Drug-device co-development in the era of precision medicine:

Approval of Tafinlar and Mekinist combination therapy and next generation sequencing companion diagnostic in non-small cell lung cancer

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What is Precision Medicine?

- Deliver **right drug** to **right patient** at **right dose** at **right time**

FROM

"One Size Fits All"

TO

"Personalized Medicine"

Precision Medicine Leverages

- Tumor Biology
- Biomarkers (PD, Predictive, Imaging)
- Translational Medicine

To Deliver

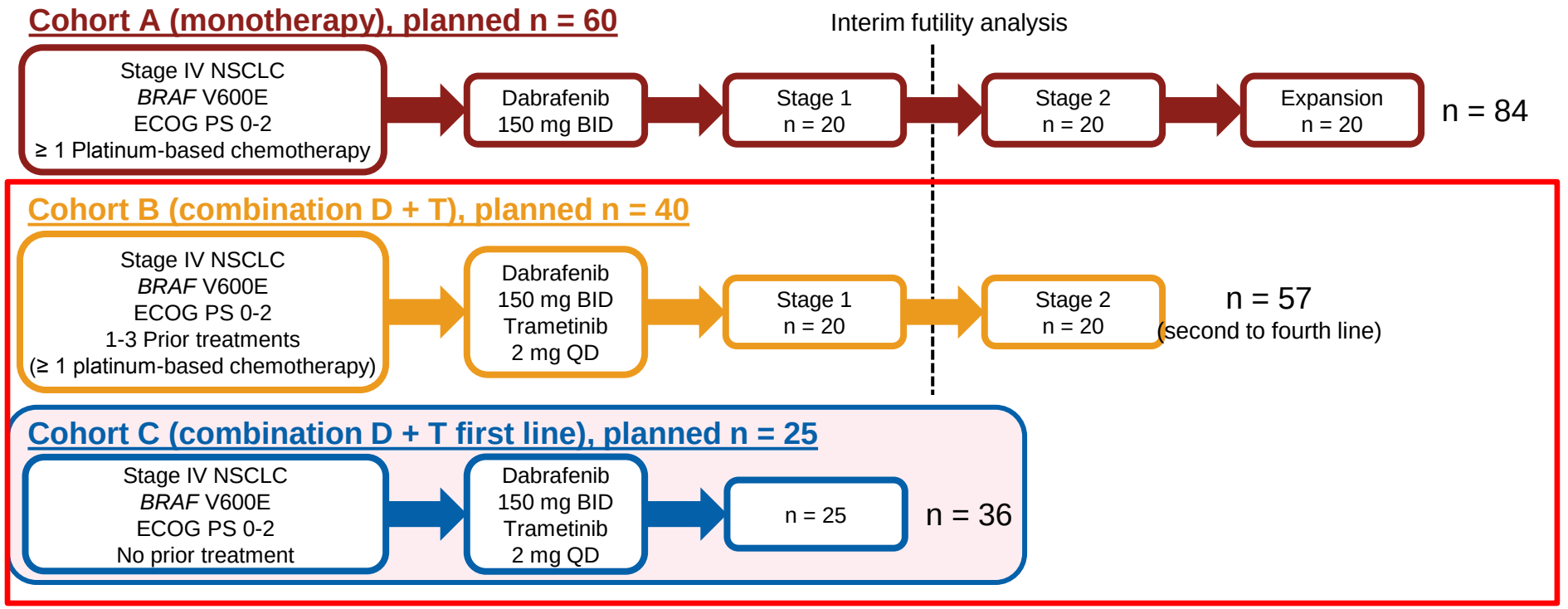
- Better Patient Selection
- Better Patient Outcomes (Efficacy/Saf)

Resulting In

- More Efficient Clinical Dev
- Improved Benefit / Risk
- Stronger Value Proposition (for PM Stakeholders)

Phase II Study BRF113928: BRAF V600E NSCLC

Dabrafenib Monotherapy / Dabrafenib + Trametinib Combination Trial



Statistical assumptions:

- **2L Cohort A**: Primary, Original (n=40) 92.6% power to detect 30% ORR. Per FDA guidance expanded to 60 pts, ORR of 30% @95% CI (18.9%, 43.2%).
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK
- **2L Cohort B**: Primary, 92.2% power to detect 55% ORR (n = 40)
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK
- **1L Cohort C**: Primary, 92.2% power to detect 60% ORR (n = 25)
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK

Primary endpoint for each cohort: **investigator-assessed ORR**

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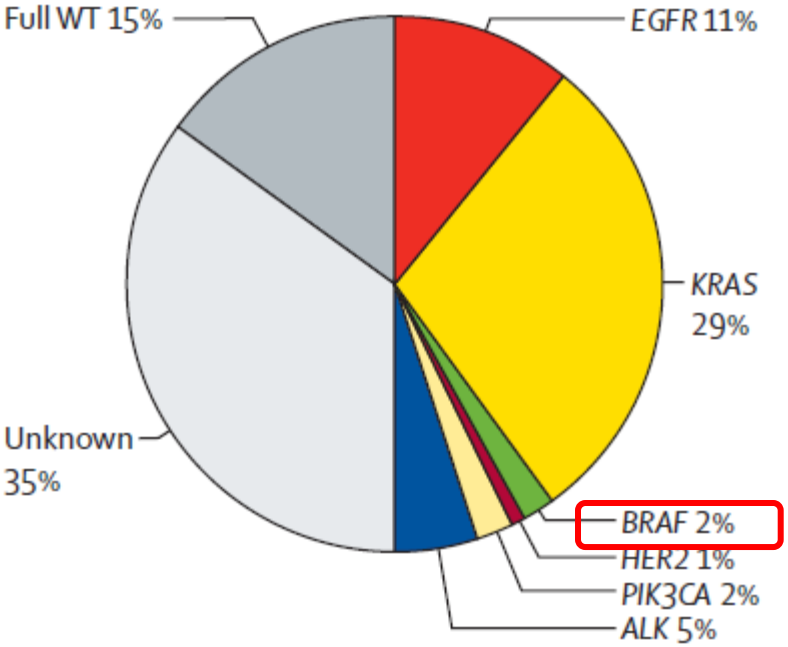
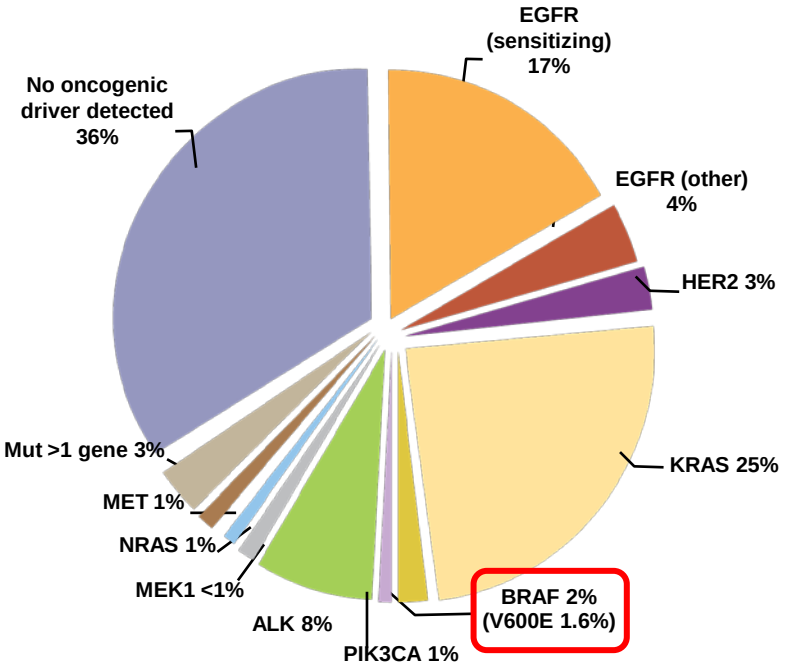
~2% BRAF mutations in NSCLC

Europe[1]
All histology
(Biomarkers France)
(n = 17,664)



US[2]
Adenocarcinoma
(Lung Cancer Mutation Consortium)
(n = 733)



1. Barlesi F, et al. *Lancet 2016*
2. Kris MG, et al. *JAMA 2014*

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What is a companion diagnostic?

