Are there new targets in advanced NSCLC?

New targets relevant after the era of EGFR and ALK

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15-18 April 2015, Geneva, Switzerland

Organisers

Partners

Disclosures

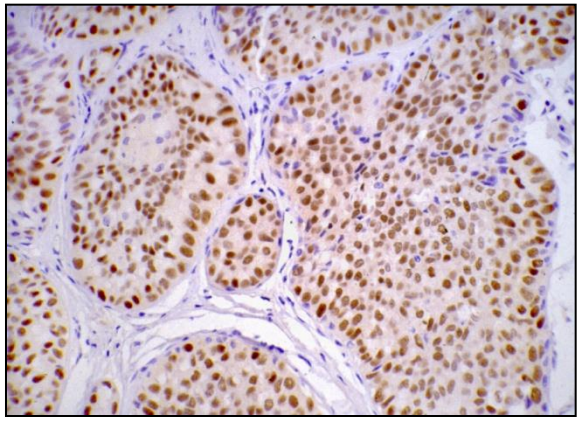
- Consultancy fees from: AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Pfizer, Roche

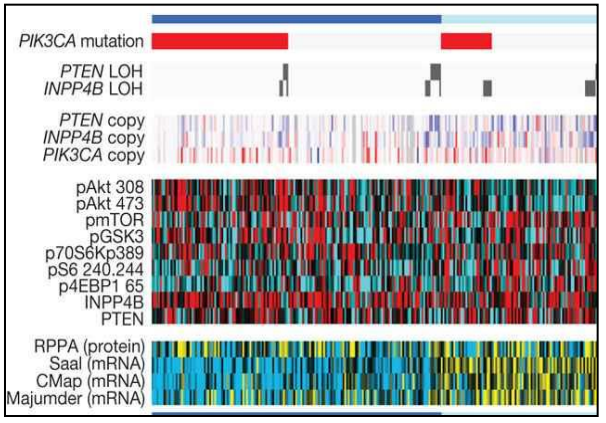
Evolution of cancer treatment

Nowadays

Clinical Oncology → Pathologic Oncology → Molecular Oncology → **Personalized Medicine**

Disease guided approach	→	Pathologic guided approach	→	Molecular approach





Few therapeutic options:
- Surgery
- Radiotherapy
- Chemotherapy

Increased therapeutic options allows specific treatments for different tumor types

Targeted agents that work in specific molecular alterations:
- Broad knowledge of molecular tumor biology
- Development of molecular analysis

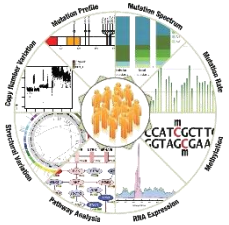
Evolution of cancer treatment

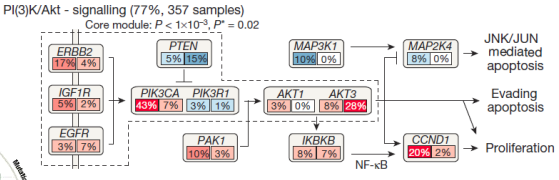
Nowadays

Clinical Oncology → Pathologic Oncology → Molecular Oncology → **Personalized Medicine**

