A case with a BRAF v600E Mutation

Paul A. Bunn, Jr, MD, Distinguished Professor and Dudley Endowed Chair, Univ. of Colorado Cancer Center, Aurora, CO, USA

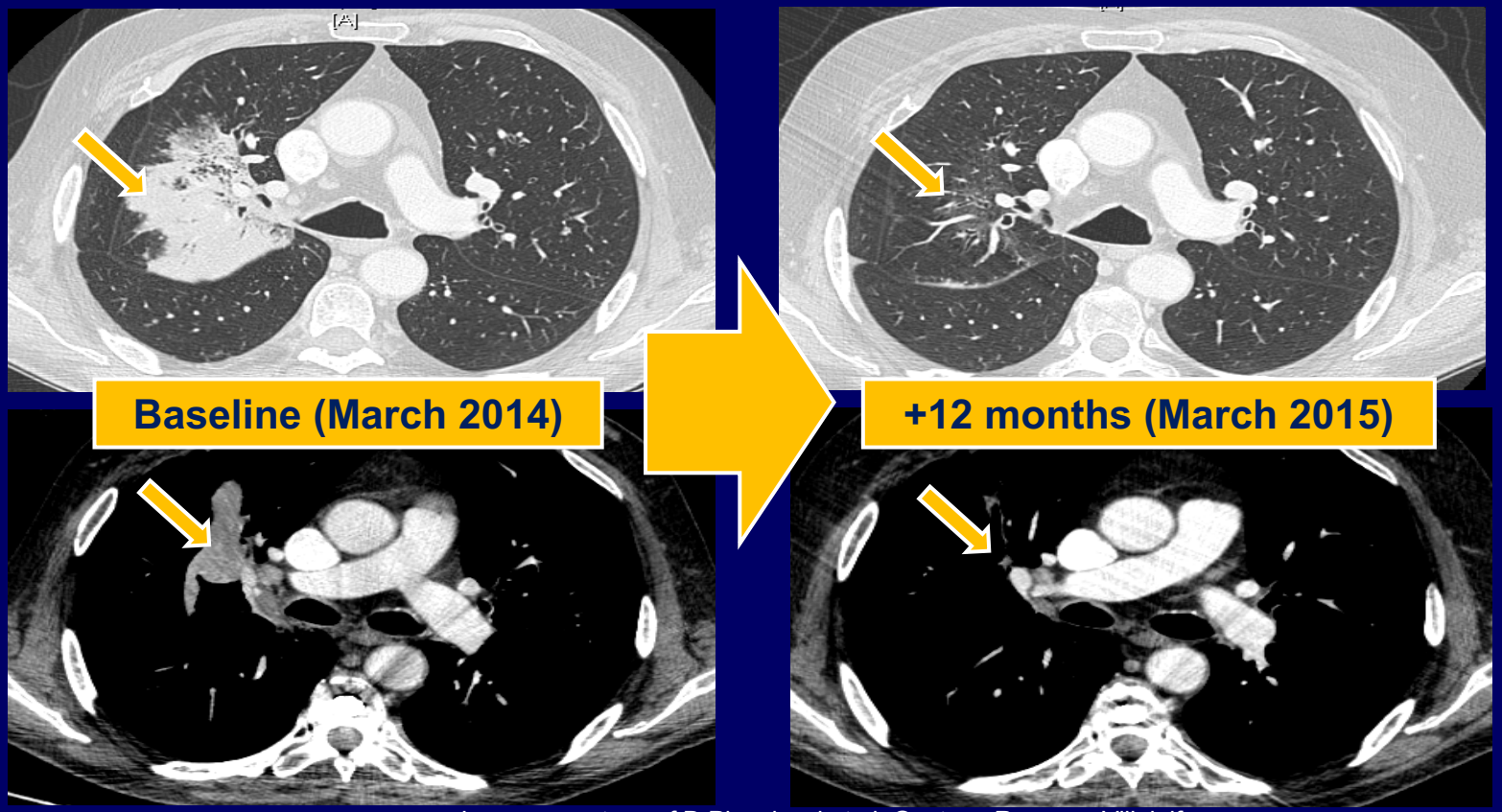
Case of Lung adenocarcinoma with BRAF mutation

- 65 yo Hispanic male former smoker presents with cough, shortness of breath and chest pain with a 10 pound weight loss. Chest CT scan shows a left lung mass and pleural effusion. A biopsy of the mass reveals an adenocarcinoma that is TTF1 positive. A CT/PET scan shows bilat lung lesions and a right adrenal mass.
- EGFR and ALK testing are negative.
- The patient is treated with pemetrexed and carboplatin and has a confirmed partial response through 6 cycles. He receives maintenance pemetrexed for 6 more cycles but has tumor progression, considerable fatigue and anemia.

Case of Lung adenocarcinoma with BRAF mutation

- He indicates that he would like to have a break from chemotherapy. His physician orders PD-L1 testing and Foundation One testing from his original biopsy. The Foundation One report shows a BRAF v600E mutation and the PD-L1 testing shows 10% positive tumor cells.

