A paradigm shift in early drug development: Individualizing to more patient benefit

THE IMPORTANCE OF PATIENT SELECTION IN TREATMENT EFFICACY

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Disclosure

No conflict of interest to declare

“Right treatment for the Right patient“
Challenges

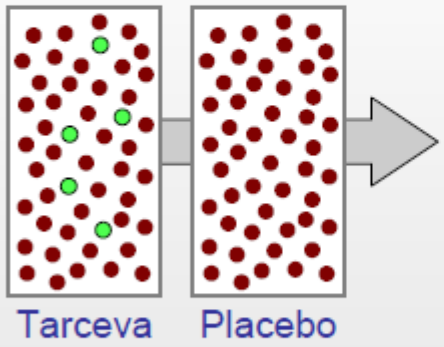
- Selecting the patients for early drug trials
- Tumor sampling
- Ethical questiones
- Tumor heterogeneity

Enrollment of patients for early drug development trials

- **“All-comers” Selecting a group of patients with frequent target mutations , example : pancreatic cancer with KRAS mutations (40-50%)**
- High number of patients at risk of exposure to study drug despite not presenting the target of interest
- Low prevalence of responsive population could result in “no go” for the drug (Gefinitib in NSCLC inhibiting only mutated EGFR)

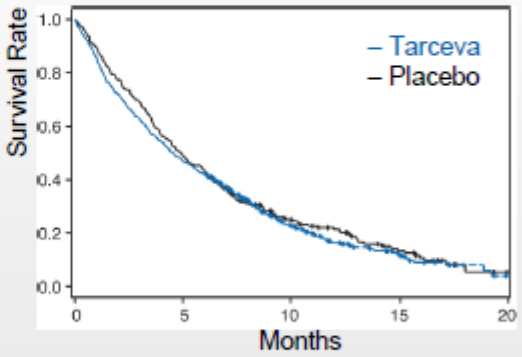
A survival benefit will not be seen in a randomized trial if benefit is restricted to 10-15% of the study population.

10% Mutation Rate



Patients with benefit -
Patients without benefit -

Representative Kaplan-Meier Curves



10000 Simulation Runs:
Median p-value = 0.36

A Bajamonde, G Fyfe, P Klein, & J Wang

Potentially active therapy could be missed

Option 1 : Enroll all patients.
Example: First Line MBC (median survival ~ 22 months)

Expected Benefit	Target Prevalence	Actual Benefit (All Patients)	Required Sample Size And Study Duration
↑ 5 months	100%	↑ 5 mos (22.7%)	1250 → 52 mos
(22.7%)	50%	↑ 2.5 mos (11.4%)	3500 → 108 mos
	25%	↑ 1.25 mos (5.7%)	11000 → 349 mos

* ***Easy to miss a potentially active new therapy as target prevalence decreases***

Kenneth Hilland

Enrollment of patients for early drug development trials

- **Restricted to patients with detected "driver mutation"**
- Predictive markers often based on preclinical studies, may not always re-capitulate the clinical setting (EGFR and gefitinib)
- Effect of drug in biomarker-negative population not detected (chemotherapy in HER2-low/breast cancer)
- In cases of infrequent driver mutations - Large number of patients needs to be screened (ALK translocation in NSCLC 4%)

Screening for ALK translocation in NSCLC patients

- **20 – 25 patients must be screened for <u>every</u> eligible patient**
- **Ethical questions - risks of sampling**
- **Reimbursment ?**