Reclassification of disease

- Cancer genome atlas
- Pangenomics





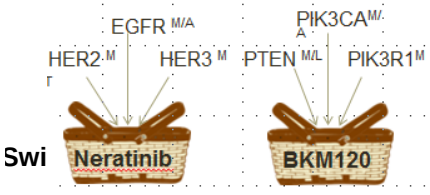
Technology development and genomics

- Multiplexing
- Next Generation Sequencing

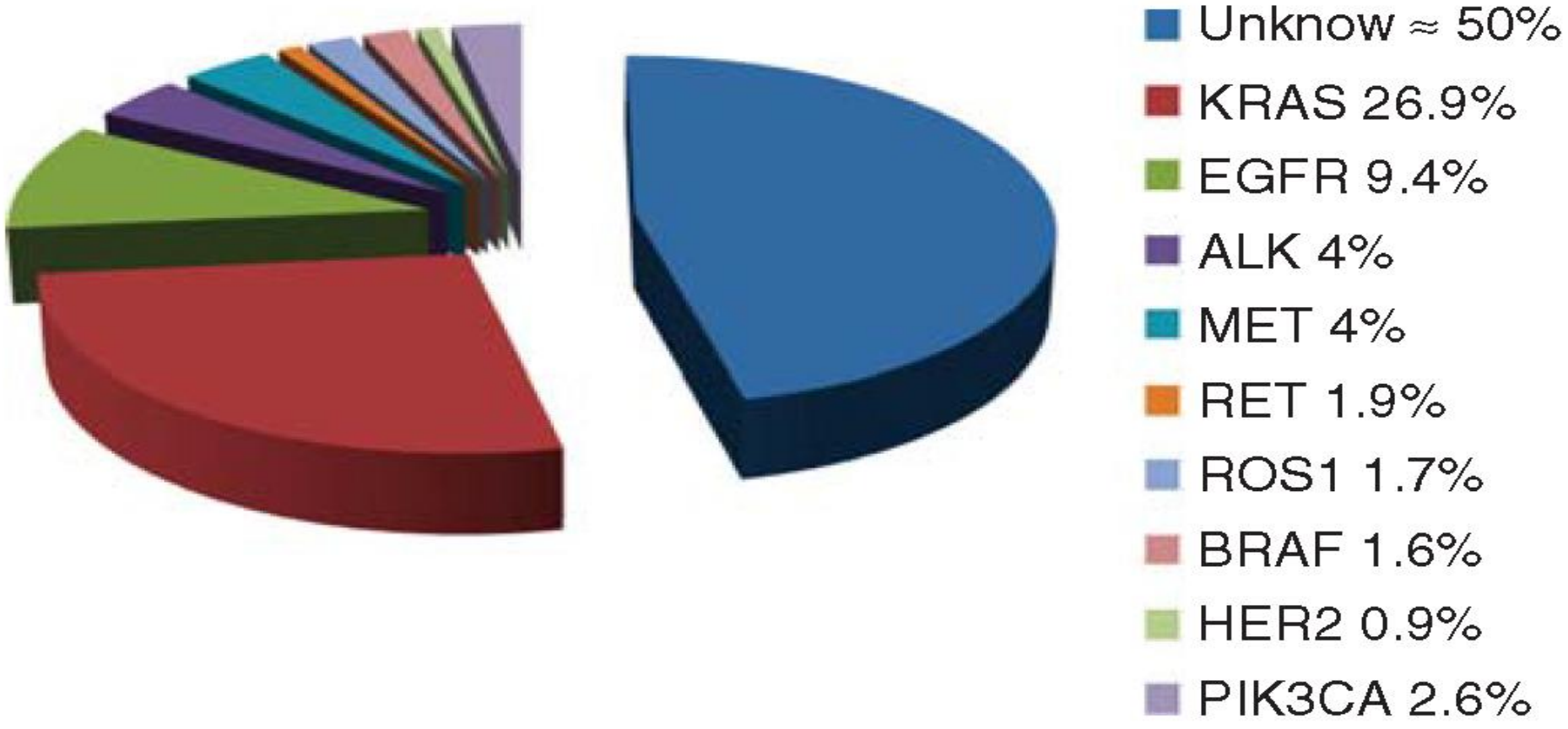
Change in paradigm of biomarker-drug development

