			3rd gen
	Crizotinib	**Alectinib**	**Brigatinib**	**Ceritinib**	**Lorlatinib**
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res [4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens [1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

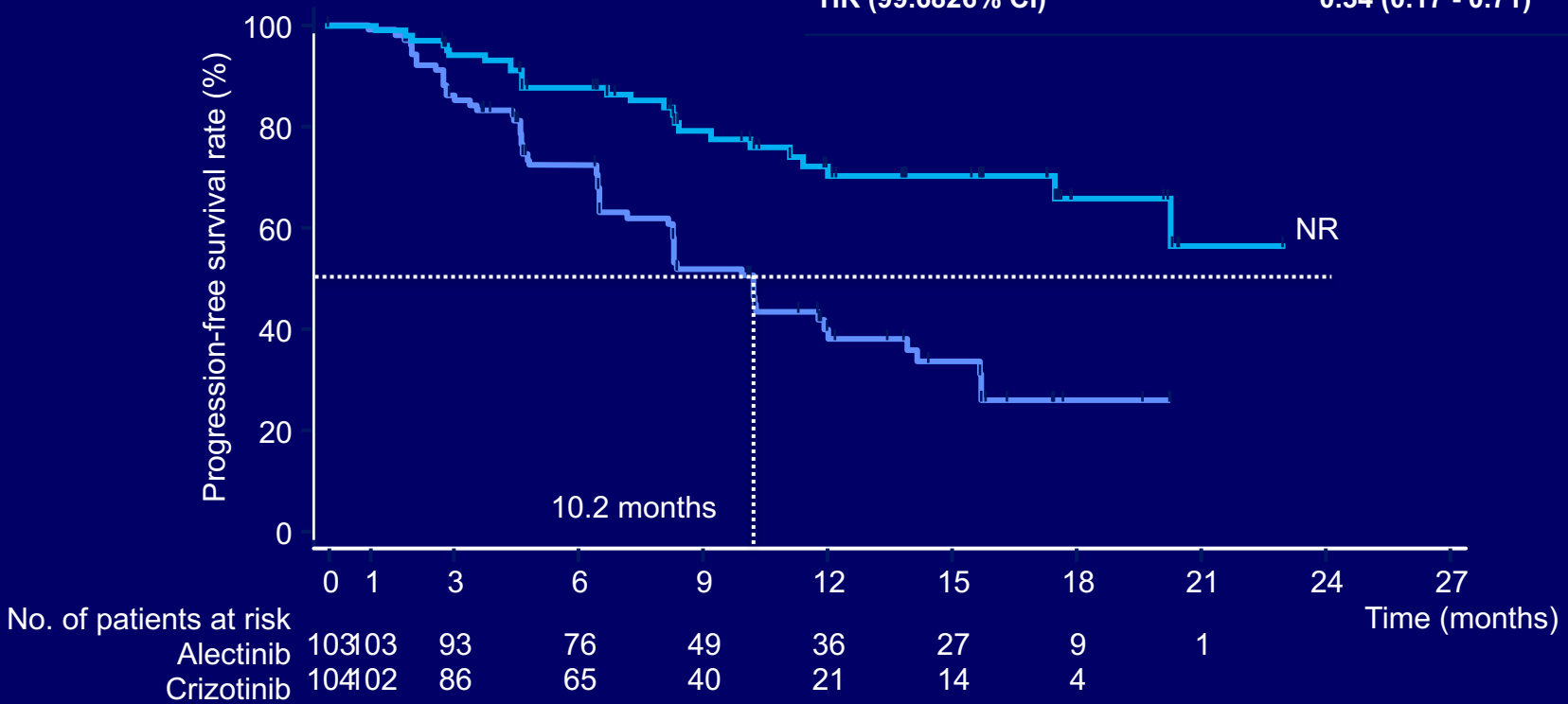
REFERENCES

1. Shaw NEJM 2016
2. Toyokawa JTO 2015
3. Katayama STM 2012
4. Katayama CCR 2014
5. Ou Lung Cancer 2015
6. Ceccon MCR 2014
7. Friboulet Cancer Discov 2014
8. Kodityal Lung Cancer 2016
9. Zou Cancer Cell 2015
10. Bayliss Cel Mol Lif Sci 2015

Slide courtesy of Dr. Christine Lovly

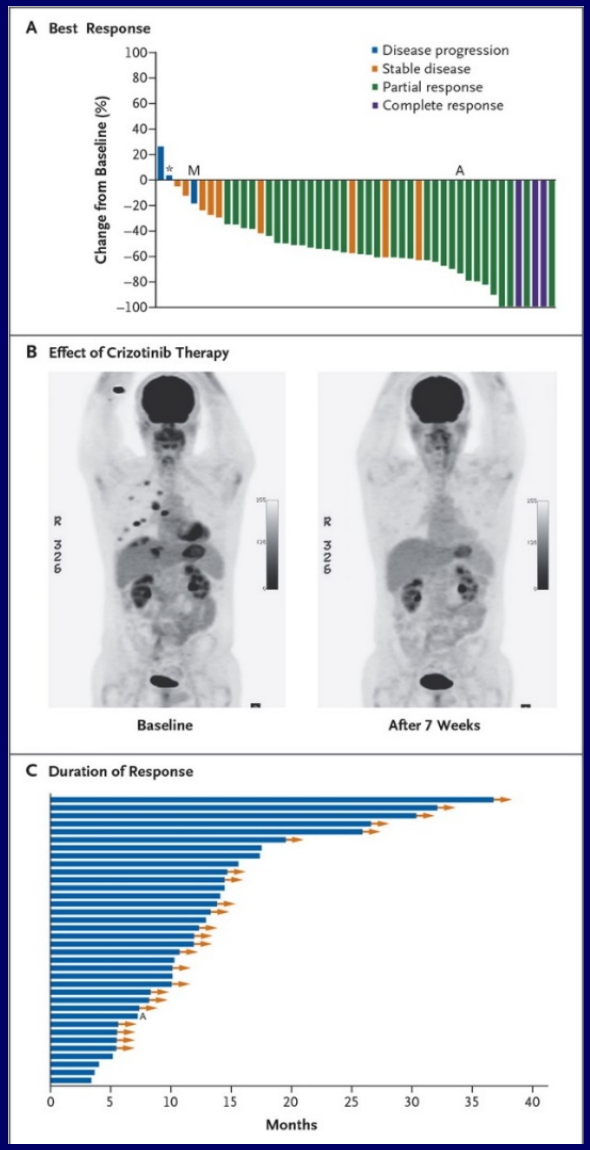
J-Alex: Primary Endpoint: PFS by IRF (ITT Population)