Enrollment of patients for early drug development trials

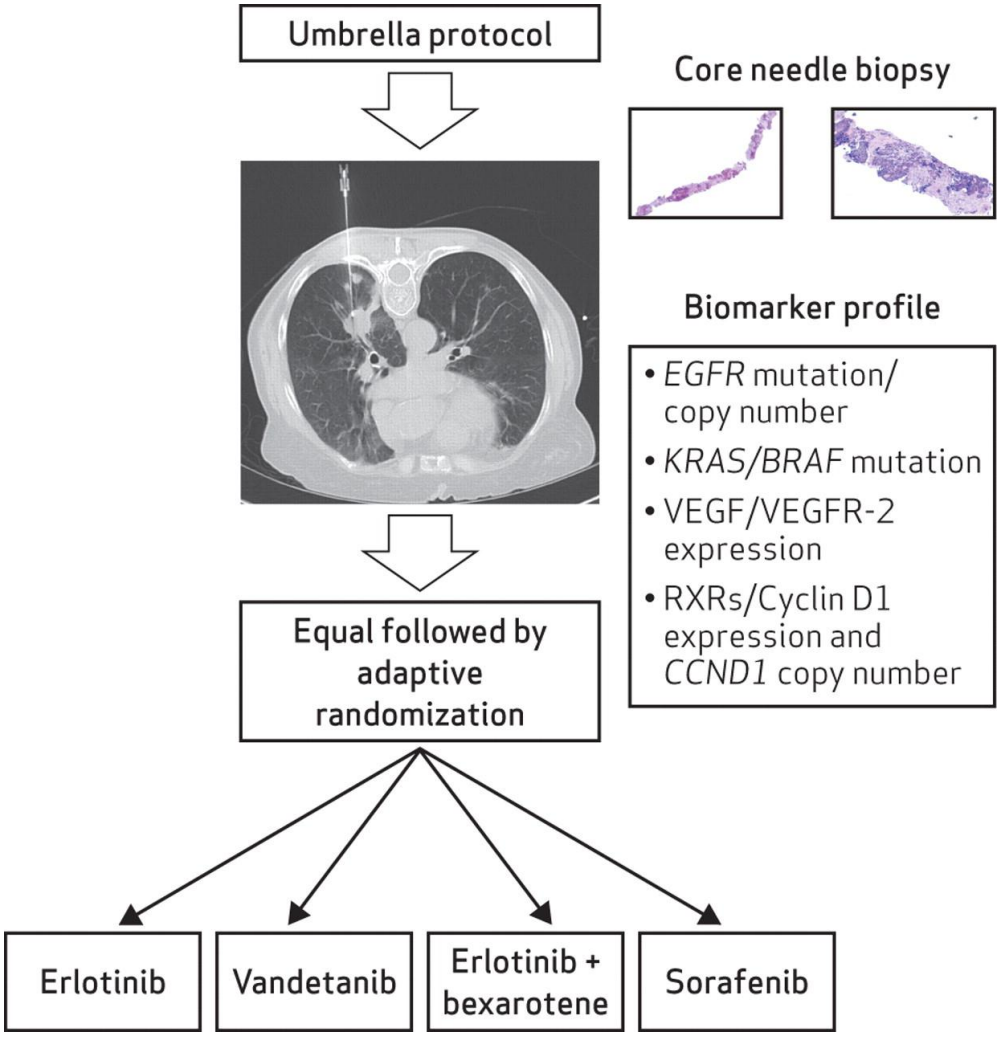
- Restricted to patients with detected "driver mutation", *limitations:*
  - Predictive markers often based on preclinical studies, may not re- capitulate the clinical setting (EGFR and IGFR1)
  - Effect of drug in biomarker-negative population not detected (chemotherapy in HER2-low breast cancer)
  - Large number of patients to be screened in cases of infrequent driver mutations (ALK translocation 4%)

- **BATTLE approach (Biomarker–integrated Approaches of Targeted Therapy for Lung cancer Elimination) - biopsy-driven adaptive trial program**

Biomarker–integrated Approaches of Targeted Therapy for Lung cancer Elimination
BATTLE

- Refractory NSCLC patients – mandated core biopsies
- Analysis of multiple biomarkers: EGFR, KRAS, BRAF mutations …
- 4 corresponding targeted therapies: erlotinib EGFR i), vandetanib dual EGFR/VEGFRi, bexacarotene + erlotinib targeting cyclin D1/XRX pathways and EGFR) and sorafenib RAF/VEGFR2PDGFR)

Schema for BATTLE study.