- Clinical trials in small p populations

New clinical trials in Personalized medicine



Targetable oncogenes in lung ADC



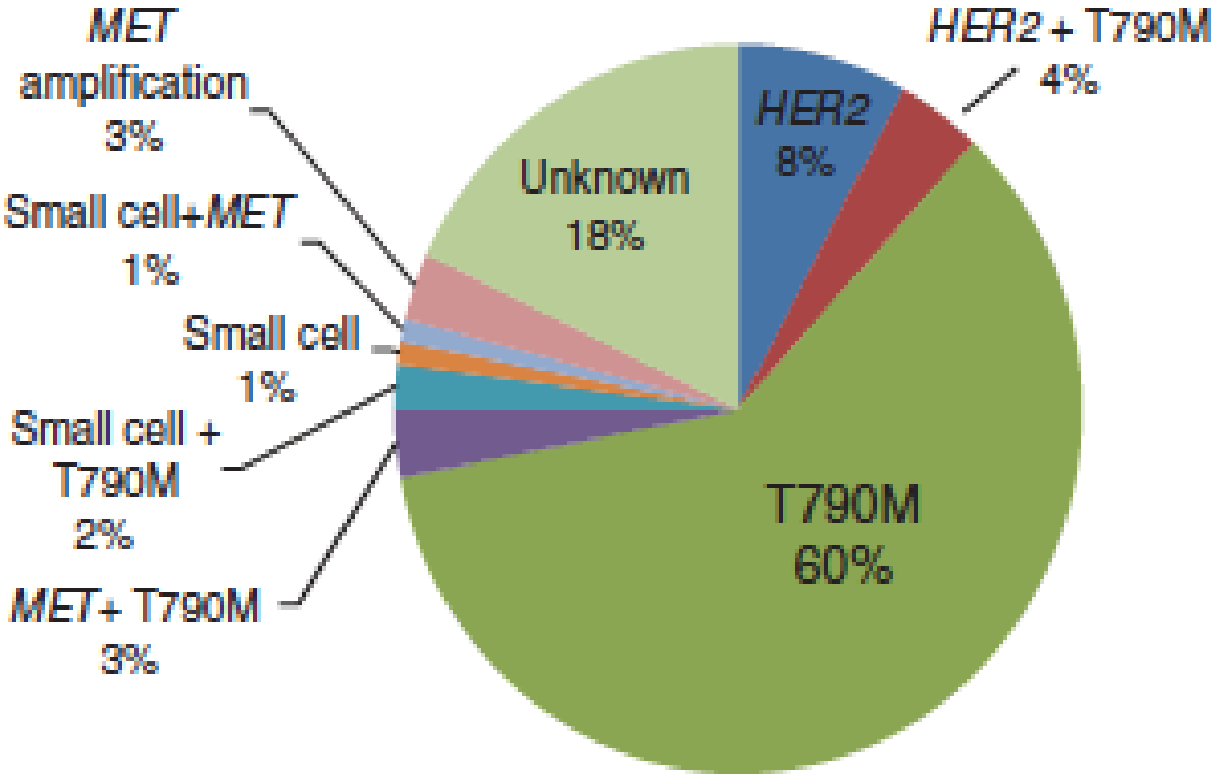
Minuti Exp Opin Biol Ther 13

97% of mutations mutually exclusive

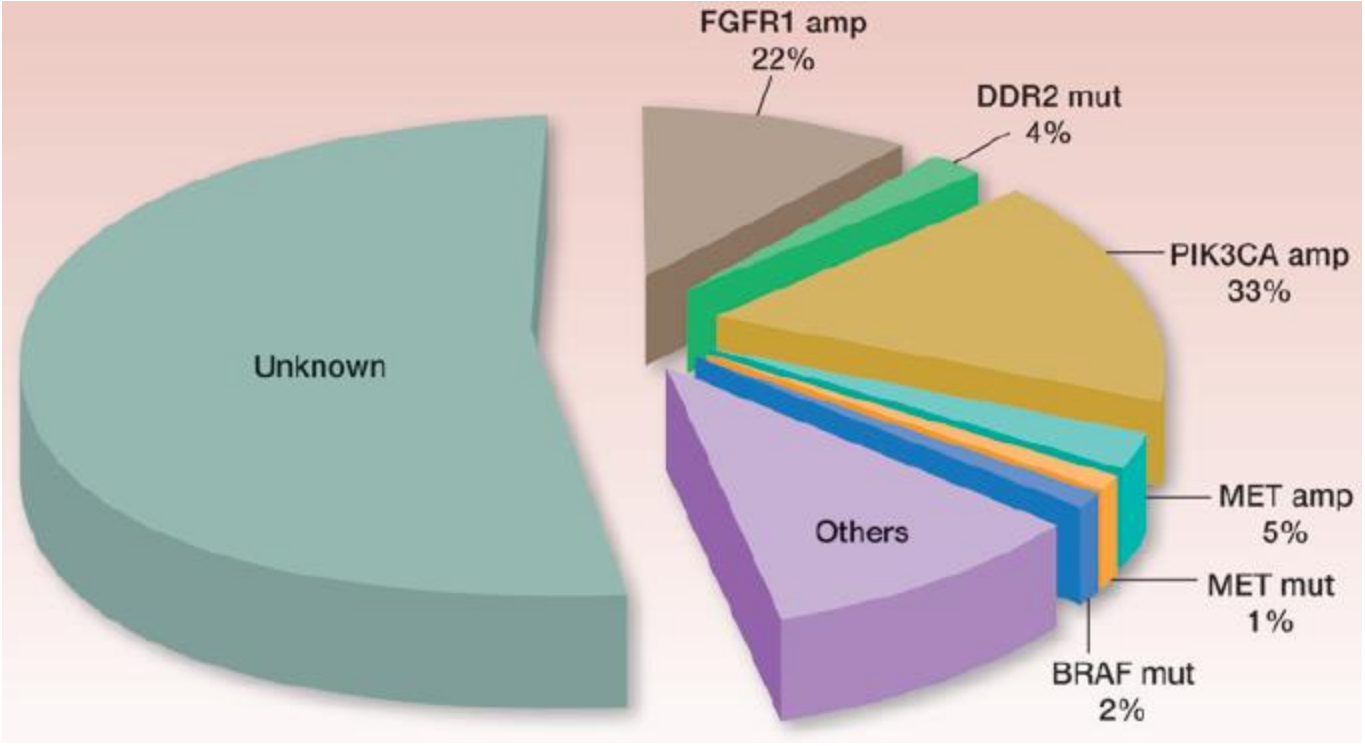
# Single Mutations	ALK	AKT	BRAF	EGFR	HER2	KRAS	MEK1	MET	NRAS	PIK3CA
ALK (38)	X		1	2		1		1		
AKT1 (0)		X								
BRAF (9)			X							1
EGFR (89)				X				1		3
HER2 (3)					X					
KRAS (114)						X		1		1
MEK1 (2)							X	1		1
MET AMP (3)								X		
NRAS (2)									X	
PIK3CA (6)										X

Number of patients with variants in indicated combination of genes , 3% (14/516)

Mechanisms of acquired resistance to EGFRTKIs



Potentially targetable mutations in SCC



Perez-Moreno P et al. Clin Cancer Res. 2012

New targets relevant after the era of EGFR and ALK
Outline

- ROS1
- HER2
- BRAF
- RET
- NTRK1
- MET
- FGFR1
- DDR2

ROS1 in NSCLC

- 50 advanced NSCLC p with ROS1 rearrangement received crizotinib
- RR 72% with 3 CR and 33 PR
- Median duration of response 17.6 mo
- Median PFS 19.2 mo
- Safety profile of crizotinib similar to that seen in p with ALK-rearranged NSCLC
- Crizotinib showed marked antitumor activity in p with advanced ROS1-rearranged NSCLC