	Alectinib (N=103)	Crizotinib (N=104)
Events, n (%)	25 (24.3%)	58 (55.8%)
Median, mo (95% CI)	NR (20.3 - NR)	10.2 (8.2 - 12.0)
P-value	<0.0001	
HR (99.6826% CI)	**0.34 (0.17 - 0.71)**	

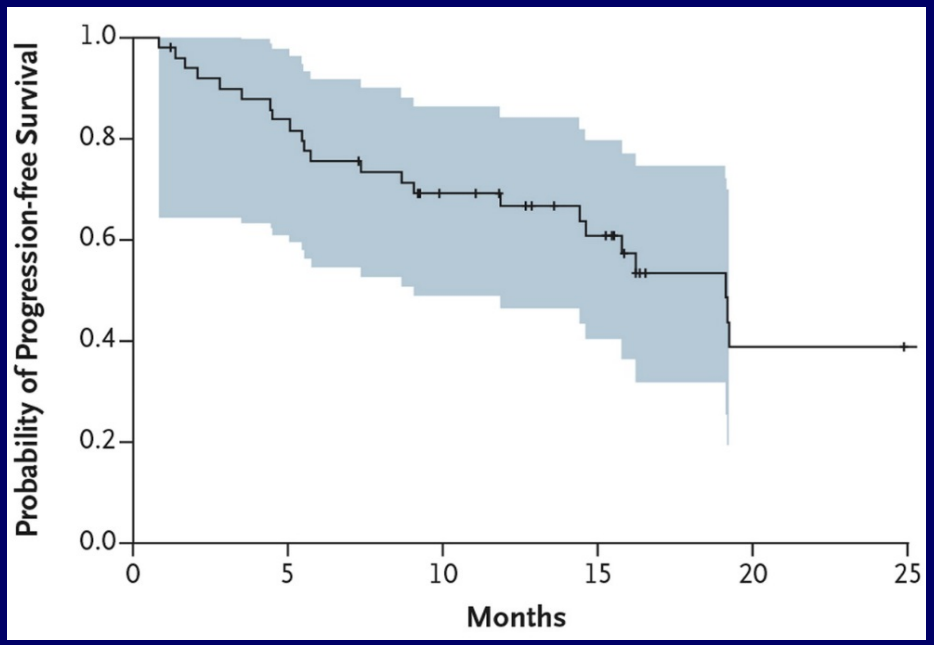


Presented by: Hiroshi Nokihara

Crizotinib in *ROS1*-Rearranged NSCLC

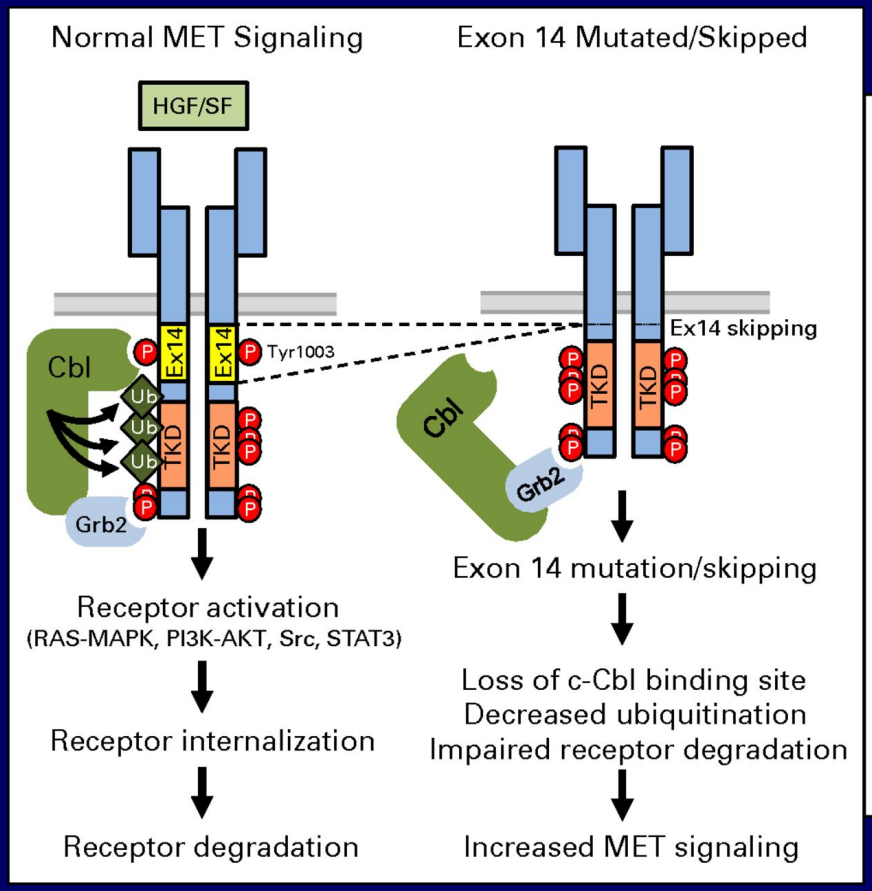


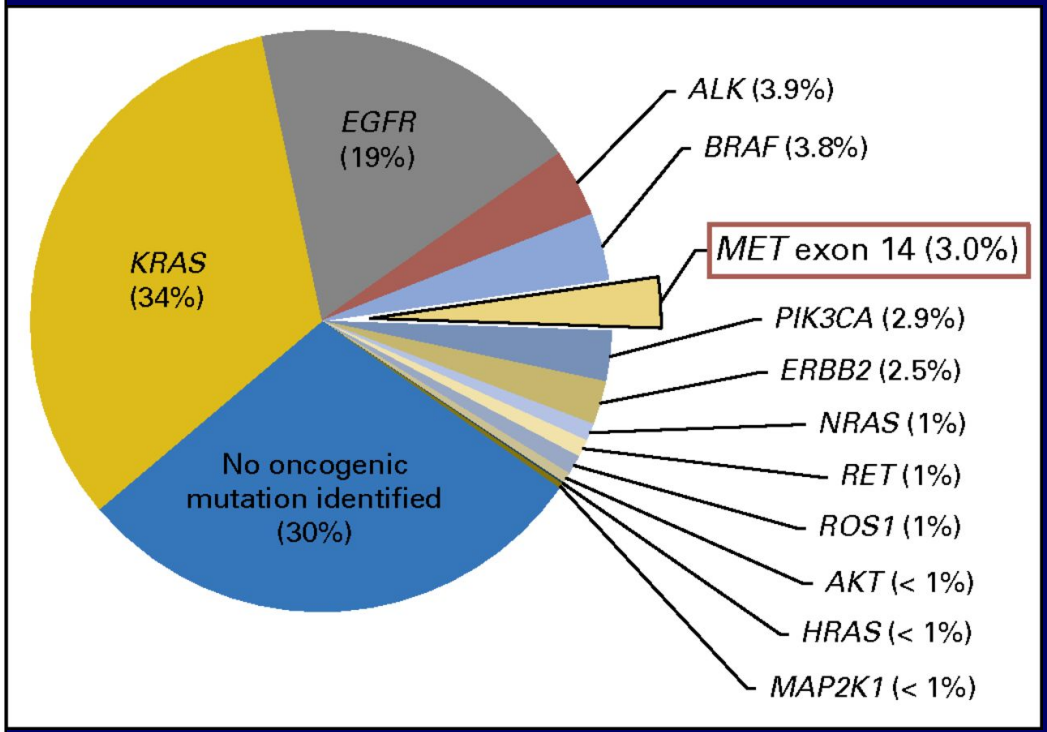
PFS



Shaw A, et al. *N Engl J Med,* 2014; 371 (21):1963-1971.

MET exon (Ex) 14 skipping results in impaired c-Met receptor degradation.





Mark M. Awad JCO 2016;34:879-881

LCMC II Goals: To determine the value of routine genomic panel testing and genomic therapy; more markers, sites and therapies

