Lung Cancer Care: The Last and The Next 5 Years Perspectives

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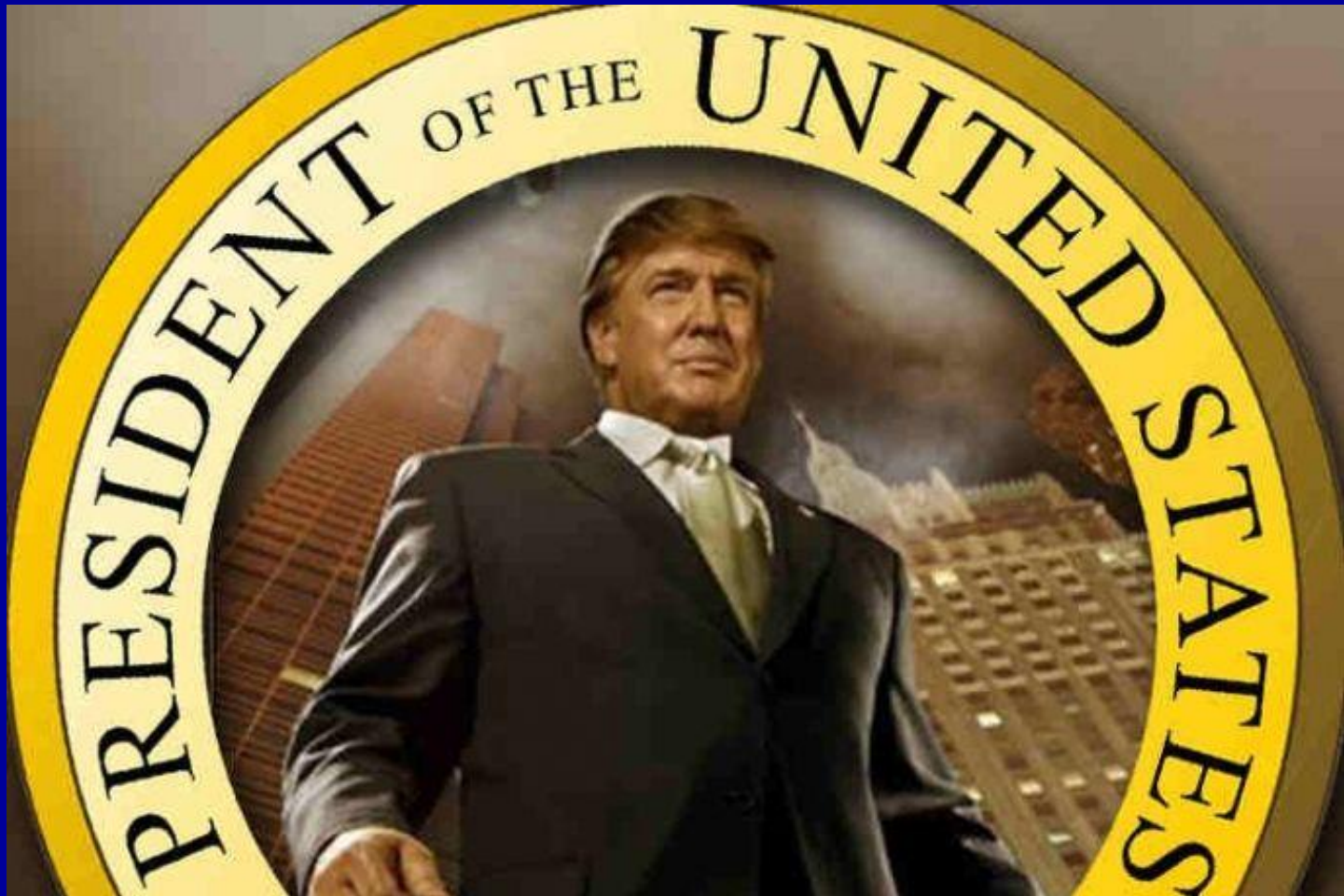# Prediction of the next 5 years based on the last 5 years

2011 to 2015 → 2016 → 2017 to 2021

This is un-predictable world

2011:
USA troop found and kill Bin Laden

2021:
Donald Trump as president of USA

"Those that fail to learn from history, are doomed to repeat it."

Winston Churchill

2011 to 2015

MADE IT	DIDN'T MAKE IT
Crizotinib for ALK positive lung cancer	MAGE A3 vaccine as adjuvant therapy for resectable lung cancer
Ramucirumab as second line therapy	Stimuvax for stage III lung cancer
Necitumumab for squmaeous cell carcinoma	Bevacizumab as adjuvant therapy for resectable lung cancer
Ceritinib/Alectinib as second line therapy for crizotinib failur	Erlotinib as adjuvant therapy for resectable lung cancer
Osimertinib for T790M positive lung cancer (post TKI failure)	
Nivolumab/pembrolizumab as second line therapy	

2011 to 2015

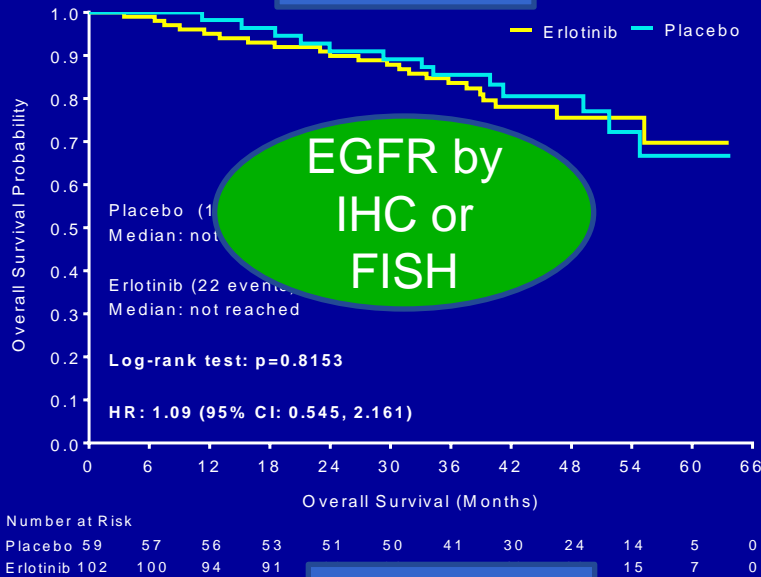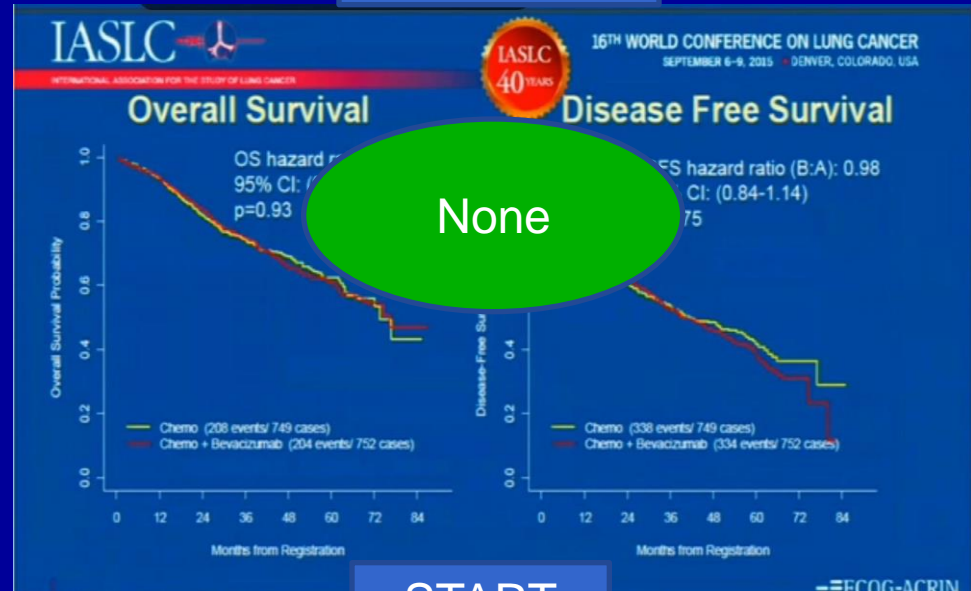| Made it	Didn't make it
Crizotinib for ALK positive lung cancer	MAGE A3 vaccine as adjuvant therapy for resectable lung cancer
Ramucirumab as second line therapy	Stimuvax for stage III lung cancer
Necitumumab for squmaeous cell carcinoma	Bevacizumab as adjuvant therapy for resectable lung cancer
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Why didn't we make it?
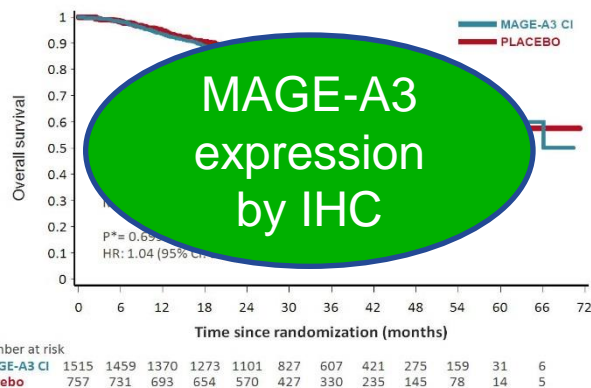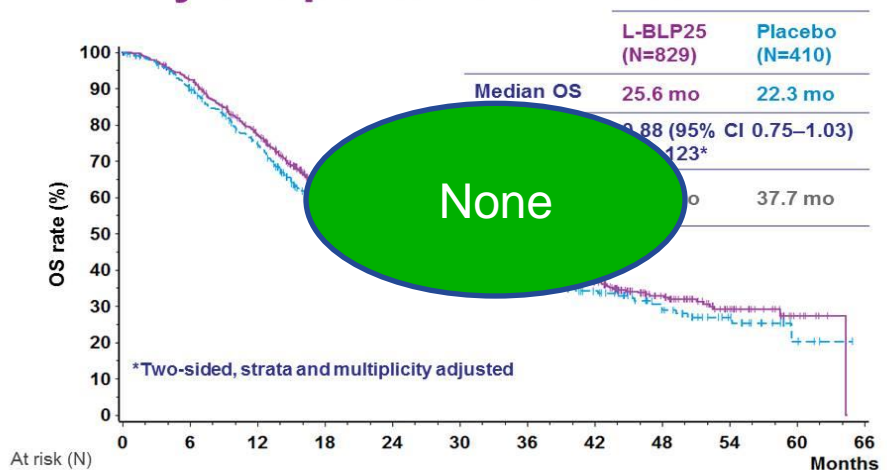
Overlap in EGFR biomarker: IPASS

High EGFR-gene-copy number

N=198

EGFR expression positive

N=242

EGFR mutation positive

N=209

25

51

13

Positive for all 3 biomarkers N=132

28

34

15

FISH+ Mut+:160
FISH+ Mut-:38
FISH- Mut+:49

=329 with known biomarker status for all 3 biomarkers

Fukuoka and Mok et al JCO 2011
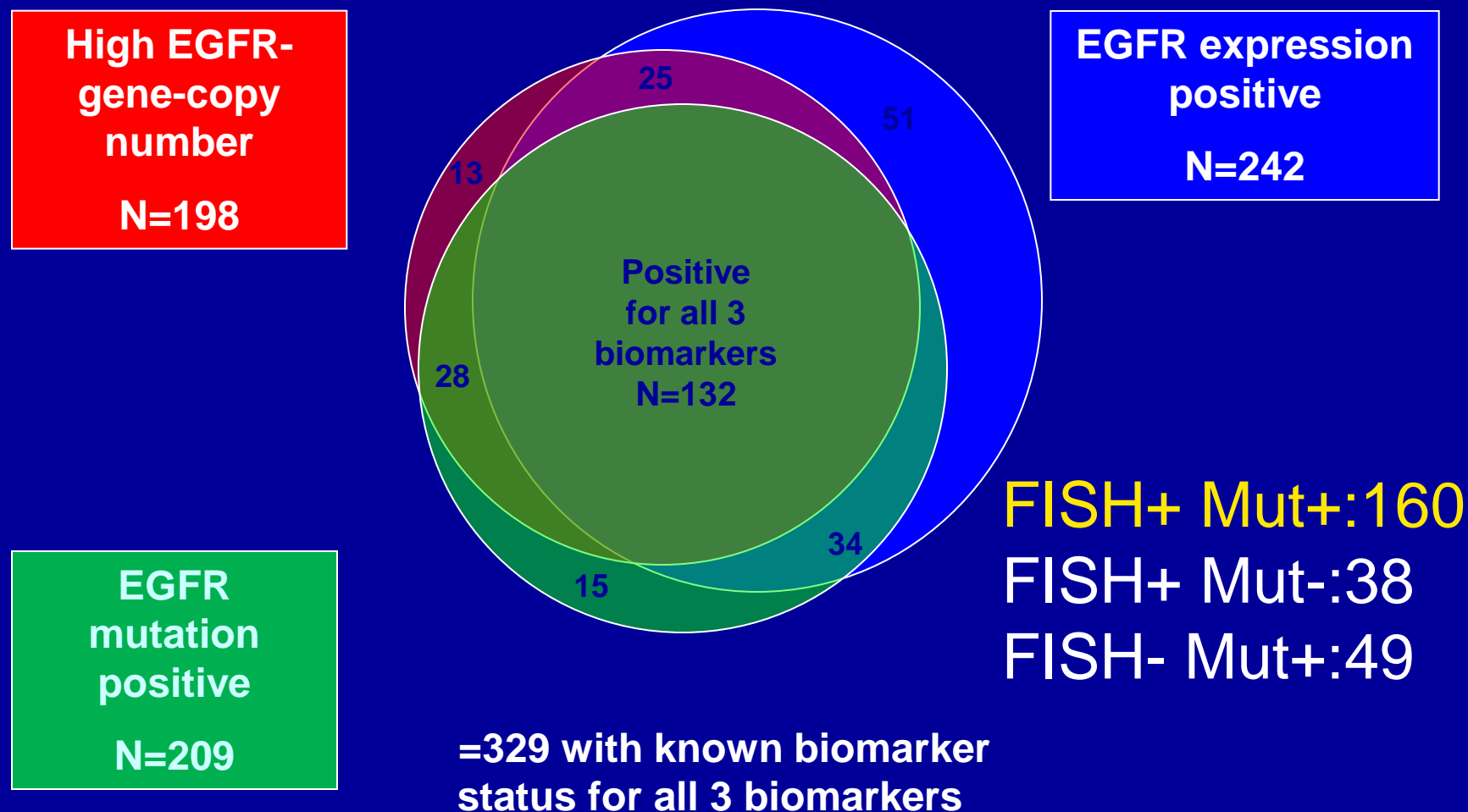
IPASS: EGFR Mutation as the true biomarker