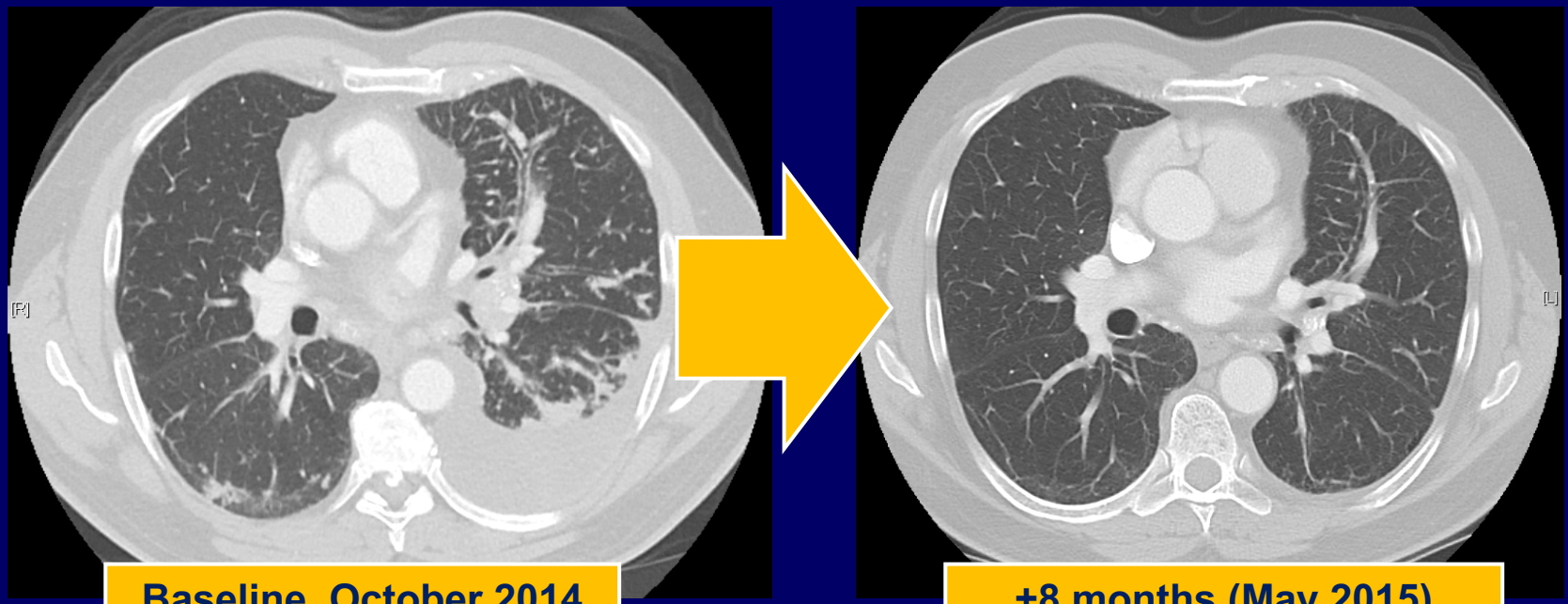
59 Year Old Male Patient (Former Smoker) With V600E BRAF Mutation Treated With Dabrafenib Plus Trametinib



Images courtesy of D.Planchard et al, Gustave Roussy - Villejuif

Case of Lung adenocarcinoma with BRAF mutation

- The patient is treated with dabrafinib plus trametinib and has a response as illustrated below.
- The response lasts for 14 months when PD is noted



Images courtesy of B. Johnson et al, Dana-Farber - Boston

Case of Lung adenocarcinoma with BRAF mutation

- The patient is now treated with atezolizumab and again has a partial response.

A case with a BRAF v600E Mutation

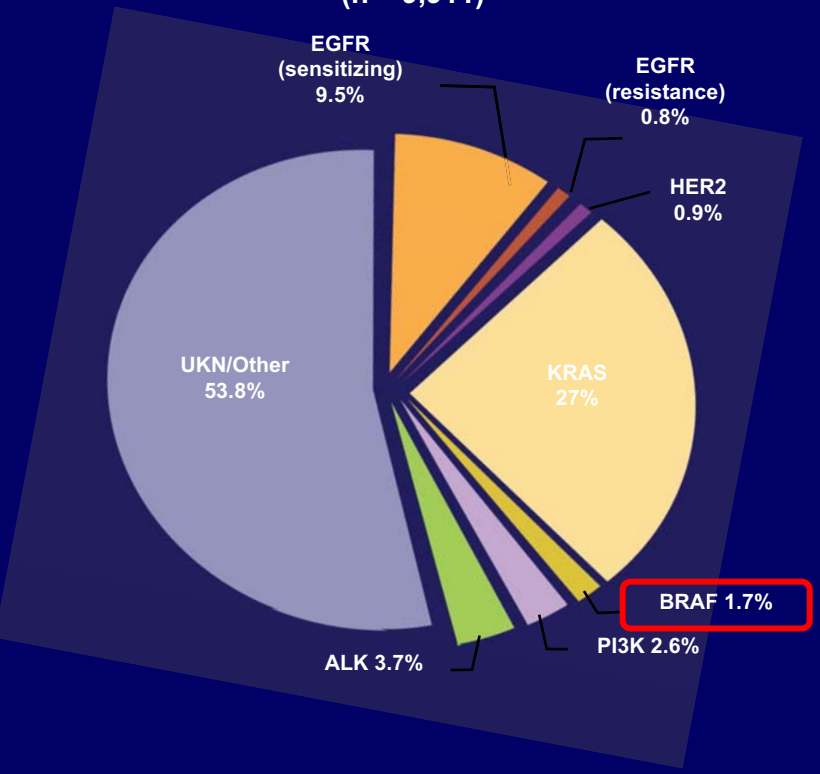
Paul A. Bunn, Jr, MD, Distinguished Professor and Dudley Endowed Chair, Univ. of Colorado Cancer Center, Aurora, CO, USA

Disclosures

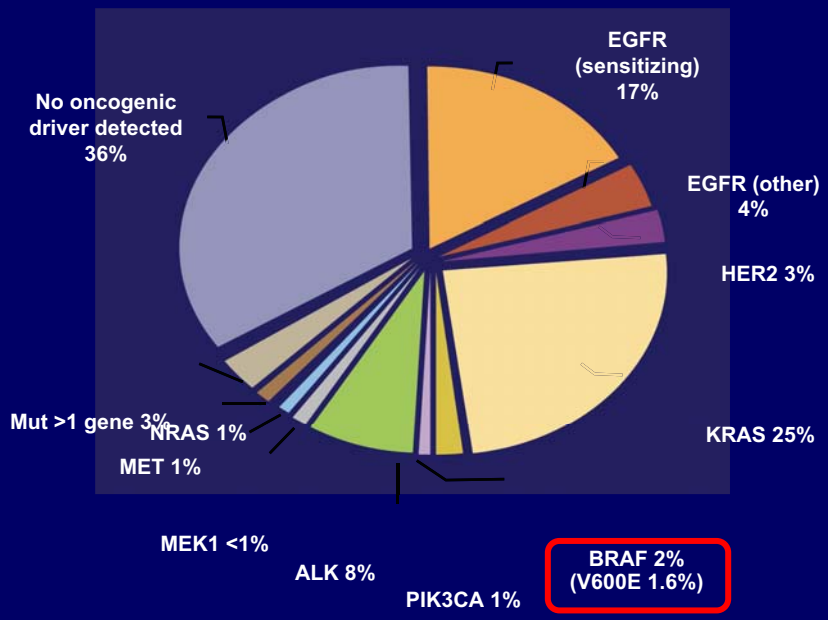
Advisory Committee	Genentech BioOncology, Lilly
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Celgene Corporation, EMD Serono Inc, Genentech BioOncology, Lilly, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc

BRAF Mutations in NSCLC

Europe[1]
All histology
(Biomarkers France)
(n = 9,911)



US[3]
Adenocarcinoma
(Lung Cancer Mutation Consortium)
(n = 733)



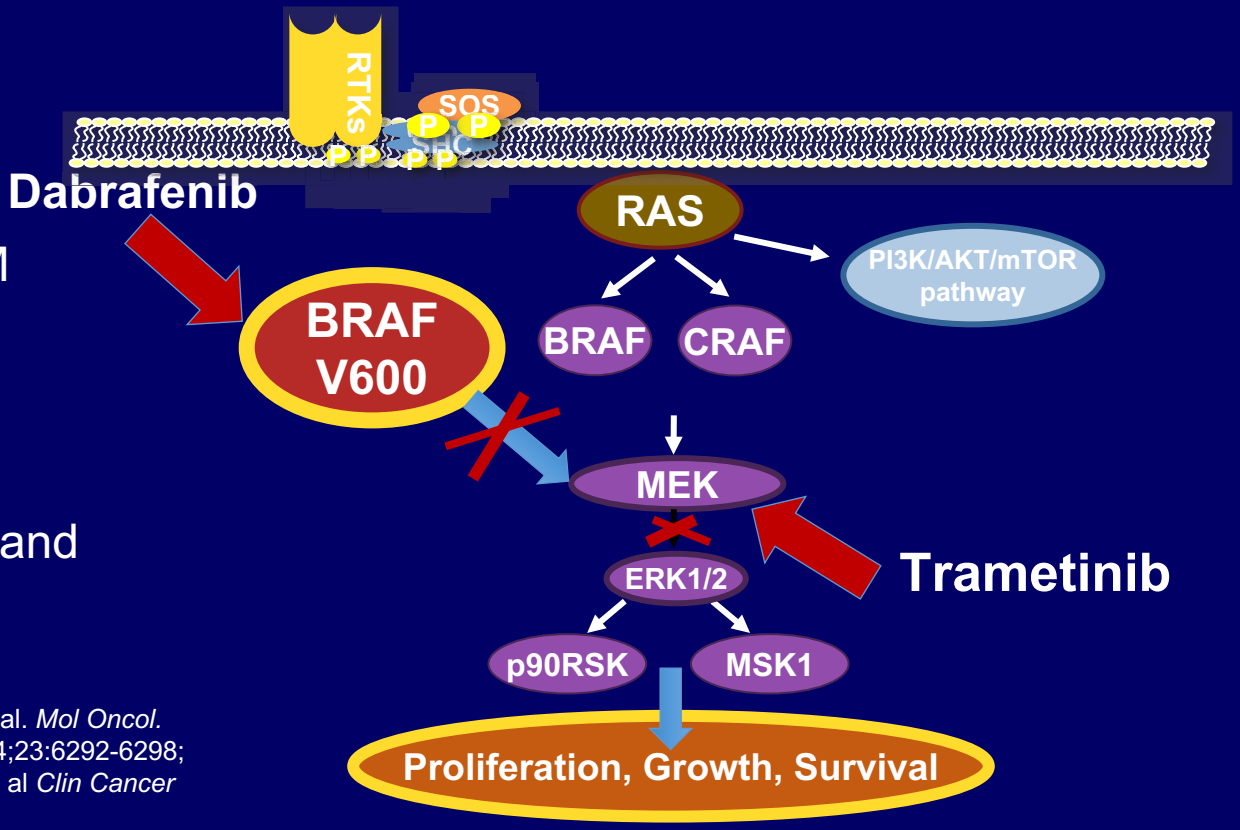
- NSCLC with BRAF V600E mutations have histologic features suggestive of an aggressive tumor[3]
- Patients with BRAF V600E mutation demonstrate less favorable outcomes with platinum based chemotherapy[3,4]

1. Barlesi F, et al. *J Clin Oncol* 2013;31:3004-3011;
2. Marchetti A, et al. *J Clin Oncol* 2011;29;3574-3579;
3. Kris MG, Johnson BE, et al. *JAMA*. 2014;311(19):1998-2006; JAMA;
4. Cardarella S, et al. *Clin Cancer Res*. 19(16):4532-4540.

Dabrafenib Inhibits BRAF V600 Kinase and Trametinib Inhibits Downstream MEK Signaling

Dabrafenib mode of action
- Reversible, small molecule
- BRAF inhibitor
- ATP competitive
- BRAF V600E: IC_{50} 0.65 nM

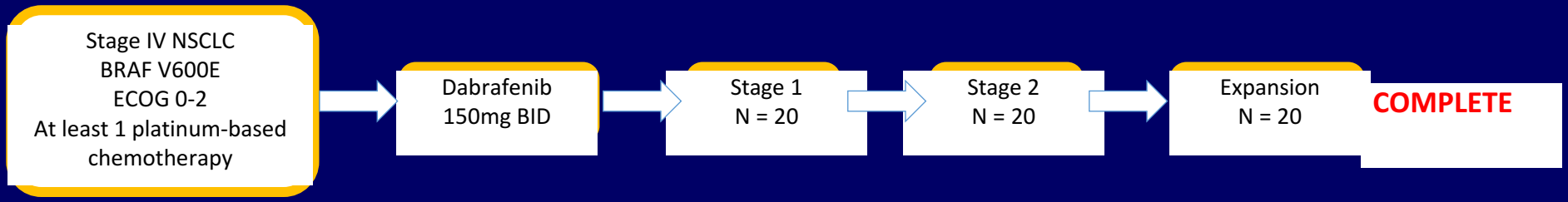
Trametinib mode of action
- Reversible, small molecule
- MEK1 and MEK2 allosteric inhibitor
- MEK1 and MEK2: IC_{50} 0.7 and 0.9 nM



Davies H, et al. *Nature*. 2002;417:949-954; Platz A, et al. *Mol Oncol*. 2008;1:395-405; Karasarides M, et al. *Oncogene*. 2004;23:6292-6298; Long, et al. *N Engl J Med*. 2014;371:1877; Gilmartin et al *Clin Cancer Res* 2011;17:989.