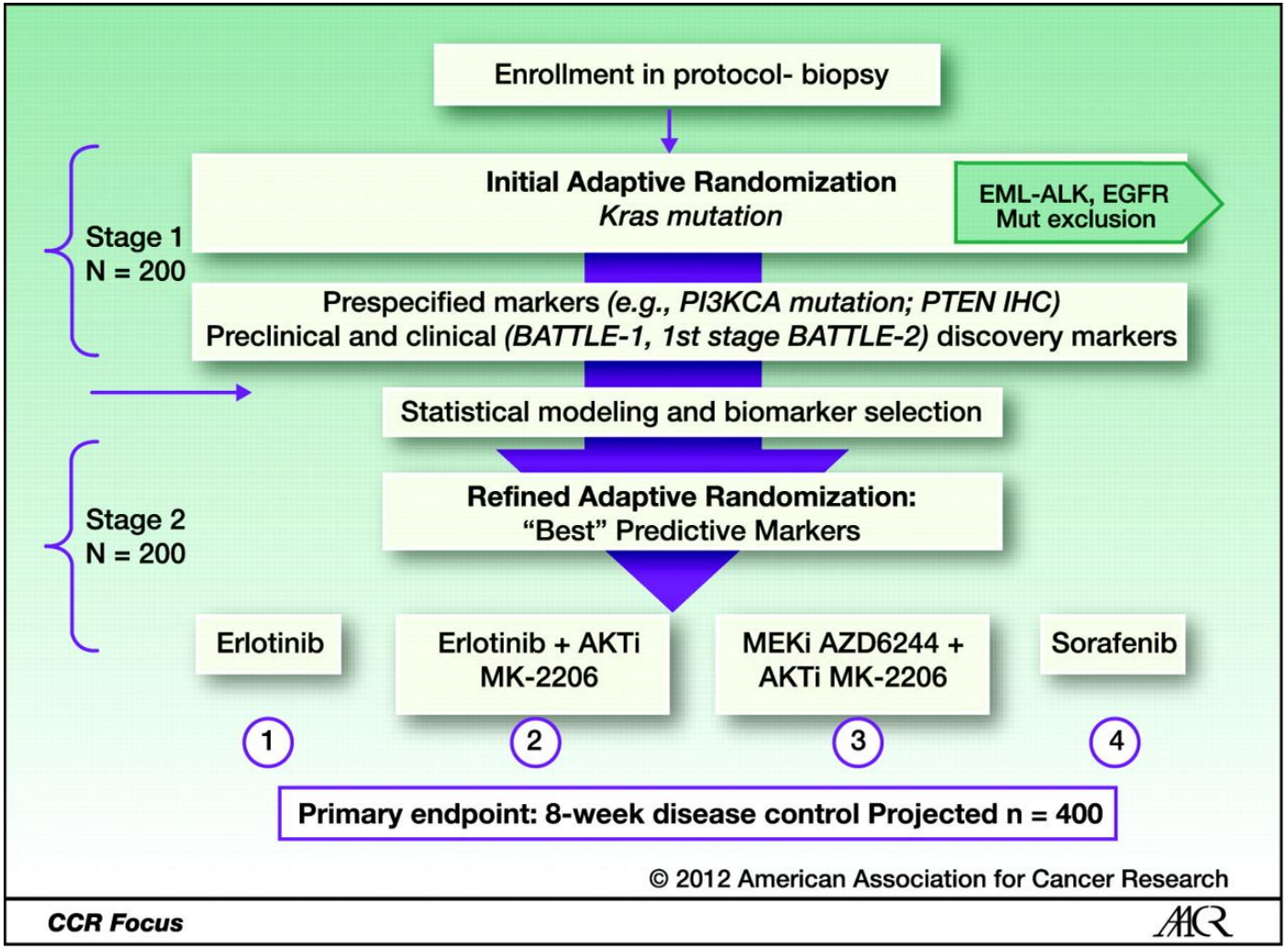
Kim E S et al. Cancer Discovery 2011;1:44-53

Biomarker–integrated Approaches of Targeted Therapy for Lung cancer Elimination

BATTLE approach

- **Advantages**
  - Each drug evaluated for efficacy in multiple markers subgroups
  - May lead to co-developing new therapeutics with matching diagnostics
- **Limitations**
  - Wrong biomarker may result in “no go”- i.e. similar to restricted enrollment
  - Biomarker cut off points
    - *Too high* - reduced ability to discriminate
    - *Too low* - dilute the effect of the treatment in biomarker-positive group