EGFR mutation positive

Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001
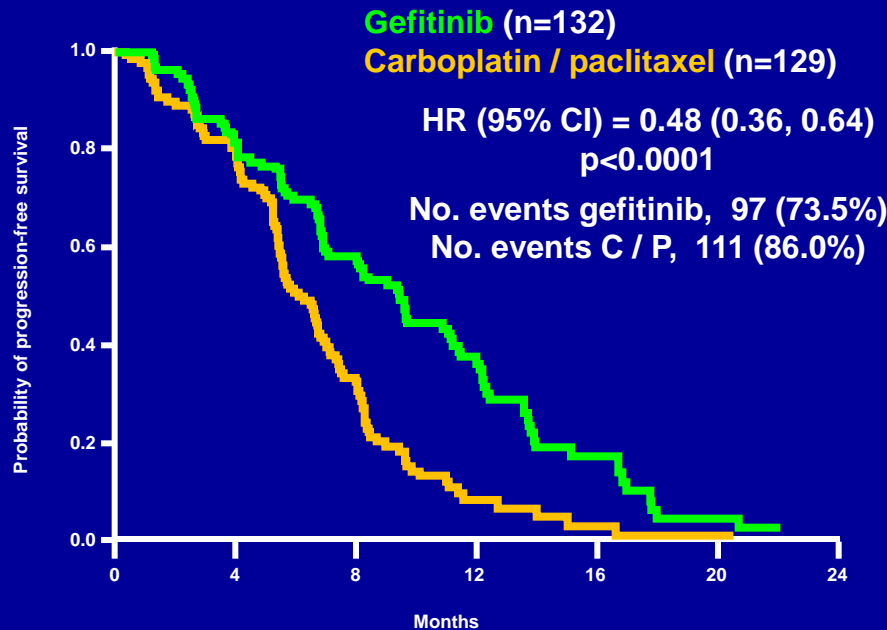
No. events gefitinib, 97 (73.5%)
No. events C / P, 111 (86.0%)

EGFR mutation negative

Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001

No. events gefitinib , 88 (96.7%)
No. events C / P, 70 (82.4%)

At risk :
Gefitinib 132 108 71 31 11 3 0   91 21 4 2 1 0 0
C / 129 103 37 7 2 1 0   85 58 14 1 0 0 0
P
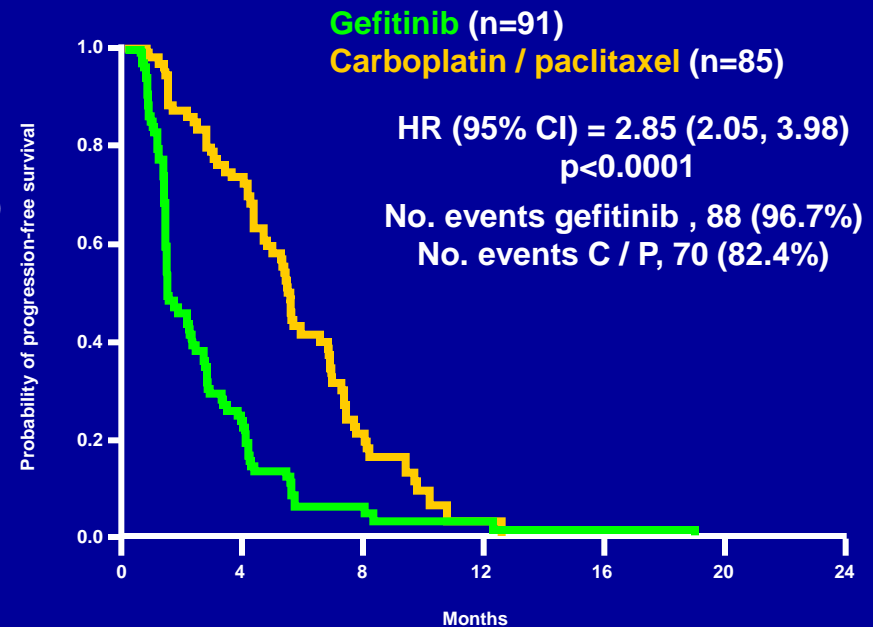
Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok et al NEJM 361:947 2009

How reliable is MAGE-A3 as biomarker?

Randomized phase II study on MAGE-A3 positive stage IB-II NSCLC

B

Disease-Free Survival (%) vs Time Since Surgery (months)

MAGE-A3 + AS02$_B$
Placebo

MAGE-A3 is not a strong predictive biomarker in adjuvant setting

No. at risk
MAGE-A3 + AS02$_B$	122	103	91	81	76	70	66	63	60	54	49	36	29	13	5
Placebo	60	53	41	35	33	32	25	24	24	21	20	15	10	3	1

MAGE-A3 + AS02$_B$
Placebo

No. at risk
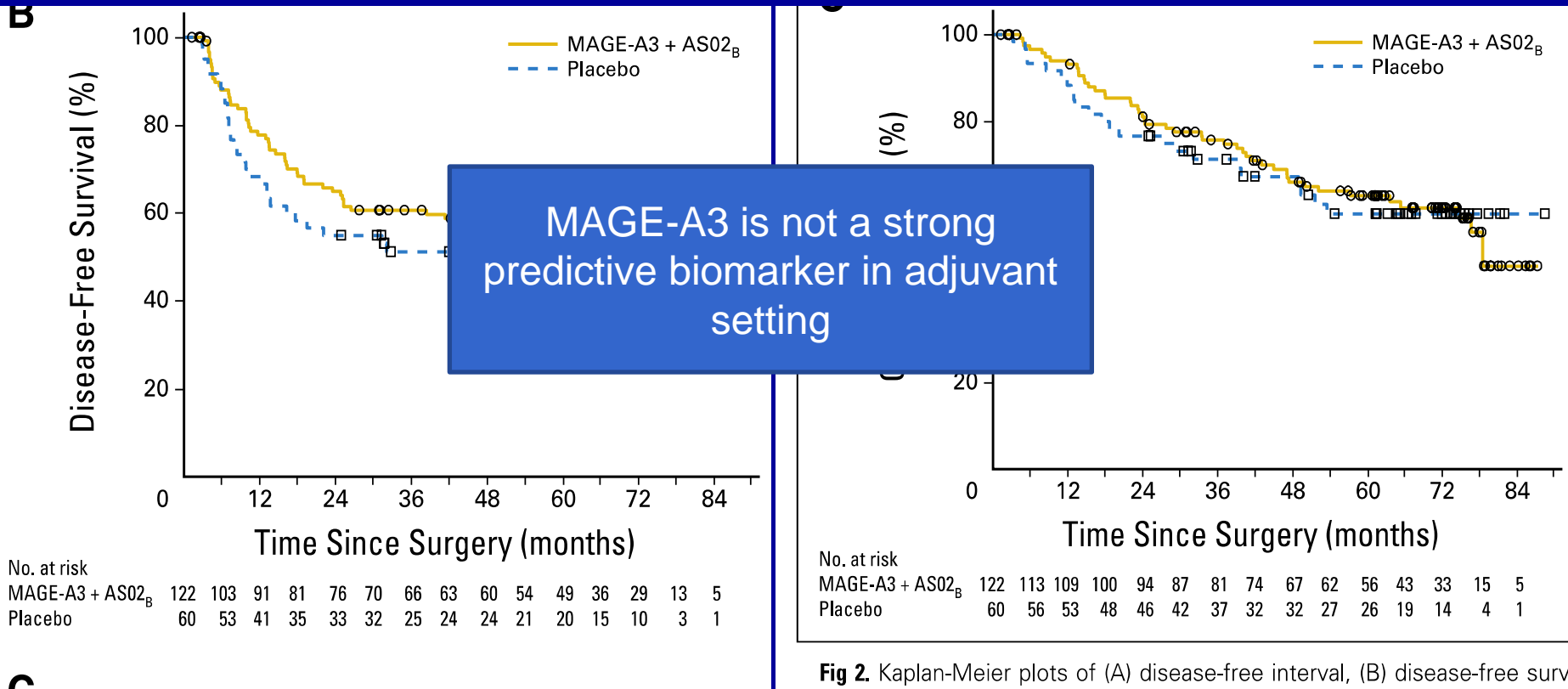|															
MAGE-A3 + AS02$_B$	122	113	109	100	94	87	81	74	67	62	56	43	33	15	5
Placebo		60	56	53	48	46	42	37	32	32	27	26	19	14	4	1

Fig 2. Kaplan-Meier plots of (A) disease-free interval, (B) disease-free survi
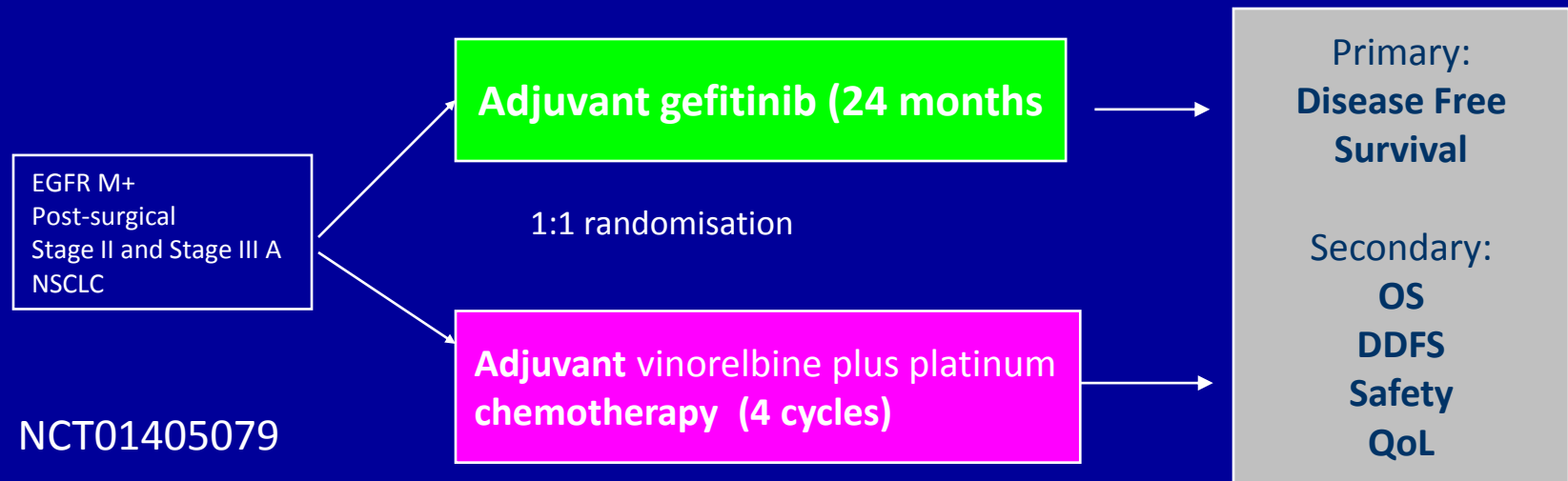
C

DFS (HR 0.76, p=0.25)   OS (HR 0.81, p=0.45)

Vansteenkriste et al JCO 2013

So we have learnt….