BRF113928: Study Design

Cohort A (monotherapy) n = 60



Reported at ESMO 2014*

*Planchard D, et al. *Ann Oncol* 2014;25(suppl 4):abstract LBA38_PR.

Rationale for Combining Dabrafenib (D) and Trametinib (T)

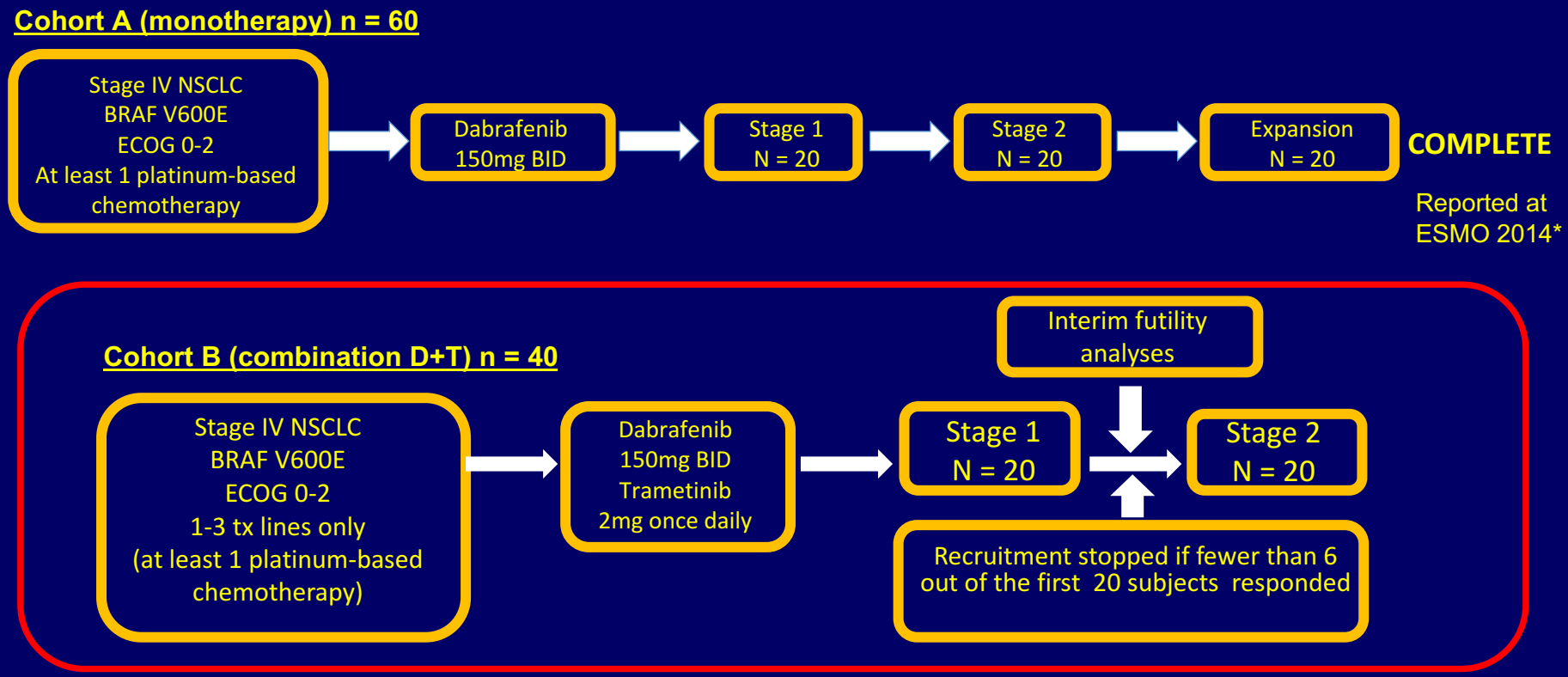
- In preclinical models, combination of D+T was more effective than either agent alone[1] at:
  - inhibiting MAPK pathway
  - Inducing apoptosis in BRAFV600E mutant NSCLC cell lines
- D+T was more efficacious than BRAF-inhibitor monotherapy in BRAFV600-mutant melanoma[2,3]
  - D+T demonstrated clinically meaningful and significant superior OS, PFS, ORR, and DoR
- Dabrafenib monotherapy demonstrated clinically meaningful antitumor activity with durable objective responses in BRAF-mutated V600E NSCLC[4]
  - ORR = 32%, and DCR = 56%
  - Median DoR = 9.6 months (95% CI, 5.4 – 15.2) with 77% responders progressed or died
  - Median PFS = 5.5 months with 62% patients progressed or died

1. GlaxoSmithKline Document Number 2013N169244_00:Cellular assays with dabrafenib and trametinib as single agents and in combination in BRAF mutant lung cancer cell lines. Report Date May 2013; 2. Long GV, et al. *N Engl J Med* 2014;371(20):1877-1888; 3. Robert C, et al. *N Engl J. Med* 2015;372(1):30-39; 4. Planchard D, et al. *Ann Oncol* 2014;25 (suppl 4):abstract LBA38_PR.