LCMC II

Presented By Dara Aisner at 2016 ASCO Annual Meeting

LCMC I vs. II

	LCMC I	LCMC II
Enrollment Dates	11/2009 – 7/2011	11/2012 – 12/2015
Number of Participating Sites	11	16
Core required target genes (selected alterations)	10	14
Available SOC therapies	0 (at start)	2 (at start)
Available linked trials	10	10
Testing sites		
Using NGS at start	0	0
Using NGS by end	0	16

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Current:

Illumina HiSeq 2000

300 – 600 Gigabases 6 – 11 days

Illumina MiSeq

1.5 Gigabases 1 day

Ion Torrent PGM

1 Gigabase 6 hours

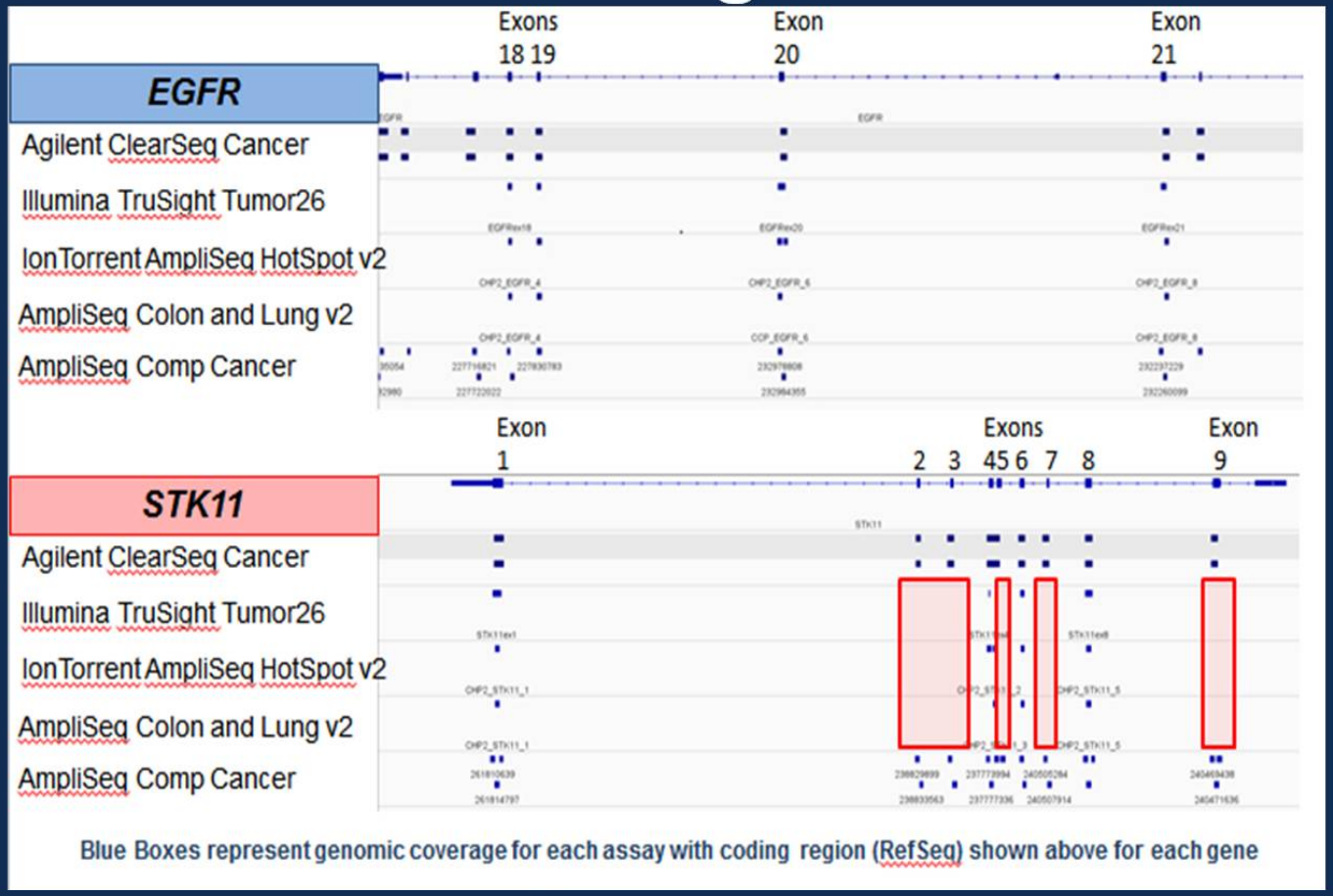
Emerging:

Illumina HiSeq 2500

Ion Torrent Proton

Human Genome in a Day

Multi-institutional NGS Data Sharing: Differences in Coverage



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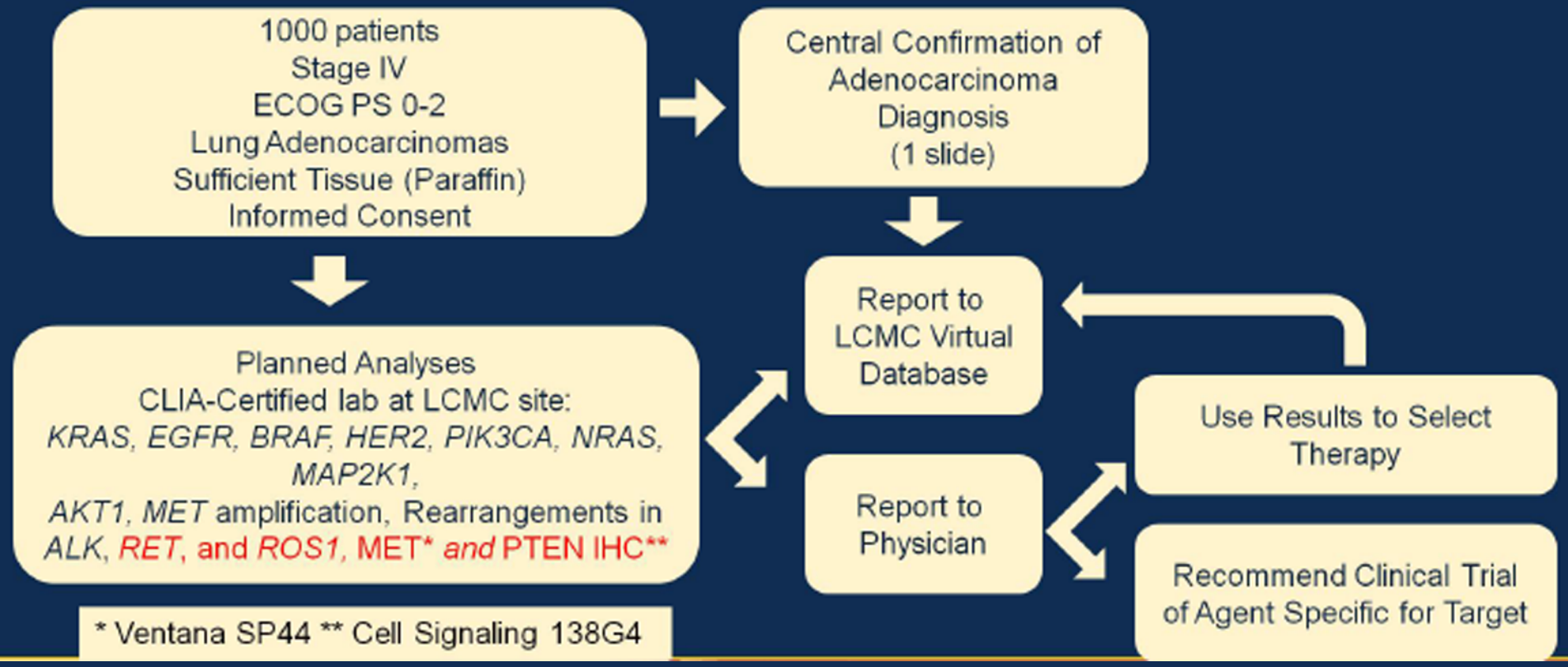
LCMC II Biomarker Targets

Point mutations in:
AKT1
BRAF
EGFR
ERBB2 (HER2)
KRAS
MAP2K1 (MEK)
PIK3CA
NRAS

Rearrangements in:
ALK (FISH or NGS)
RET (FISH or NGS)
ROS1 (FISH or NGS)

Other alterations:
METamp (FISH)
PTENexp (IHC)
METexp (IHC)

Study Design



Patient Characteristics

N = 875

Median Age (Range)	64 (23-91)
Gender	
Men	398 (45%)
Women	477 (55%)
Smoking Status	
Never	217 (25%)
Former	535 (61%)
Current	106 (12%)
Not reported	17 (2%)
Adenocarcinoma	875 (100%)
Stage IV	875 (100%)
Performance Status	
0	239 (27%)
1	546 (63%)
2	72 (8%)
Not reported	18 (2%)