CTONG1104: A national, multi center, randomized, open-label, phase III trial of gefitinib versus combination of vinorelbine plus platinum as adjuvant treatment in pathological stage II-IIIA(N1-N2) NSCLC with EGFR activating mutation (**ADJUVANT**)

EGFR M+
Post-surgical
Stage II and Stage III A
NSCLC

Adjuvant gefitinib (24 months

1:1 randomisation

Adjuvant vinorelbine plus platinum **chemotherapy (4 cycles)**

Primary:
Disease Free Survival

Secondary:
OS
DDFS
Safety
QoL

NCT01405079

FPI: Sep.15, 2011

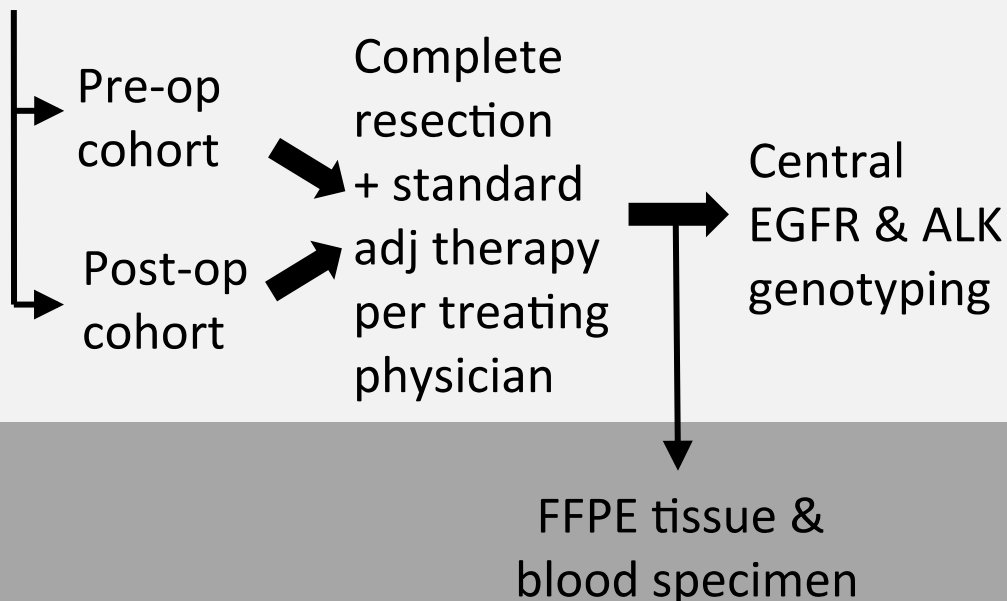- Sample size was estimated to be 220 when HR of DFS, the primary endpoint, was estimated to be 0.6, the enrollment period was to be 2 years, the period of follow-up after the final enrollment was to be 5 years, statistically significant level (α) was to be 0.05, and the statistical power was to be 80%. The estimated total events is 122 from 208 analysed patients

24 sites, 41 patients randomized (2012/9)

ALCHEMIST-SCREENING Trial Schema

Trials conducted at sites in the
NCI Clinical Trials Networks: NCTN & NCORP

Non-squamous NSCLC (n=6,000 to 8,000 pts)
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA
Post-Op cohort with negative surgical margins

Pre-op cohort

Post-op cohort

Complete resection + standard adj therapy per treating physician

Central EGFR & ALK genotyping

FFPE tissue & blood specimen

EGFR-mutation:
Phase III trial of erlotinib vs placebo x 2 years (n=410) after any adj tx

ALK-rearranged:
Phase III trial of crizotinib vs placebo x 2 years (n=360) after any adj tx

Without Molecular Alterations: Followed q6 months x 5 years after any adj tx

FFPE tissue from biopsy done at recurrence

Advanced genomics at the NCI

ALCHEMIST EGFR Treatment Trial A081105

Resected NSCLC tissue tested on ALCHEMIST Screening Trial

↓

Patients with tumors with an EGFR mutation

→

R A N D O M I Z E

1 cycle =21 days

Erlotinib
150 mg po BID x
2 years

→ Long Term Follow-up

Placebo
po BID x
2 years

→ Long Term Follow-up
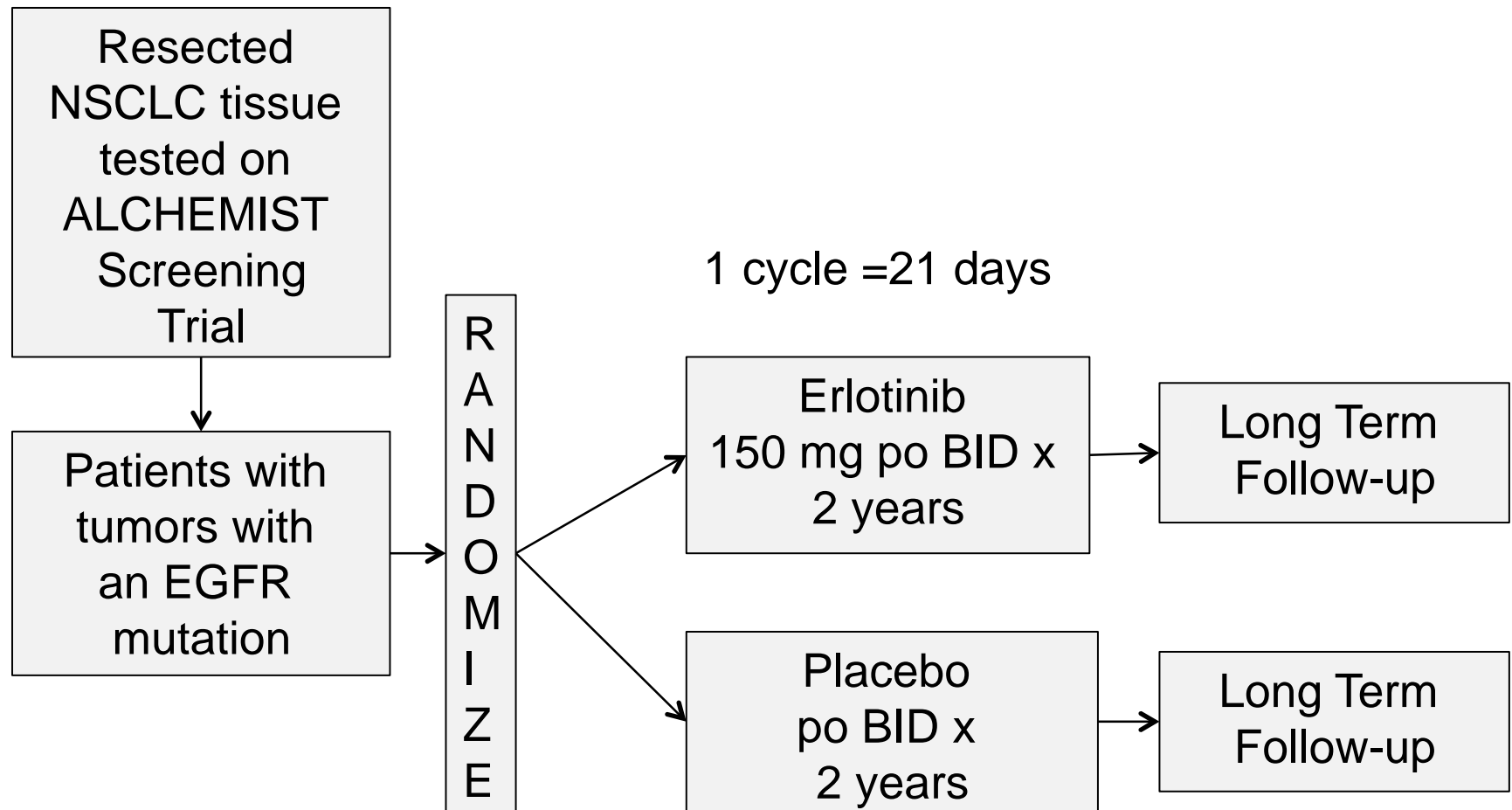
Primary endpoint is overall survival

ADAURA: Phase III study on AZD9291 vs Placebo

Stage IB, II ort IIIa Priminary NSCLC

EGFR mutation positive including the atypical mutations

WHO PS0,1 Completed resection and adjuvant chemotherapy

AZD9291

Placebo
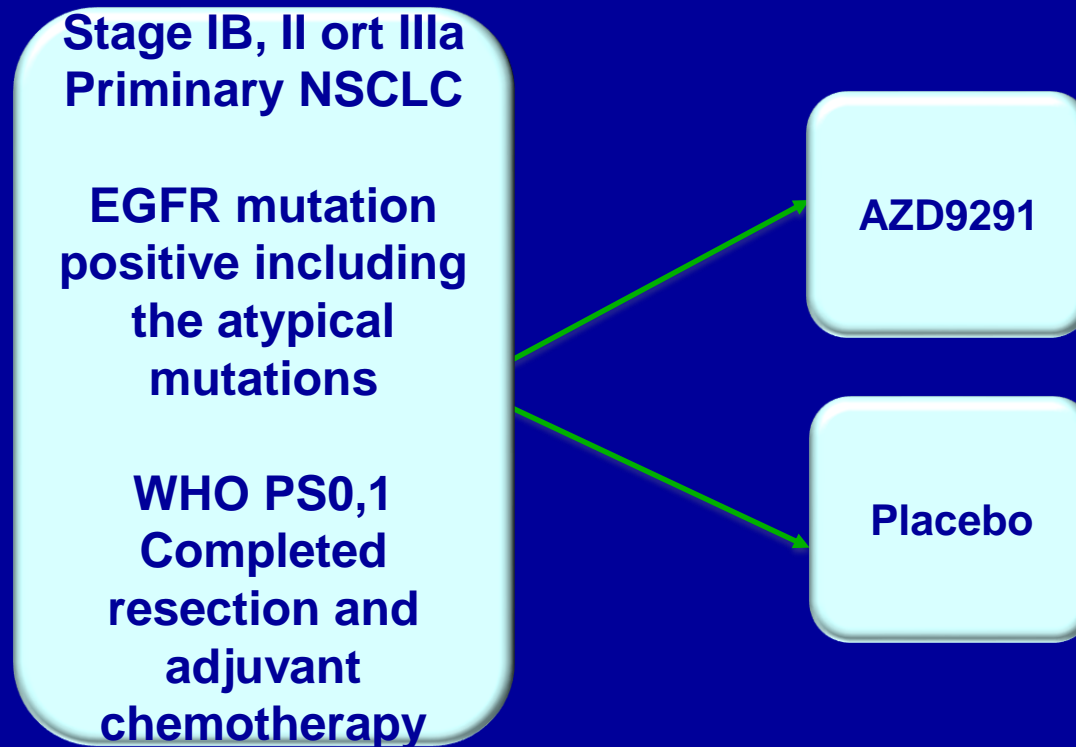
- Primary endpoint: disease-free survival (DFS)
- Secondary endpoints: OS; DFS and OS in patients with del19/L858R (*EGFR* M+)

2011 to 2015

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What is the reason(s) for success?
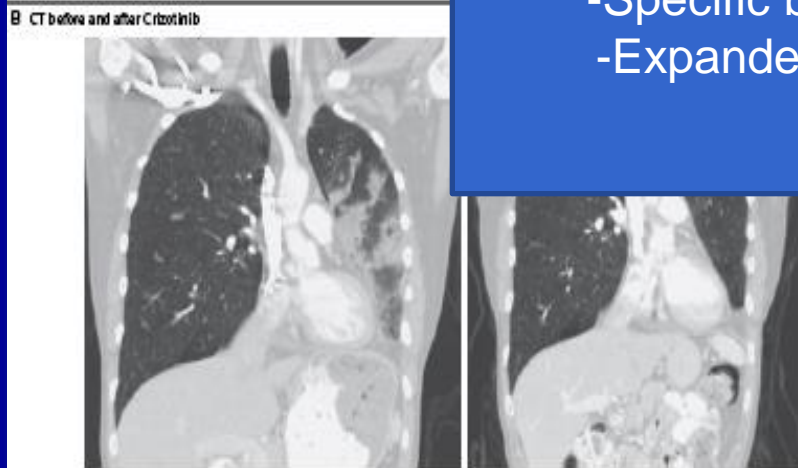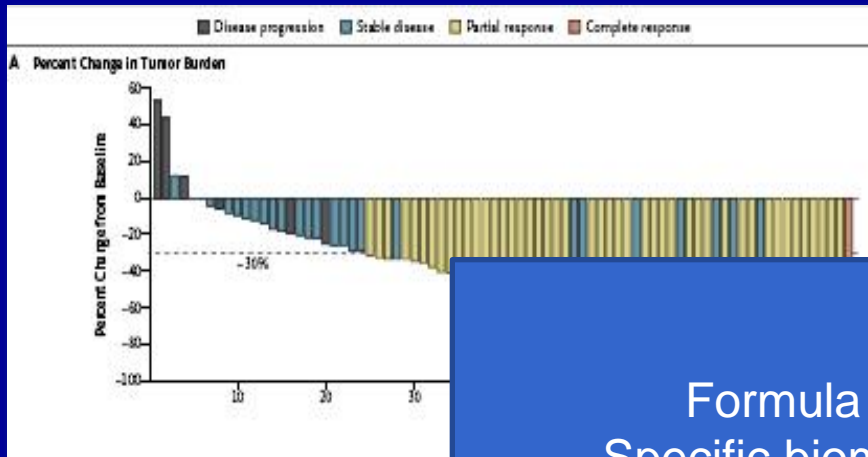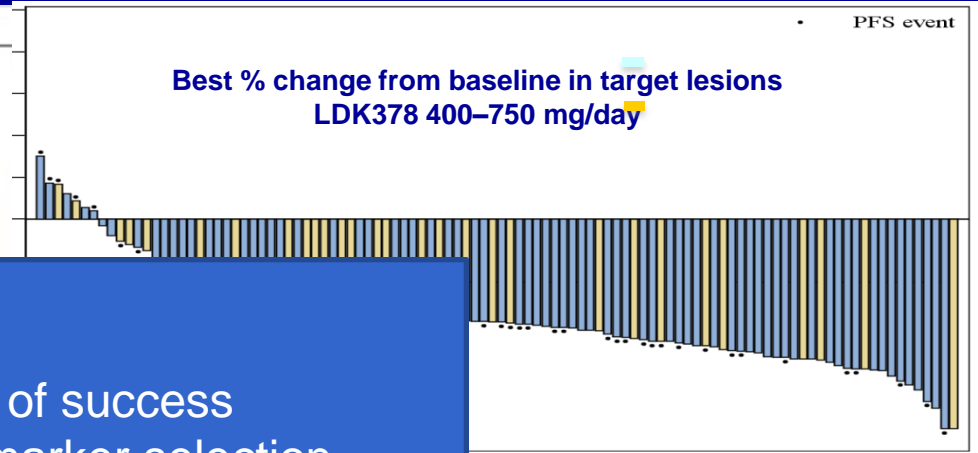
Formula of success
-Specific biomarker selection
-Expanded phase I program