BRF113928: Study Objectives

- Primary objective: Investigator-assessed ORR
- Secondary objectives: PFS, DoR, OS, safety, tolerability, and population PK
- Cohort B analysis populations:
  - Efficacy population (≥ 2nd line), N = 24
    - Defined as having had either 2 post-baseline scans or discontinued study treatment
  - Safety population (all treated), N = 33

BRF113928: Study Design



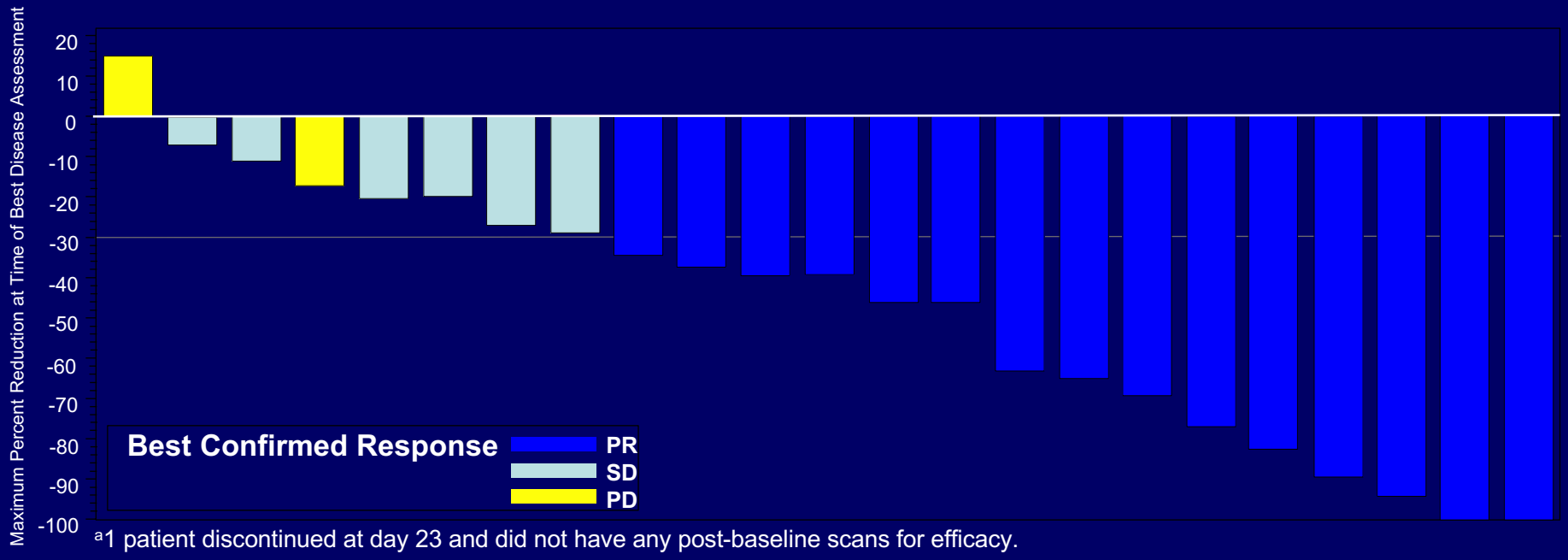
*Planchard D, et al. *Ann Oncol* 2014;25(suppl 4):abstract LBA38_PR.

Patient Population

		All Treated (N = 33)
Age, years	Median (range)	66 (49-88)
Sex, (%)	Female/male	21 (64)/12 (36)
Race,[a] n (%)	White	27 (82)
	Asian	3 (9)
	African American/Mixed	2 (6)
ECOG PS at baseline, n (%)	0 or 1	31 (94)
	2	2 (6)
Smoking history,[b] n (%)	Never smoked	9 (27)
	≤ 30 pack-years	13 (39)
	> 30 pack-years	10 (30)
Number of prior systemic regimens for metastatic disease,[c] n (%)	1	19 (58)
	2	6 (18)
	3	5 (15)

[a]One patient had missing race data; [b] One patient had missing smoking history information; [c] Three patients had missing information for prior systemic regimen for metastatic disease.

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 24[a])



[a]1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

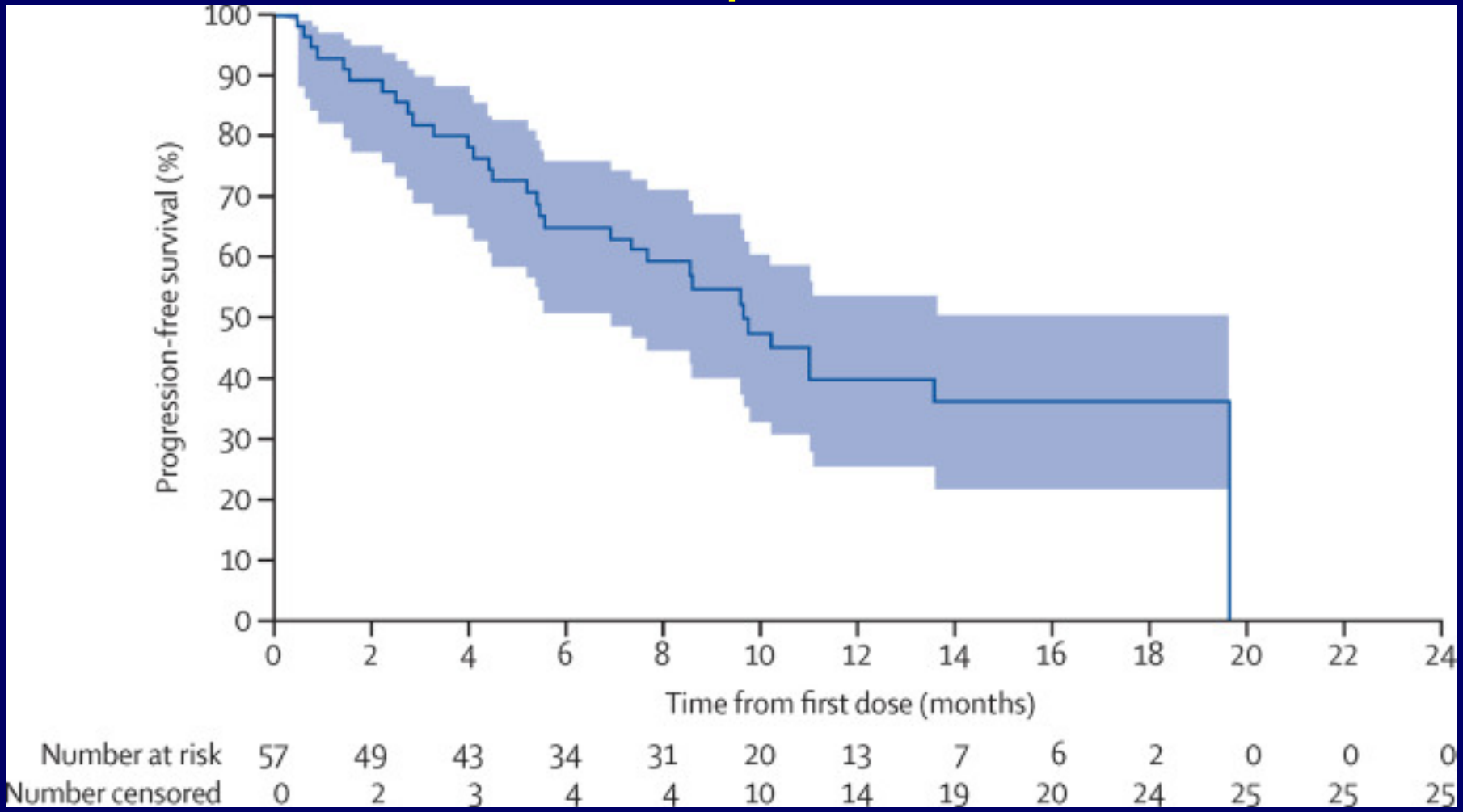
- The median duration of response was not reached