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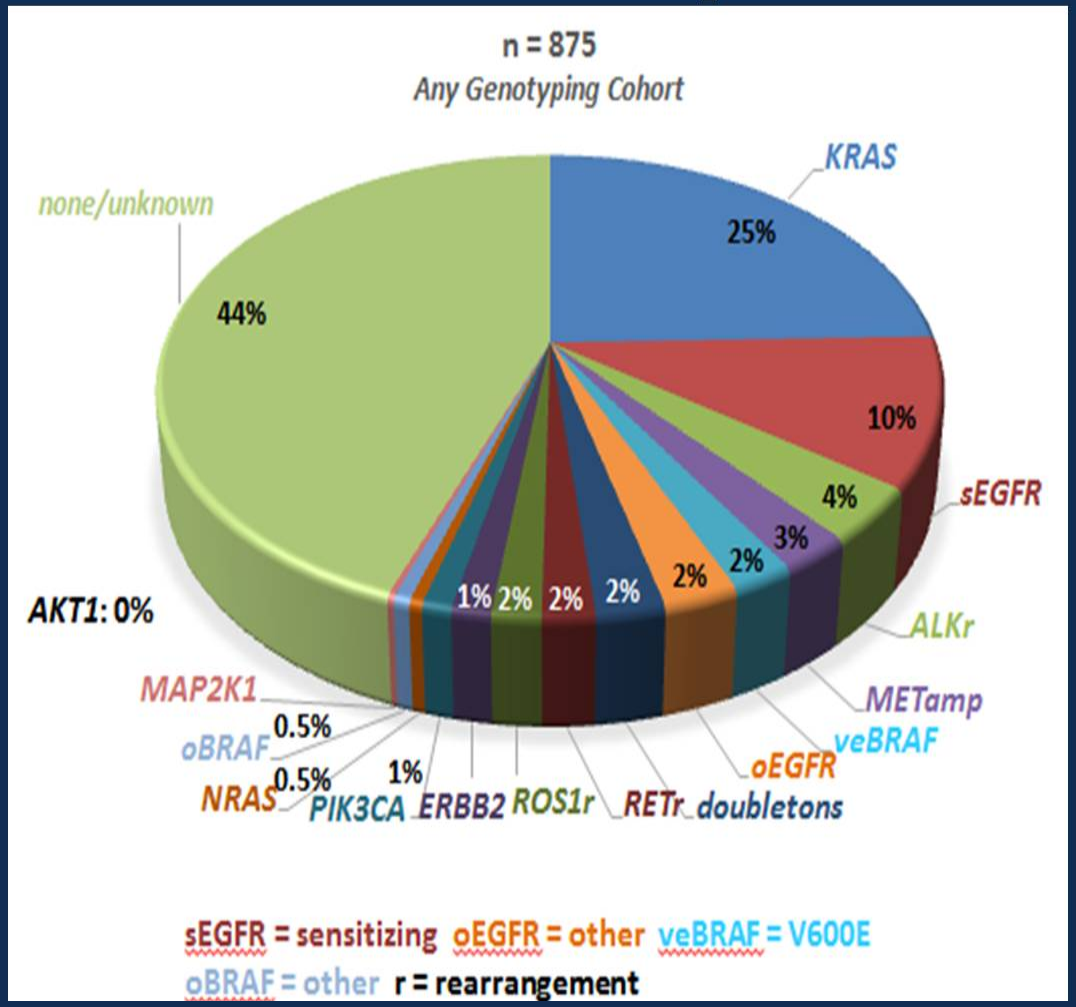
Mutational Frequencies in LCMC II



IHC assays	% pos cases
PTEN loss	15%
MET exp	59%
Pending central review	

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

free to breathe
a partnership for lung cancer survival

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Doubleton Mutations in 4.1%

n = 36/875 including *PIK3CA*

Gene	*AKT1*	*BRAF*	*ERBB2*	*KRAS*	*MAP2K1*	*NRAS*	*EGFR*	*ALKr*	*METa*	*ROS1r*	*RETr*	*PIK3CA*
AKT1	X											
BRAF		X		1					2	1		
ERBB2			X									
KRAS				X		1	2		6			8
MAP2K1					X							
NRAS						X						
EGFR							X	1	4*		1*	4
ALKr								X		1		1
METa									X	1	1	1
ROS1r										X	1	
RETr											X	1
PIK3CA												X

* *Triple mutation – EGFR/RET/MET*

LCMC I vs. II Mutation Frequencies

Based on testing for each gene separately

Gene	LCMC I	LCMC II	P value
EGFR	23%	16%	.001
ALK	9%	4%	<.001
KRAS	25%	27%	.434
ERBB2	3%	2%	.653
veBRAF	2%	3%	.074

- Why?
- Selection bias

Smoking Status	LCMC I	LCMC II	P value
Current	7%	12%	< 0.001
Former	59%	62%	
Never	34%	25%	

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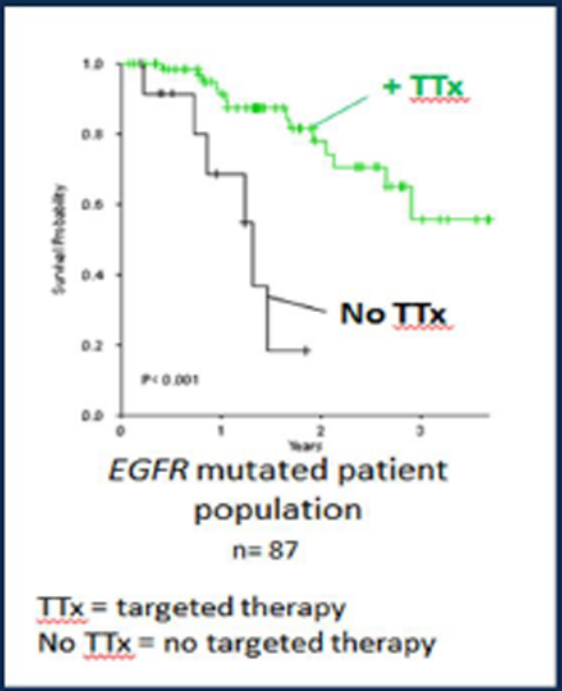
Expected Outcomes & Associations Were Seen



EGFR mutated patient population

n= 87

TTx = targeted therapy

No TTx = no targeted therapy

Variable 1	Variable 2	P value
Smoking Status	*KRAS* mutation	P<.001
Non-smoking Status	*EGFR* mutation	P<.001
Non-smoking Status	*ALK* rearrangement	P<.001
Asian Ethnicity	*EGFR* mutation	P<.001