Best % change from baseline in target lesions
LDK378 400–750 mg/day

Crizotinib

Osimertinib

Kwak NEJM 2011, Shaw et al 2014, Janne et al NEJM 2015
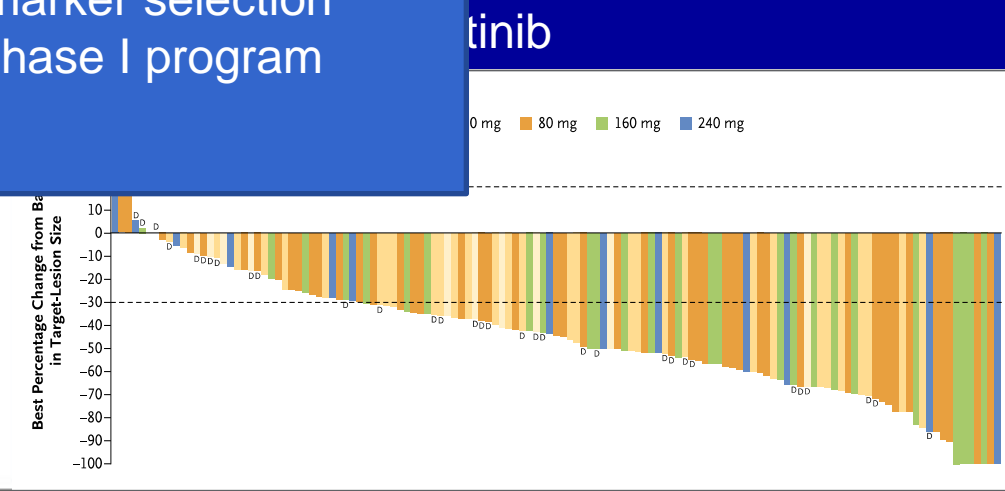
Common factors in these phase I studies

- Proven driver oncogene (pre-clinical)
- Known incidence of the driver oncogene in population
- Biomarker with established predictive power
- Convincing waterfall plot (High single agent response rate)

Traditional clinical trial design

Definition	Study types included
Phase I Tolerability or PK as primary endpoint in the protocol, independent of the study population and secondary parameters	• Safety & Tolerability studies (Single/ multiple dose in patients or healthy volunteers) • Oncology studies in patients with tolerability / MTD as primary endpoint (efficacy might be a secondary endpoint) • Drug-Drug interaction & Food Effect • PK in renal or hepatic impaired patients
Phase IIA Exploratory (non-pivotal) study that has clinical efficacy, Pharmacodynamics or biological activity as primary endpoint, conducted in patients or healthy volunteers.	• Proof of concept, efficacy, or mechanism • Mechanistic studies • Dose range exploration • Pilot studies
Phase IIB Definite dose range finding study in patients with efficacy as primary endpoint. Exceptionally, Phase II studies can be used as pivotal trials, if the drug is intended to treat life-threatening or severely-debilitating illnesses as in oncology indications	• Definite dose finding studies • Extension studies of Phase IIB studies

Algorithm for Biomarker-Driven Trial Designs of Targeted Therapies
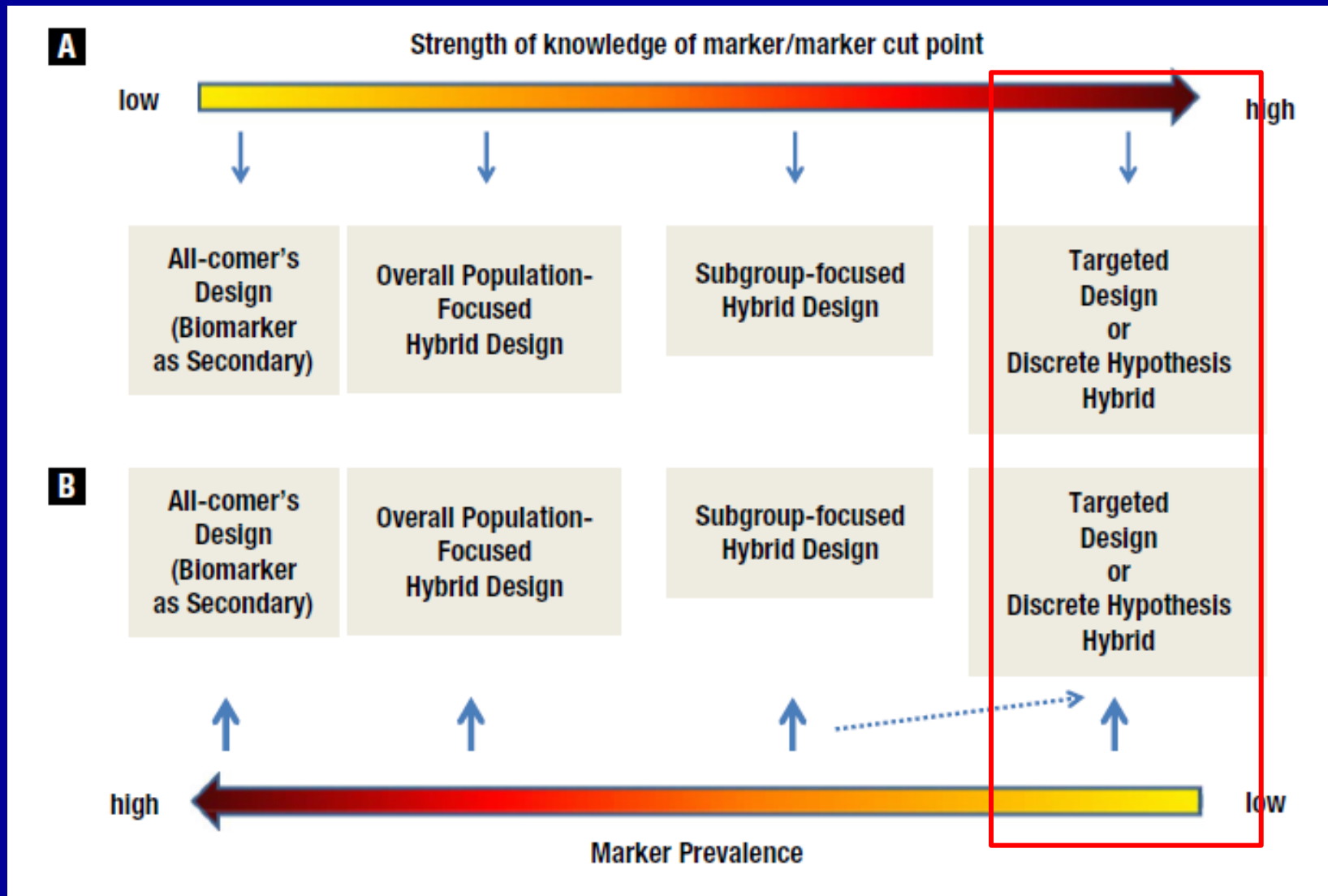
from Redman, Gandara et al: Clin Cancer Res 2012
& Gandara et al: Clin Lung Cancer 2012

Biomarker driven phase I study

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                              ┌─────────────┐      ┌──────────┐
                              │ Biomarker-  │ ───► │   Off-   │
                              │             │      │  study   │
                              └─────────────┘      └──────────┘
        ┌──────────────────┐
        │ Mandatory biopsy │
        └──────────────────┘
                              ┌─────────────┐      ┌──────────┐
                              │ Biomarker + │ ───► │ New TKI  │
                              └─────────────┘      └──────────┘
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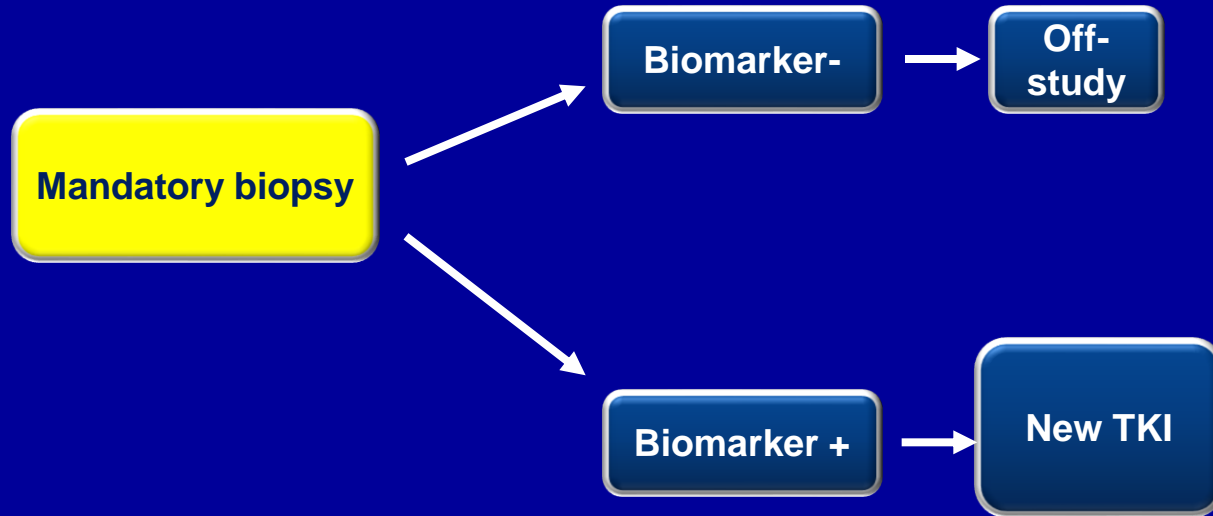
Primary endpoint:
ORR

Secondary endpoints:
PFS, OS, safety, exploratory biomarkers

2016 | **2017 to 2021** →

How may this translate into future success?

a

Tumour type A (lung cancer)
→ Tumour molecular analysis
→ Biomarker 1, Biomarker 2, Biomarker 3, Biomarker 4
→ Drug 1, Drug 2, Drug 3, Drug 4

b

Tumour type A (lung cancer), Tumour type B (gastric cancer), Tumour type C (colon cancer), Tumour type D (breast cancer)
→ Tumour molecular analysis
→ Biomarker 1, Biomarker 2
→ Drug 1, Drug 2

c

Tumour organ of origin

Breast, Colorectal, NSCLC, Prostate, Melanoma, Ovarian, GIST, Gastric, PDAC

ER positive: Luminal A, Luminal B
ER negative: HER2, Normal-like, Basal
BRCA

Anti-EGFR responsive Ras WT, MMR, CIMP, EML-ALK, EGFR, TMPRSS2-erg, BRAF mutated, BRCA, c-kit mutated, HER2

Molecular characteristics (biotype)

Oestrogen dependent: BREAST
Abl-like kinase dependant: CML, GIST, RCC
EGFR dependent: NSCLC, COLON, SCCHN
HER2 amplified: BREAST, GASTRIC, Pa
ALK-inhibitor responsive: NSCLC, NHL, NB
DDR defective: BREAST, OVARY, Pa
BRAF mutant: MELANOMA
NOVEL mutant
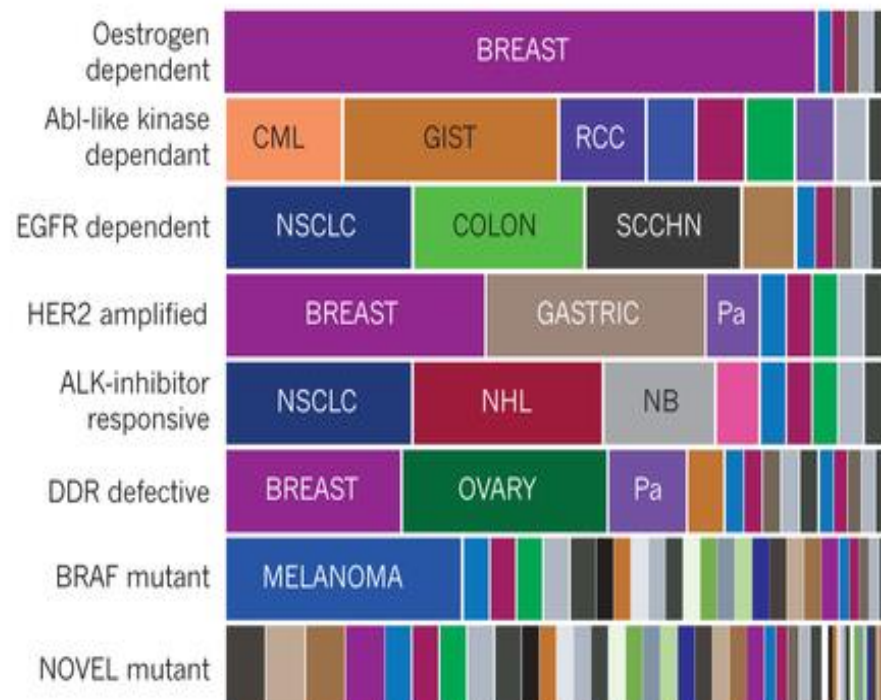
Updated Lung-MAP Trial Schema (2016)

