Incorporation of Biomarkers and Biological Correlative Studies into Early Phase Clinical Trials

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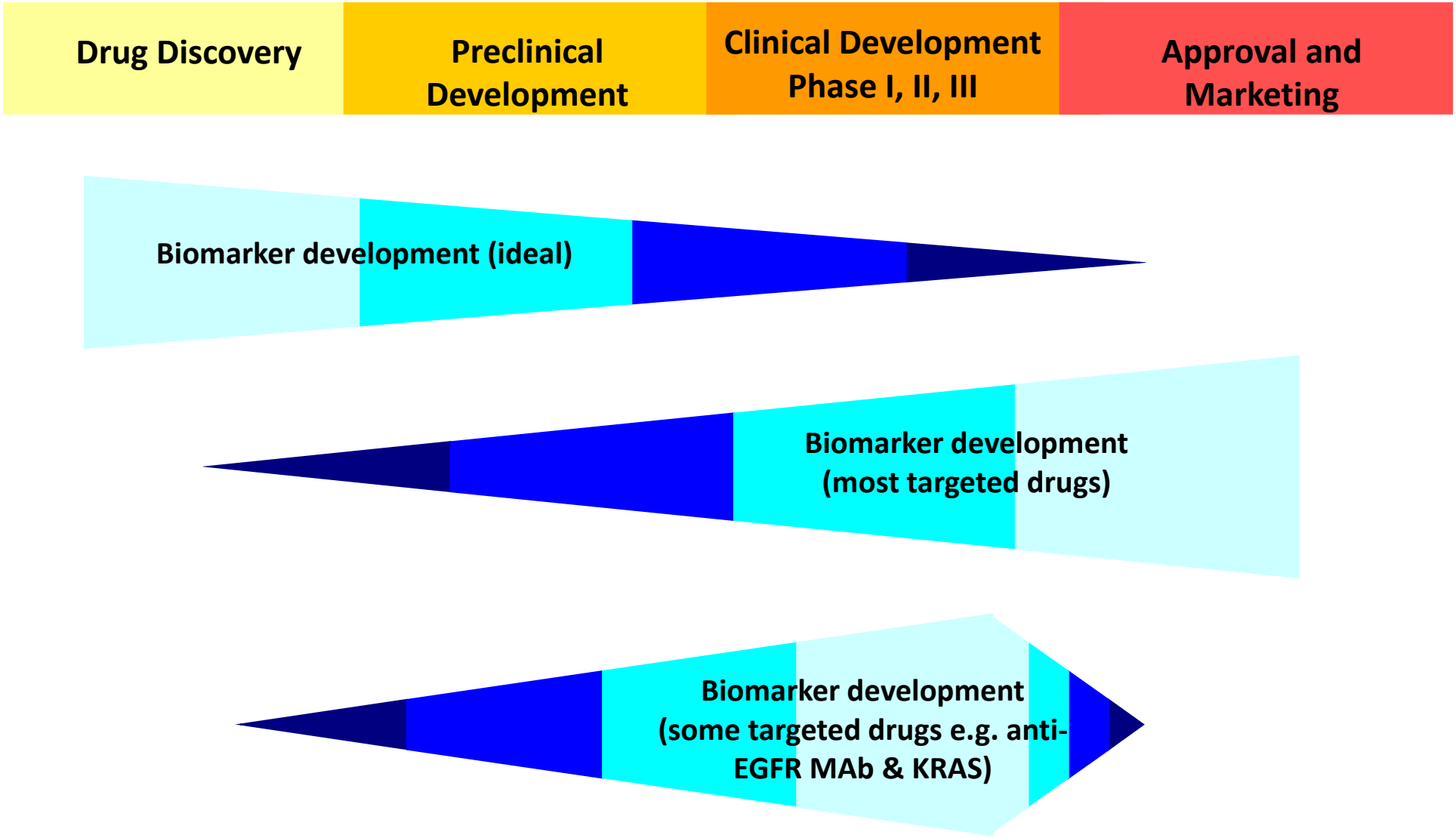
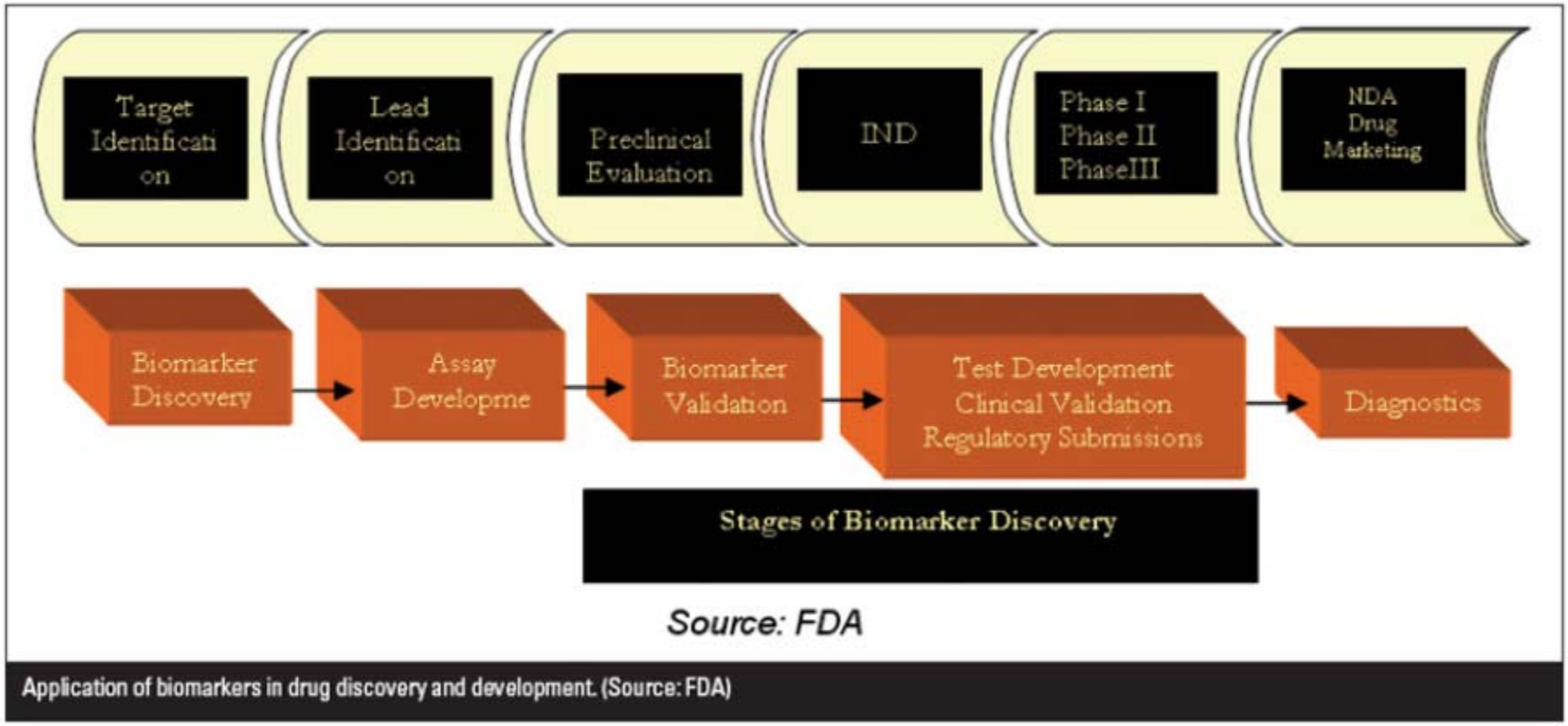
Drug and Biomarker Developments