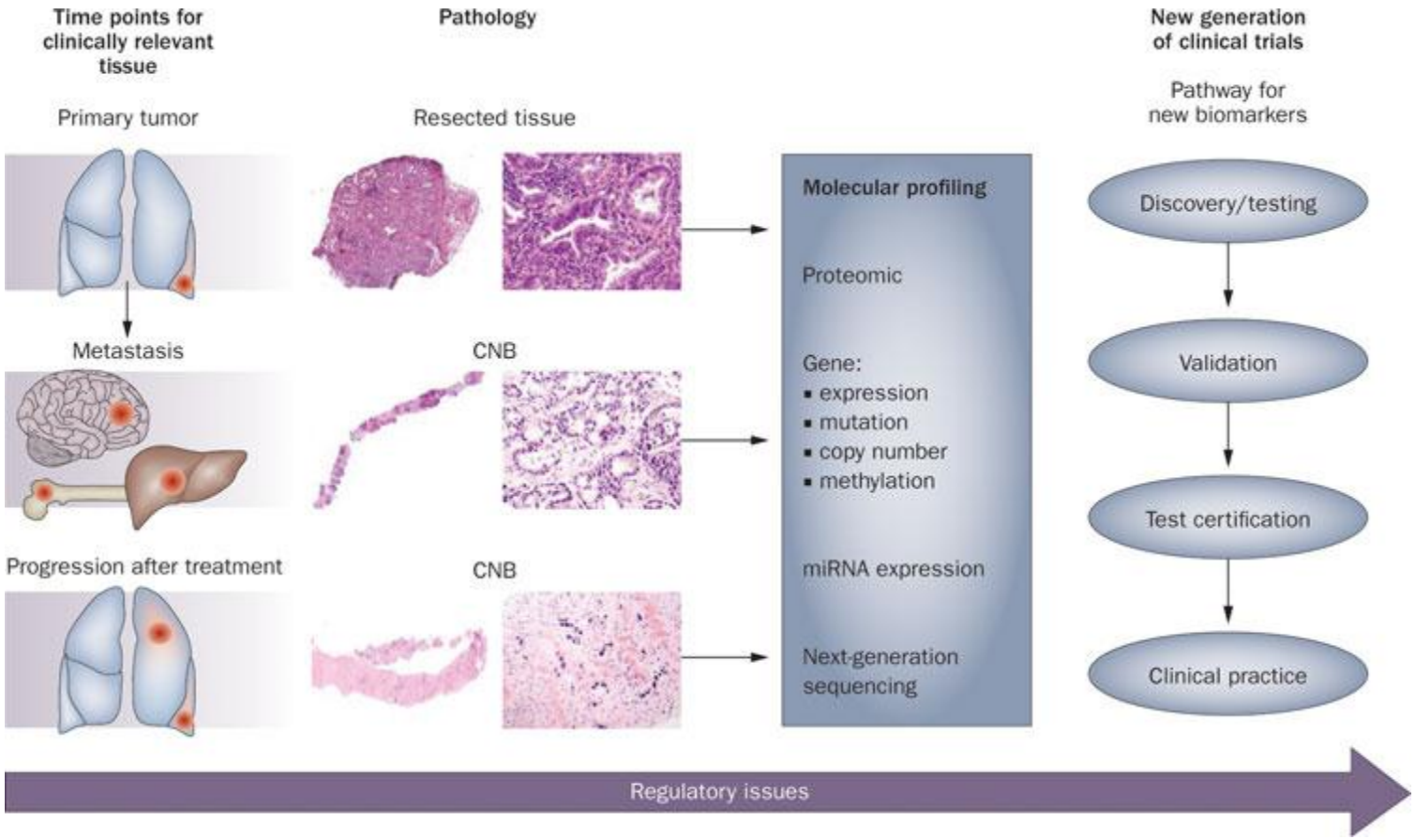
Battle-2 schema: advanced refractory NSCLC.