Matched Sub-studies

Non-match Sub-studies

PI3K	CDK4/6	FGFR[1]	HRD

Checkpoint Naive	Checkpoint Refractory

Stage 1

GDC-0032	Palbociclib	AZD4547	BMN 673*

Nivo/Ipi Nivolumab	MEDI4736/ Treme*

Stage 2

GDC-0032 Vs SoC	Palbociclib Vs Soc	AZD4547 Vs SoC	BMN 673 Vs SoC*
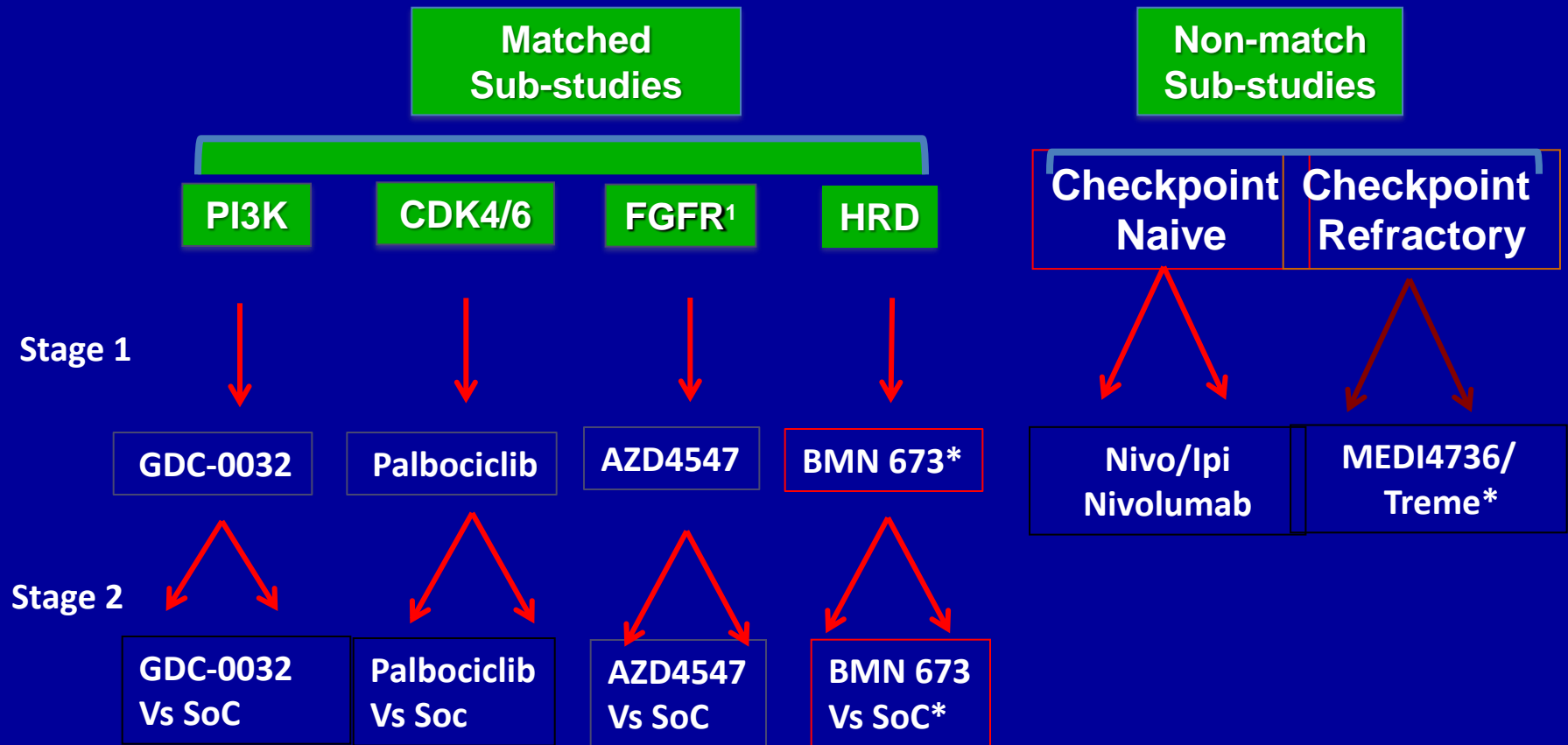
- Lung-MAP amended to 2nd line therapy and beyond to accommodate Nivolumab approval
- Pre-screening added back
- Eligibility criteria broadened;   *Sub-studies in development

Biomarker trial design based on comprehensive genomic profiling

Screen success rate: up to ~80% of patients, depending on biomarkers selected

% of lung squamous patients with alteration

PI3K/AKT/mTOR:
- PIK3R1/2, TSC1/2, AKT1/2
- STK11 loss
- FBXW7 loss
- PTEN loss
- PIK3CA amp
- PIK3CA mutation

Cell Cycle:
- CCND3 amp
- CCNE1 amp
- CDK6 amp
- CCND2 amp
- CCND1 amp
- CDKN2A/B loss

FGFR:
- FGFR3 amp
- FGFR1 amp/mutation

lead candidate biomarkers

additional potential biomarkers

Cell Cycle 46% — FGFR 4% (5%)

PI3K 26% — Cell Cycle 25% (26%)

PI3K 47% — FGFR 4% (5%)

Non-Match 18%

NCI-MATCH Schema

Genetic sequencing PTEN IHC → Actionable mutation detected → Study agent

Study agent → Stable disease, complete or partial response (CR+PR)[1] → Continue on study agent until progression → PD → Repeat biopsy and sequencing

Study agent → Progressive disease (PD)[1] → Check for additional actionable mutations[2]

Check for additional actionable mutations[2] — Yes → (back to Actionable mutation detected)

Check for additional actionable mutations[2] — No → No additional actionable mutations, or withdraw consent

Repeat biopsy and sequencing → No additional actionable mutations, or withdraw consent

No additional actionable mutations, or withdraw consent → 3 Year Follow Up

[1]CR, PR, SD, and PD as defined by RECIST

[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

NCI-MATCH Subprotocols - Activated August 2015

Molecular Target	Estimated % Prevalence	Agent(s) for Molecular Target	Subprotocol ID
EGFR activating mutations	1 - 4	Afatinib	EAY131-A
HER2 activating mutations	2 - 5	Afatinib	EAY131-B
EGFR T790M mutations and rare activating mutations of EGFR	1 - 2	AZD9291	EAY131-E
ALK translocations	<2	Crizotinib	EAY131-F
ROS1 translocations	<2	Crizotinib	EAY131-G
BRAF V600E or V600K mutations	1-12	Dabrafenib and trametinib	EAY131-H
HER2 amplification	5	Ado-trastuzumab emtansine	EAY131-Q
BRAF fusions, or non-V600E, non-600K BRAF mutations	2.79	Trametinib	EAY131-R
NF2 loss	2	Defactinib	EAY131-U
cKIT mutations	<2	Sunitinib	EAY131-V

Santa Monica 2016

Studies Targeting Alterations Responsive to Targeted Receptor Kinase inhibition

STARTRK-2 Basket Study initiated at clinical sites globally

Patients with Solid Tumors (any line of therapy)

Possible chemotherapy per MD

Tumor sample submission for CDx analysis at Ignyta's central lab

Separate by molecular alteration and solid tumor type

NSCLC

| NTRK1/2/3 fusions | ROS1 fusions |

CRC

| NTRK1/2/3 fusions | ROS1 fusions | ALK fusions |

All other non-NSCLC, non-CRC solid tumors

| NTRK1/2/3 fusions | ROS1 fusions | ALK fusions |

All solid tumors

NTRK1/2/3, ROS1, and ALK *non-fusion* alterations

Separate analyses by Cohort (basket)
Primary endpoint = ORR
Key secondary endpoint = DOR

SIMON 2-STAGE RULES:
1st stage: 6 pts (≥1 response)
2nd stage: + 8 pts (≥ 5 responses)
Open new "basket"

Second generation: Dacomitinib

ARCHER 1050:

Advanced NSCLC
- Adenocarcinoma
- EGFR exon 19/21 mut+
- First-line treatment
- PS 0-1

N= 440 patients

R A N D O M I Z E

1 → **Dacomitinib 45mg qd**

1 → **Gefitinib 250mg qd**

Primary endpoint in PFS 14.8 vs 9.5 months

Stratification
-Race
-Exon 19 v 21

Completed accrual in March 2015

Third Generation EGFR TKI with expected outcomes in 5 years

"3rd" gen	N	RR* T790M-	RR T790M+	PFS	Registration study
Rociletinib (CO-1686)	256	37%	53%^	~8.0 mo	TIGER 3
Osimertinib (AZD9291)	253	21%	61%	~8.2 mo	AURA 3
HM61713 (800mg)	62	12% (300 mg)	55%	NR	ELUXA 2/3
EGF816X*	53	-	60%	NR	Phase I
PF-06747775	XX	XX	XX	XX	Phase I dose escalation

*T790M- subgroups are very small **Multiple other agents earlier in development**
^ many unconfirmed

Sequist PASCO 2015 -8001;Janne NEJM 2015; Park PASCO 2015 ; Tan PASCO 2015; Goto PASCO 2015

FLAURA study design

Enrollment by local* or central# *EGFR* mutation testing of biopsy sample

→

Stratified by:

Asian / non-Asian

Ex19del / L858R

→

AZD9291 (80 mg p.o. qd)

→

RECIST 1.1 assessment every 6 weeks until objective progressive disease

Patients randomized to standard of care may receive AZD9291 after progression §

→

Primary objective: efficacy by PFS

→

EGFR-TKI standard of care##: gefitinib (250 mg p.o. qd) or erlotinib (150 mg p.o. qd)

→

Combination of EGFR TKI and Bevacizumab NEJ026

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                        ┌─────────────────────┐   ╭───╮   ┌─────────────────────┐
                        │  Erlotnib +         │──▶│PD1│──▶│  Recommend          │
                   ┌───▶│  Bevacizumab        │   ╰───╯   │  Pem/Platinum       │
                   │    └─────────────────────┘           └─────────────────────┘
┌────────────────┐ │
│ Non-sq NSCLC   │─┤
│ Previously     │ │
│ untreated      │ │
│ Age 20 or above│ │
│ EGFR M+        │ │
│ N=214          │ │    ┌─────────────────────┐   ╭───╮   ┌─────────────────────┐
└────────────────┘ └───▶│  Erlotinib          │──▶│PD1│──▶│  Recommend          │
                        └─────────────────────┘   ╰───╯   │  Pem/Platinum +     │
                                                          │  Bevacizumab        │
                                                          └─────────────────────┘
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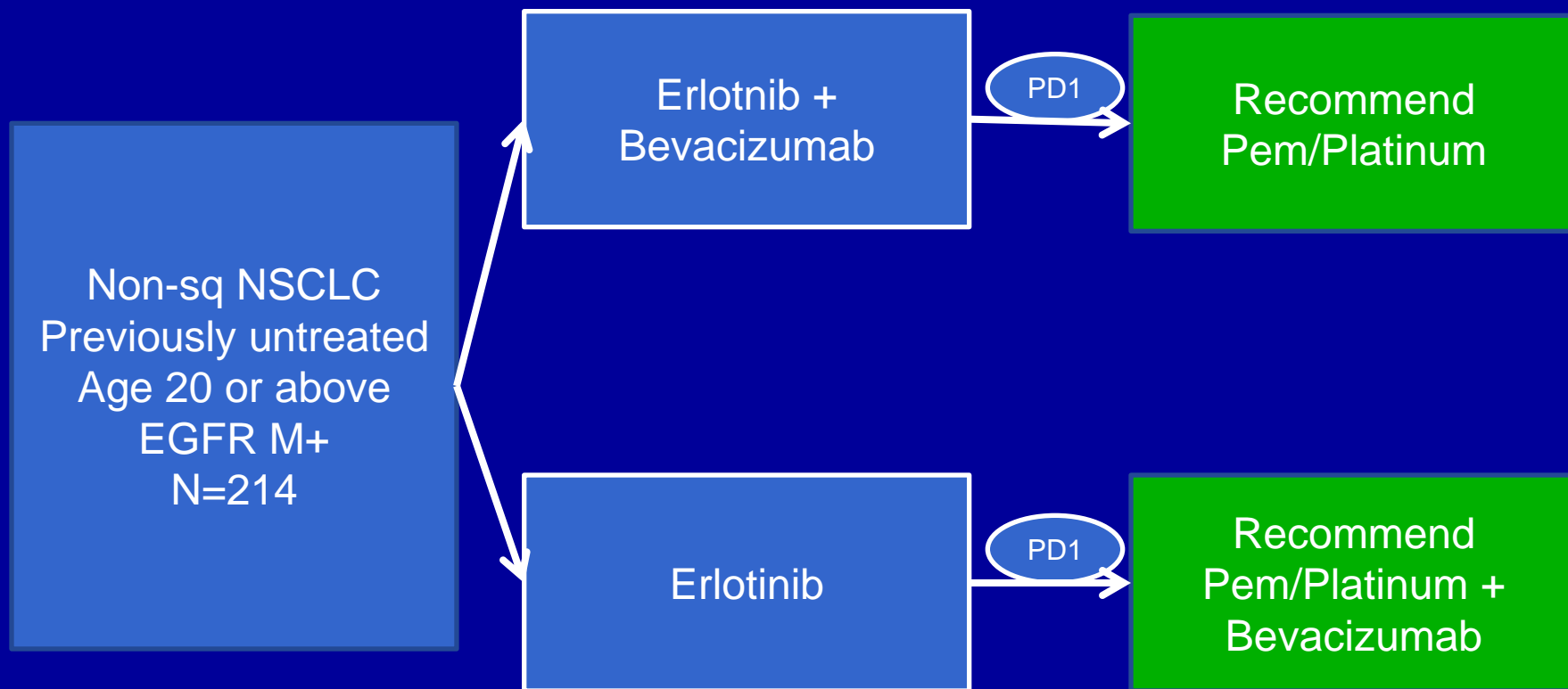
Primary endpoint: PFS
Secondary endpoint: OS, RR, Safety