Overview of Best Confirmed Response for ≥ 2nd Line Patients

Best response	Investigator Assessed N = 24	Independent Review N = 22[a]
PR, n (%)	15 (63)	15 (68)
SD[b], n (%)	6 (25)	2 (9)
PD, n (%)	2 (8)	2 (9)
Non-CR, non-PD, n (%)	0 (0)	2[c] (9)
Not evaluable	1 (4)	1 (5)
Response rate (confirmed CR + PR)	63%	68%
95% CI	(40.6–81.2)	(45.1–86.1)
Disease control rate (CR + PR + SD + non-CR, non-PD)	88%	86%
95% CI	(67.6–97.3)	(65.1–97.1)

[a]The independent review sample size was 22 rather than 24 because the scans for 2 subjects were not available for independent review at the time of the data cut.
[b]SD is defined as meeting SD ≥ 12 weeks.
[c]Two patients did not have measurable disease at baseline, per independent review.

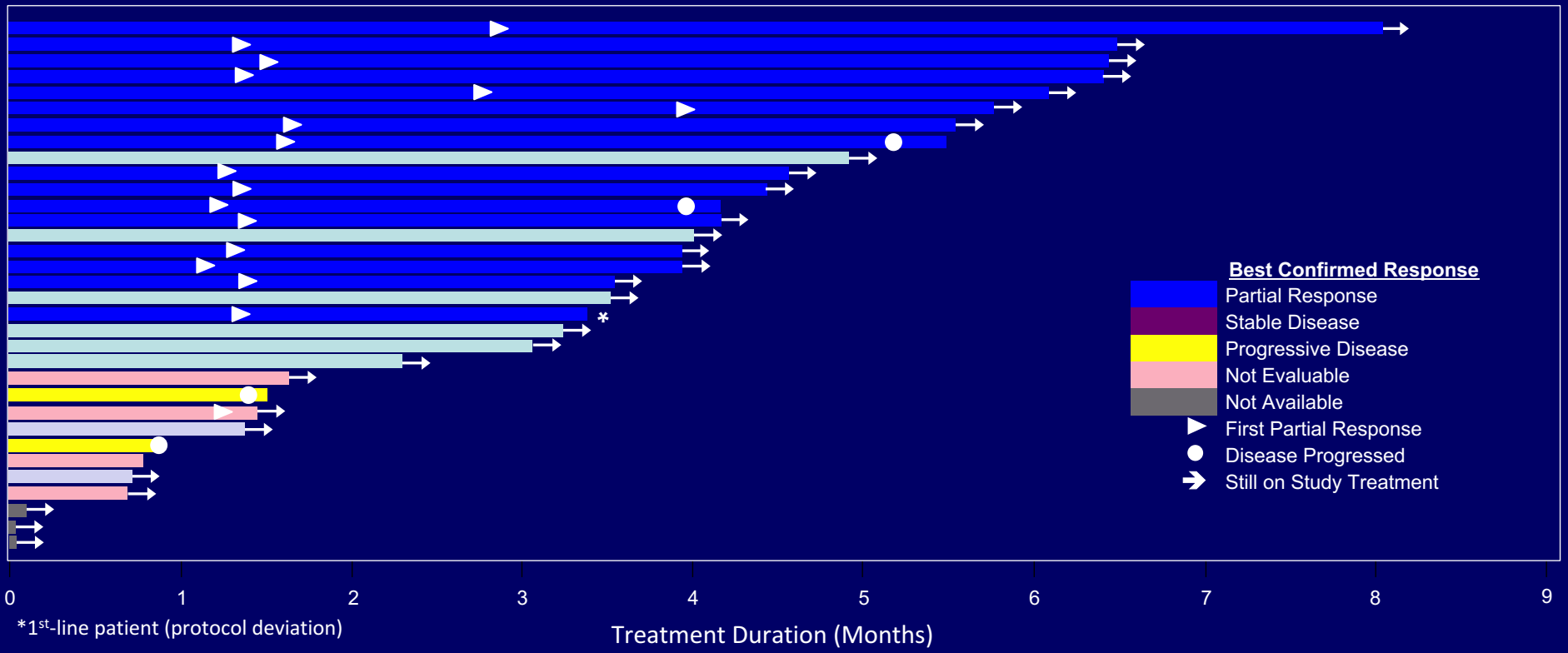
Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial:PFS



David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

, Volume 17, Issue 7, 2016, 984–993
http://dx.doi.org/10.1016/S1470-2045(16)30146-2

Duration of Treatment for All Enrolled Patients in the Interim Analysis (n = 33)



*1st-line patient (protocol deviation)

- Median time on study treatment (dabrafenib and trametinib) = 108 days (range,1 to 244 days)

Adverse Event Overview

	No. of Patients All Treated, n (%) (N = 33)
Any adverse event (AE)	29 (88)
Max grade 3 Max grade 4 Max grade 5	13 (39) 1 (3)[a] 1 (3)[b]
Any serious AE (SAE) Fatal SAEs	14 (42) 1 (3)
AEs leading to study treatment discontinuation	2 (6)
AEs leading to dose reduction	9 (27)
AEs leading to dose interruption	17 (52)

[a]Hyponatremia; [b]Pleural effusion and disease progression.