Berry D A et al. Clin Cancer Res 2012;18:638-644

Tumor tissue availability

Tissue availability for biomarker discovery



Wistuba, I. I. *et al.* (2011) Methodological and practical challenges for personalized cancer therapies *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2011.2

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Enrollment of patients for early drug development trials

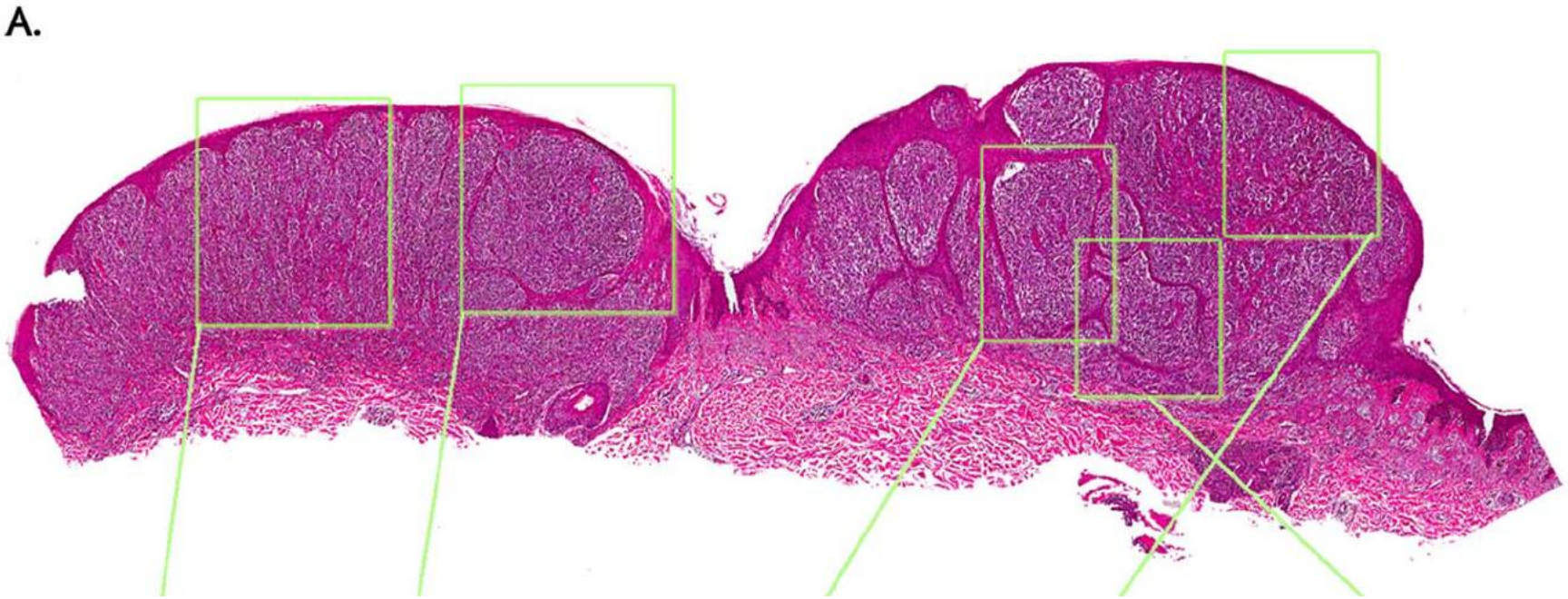
Challenges

- Accessability of tissue and blood for multiple sampling, mandatory at:
  - Baseline/pretreatment
  - Time of treatment
  - Time of stable disease
  - Time of refractory tumor
- Broad informed consent allowing acquisition of bio-specimens and subsequent tissue banking and later research
- Amount of available tumor tissue
  - Core biopsies
  - Fine Needle Aspiration Cytology (FNAC)
- Prescreening before inclusion in the trial
  - Central laboratory review, ensuring state of the art analyses, involves shipment of samples
  - Turnaround time between molecular analysis and trial initiation

Tumour heterogeneity

Intratumor - and intertumor heterogeneity

Intratumor heterogeneity of $BRAF_{V600}$ mutations in primary melanoma



Yancovitz M 2012

Intratumor heterogeneity of BRAF$_{V600}$ mutations in primary melanoma

Table 3. Detection of intratumor variation in BRAF mutation rates via laser capture microdissection.