List of second generation ALK inhibitors

Ceritinib

Alectinib

Loratinib

Brigatinib

TSR-011

X-396

CEP-37440

RXDX-101

ASP3026

List of second generation ALK inhibitors

Ceritinib **Alectinib** **Loratinib** **Brigatinib**

List of second generation ALK inhibitors

Ceritinib
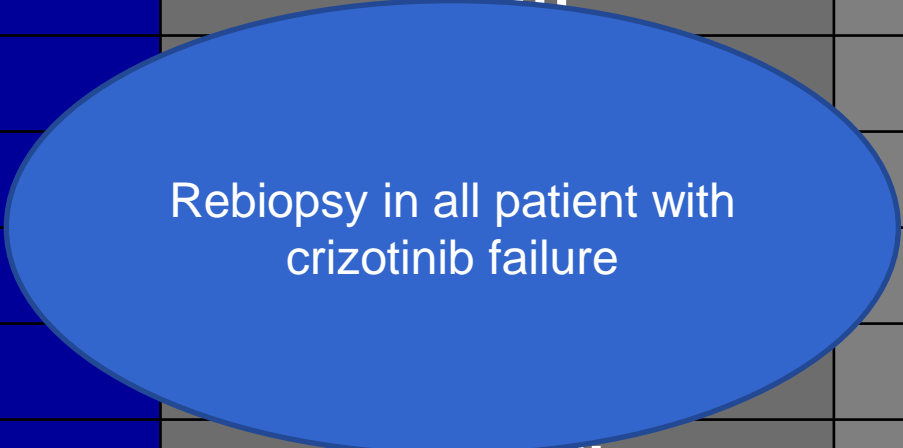
Alectinib

Loratinib

Brigatinib

Differential inhibitory activities among ALK inhibitors
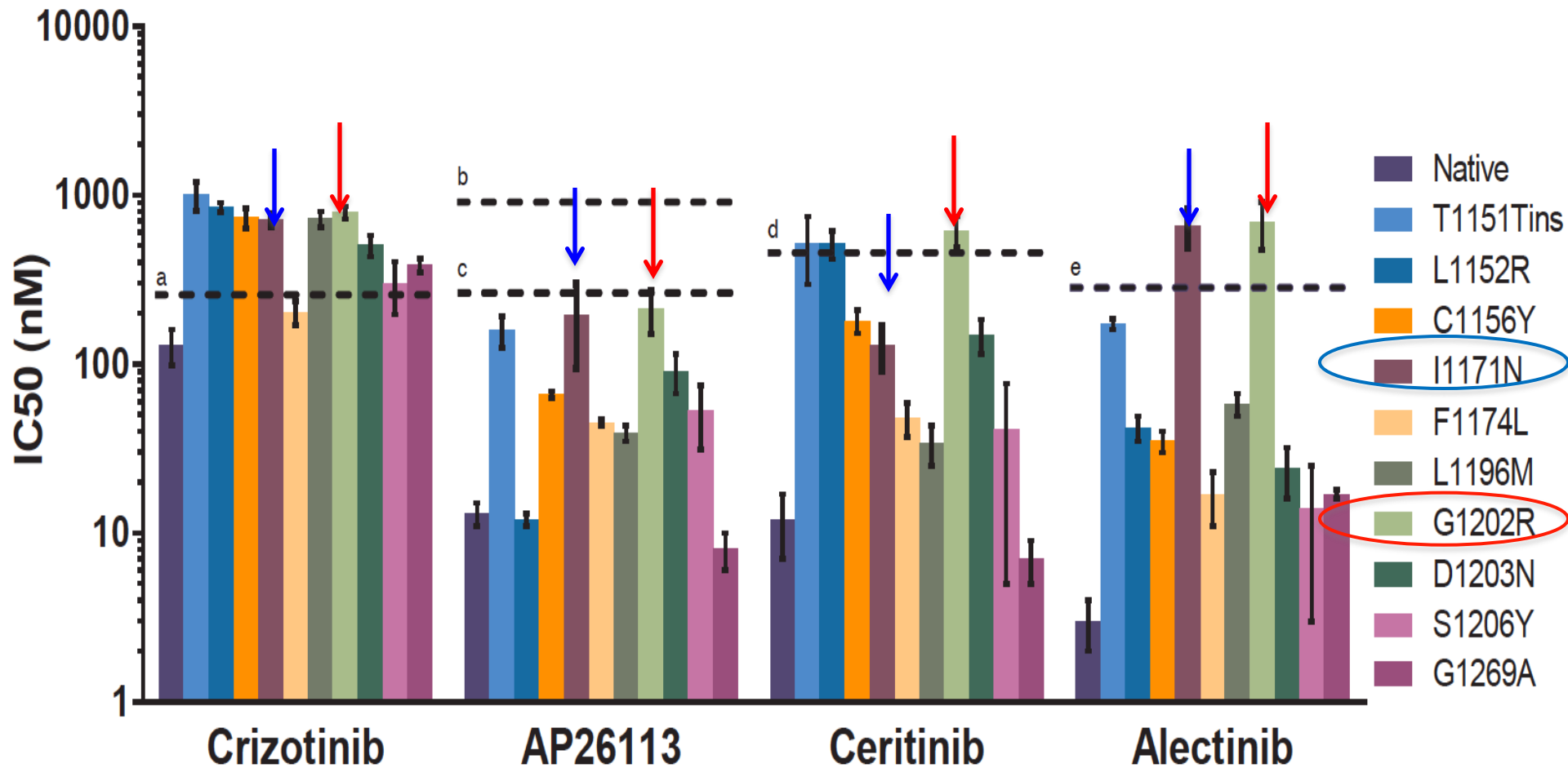
Differential sensitivities of Alectinib & Ceritinib to acquired ALK resistance to ALK inhibitors

Resistance mutation	Yes	No
L1196M	Both	
G1269A	Both	
G1206Y		
1151T ins		Ceritinib
F1174C/V		Ceritinib
C1156Y		Ceritinib
I1171T	Ceritinib	Alectinib
I1171N	?Ceritinib	Alectinib
I1171S	? Ceritinib	Alectinib
G1202R		Both

Rebiopsy in all patient with crizotinib failure

Moving second generation to first line

Alectinib

Eligibility criteria:
- *ALK*-positive locally advanced/metastatic NSCLC
- No prior treatment for advanced disease

R A N D O M I S E

Alectinib 600mg b.i.d.
(n=143)

Crizotinib 250mg b.i.d.
(n=143)

Primary endpoint = PFS*

*Determined by investigators, based on RECIST v1.1

Ceritinib

Eligibility criteria:
- *ALK*-positive locally advanced/metastatic non-squamous NSCLC
- No prior treatment for advanced disease

R A N D O M I S E

Ceritinib 750mg
(n=174)

Pemetrexed/cisplatin OR pemetrexed/carboplatin q3w (n=174)

Pemetrexed q3w

Primary endpoint = PFS

1. NCT02075840   2. NCT01828099

Combination with immunotherapy

- **Cohorts**
  - [-1 dose cohort] ceritinib 300 mg qd + nivolumab (3 mg/kg q2w)
  - [1st dose cohort] ceritinib 450 mg qd+ nivolumab (3 mg/kg q2w) [starting dose level]
  - [2nd dose cohort] ceritinib 600 mg qd + nivolumab (3 mg/kg q2w)
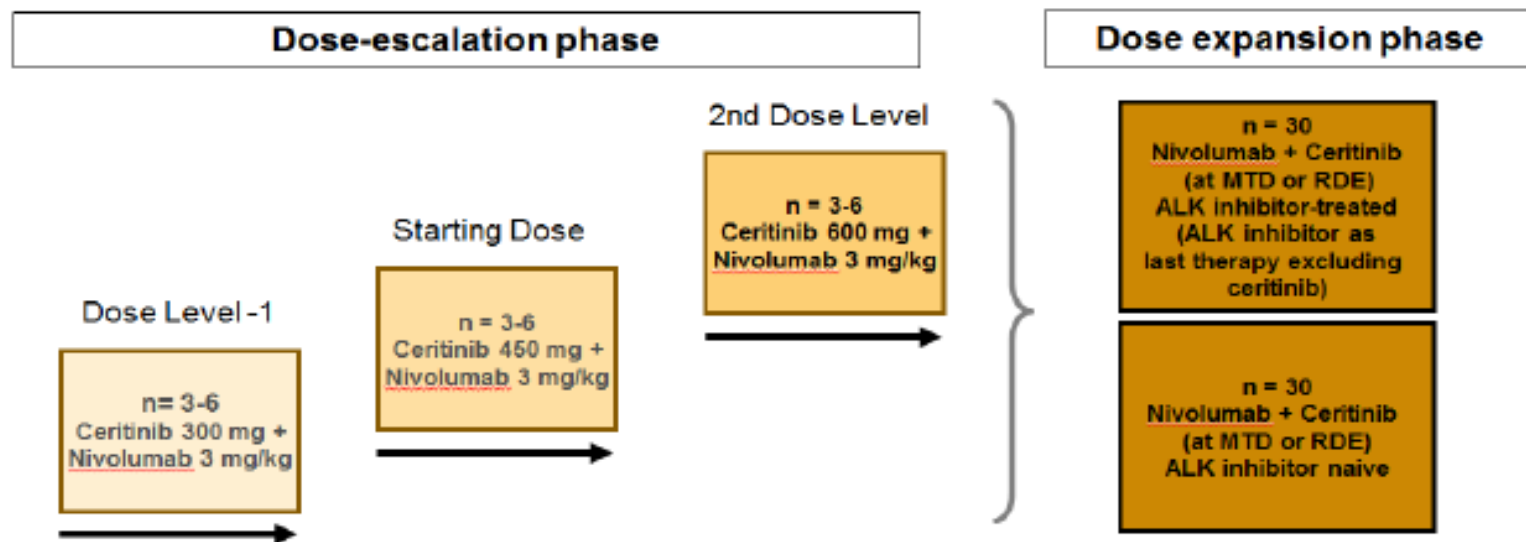
What the EGFR family may look like in 2021
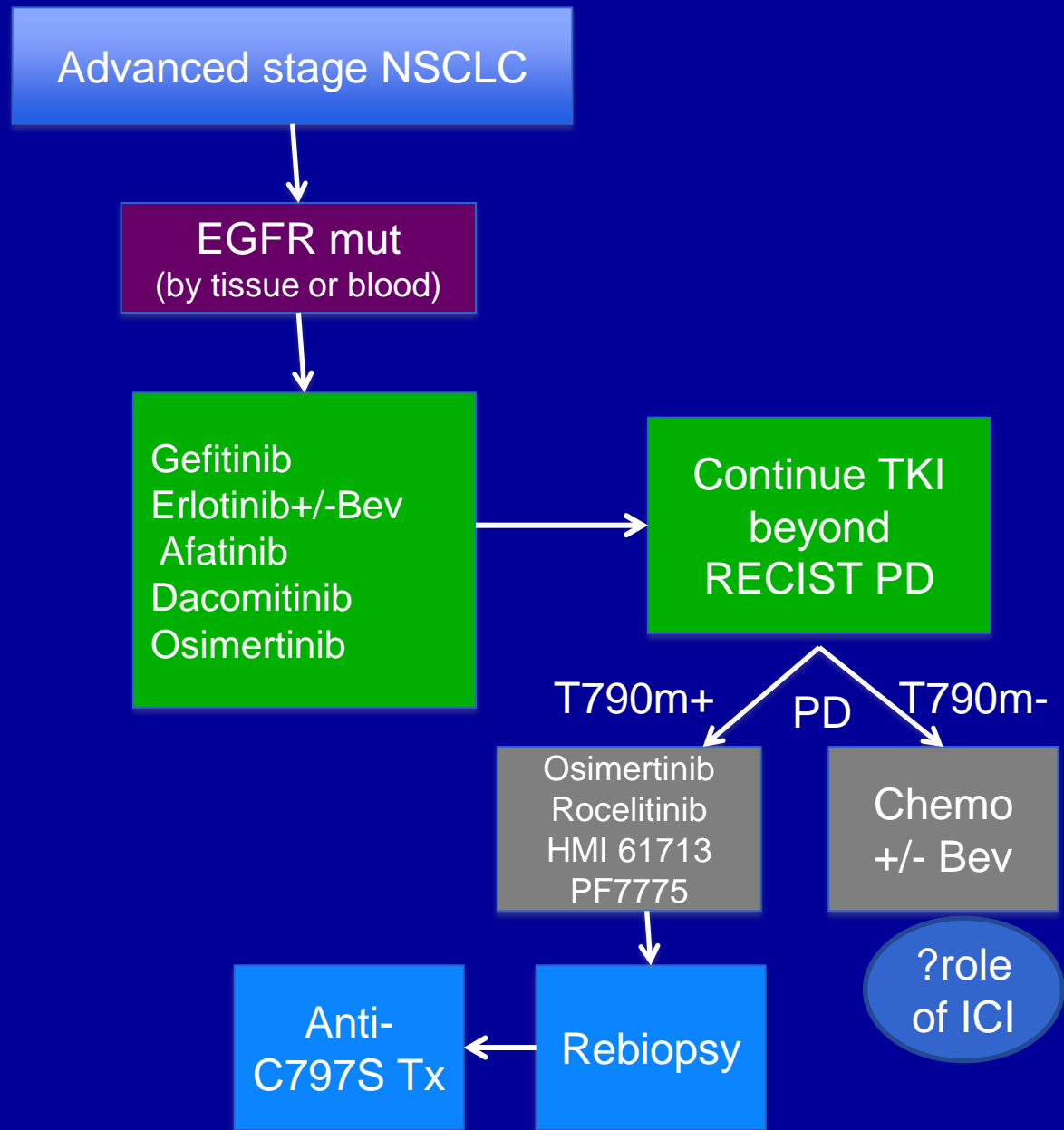
What the ALK family may look like in 2021
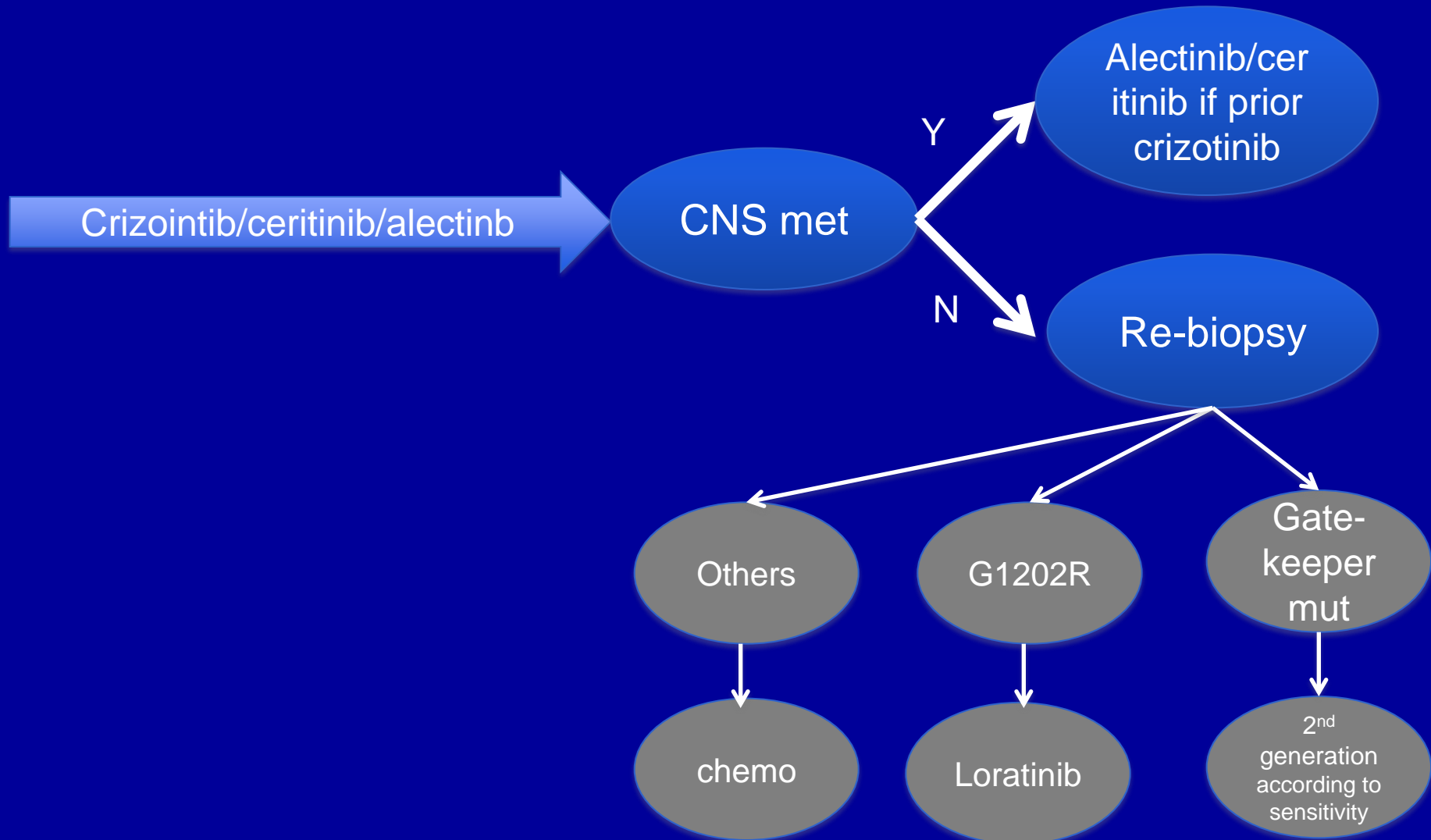
2011 to 2015