Most Common Adverse Events (≥ 20%)

AE	No. of Patients All Treated (N = 33)	
	All n (%)	≥ Grade 3 n (%)
Pyrexia	13 (39)	1 (3)
Diarrhea	11 (33)	1 (3)
Nausea	11 (33)	0 (0)
Vomiting	11 (33)	0 (0)
Decreased appetite	8 (24)	0 (0)
Asthenia	7 (21)	0 (0)
Cough	7 (21)	0 (0)
Edema, peripheral	7 (21)	0 (0)
Rash	7 (21)	1 (3)

Serious Adverse Events

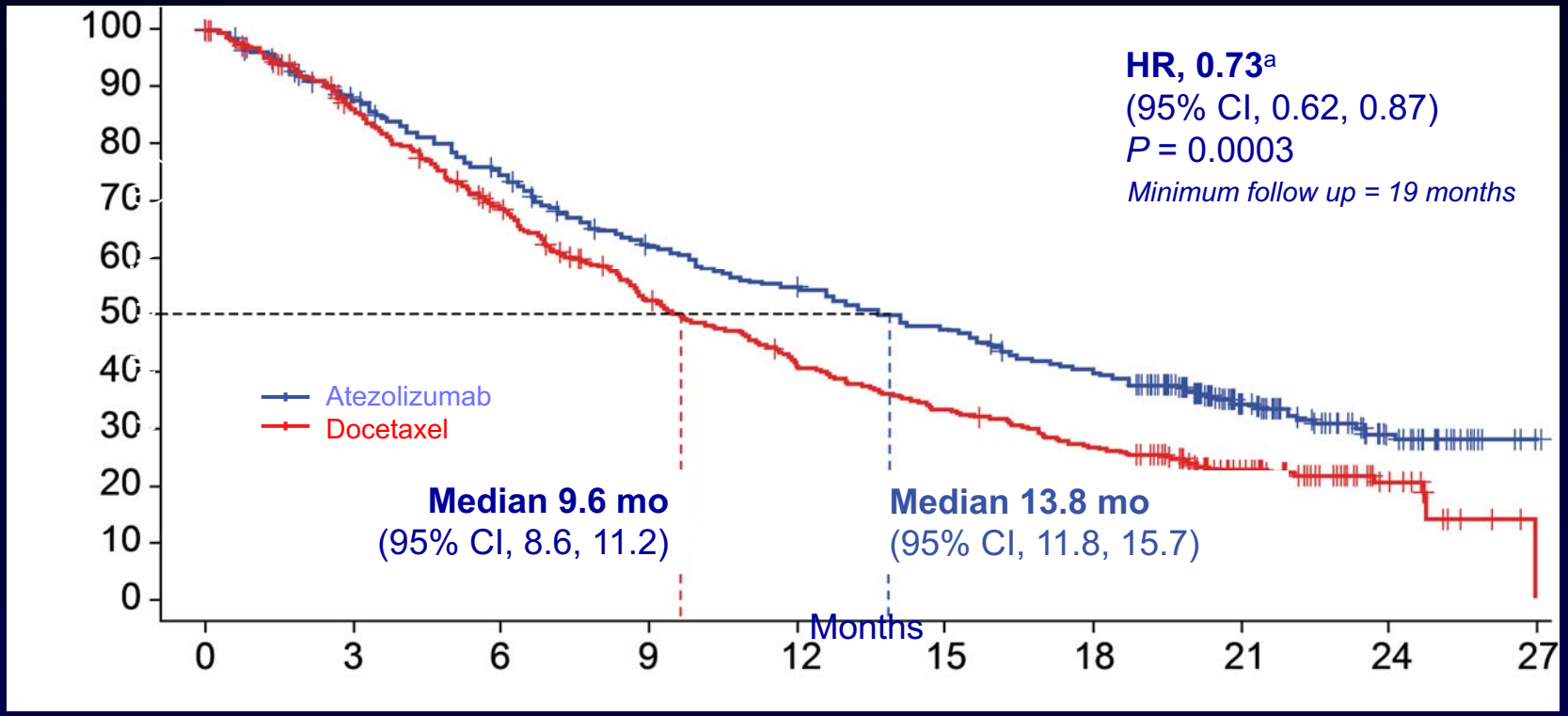
SAE	No. of Patients All Treated, n (%) (N = 33)
Any	14 (42)
Fatal (grade 5): Pleural effusion and disease progression	1 (3)
≥ 2 patients	
Pyrexia	6 (18)
Confusional state	2 (6)
Hyponatremia	2 (6)

Summary

- D + T demonstrated clinically meaningful anti-tumor activity with a higher ORR when compared indirectly with dabrafenib monotherapy in BRAF V600E mutated NSCLC
  - ORR = 63% and DCR = 88% for dabrafenib plus trametinib
  - ORR = 32% and DCR = 56% for dabrafenib as monotherapy[1]
- Safety profile is manageable and similar to previous studies in melanoma
- Cohort B has completed recruitment with 59 subjects
- A third cohort investigating D + T in previously untreated V600E mutant Stage IV NSCLC is actively recruiting

1. Planchard D, et al. *Ann Oncol* 2014;25 (suppl 4):abstract LBA38_PR

OAK:Atezo vs Doce OS, ITT (n = 850)

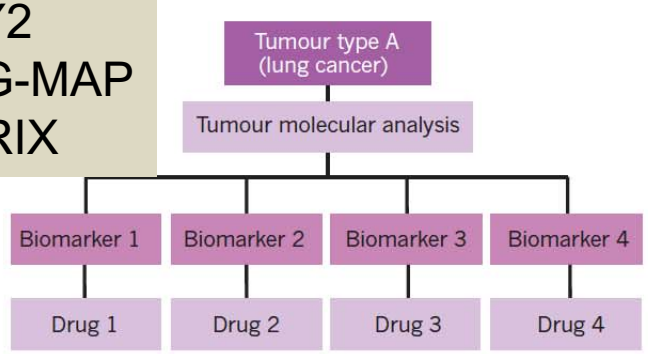


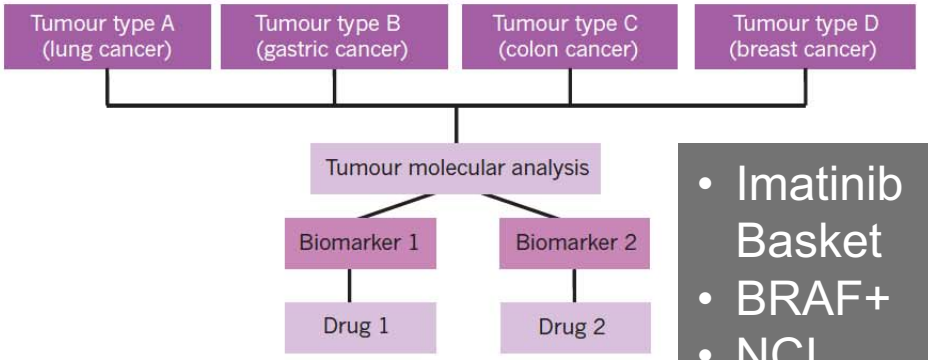
- Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