Shaw NEJM 14

ROS1 in NSCLC

- Retrospective study of stage IV lung ADC p with ROS1 rearrangement (FISH) who had received crizotinib (individual off-label use)
- 32 p
  - Median age 50.5 yrs
  - 64.5% women
  - 67.7% never-smokers
  - RR 80%
  - Median PFS 9.1 months
  - No unexpected AEs observed
- Crizotinib highly active in lung cancer p with ROS1 rearrangement, suggesting that p with lung ADC should be tested for ROS1

ROS1 in lung cancer, next steps

- IHC, high sensitivity and specificity for detecting ROS1 rearrangements ***(Boyle Clin Lung Cancer 15)***
- Cabozantinib overcomes crizotinib resistance in ROS1+ ***(Katayama CCR 15)***
- PF-06463922, a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations ***(Zou PNAS 15)***
- Clinical trials
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity
  - LDK378 in p with NSCLC harboring ROS1 rearrangement
  - PF-06463922 in p with advanced NSCLC with ALK+ or ROS1+

HER2 in NSCLC

- Somatic mutations of HER2 kinase domain in lung ADC *(Shigematsu Cancer Res 05)*
- HER2 mutation and response to trastuzumab *(Cappuzzo NEJM 06)*
- 16 p receiving HER2-tageted therapies; 22 evaluable individual anti-HER2 treatments, 50% RR (majority received trastuzumab+CT) *(Mazières JCO 13)*
- Dacomitinib *(Kris WLCC Sydney 13)*
  - 26 p with HER2 mutation
    - 3 PR (13%), duration of response 4+, 13, 14 mo
    - Median PFS 3 mo, median OS 10 mo
  - 4 p with HER2 amplification, no responses

HER2 in NSCLC

- Afatinib
  - Induced regressions in transgenic mouse models, effect increased with rapamycin (mTOR inhibitor) ***(Perera PNAS 09)***
  - PR in 3 / 3 evaluable p with HER2-mut ***(De Grève Lung Cancer 12)***

- Neratinib
  - Phase I neratinib/temsirolimus, 7 NSCLC p with HER2 mutations (2 previously treated with trastuzumab): 2 PR / no PD ***(Gandhi JCO 14)***

- Trastuzumab emtansine
  - Rapid response to trastuzumab emtansine in a p with HER2-driven lung cancer ***(Weiler JTO 15)***

Neratinib with/without temsirolimus in p with NSCLC carrying HER2 somatic mutations

- 13 p received neratinib, 14 p neratinib/temsirolimus
- Neratinib arm: 54% SD / 46% PD; PFS 2.9 mo
- Neratinib/temsirolimus: 21% PR / 79% SD; PFS 4.0 mo
- G3 toxicity neratinib/temsirolimus: vomiting 21%; diarrhea 14%

HER2 in lung cancer, next steps

- RR in HER2 mutated p treated prospectively with HER2 inhibitors seems lower to that observed in other oncogenic-driven subsets

- Other predictive markers?
  - Insertions *vs* other
  - p95HER2

- Ongoing treatment strategies
  - Neratinib/temsirolimus combination, further study
  - Afatinib phase II ETOP trial
  - TDM1 phase II trial

BRAF in NSCLC

- BRAF mutations occurred in 2.2% of advanced-stage lung ADC, most commonly V600E ***(Villaruz Cancer 15)***

- Vemurafenib, case reports
  - P with BRAF V600E lung ADC responding to vemurafenib (***Gautschi JTO 12)***
  - Dramatic response induced by vemurafenib in a BRAF V600E mutated lung ADC ***(Peters JCO 13)***
  - Lung ADC with BRAF G469L mutation refractory to vemurafenib ***(Gautschi Lung Cancer 13)***

- Dabrafenib
  - Preliminary efficacy data from 20 BRAF V600E p promising, 60% DCR ***(Planchard ASCO 13)***

Dabrafenib in p with BRAF V600Emutant advanced NSCLC: a phase II trial

- 78 previously treated p; median age 66 yrs, 50% female, 15% ECOG 2, 37% never-smoker
- 32% PR / 24% SD ≥ 12 weeks / 29% PD / 14% NE
- Disease control rate: 51% independent review *vs* 56% investigator
- Median duration of response 11.8 mo
- PFS 5.5 mo
- Tolerable treatment-related toxicity, special attention to cutaneous squamous cell-carcinoma needed