SUCCESS	FAILURE
Crizotinib for ALK positive lung cancer	MAGE A3 vaccine as adjuvant therapy for resectable lung cancer
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Key outcomes from randomized studies

	KEYNOTE 010		Checkmate 057		Checkmate 017	
RR	Pembro 2mg/kg	18%	Nivo	19%	Nivo	20%
	Pembro 10mg/kg	18.5%	Doc	9%	Doc	9%
	Docetaxel	9.3%				
PFS (Total)	Pembro 2mg/kg	3.9m	Nivo	4.2m	Nivo	3.5m
	Pembro 10mg/kg	4.0m	Doc	2.3m	Doc	2.8m
	Docetaxel	4.0m				
OS (Total)	Pembro 2mg/kg	10.4m	Nivo	12.2m	Nivo	9.2m
	Pembro 10mg/kg	12.7m	Doc	9.2m	Doc	6.0m
	Docetaxel	8.5m				

Select phase 3 studies with immune checkpoint inhibitors in 1st-line advanced NSCLC

Anti-PD-1/PD-L1

Nivolumab

CheckMate 227 — Treatment-naïve or recurrent NSCLC N=1980
- Nivolumab
- Nivolumab + ipilimumab
- Platinum-based chemotherapy
→ Primary endpoints: OS, PFS

CheckMate 026 — Treatment-naïve or recurrent PD-L1+ NSCLC N=535
- Nivolumab
- Investigator's choice chemotherapy
→ Primary endpoint: PFS

Pembrolizumab

KEYNOTE-024 — PD-L1 strong NSCLC N=300
- Pembrolizumab
- Platinum-based chemotherapy
→ Primary endpoint: PFS

KEYNOTE-042 — PD-L1+ NSCLC N=1240
- Pembrolizumab
- SOC chemotherapy
→ Primary endpoint: OS

MEDI4736

MYSTIC — Advanced NSCLC N=675
- MEDI4736
- MEDI4736 + tremelimumab
- SOC chemotherapy
→ Primary endpoint: PFS

Atezolizumab

IMpower 110 — Stage IV non-squamous PD-L1+ NSCLC N=400
- Atezolizumab
- Carboplatin or carboplatin + pemetrexed
→ Primary endpoint: PFS

IMpower 111 — Stage IV squamous PD-L1+ NSCLC N=400
- Atezolizumab
- Gemcitabine + cisplatin or carboplatin
→ Primary endpoint: PFS

IMpower 130 — Stage IV non-squamous NSCLC N=550
- Atezolizumab + carboplatin + nab-paclitaxel
- Carboplatin + nab-paclitaxel
→ Primary endpoint: PFS

IMpower 131 — Stage IV squamous NSCLC N=1200
- Atezolizumab + carboplatin + nab-paclitaxel
- Atezolizumab + carboplatin + paclitaxel
- Carboplatin + nab-paclitaxel
→ Primary endpoint: PFS

IMpower 150 — Stage IV non-squamous NSCLC N=1200
- Atezolizumab + carboplatin + paclitaxel
- Atezolizumab + bevacizumab + paclitaxel + carboplatin
- Bevacizumab + paclitaxel + carboplatin
→ Primary endpoint: PFS

Anti-CTLA-4

Ipilimumab

CA184-104 — Squamous NSCLC N=920
- Ipilimumab + paclitaxel/carboplatin → ipilimumab
- Placebo + paclitaxel/carboplatin → placebo
→ Primary endpoint: OS

CA184-153 — Squamous NSCLC N=867
- Ipilimumab + paclitaxel/carboplatin → ipilimumab
- Placebo + paclitaxel/carboplatin → placebo
→ Primary endpoint: OS

SOC=standard of care. ClinicalTrials.gov. http://www.clinicaltrials.gov/. Accessed August 2015.

First line immunotherapy

Single agent in PD-L1 positive population

Combination with chemotherapy in selected/unselected population

Combination with CTLA-4 inhibitor in selected/unselected population

Single agent in PD-L1 positive population

KEYNOTE-024
- **Strongly PD-L1[+] advanced NSCLC[a]**
- **No prior therapy**

R
1:1
N = 300

Pembro 200 mg Q3W

Platinum-Based Chemo

- **Primary end point: PFS**

KEYNOTE-042
- **Strongly/weakly PD-L1[+] advanced NSCLC[a]**
- **No prior therapy**
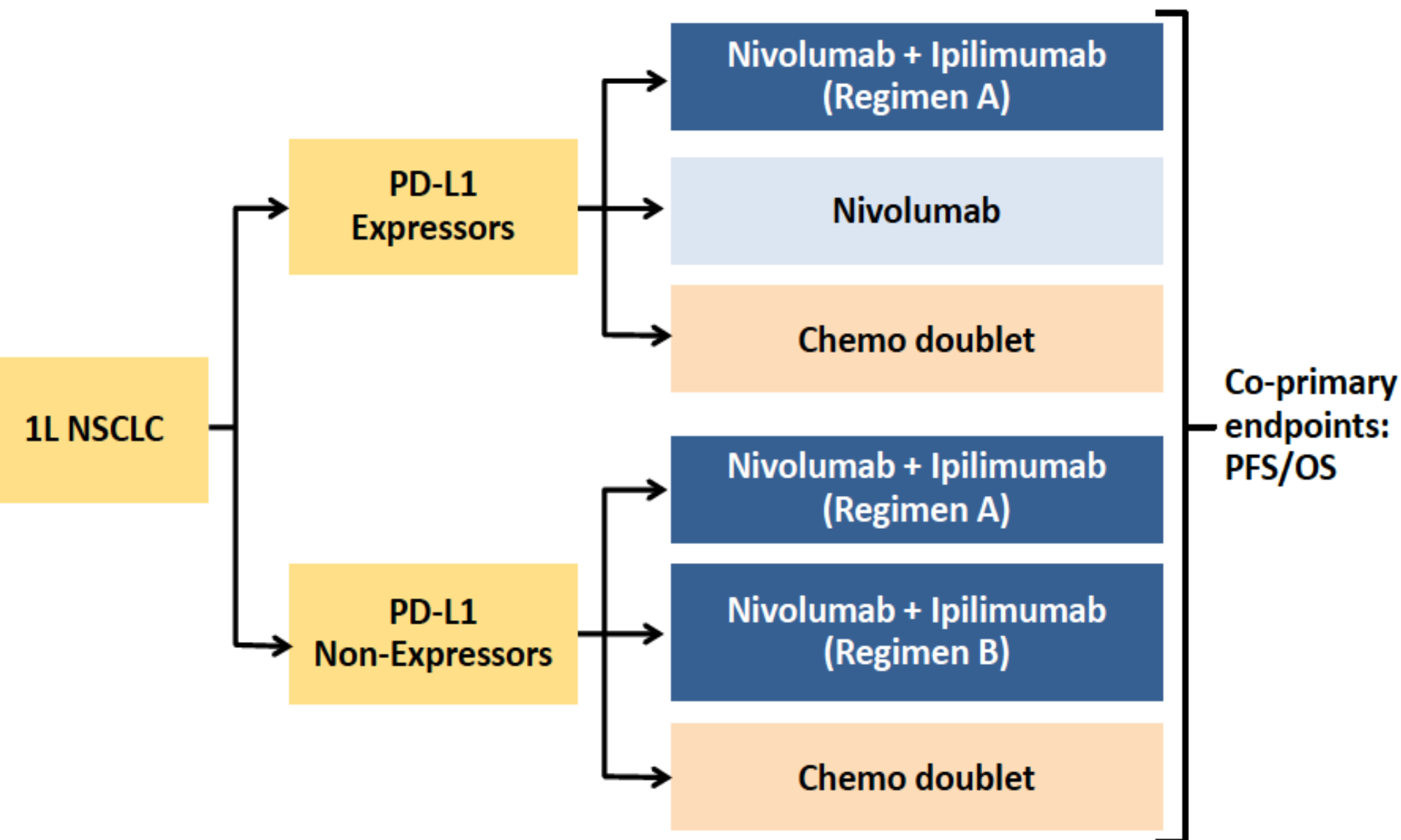
R
1:1
N = 1240

Pembro 200 mg Q3W

Platinum-Based Chemo
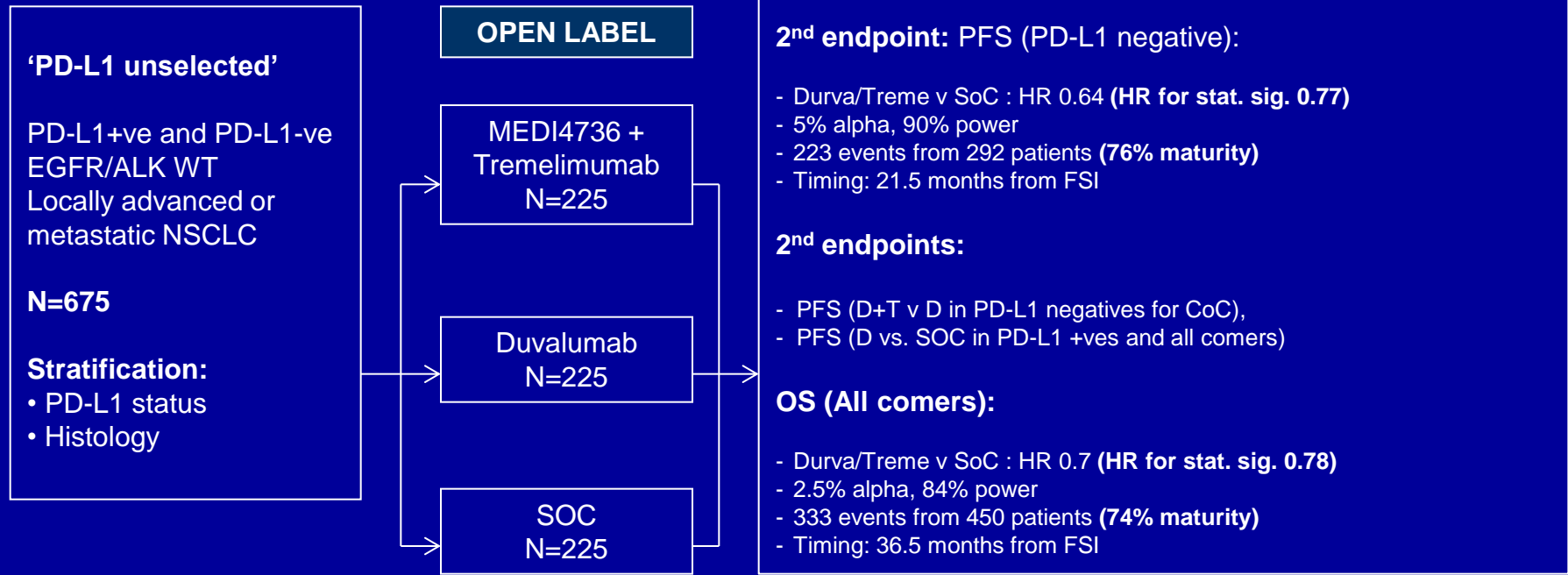
Primary end point: OS