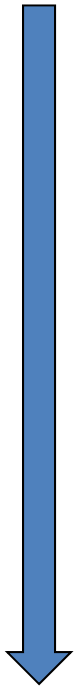
Stages of Biomarker Discovery and Development



Application of biomarkers in drug discovery and development. (Source: FDA)

What makes an omics test clinically useful and how do we get there?

Discovery



Clinical validity:
The test result shows an association with a clinical outcome of interest.

Analytical validity:
The test's performance is established to be accurate, reliable, and reproducible.

Clinical utility:
Use of the test results in a favorable benefit to risk ratio for the patient

Target Assessment

- **What is the status of the target in tissues (tumor or surrogate) pre-treatment?**
  - **Present vs absent**
  - **Activated vs inhibited**
  - **Gene amplified vs not**
  - **Wild-type vs mutated**
  - **What is the cut-off (for IHC)**

Target Assessment

- **What happens to the target in tissues (tumor or surrogate) during treatment?**
  - **If there is a "change" →**
    - **How can you validly measure and quantitate the "change"?**
    - **Is the assay reproducible?**
    - **When do you measure the "change"?**
    - **How do you report the "change"?**
    - **Does the "change" in surrogate tissues reflect same "change" in tumor tissues?**
    - **Does the "change" correlate with clinical outcome?**

The Key Players

- **Pathologists and translational scientists**
- **Lab technicians**
- **Correlative studies coordinators**
- **Interventional radiologists**
- **Biostatisticians**
- **Bioinformatics experts**
- **Clinical trial nurses and coordinators**
- **Clinical investigators**
- **Patients – who give informed consent**

Types of Biomarkers

- **Prognostic Biomarkers provide information about the patient's overall cancer outcome regardless of therapy**

- **Examples: ECOG status in lung cancer, LDH in non-Hodgkin's lymphoma, cytogenetics in AML**

Types of Biomarkers

- **Predictive Biomakers provide information regarding the probability of benefit or toxicity from a specific therapy**

- **Examples: HER2 overexpression in breast cancer (trastuzumab), *K-RAS* mutational status in colorectal cancer (anti-EGFR antibodies), ALK translocation in NSCLC (ALK inhibitors)**