- "An *in vitro* diagnostic device (IVD) provides information that is essential for the safe and effective use of a corresponding therapeutic product".
  - Identifying patients most likely to benefit from therapy
  - Identifying patients likely to be at increased risk of serious adverse reactions as a result of therapy
  - Monitoring therapeutic response for the purpose of adjusting treatment (schedule, dose, discontinuation) to achieve improved safety or effectiveness
- FDA assesses, through premarket approval (PMA), the safety and effectiveness of the IVD companion diagnostic device
  - Analytical validation: precision, accuracy, detection capability....
  - Clinical validation: pivotal drug-device clinical trial
  - Submission to Center for Devices and Radiological Health (CDRH)

What is PMA IVD

- Total System (Not Just Assay or Biomarker)
  - Sample collection devices, transport, stability
  - Sample processing and assay reagents/disposables
  - Hardware and software
- IVDs have to be compliant with:
  - Specific Labeling Requirements
  - 510(k)/PMA
  - Registration & Listing
  - Import/Export regulations
  - IDE principles

Oncomine Dx Target Test

- Collaboration with Thermo Fisher and Pfizer.
- First NGS for multiple indications in NSCLC

Gene	Variant	Targeted therapy
BRAF	BRAF V600E	TAFINALAR (dabrafenib) in combination with MEKINIST (trametinib)
ROS1	ROS1 fusions	XALKORI (crizotinib)
EGFR	L858R, Exon 19 deletions	IRESSA (gefitinib)

- Detects actionable mutations in one test which reduces turnaround time, delay of target treatment, and avoids hierarchical testing
- PMA includes analytical validation studies and clinical bridging study

Efficacy in BRAF V600E populations (ITT and BRAFV600E)

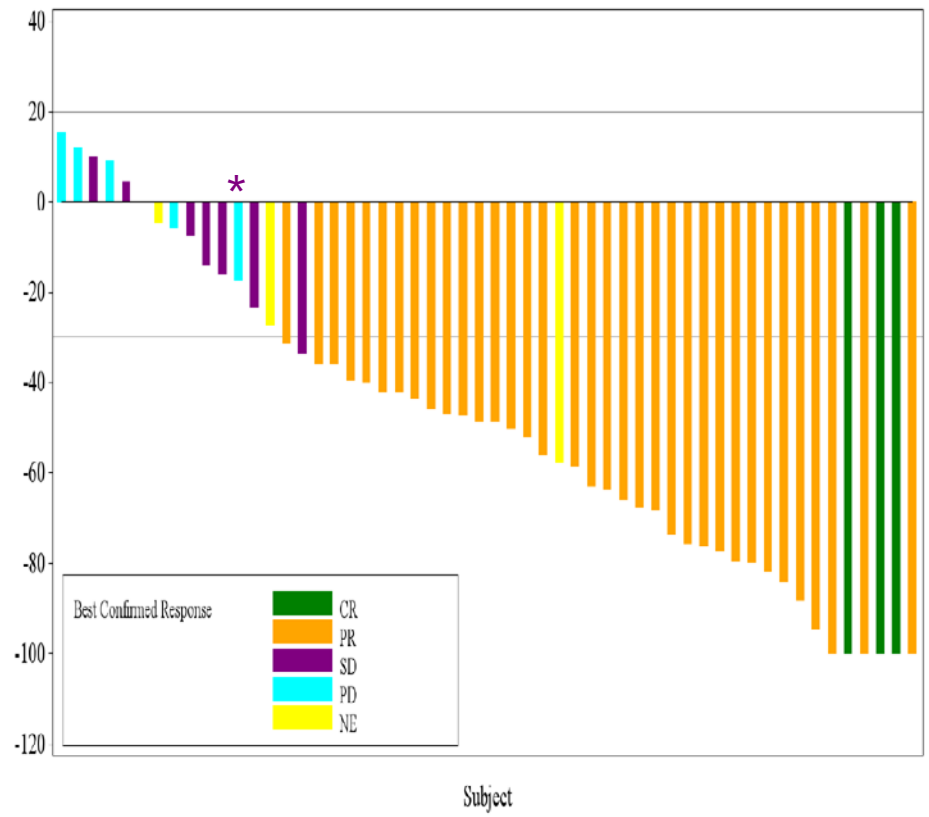
- ORR in BRAF V600E centrally confirmed population is consistent with ORR in ITT