BRAF in NSCLC, next steps

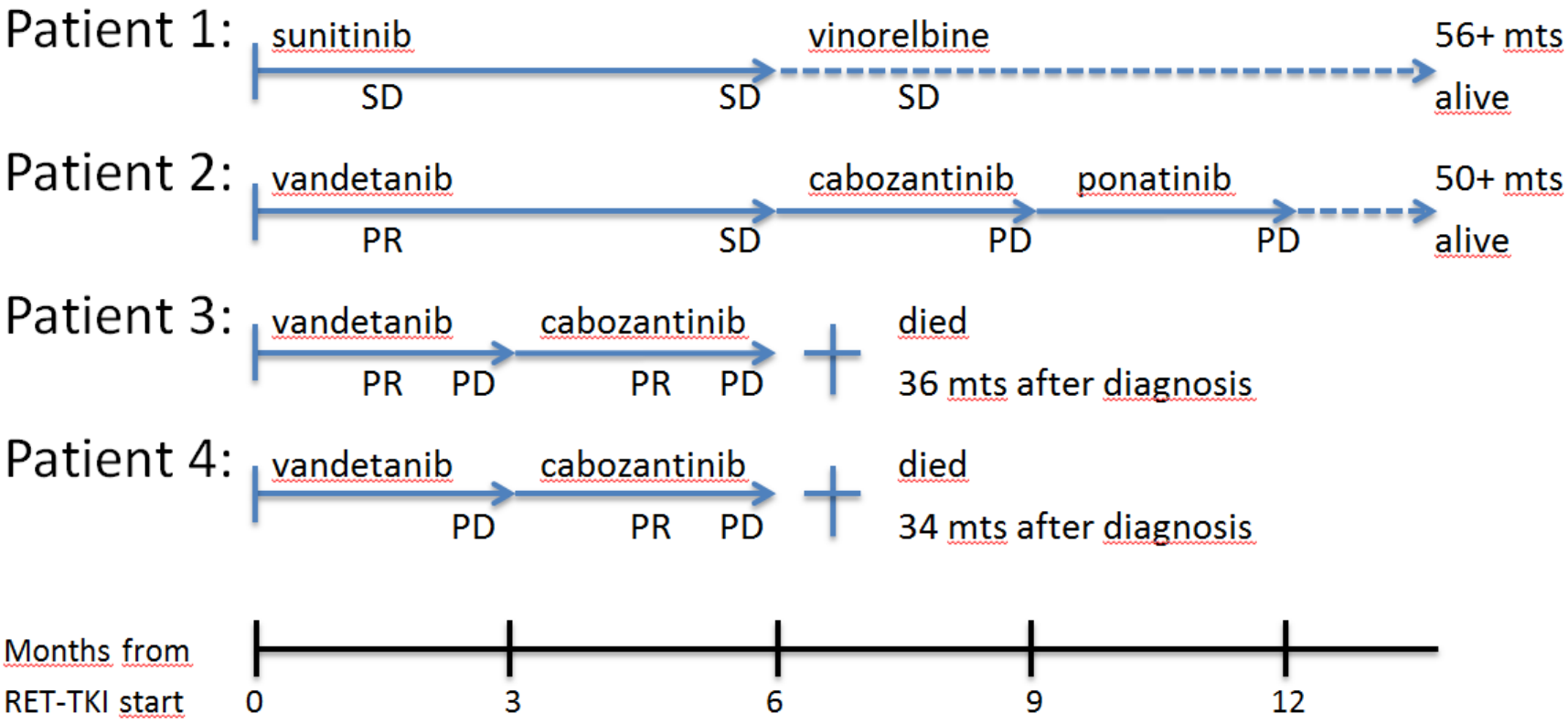
- Identification of acquired resistance mechanisms to BRAF inhibitors
  - After PR with dabrafenib, biopsy at PD showed KRAS G12D mutation ***(Rudin JTO 13)***
  - BRAF V600E NSCLC cells acquire resistance to BRAF inhibition ***(Lin PNAS 14)***
    - Simultaneous loss of full-length BRAF V600E, and aberrant BRAF pathway expression
    - Engagement of EGFR signaling pathway

- Combination of targeted therapies
  - Cohort B with dabrafenib/trametinib actively recruiting

Lung ADC with RET fusion: early experience with diagnosis and targeted therapy

- 529 tumor samples analyzed in 12 mo
- 12 (2%) tumors *RET*-positive by FISH
- No coincident mutations in *EGFR, HER2, KRAS, BRAF, ALK, or ROS1*
- 4 p with *RET* fusion received one or more RET inhibitors; PR seen with cabozantinib and vandetanib

Patients with targeted therapy



RET in NSCLC, next steps

- Responses to cabozantinib in p with RET fusion-positive lung ADC ***(Drilon Cancer Discov 13)***

- Clinical trials
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity
  - Vandetanib in advanced NSCLC with RET rearrangement
  - Ponatinib in advanced NSCLC with RET translocation
  - Safety and activity of lenvatinib (E7080) in subjects with KIF5B-RET+ ADC of the lung