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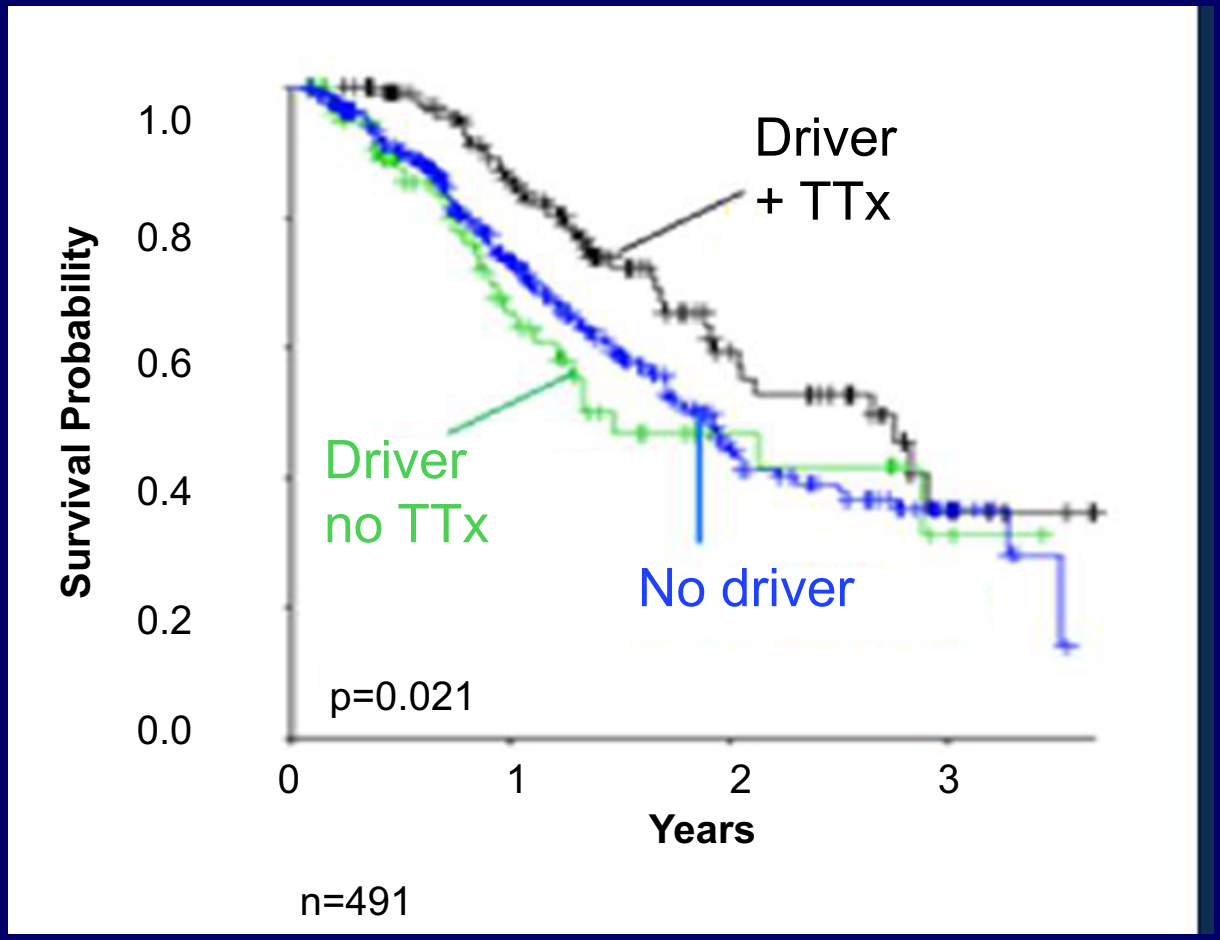
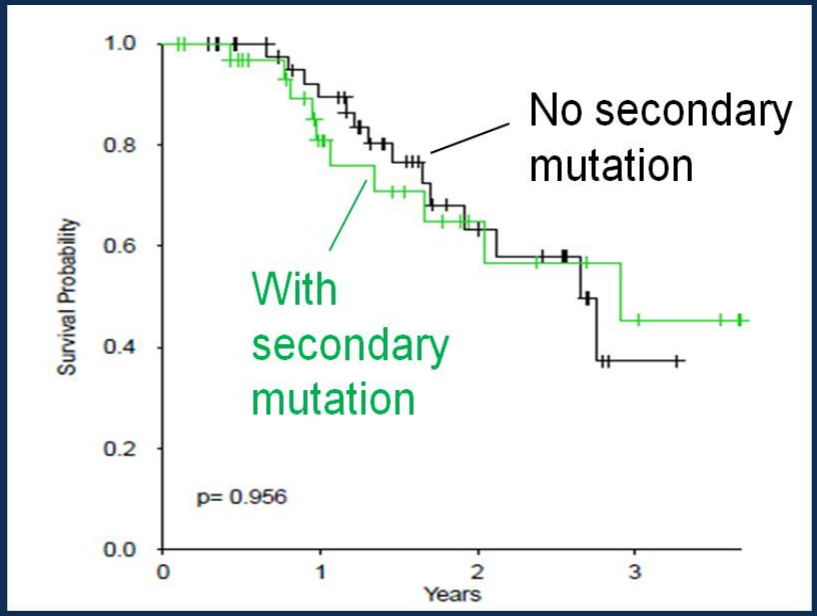
LCMC II: Driver Mutation Treatment Leads to Improved Survival



Is There a Clear Modulator of Response?

n= 79
Median survival
2.7 vs 2.9



Secondary mutation = any detected alteration in *TP53* and/or *PTEN* and/or *PIK3CA*

All patients with driver and targeted therapy

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Matching Patients with the Best Possible Therapies

free to breathe
a partnership for lung cancer survival

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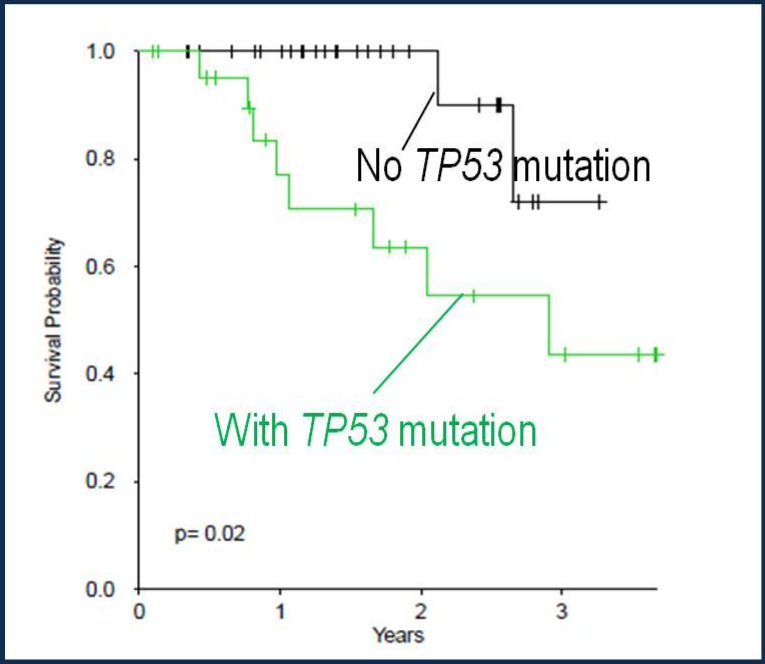
Some Modulators Can Be Identified



EGFR sensitizing mutation with targeted therapy

n= 51
Median survival 2.9 vs. NA

121 cases *EGFR* (+)