Types of Biomarkers

- **Pharmacokinetic (PK): provide information about the absorption, distribution, metabolism and elimination (ADME) of the drug and/or its metabolites in the patient and/or tumor**

- **Examples: Cmax (peak concentration), Cl (clearance), t1/2 (half-life), AUC (exposure = area under concentration x time curve)**

Types of Biomarkers

- **Pharmacodynamic (PD): provide information about the effect of a therapeutic intervention on the patient and/or tumor**

- **Examples: neutrophil count, skin rash, tumor expression of a downstream marker (e.g. pERK post administration of a MEK inhibitor), decrease in FDG uptake on PET scan post treatment**

Biomarkers: regulatory definitions

Integral Markers

- **Used for patient selection or treatment stratification**
- **Used to determine patient treatment**
- **Performed in CLIA environment**
- **e.g. mutated BRaf (V600) with a targeted agent (dabrafinib, vemurafinib)**

Integrated Markers

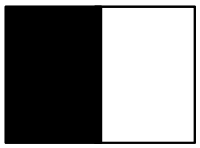
- **Used for patient description**
- **Provide evidence of pathway activation**
- **CLIA ready**
- **e.g. study of biomarkers for Ras/Raf/MEK signaling**

Exploratory Markers

- **Descriptive biomarkers, hypothesis generation**
- **Not validated**
- **e.g. study of cross talk between Ras/Raf/MEK and PI3K signaling cascades**

Courtesy of Percy Ivy, CTEP/NCI

“Companion” vs “Complementary” Diagnostic



- **Companion Diagnostic:**
  - “Provides information that is essential for the safe and effective use of a corresponding drug or biological product”
  - e.g. PD-L1 IHC 22C3 for pembrolizumab in NSCLC

- **Complementary Diagnostic:**
  - ”Not required but aids risk/benefit assessment fro drug use in individual patients”
  - e.g. PD-L1 IHC 28-8 for nivolumab in NSCLC and melanoma, PD-L1 IHC SP142 for atezolizumab in bladder cancer

List of FDA Cleared or Approved Companion Diagnostic Devices

Drug Name	Device Trade Name
Trastuzumab Pertuzumab	**HER2** FISH PharmDx Kit
	HERCEPTEST
Trastuzumab	INSITE **HER-2/NEU** KIT
	Bond Oracle **Her2** IHC System
	SPOT-LIGHT **HER2** CISH Kit
	HER2 CISH PharmDx Kit
	INFORM **HER2** DUAL ISH DNA Probe Cocktail
	PATHVYSION **HER2** DNA Probe Kit
	PATHWAY **ANTI-HER2/NEU** (4B5) Rabbit Monoclonal Primary Antibody
Olaparib	**BRACA**nalysis CDx™
Imatinib	DAKO **C-KIT** PharmDx

Drug Name	Device Trade Name
Gefitinib	Therascreen® **EGFR** RGQ PCR Kit
Afatinib	
Erlotinib	cobas **EGFR** Mutation Test
Crizotinib	VENTANA **ALK** (D5F3) CDx Assay
	VYSIS **ALK** Break Apart FISH Probe Kit
Cetuximab and Panitumumab	cobas® **KRAS** Mutation Test
Vemurafenib	COBAS 4800 **BRAF V600** Mutation Test
Trametinib Dabrafenib	THxID™ **BRAF** Kit

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

Comparison of PD-L1 Assays

		pembrolizumab (Keytruda, MK-3475)	nivolumab (Opdivo, BMS-936558)	durvalumab (MEDI-4736)	atezolizumab (MPDL3280A, RG7446)
Drug	Manufacturer	Merck Sharp & Dohme	Bristol-Myers-Squibb	MedImmune/ AstraZeneca	Genentech/ Roche
	mAb	humanized IgG4	human IgG4	human Fc-modified IgG1	human Fc-modified IgG1
	Target	PD-1	PD-1	PD-L1	PD-L1
	FDA approved	Melanoma, NSCLC, SCCHN	Melanoma, NSCLC, renal, HD	Bladder*	Bladder, NSCLC*
Companion Diagnostic Assay PD-L1+	IHC assay developer	Dako	Dako	Ventana	Ventana
	Antibody clone	22C3 mouse	28-8 rabbit	SP263 rabbit	SP142
	Expression on	TCs and stroma	TCs	TCs	TICs and TCs
	Cut-off	▪ Melanoma, Bladder, NSCLC: ≥1% TC (or any tumor stroma cell)	▪ NSCLC: ≥1-5% TC ▪ Renal: ≥5% TC	▪ NSCLC, SCCHN: ≥25% TC	▪ Bladder, NSCLC, Breast: IHC 2+ ≥5%-<10% TC or TIC or IHC 3+ ≥10% TC or TIC