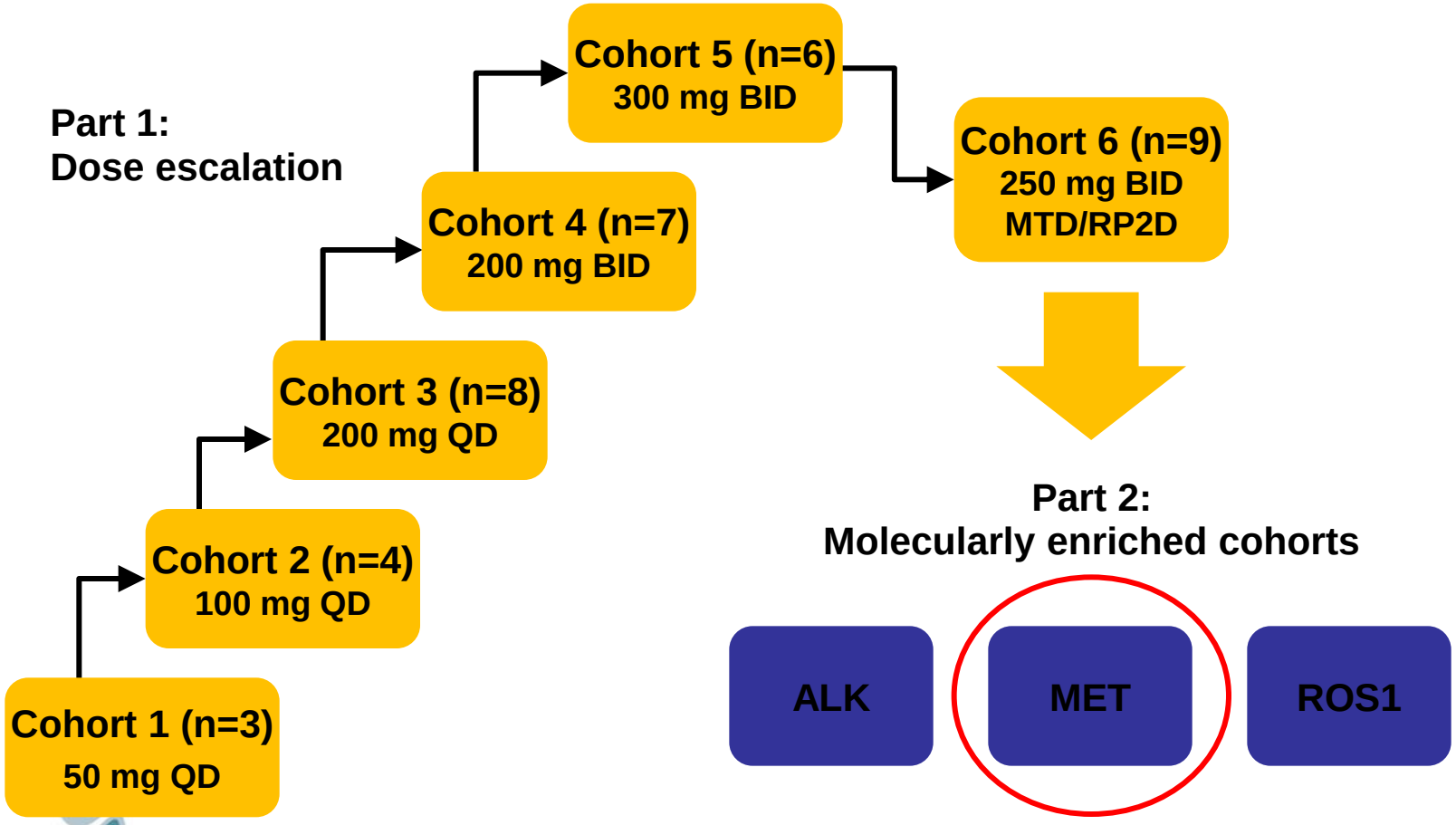
NTRK1 in NSCLC

- *NTRK1* rearrangements, which encode TRKA protein, identified in tumor samples from 3/91 (3%) p (never-smokers) with lung cancer without known oncogenic alterations ***(Vaishnavi Nat Med 13)***

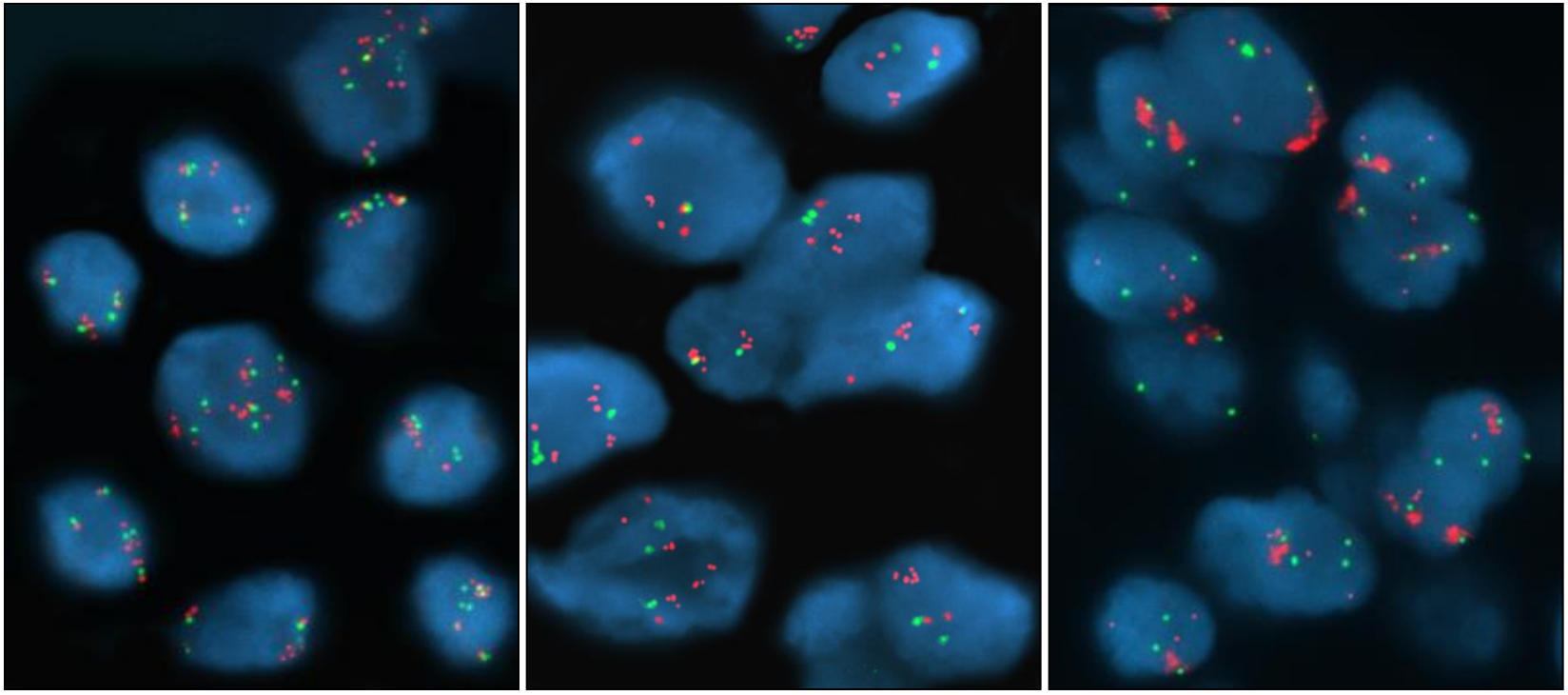
- In preclinical models, kinase inhibitors with activity against TKRA—including ARRY-470, lestaurtinib (CEP-701), and crizotinib induced cell-cycle arrest and inhibited proliferation