Only Sens*EGFR* (+) = 91

With TTx = 72
15 with no TTx or missing information

With survival AND *TP53* data = 51

Of these, 40 by NGS

Assay Coverage Matters

Of NGS cases:
TP53 positive rate= 48%

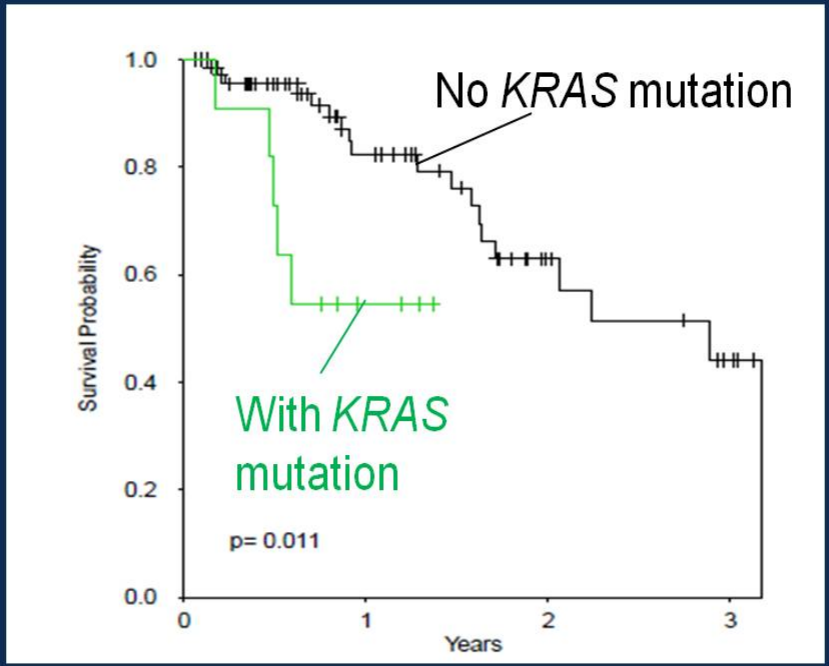
Of non-NGS cases:
TP53 positive rate= 8% (4 hotspots)

We are likely under-observing *TP53* mutation status

Presented By Dara Aisner at 2016 ASCO Annual Meeting

KRAS in Never Smokers

n= 82
Median survival
2.9 vs NA



Never smokers, no targeted therapy

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

free to breathe
a partnership for lung cancer survival

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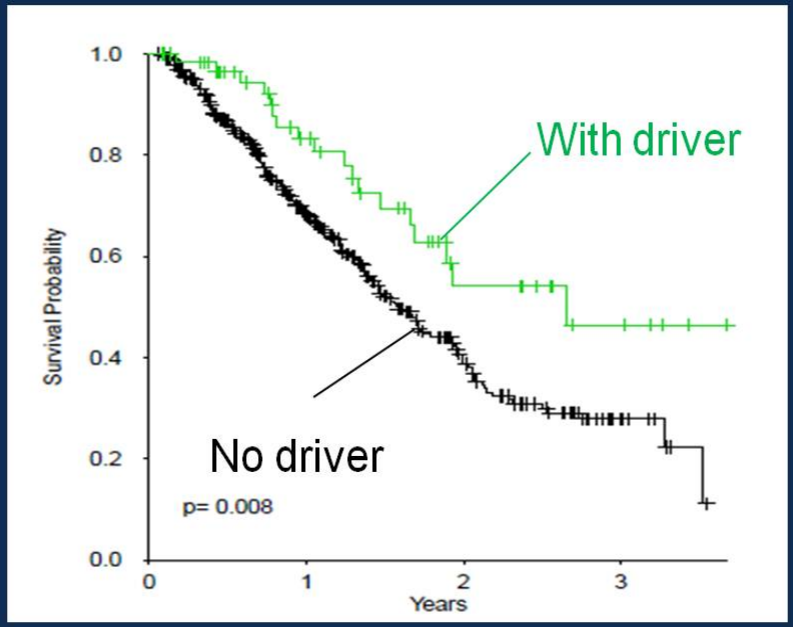
Drivers in Smokers

n= 447
Median survival
1.6 vs 2.7



Smokers

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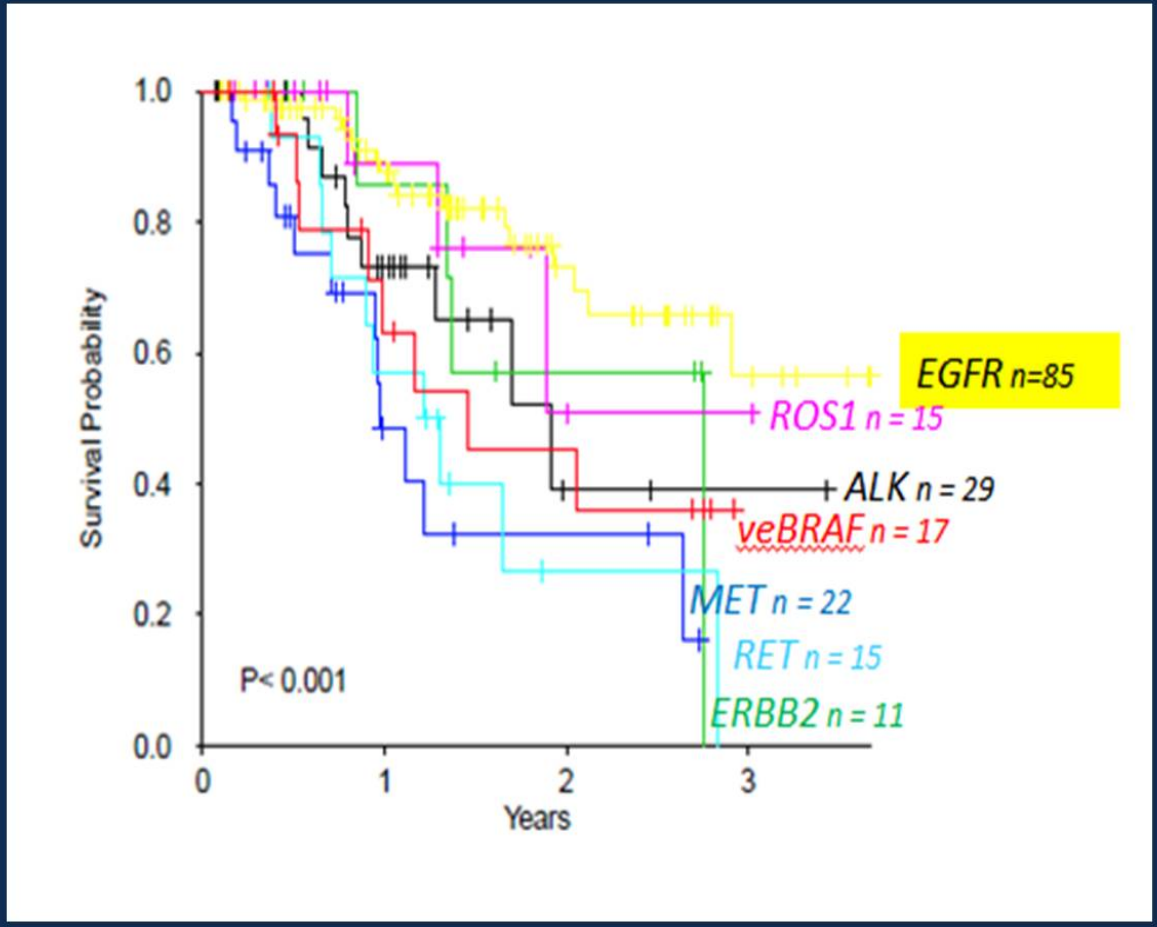
Survival by Driver