* FDA Breakthrough Designation Therapy status

TCs = tumor cells; TIC= tumor-infiltrating immune cells; n/a, not applicable

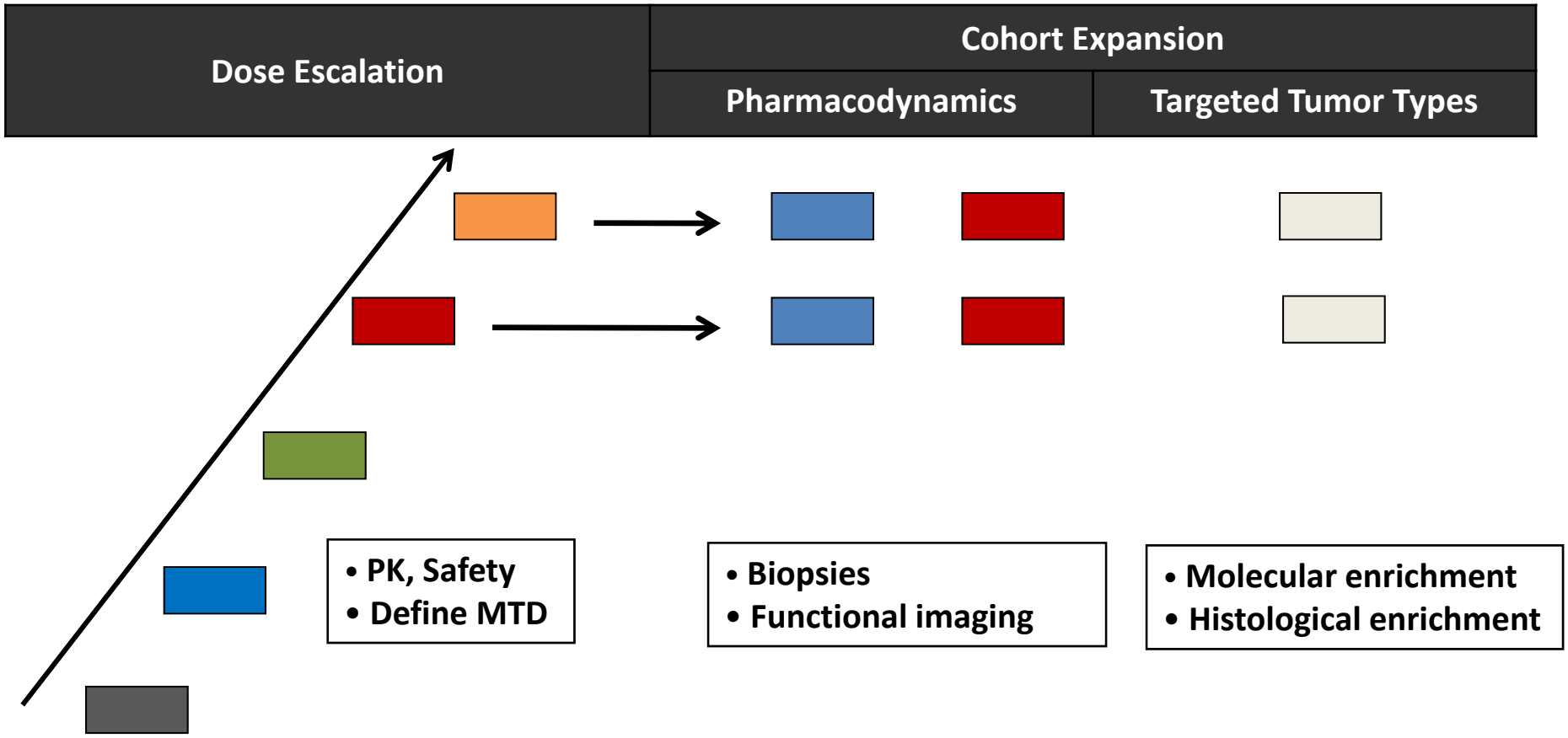
Hansen, Siu JAMA Oncology, 2016

PD-L1 Assays

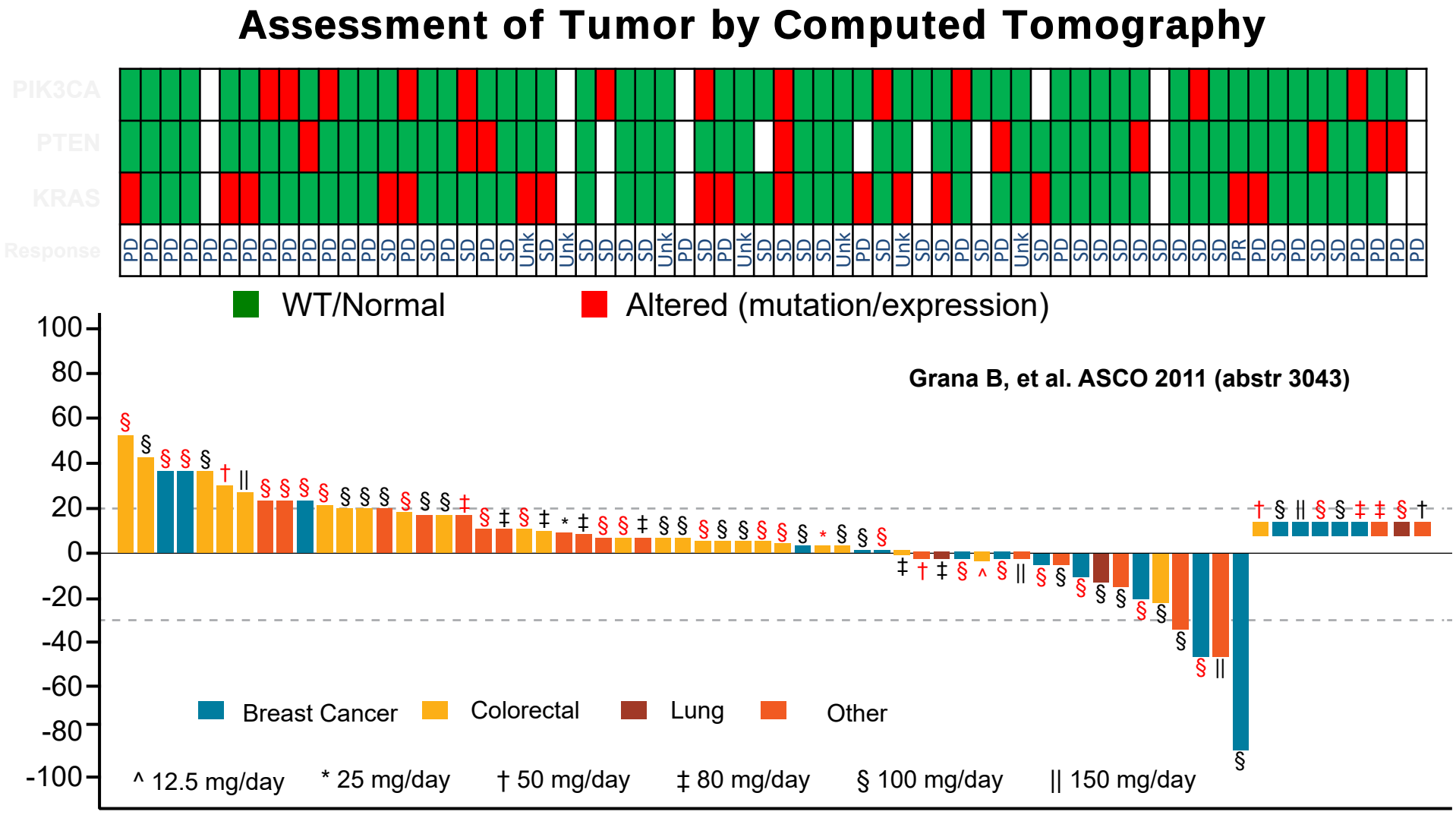
Challenges:

- **Different antibodies being used**
- **Variable definitions for biomarker positivity (which cells/tissue components, different staining thresholds used as cut-offs)**
- **Lack of standardization and harmonization**
- **Challenging to make comparisons across trials that used different assays with different definitions**

Phase I Study Design – Unselected Patients in Dose Escalation followed by Specific Expansion Cohorts