[a]Stratified HR

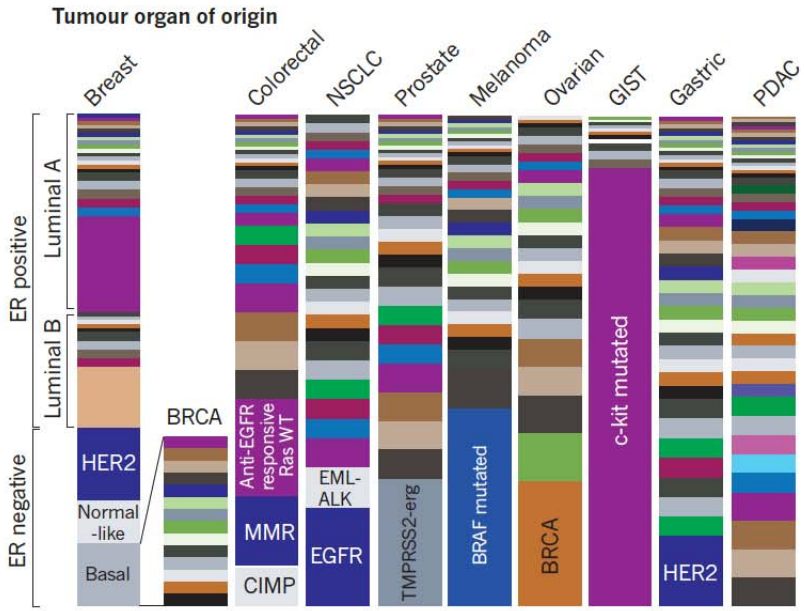
Umbrella & basket studies

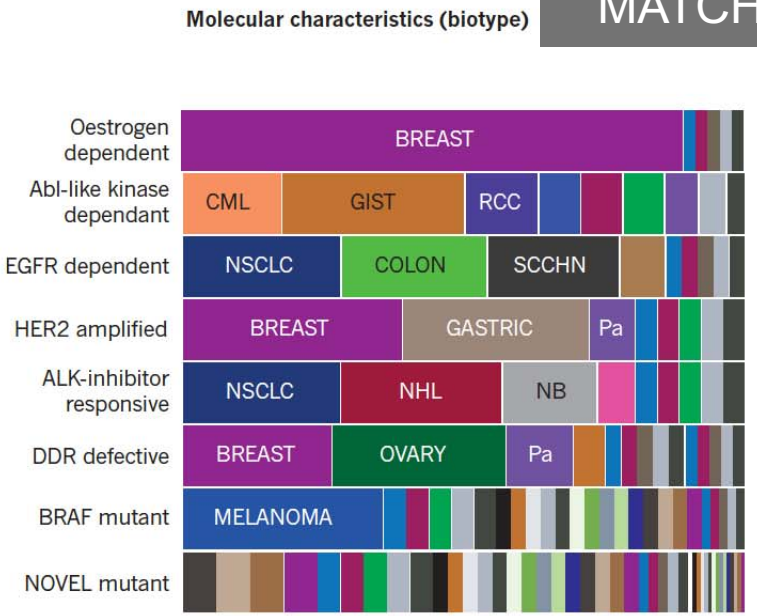
- BATTLE
- I-SPY2
- LUNG-MAP
- MATRIX





- Imatinib Basket
- BRAF+
- NCI MATCH





Biankin AV et al. Nature 2015; 526:361

Basket example: NCI-MATCH
NCI Molecular Analysis for Therapy Choice

- Phase II
- Advanced solid tumors, lymphomas
- 2400 sites
- Screening of patients (n=5000)
- Patients assigned to ~24 sub-studies
- Primary endpoint: Response rate

Conley BA & Doroshow JH. Semin Oncol 2014, 41, 297

Treatment Assignments by Arm, Cancer Type

	Assigned to Rx	Uncommon Cancers	Common Cancers
Q: Ado-trastuzumab emtansine in HER2 amplifications	11	Adeno Esophageal (2) Ovarian (3) Cholangio (1) TCC Urothelium (1)	Colon Adeno (3) Colon NOS (1)
U: Defactinib in NF2 loss	7	Mesothelioma (2) Ovarian (2) Pancreas/Adeno NOS (1)	Colon Adeno (1) Lung Adeno (1)
B: Afatinib in HER2 mutations	5	Gastric Adeno (1) Adeno Esophageal (1)	Breast (2) Prostate (1)
H: Dabrefenib+Trametinib in BRAF V600	5	Neuroendocrine (1)	Lung Adeno (3) Lung Adeno w. BAF (1)
R: Trametinib in BRAF non-V600	2	Ovarian (1)	Colon Adeno (1)
E: AZD9291 in EGFR T790M	1	Neuroendocrine NOS (1)	--
F: Crizotinib in ALK translocations	1	Mets to Peritoneum NOS (1)	--
V: Sunitinib in cKIT mutations	1	Thymoma (1)	--
A: Afatinib in EGFR mutations	--	--	--
G: Crizotinib in ROS1 translocations	--	--	--
Total	**33**	**19 (58%)**	**14 (42%)**

A case with a BRAF v600E Mutation

Paul A. Bunn, Jr, MD, Distinguished Professor and Dudley Endowed Chair, Univ. of Colorado Cancer Center, Aurora, CO, USA