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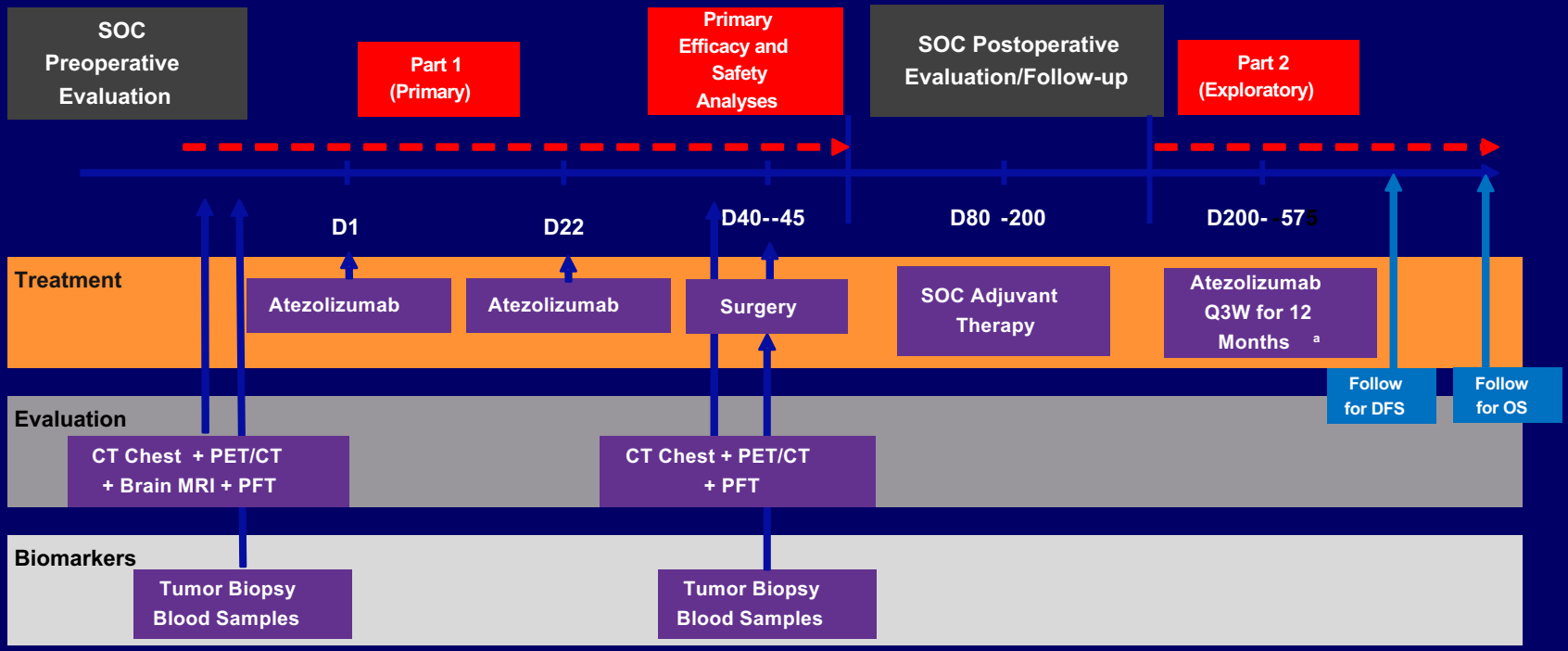
LCMC II: Conclusions

- Nex Gen Panel testing can easily (and should) be done in patients with advanced adenoca of lung with standard biopsies in a relevant time frame.
- First line molecularly targeted therapy improves survival.
- Passenger mutations do not influence outcome.
- Suppressor gene mutations such as p53 may worsen outcome from molecular therapy.
- KRAS mutations may impart a worse prognosis in never smokers.
- New guidelines will likely recommend NGS panel testing and additional molecular therapies.

LCMC 3: Neoadjuvant Atezolizumab



D. Carbone, PI

CT = computed tomography; PET = positron emission tomography; SOC = standard of care.

[a]Part 2 of this study is only for patients who demonstrate clinical benefit with neoadjuvant atezolizumab therapy in Part 1. Adjuvant atezolizumab treatment may be started directly within 60 – 90 days after surgery or within 30 days after adjuvant SOC chemotherapy (with or without radiation).

Choice of adjuvant SOC chemotherapy will be at the discretion of the treating physician, depending on the disease stage, as deemed clinically appropriate.

LCMC 4: Neoadjuvant TK

In planning for EGFR, ALK, ROS1, MET and others

LCMC II Acknowledgements

- LCMC sites, coordinators, and investigators
- LCMC coordinating center staff
- LCMC executive committee
- LCMC Clinical committee chaired by M. Kris
- LCMC Pathology committee chaired by D. Kiatkowski, L. Scholl and D. Aisner
- LCMC statistical center with Y. Shyr and L. Berry
- Patients and family who volunteered for the studies