Tumor	No. regions dissected	*BRAF*^{V600E} DNA percentages					Statistical variance (×100)	Presence of heterogeneity[1]
		Dissected region						
		1	2	3	4	5		
1	5	39.4%	42.8%	43.6%	48.1%	56.1%	0.419	Unlikely
2	4	7.4%	13.4%	16.3%	31.3%		1.038	Unlikely
3	3	6.7%	7.9%	29.0%			1.575	Unlikely
4	3	0.0%	16.8%	33.4%			2.787	Likely
5	4	0.0%	21.9%	32.5%	39.7%		2.991	Likely
6	4	9.7%	42.5%	52.9%	53.6%		4.247	Marked
7	4	0.0%	0.0%	22.2%	48.3%		5.286	Marked
8	4	0.0%	0.0%	0.0%	48.9%		5.969	Marked
9	5	4.9%	13.9%	18.8%	77.7%	81.2%	13.691	Marked

[1]Qualitative judgment based on variance values, see text for full explanation.

doi:10.1371/journal.pone.0029336.t003

SNaPshot assay

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SNaPshot assay

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BRAF mutations concordance between primary and metastases

Table 4. BRAF mutation concordance between primary and metastatic specimens using MS-PCR.

Patient	Primary tumor	Metastatic tumor
1	Wild Type	Mutant
2	Wild Type	Mutant
3	Wild Type	Mutant
4	Wild Type	Mutant
5	Wild Type	Mutant
6	Wild Type	Mutant
7	Mutant	Mutant
8	Mutant	Mutant
9	Mutant	Mutant
10	Mutant	Mutant
11	Mutant	Mutant
12	Mutant	Mutant
13	Mutant	Mutant
14	Mutant	Mutant
15	Mutant	Mutant
16	Mutant	Mutant
17	Mutant	Wild Type
18	Mutant	Wild Type

doi:10.1371/journal.pone.0029336.t004

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Patient	Primary tumor	Metastatic tumor
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3	Wild Type	Mutant
4	Wild Type	Mutant
5	Wild Type	Mutant
6	Wild Type	Mutant
7	Mutant	Mutant
8	Mutant	Mutant
9	Mutant	Mutant
10	Mutant	Mutant
11	Mutant	Mutant
12	Mutant	Mutant
13	Mutant	Mutant
14	Mutant	Mutant
15	Mutant	Mutant
16	Mutant	Mutant
17	Mutant	Wild Type
18	Mutant	Wild Type

doi:10.1371/journal.pone.0029336.t004

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BRAF mutations concordance between metastases

Table 5. BRAF mutation concordance between multiple metastatic specimens using MS-PCR.

Patient	Metastasis 1	Metastasis 2
19	Wild Type	Wild Type
9	Wild Type	Mutant
20	Wild Type	Mutant
21	Wild Type	Mutant
22	Wild Type	Mutant
23	Wild Type	Mutant*
2	Mutant	Mutant
6	Mutant	Mutant
14	Mutant	Mutant
15	Mutant	Mutant
24	Mutant	Mutant
25	Mutant	Mutant
26	Mutant	Mutant
27	Mutant	Mutant
28	Mutant	Mutant
29	Mutant	Mutant
30	Mutant	Mutant
31	Mutant	Mutant*
32	Mutant	Mutant

*patient had a third metastasis which was mutant by MS-PCR.
doi:10.1371/journal.pone.0029336.t005

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Targeting driver mutations

Target	Disease	Agent	Regimen	Response rate (%)
Mutant EGFR	NSCLC	Gefitinib, erlotinib	Monotherapy	70-90
EML4-ALK	NSCLC	Crizotinib	Monotherapy	70-90
BCR/ABL	CML	Imatinib	Monotherapy	70-90
c-KIT	GIST	Imatinib	Monotherapy	45
Mutant BRAF	Melanoma	Vemurafenib	Monotherapy	50

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; BCR-ABL, breakpoint cluster region-abelson; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; BRAF, B-type Raf kinase.

Saijo et al, Cancer Res Treat.2012,

Targeting driver mutations

- **Subsets of patients with mutation still fail to respond**
- **Often transient response**
- **Resistance develop – heterogeneity, activation of compensatory pathways, new mutations**
- **Responses often shortlived**
- **Prolong PFS and some prolongs OS**
- **Cures are rare**

- **Combination of targeted therapies**
- **Chemotherapy still the backbone of cancer therapy in a number of solid cancers**