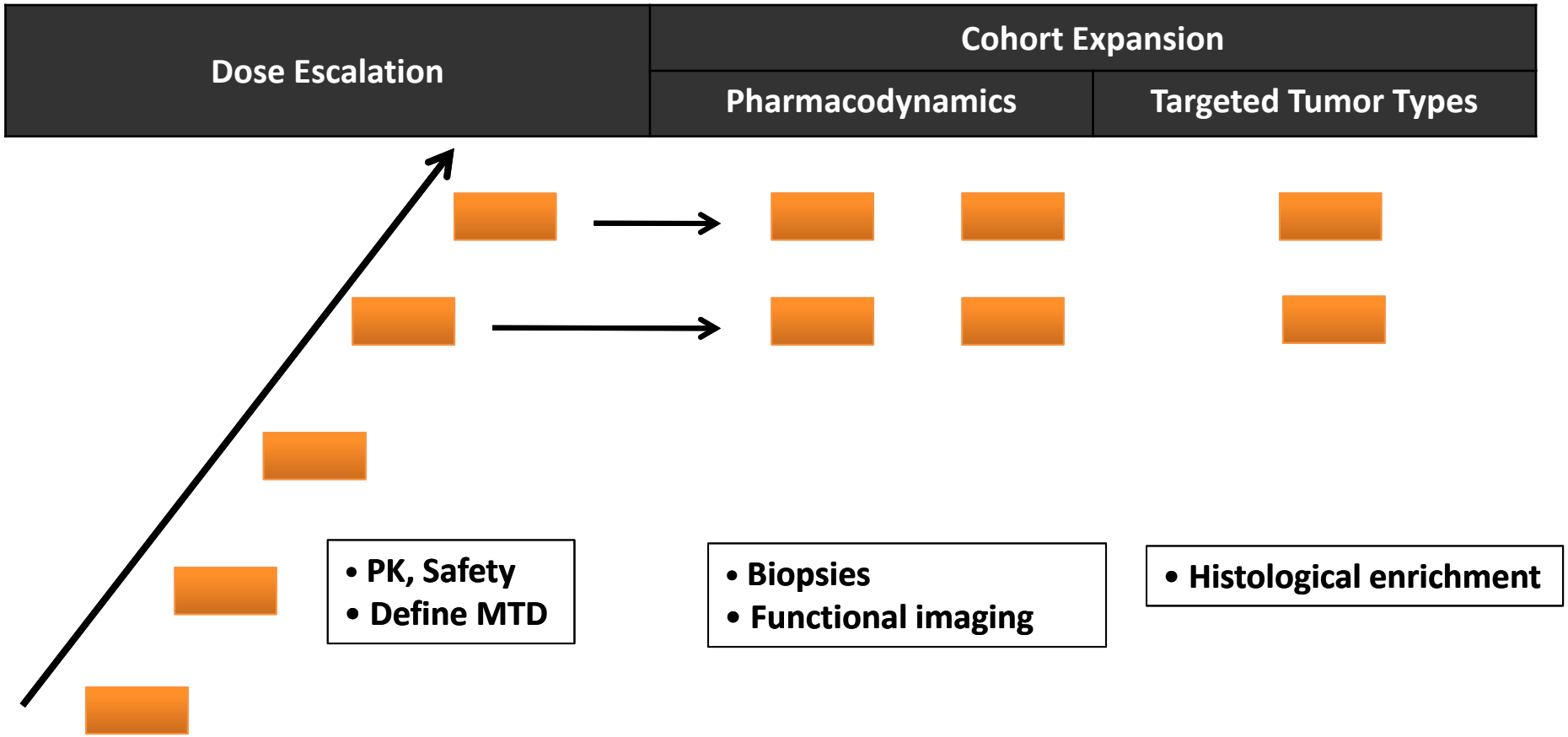


Searching for Target Populations (BKM120)

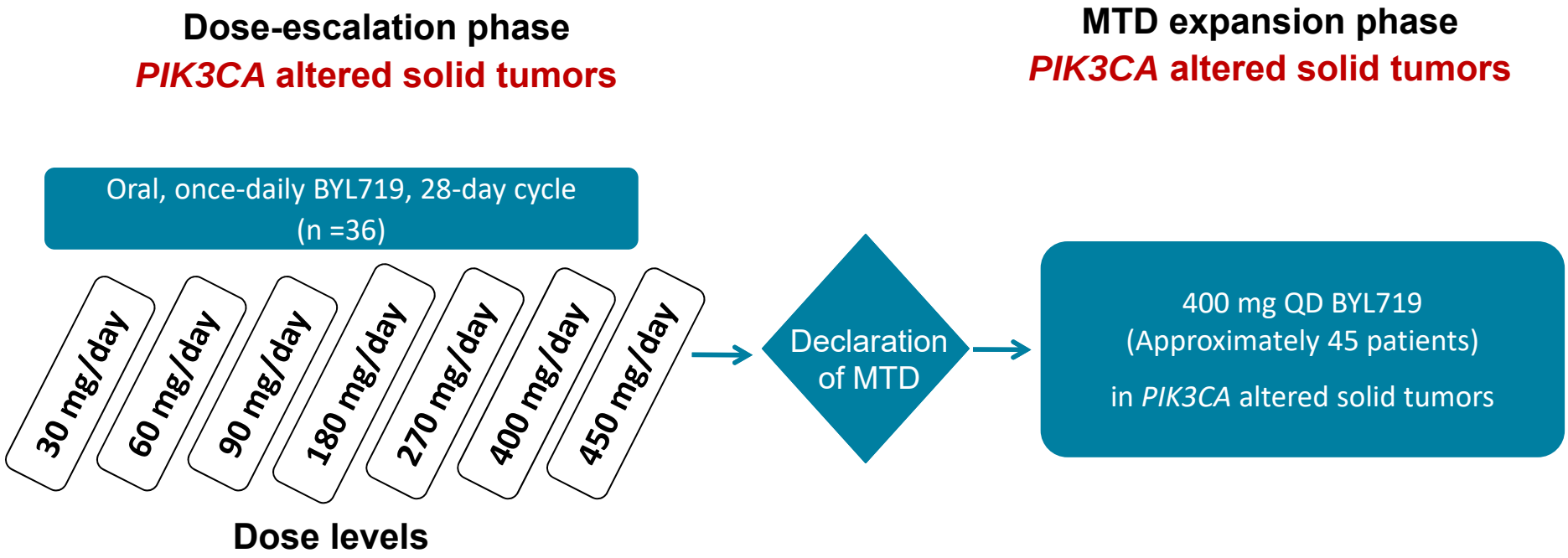


Symbols in red indicate activated PI3K pathway, defined as at least one of the following: PIK3CA mutation or amplification, PTEN mutation or PTEN null or low expression.
PD, disease progression; SD, stable disease; PR, partial response; Unk, unknown.