Population		Investigator assessment		IRC assessment	
		Responder n (%)	95% CI	Responder n (%)	95% CI
Combination 2L+	ITT (N=57)	38 (66.7)	(52.9, 78.6)	36 (63.2)	(49.3, 75.6)
	BRAF V600E centrally confirmed (N=22)	16 (72.7)	(49.8, 89.3)	15 (68.2)	(45.1, 86.1)
Combination 1L	ITT (N=36)	22 (61.1)	(43.5, 76.9)	22 (61.1)	(43.5, 76.9)
	BRAF V600E centrally confirmed (N=23)	14 (60.9)	(38.5, 80.3)	14 (60.9)	(38.5, 80.3)

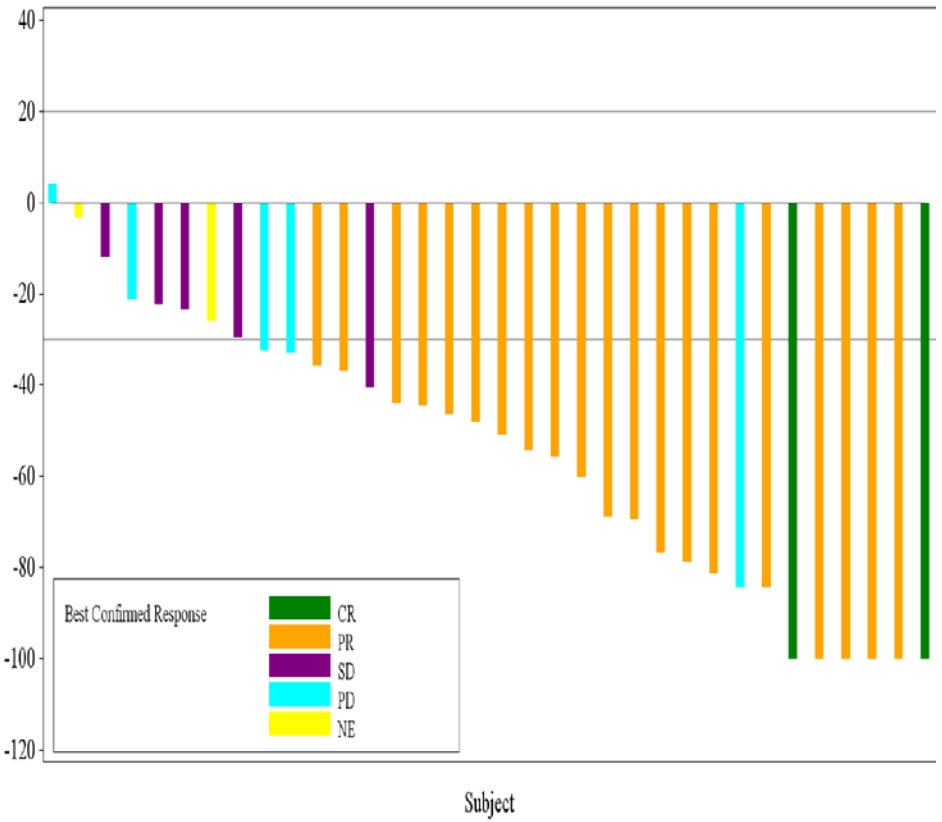
Max. Target Lesion Reduction

From Baseline Sum of diameters by Best Confirmed Response by Investigator

Combination 2nd line plus



Combination 1st line



* Maximum change from baseline was 0%

Some patients were evaluated as PD due to new lesion, despite the target lesions were SD