Indication	1L non-squamous NSCLC PD-L1-selected patients	1L non-squamous NSCLC	1L non-squamous NSCLC
Phase/study	Phase III IMpower 110	Phase III IMpower 150	Phase III IMpower 130
# of patients	N=400	N=1200	N=550
Design	• **ARM A:** atezolizumab monotherapy • **ARM B:** carboplatin or cisplatin + pemetrexed	• **ARM A:** atezolizumab + Avastin + paclitaxel + carboplatin • **ARM B:** atezolizumab + paclitaxel + carboplatin • **ARM C:** Avastin + paclitaxel + carboplatin	• **ARM A:** atezolizumab + nab-paclitaxel + carboplatin • **ARM B:** nab-paclitaxel + carboplatin
Primary endpoint	• Progression-free survival	• Progression-free survival	• Progression-free survival
Status	• FPI Q3 2015	• FPI Q2 2015	• FPI Q1 2015

Combination with chemotherapy in selected/unselected population

Checkmate-227: Phase 3 Opdivo + Yervoy

MYSTIC: PFS

'PD-L1 unselected'

PD-L1+ve and PD-L1-ve
EGFR/ALK WT
Locally advanced or
metastatic NSCLC

N=675

Stratification:
• PD-L1 status
• Histology

OPEN LABEL

MEDI4736 +
Tremelimumab
N=225

Duvalumab
N=225

SOC
N=225

Primary endpoint: PFS (All comers)

- Durva/Treme v SOC HR 0.59 **(HR for stat. sig. 0.81)**
- 5% alpha, > 90% power
- 338 events from 450 patients **(75% maturity)**
- Timing: 21.5 months from FSI

2nd endpoint: PFS (PD-L1 negative):

- Durva/Treme v SoC : HR 0.64 **(HR for stat. sig. 0.77)**
- 5% alpha, 90% power
- 223 events from 292 patients **(76% maturity)**
- Timing: 21.5 months from FSI

2nd endpoints:

- PFS (D+T v D in PD-L1 negatives for CoC),
- PFS (D vs. SOC in PD-L1 +ves and all comers)

OS (All comers):

- Durva/Treme v SoC : HR 0.7 **(HR for stat. sig. 0.78)**
- 2.5% alpha, 84% power
- 333 events from 450 patients **(74% maturity)**
- Timing: 36.5 months from FSI
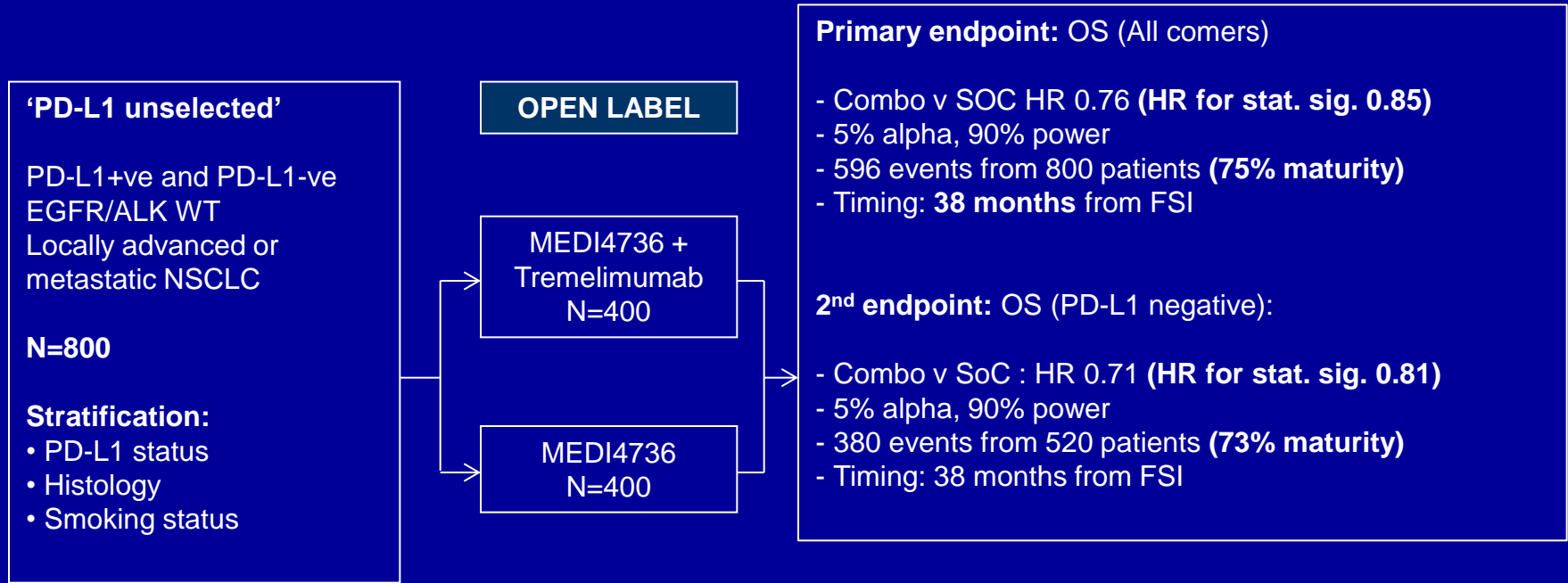
• Assumes a 3 month (2 tumor assessment) delay in PFS before separation of KM curves
• Median PFS of 5.8 months in SoC and 7.3 months in experimental arm in all comers (Improvement of 0.8 months)
• Median OS of 12.9 months in SoC and 16.3 months in experimental arm in all comers (Improvement of 1.9 months)

NEPTUNE: OS

'PD-L1 unselected'

PD-L1+ve and PD-L1-ve
EGFR/ALK WT
Locally advanced or
metastatic NSCLC

N=800

Stratification:
• PD-L1 status
• Histology
• Smoking status

OPEN LABEL

MEDI4736 +
Tremelimumab
N=400

MEDI4736
N=400

Primary endpoint: OS (All comers)

- Combo v SOC HR 0.76 **(HR for stat. sig. 0.85)**
- 5% alpha, 90% power
- 596 events from 800 patients **(75% maturity)**
- Timing: **38 months** from FSI

2nd endpoint: OS (PD-L1 negative):

- Combo v SoC : HR 0.71 **(HR for stat. sig. 0.81)**
- 5% alpha, 90% power
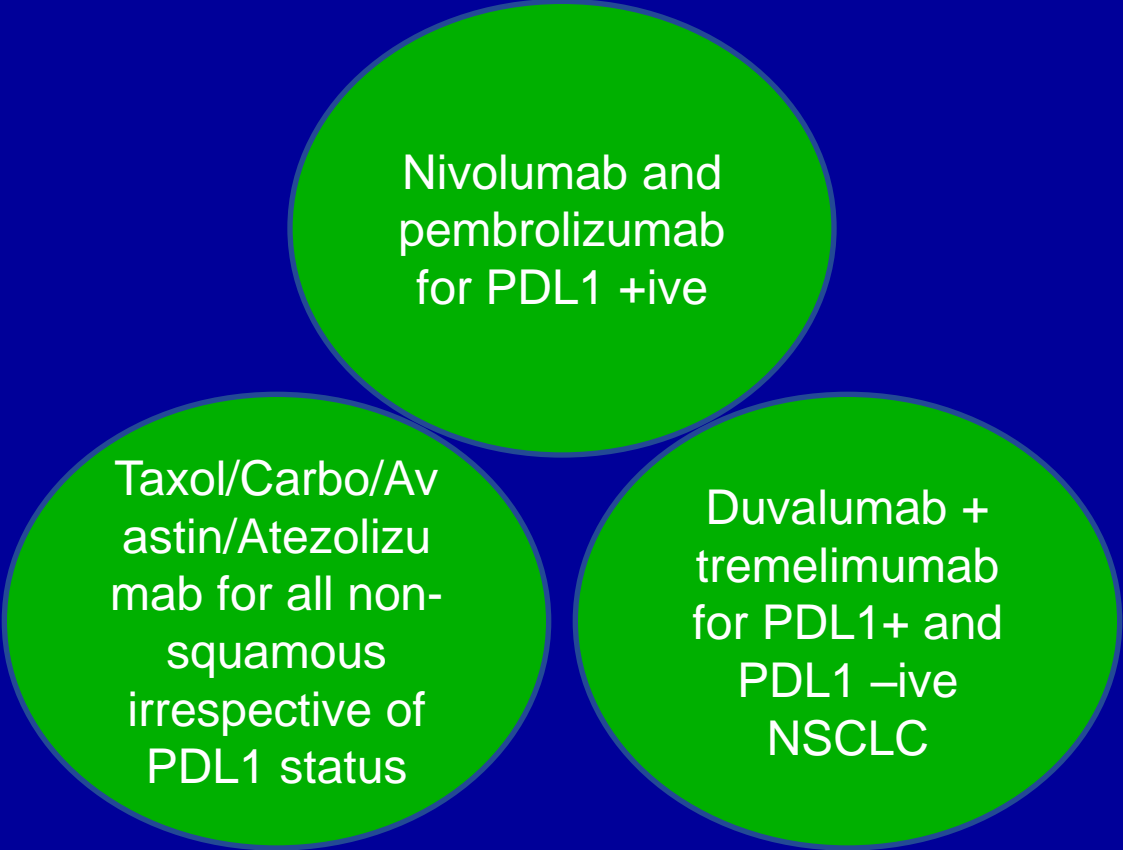- 380 events from 520 patients **(73% maturity)**
- Timing: 38 months from FSI

• Assumes a 3 month delay in OS before separation of KM curves
• Median OS of 12.9 months in SoC and 16.3 months in experimental arm in all comers (Improvement of 1.9 months)
• **Two interim analyses of OS are planned after 60% and 80% of the planned events**

AstraZeneca Confidential

What may happen if the following studies are positive

Checkmate26 and Keynote 24

IMpower 150

MYSTICS
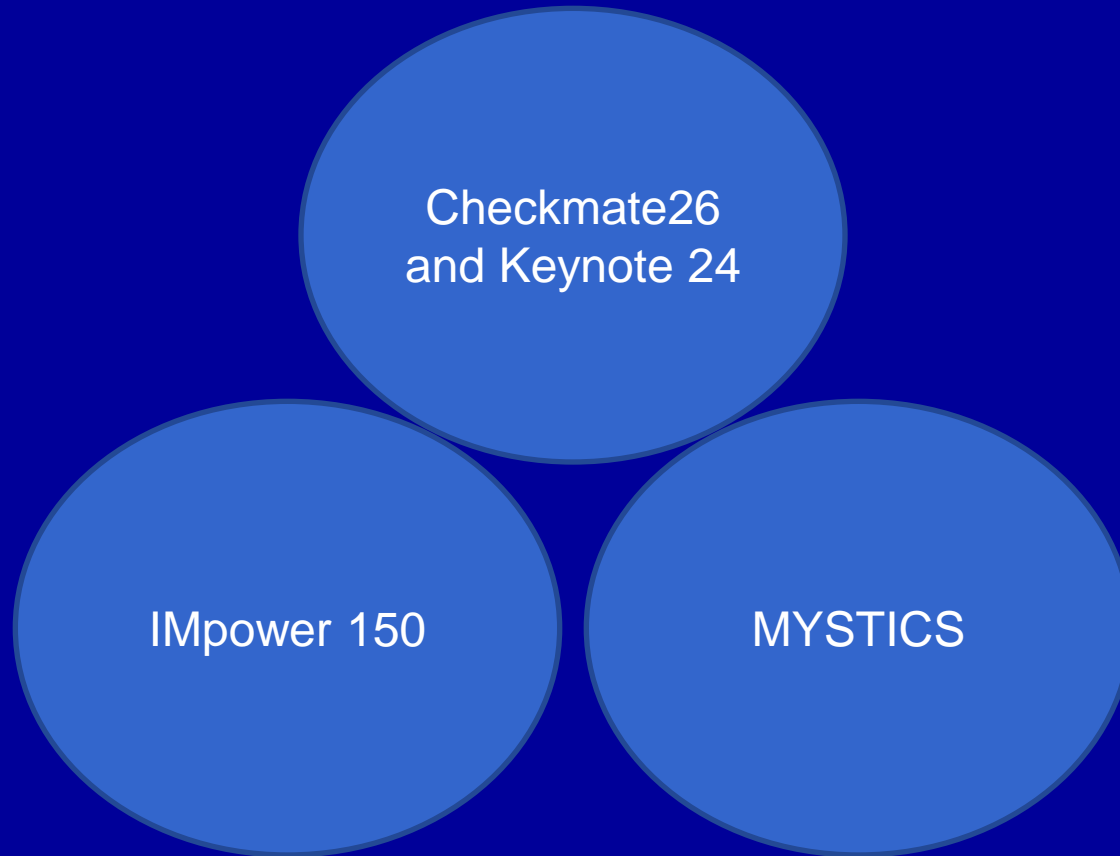
New first line options

Nivolumab and pembrolizumab for PDL1 +ive

Taxol/Carbo/Avastin/Atezolizumab for all non-squamous irrespective of PDL1 status

Duvalumab + tremelimumab for PDL1+ and PDL1 –ive NSCLC

The implication

- All EGFR/ALK/ROS1 negative patients should have PD-L1 status tested (by one of the platforms)
- No patient should have first line chemotherapy if he/she/government can afford it
  - If PDL1+, it is the choice between single agent anti-PDL1 or combination with anti-CTLA4
  - If PDL1-, it is the choice between chemotherapy with anti-PDL1 or combination of anti-PDL1 and anti-CTLA4

Summary

2011 to 2015 → 2016 → 2017 to 2021

Science speaks

Competition without strong science may create chaos and disappointment

President of IASLC