Phase I Study Design – Only Molecularly Enriched Patients



Phase I Trial of BYL719 (PI3K alpha inhibitor): Study design



Juric et al. AACR 2012

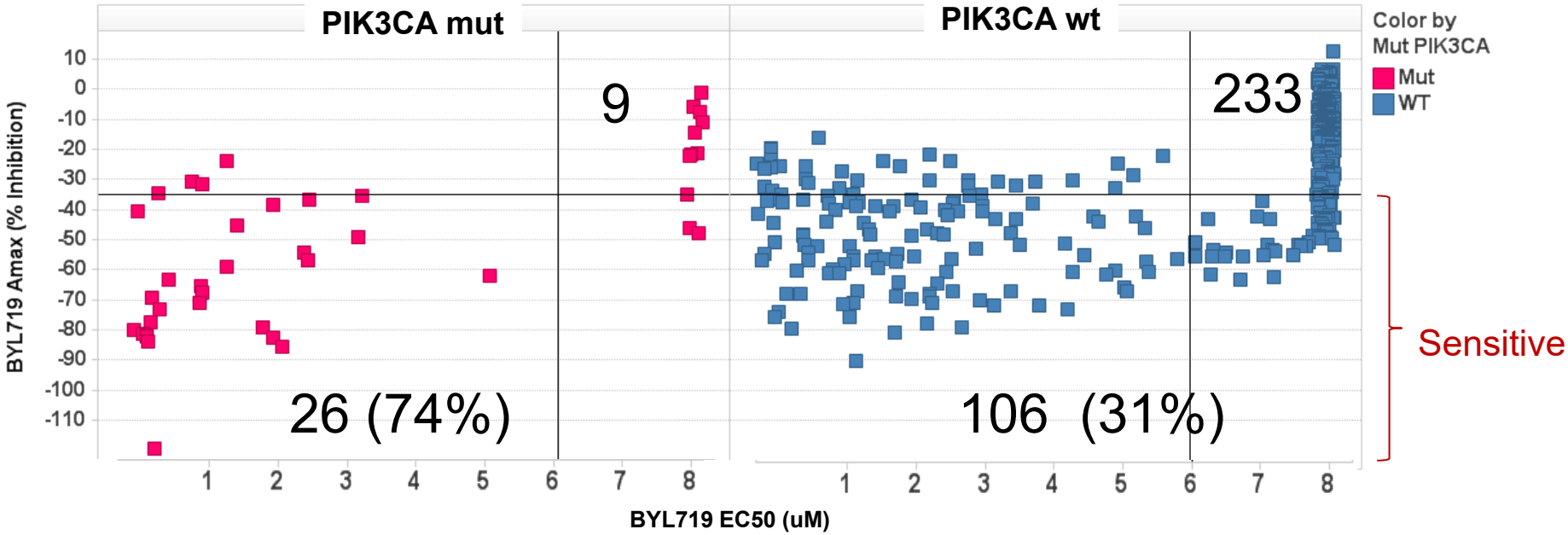
BYL719 : A Selective Inhibitor of PI3Kα

Biochemical IC_{50} (nM)	BYL719
Alpha wt	4.6
Alpha E545K	4
Alpha H1047R	5
Beta	1‘156
Delta	290
Gamma	250
Vps34	>9‘100
mTOR	>9‘100

Cellular IC_{50} (nM)	BYL719
Alpha	74
Beta	2‘249
Delta	1‘213
mTOR	>10‘000
pP53Ser15	>30‘000
pATMSer1981	>10‘000