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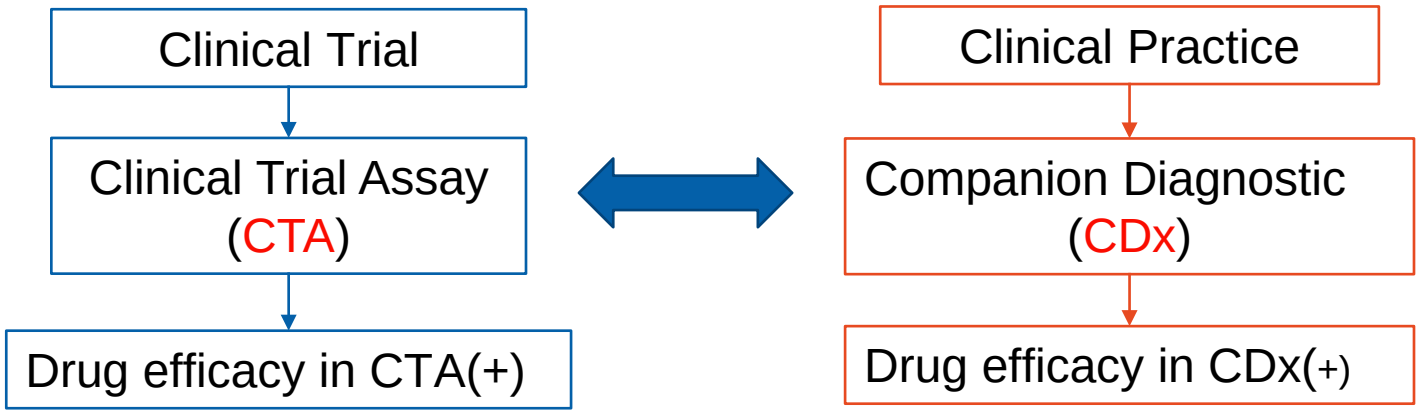
Large scale analytical validation studies

- 32 validation studies for hundreds of variants

ID	Study	ID	Study
1	Analytical accuracy	17	External panel reproducibility
2	Limit of Blank	18	External sample processing reproducibility
3	Limit of Detection	19	Tissue heterogeneity
4	DNA/RNA input	20	Extraction method equivalency (DNA, RNA)
5	Tissue input	21	Specimen equivalency
6	Tumor content	22	Workflow toleratnces
7	Inclusivity/Cross-reactivity	23	Tissue Fixation
8	Endogenous Interference	24	Contamination
9	Exogenous interference	25	Stability
10	Anti-microbial testing	26	Shelf-life stability
11	External panel reproducibility	27	Designated hold times in-use stability
12	External sample processing reproducibility	28	Kit lot interchangeability
13	Precision	29	Sample stability (extracted DNA and RNA)
14	Tissue heterogeneity	30	Stored slide stability
15	Extraction method equivalency (DNA, RNA)	31	Stored block stability
16	Specimen equivalency	32	Transport stability

Bridging Study for MEK-TAF



- Primary objectives
  - Concordance between CTA and CDx
  - Efficacy in CDx(+) patients in Cohort B and Cohort C

Challenges and Mitigation Strategies

Challenge	Mitigation Strategy
CDx development delayed - due to GSK-Novartis Oncology acquisition	- Alerted the regulatory authorities, and kept them informed of the progress - Staggered submissions worldwide depending on need for CDx
Different data structures - CDx data in Novartis standards - Clinical data in GSK standards	- Maintained constant contact between CDx and clinical teams - Ensure delivery of CDx related data was in appropriate formats dependent on specific analysis
Sequential study design - Cohorts were not randomized and were not run in parallel	- Engaged HAs before 1st patient was enrolled in combination cohorts - Emphasized the rarity of BRAF V600E NSCLC

Challenges and Mitigation Strategies

Challenge	Mitigation strategy
Missing CDx results - Some patients had no leftover specimen for re-testing - Some specimen did not yield valid CDx results	- Propensity score, t-test, Fisher exact test to check covariate imbalance - Logistic regression to identify covariates correlated with CDx results and clinical outcome - Multiple imputation to impute missing CDx results
Missing CTA(-) results - No CTA (-) patients enrolled in original trial	- Sensitivity analysis assuming different negative percent agreement (NPA)

Conclusions

- In BRAF V600E mutation-positive metastatic NSCLC, dabrafenib in combination with trametinib demonstrated:
  - Clinically meaningful efficacy
    - High and durable response rate
    - Overall efficacy consistent among ITT and BRAF V600E populations and also consistent between IRC and Investigator assessment
    - Results demonstrate clinical efficacy in CDx(+) patients
  - Manageable safety profile
- The clinical and CDx data from BRF113928 support the indication of dabrafenib plus trametinib as a treatment for advanced or metastatic NSCLC patients with BRAF V600E mutation plus the approval of the Oncomine NGS test

Thank you

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