- Clinical trials:
  - Phase I study of RXDX-101, an oral Pan-Trk, ROS1, and ALK inhibitor ***(De Braud ESMO 14)***
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity

MET: study A8081001 with crizotinib



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

Objective response rate

	Low *MET*, n=2	Intermediate *MET*, n=6	High *MET*, n=6
ORR, % (95% CI)[b]	0 (0–84)	17 (0–64)	67 (22–96)
Best response, n (%)			
Complete response	0	0	1 (17)
Partial response	0	1 (17)	3 (50)
Stable disease	0	4 (67)	1 (17)
Objective progression	2 (100)	1 (17)	1 (17)
Median duration of response, weeks (range)[c]	–	16	73.6 (24.1–128.0)
Duration of stable disease, n (%)[d]			
0–<3 months	–	3 (75)	0
3–<6 months	–	1 (25)	1 (100)

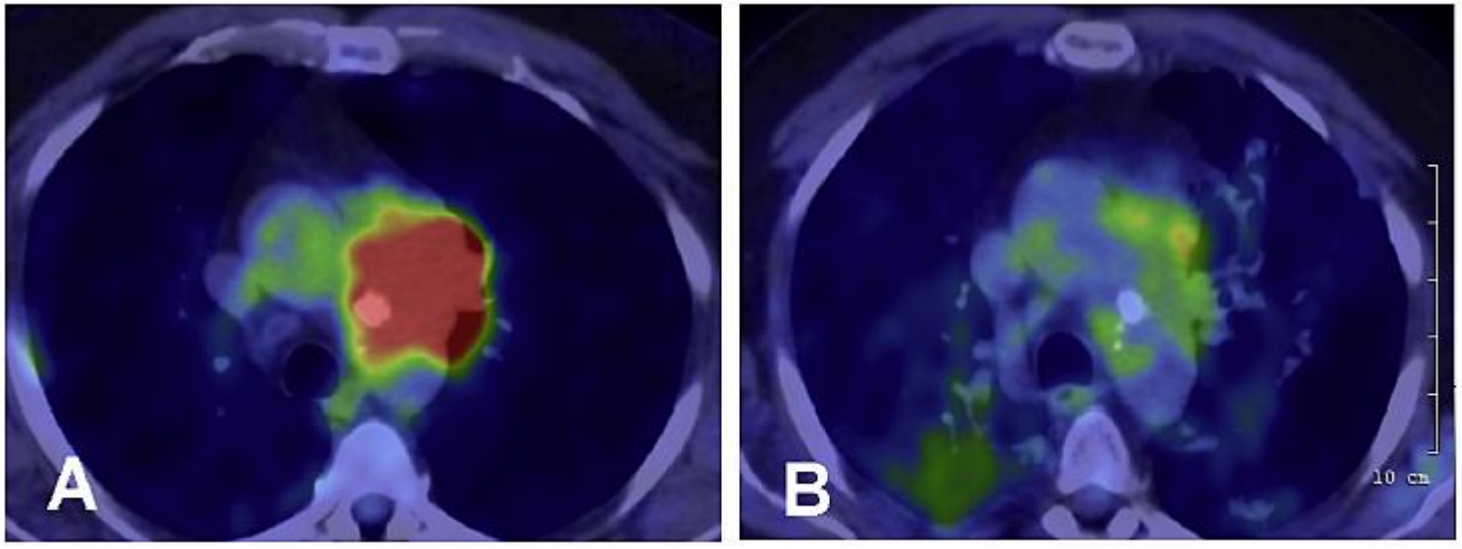
- **Lung Cancer Mutation Consortium *(Varella-Garcia ASCO 12)* MET gene amplification defined by ratio mean MET/mean CEP7≥2 in 4% of ADC**

c-MET Inhibition in SCC: crizotinib

c-Met amplified SCC

Before

After



MET amplification, a mechanism of AR to EGFTKIs

- Phase Ib/II of cabozantinib +/- erlotinib, encouraging activity in erlotinib-pretreated population, including PR in one p with MET amplification ***(Wakelee ASCO 12)***