PIK3CA mutation is associated with sensitivity to BYL719

Compound profiling results for BYL719

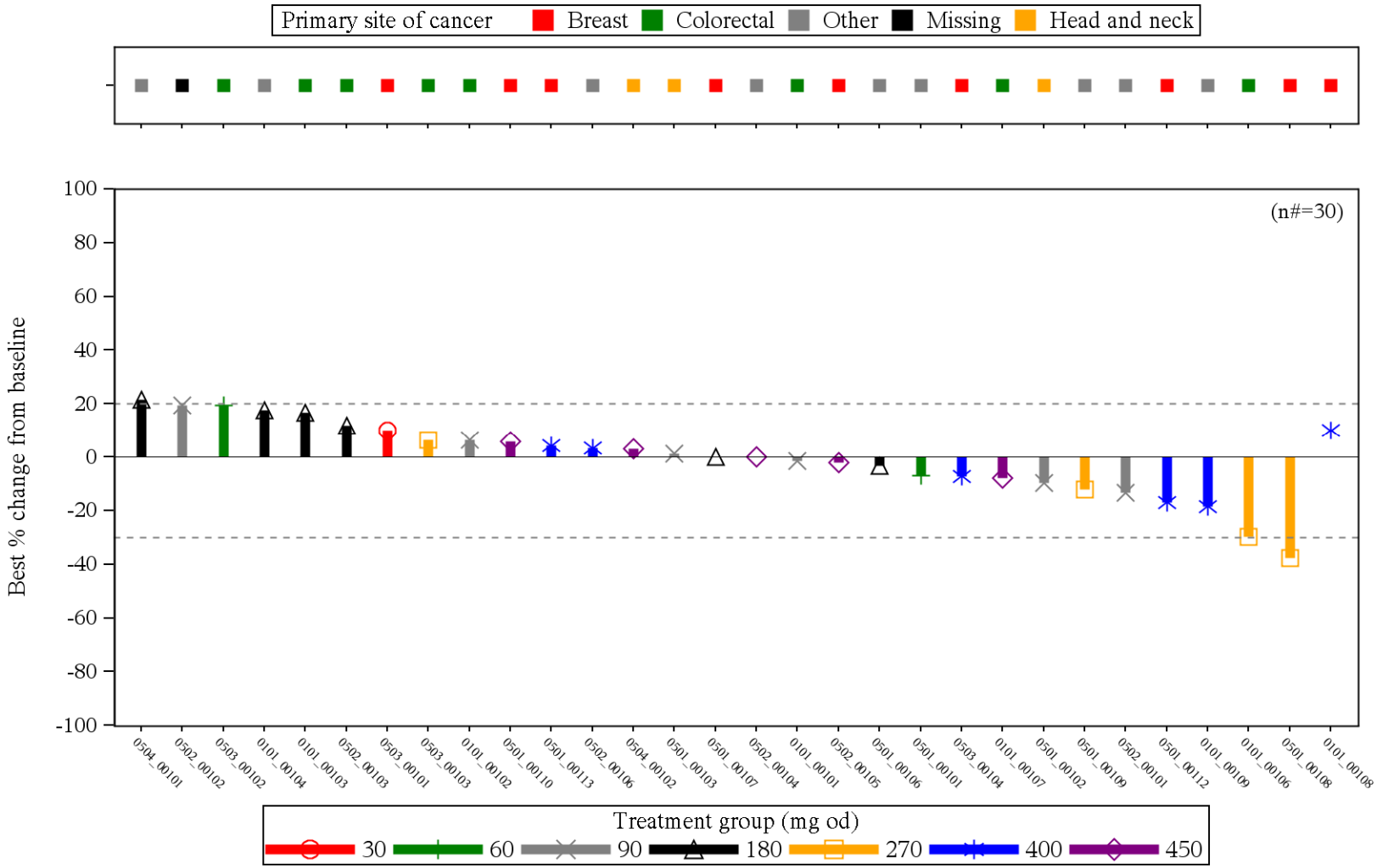


P=1x10^{-6} by Fisher's Exact Test (two tailed)

- *PIK3CA* mutation is associated with sensitivity across different indications
- *PIK3CA or* ERBB2 amplification are associated with BYL719 sensitivity as well (p=0.001)

Preliminary Efficacy

Best percentage change from baseline in sum of longest diameters



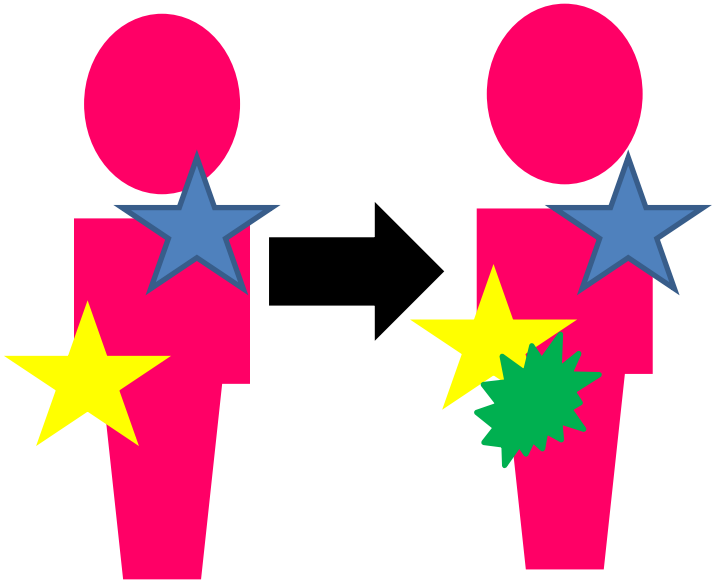
Number of Patients Needed to be Screened for 70 Marker + Patients

Prevalence of Marker	Expected Number to be Screened
0.05	1394
0.1	697
0.2	349
0.3	232
0.4	174
0.5	139
0.6	116
0.7	100
0.8	87
1	70

Sleijfer S, Bogaerts J, Siu LL. J Clin Oncol 2013

Interpatient Heterogeneity versus Intratumor Heterogeneity

Interpatient Heterogeneity



Intratumor Heterogeneity (geographic/spatial heterogeneity and temporal heterogeneity)

Conclusions

- Incorporation of biomarkers into clinical trials may serve different purposes:
  - Selecting the ‘most suitable’ patients to go on
  - Proof of pharmacodynamic effects
  - Understand mechanisms of resistance
  - Discovery and hypothesis generation

- Challenges: Biological, technical, regulatory