- Phase Ib/II trial of INC280/gefitinib in p with EGFR mutation and MET-positive (IHC) ***(Wu ASCO 14)***
  - PR seen in 8/46 (17%) evaluable p
  - All responding p had high MET status by IHC or FISH

- Phase I of EGF816 in combination with INC280 in NSCLC p with EGFR mutation and AR

FGFR inhibition in SCC, BGJ398

- Phase I dose-escalation study of p with any *FGFR* genetically altered tumor, progressed at least 1line, including platinum (SCC cohort: N=21)
  - FGFR 1-amplified tumors by FISH/CISH
- **Results:** 17 evaluable p
  - 2 PR
  - 2 additional PRs after the data cutoff date
  - 3 additional p had SD with tumor regression (up to 11% reduction)
- **Safety:**
  - Manageable and reversible hyperphosphatemia, stomatitis, decreased appetite, and fatigue
- **Conclusion:**
  - These data encourage further development of BGJ398 in *FGFR1*-amplified SCC and efforts to optimize predictive biomarkers for FGFR inhibitor sensitivity

Nogova J Clin Oncol 2014

FGFR Inhibition in SCC, AZD4547

- Phase I expansion of AZD4547 in previously-treated p with *FGFR1* amplified SCC
- **Results:**
  - 15 p: 1 PR, 4 SD, 9 PD (7 progressions and 2 deaths)
    - The PR observed in a p with high *FGFR1* amplification
- **Safety:**
  - Most common related AEs were GI and dermatologic
  - Grade ≥ 3 related AEs in 3 p (20%) (central serous retinopathy, hyponatremia, dehydration)
- **Conclusion:**
  - AZD4547, well-tolerated in p with *FGFR1* amplified SCC but pre-specified efficacy endpoint in terms of ORR for continuation not met

Paik *J Clin Oncol* 2014

FGFR inhibitors in clinical trials in NSCLC

DRUG	TARGET
Dovitinib	VEGFR1-2-3, PDGFRβ, FGFR1-2-3, FLT3, KIT, RET
Ponatinib	VEGFR2, FLT3 PDGFRα, FGFR1-2-3-4, BCR-ABL
Lucitanib	VEGFR1-2-3, PDGFRα-β, FGFR1
AZD4547	FGFR1-2-3
BGJ398	FGFR1-2-3
LY2874455	FGFR1-2-3-4
JNJ-42756493	FGFR1-2-3-4
Debio1347	FGFR1-2-3
TAS120	FGFR1-2-3-4
GSK3052230/FP-1039	FGF trap

DDR2 in SCC

- In 290 SCC tissue samples, frequency of *DDR2* mutations, 3.8% ***(Hammerman Cancer Disc 2011)***
  - *DDR2* mutations drive molecular alterations whose activation has been inhibited by dasatinib
  - SCC p harboring a *DDR2* kinase domain mutation who responded to dasatinib and erlotinib treatment

- Trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation
  - Study terminated *(lack of efficacy and slow accrual)*

New targets relevant after the era of EGFR and ALK

- **What is the optimal treatment for p with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment?**
  - 2nd ESMO Consensus Conference on Lung Cancer ***(B Besse and Panel members, Ann Oncol 14)***:
    - **Recommendation:** Specific targeted treatments should be discussed with the p and may be considered in individual p based on expected risk-benefit, biological plausibility, preclinical data, and limited clinical efficacy data for authorised therapies in different indications

New targets relevant after the era of EGFR and ALK

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2015
Non-Small Cell Lung Cancer

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF V600E mutation*	vemurafenib[1] dabrafenib[2]
MET amplification	crizotinib[3,4]
ROS1 rearrangements	crizotinib[5]
HER2 mutations	trastuzumab[6] (category 2B) afatinib[7] (category 2B)
RET rearrangements	cabozantinib[8] (category 2B)

*Non-V600E mutations have variable kinase activity and response to these agents.

New targets relevant after the era of EGFR and ALK

- NSCLC is divided in subsets by the presence of targetable molecular alterations (EGFR, ALK, KRAS, ROS1, RET, HER2, BRAF, NTRK1, FGFR, among others)

- At present, EGFR, ALK and ROS1 should be tested in non-SCC

- Challenges
  - Genotyping
  - Some molecularly defined subsets are infrequent; a clear effort required to identify these p
  - Few trials in these uncommon molecular alterations
  - International collaboration

Thanks!!!

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