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Backups Session 4

Only In Few Cases Have Subgroups Been Defined in Advance With Formal Analysis

Imatinib and Kit + GIST (prospective, preapproval)

Dasatinib and PH + ALL (prospective, preapproval)

Maraviroc and CCR5 + (tropic) HIV-1 (prospective, preapproval)

Tetrabenazine and 2D6 dosing (prospective, preapproval)

Trastuzumab and HER2+ Br Ca ("prospective", preapproval)

Nilotinib and UGT hyperbilirubin (retrospective, preapproval)

Abacavir and HLAB*5701 HAS (prospective, post-approval)

Clopidogrel and 2C19 "resistance" (prospective, post-approval)

Cetuximab / Panitumamab and KRAS (retrospective, post-approval)

Carbamazepine and HLAB*1502 SJS (retrospective, post-approval)

Warfarin and 2C9/VKORC1 dosing (retrospective, post-approval)

L. Lesko, FDA

Timelines for the development of an Dx assay (Immunoassay, existing platform/instrument)

Phase	Activity	Milestone	Time (months)
1	Initial R&D	Lab prototype	12–24
2	Technical review; design concept and specifications	Development plan	6–10
3	Test to specifications	Meet performance specifications	8–10
4	Final design and testing	Manufacturing prototype	6–8
5	Clinical trials	PMA or 510(k) approval	6–12
6	Transfer to manufacturing	Final product	4–8
7	Full production	Product release	4–6
Total, 2–7			34–54

[a]LOE = Level of Effort
[b]The higher estimate range reflects the requirements for a new product, PMA submission.

Assessable Tumor Samples in Recent NSCLC Trials

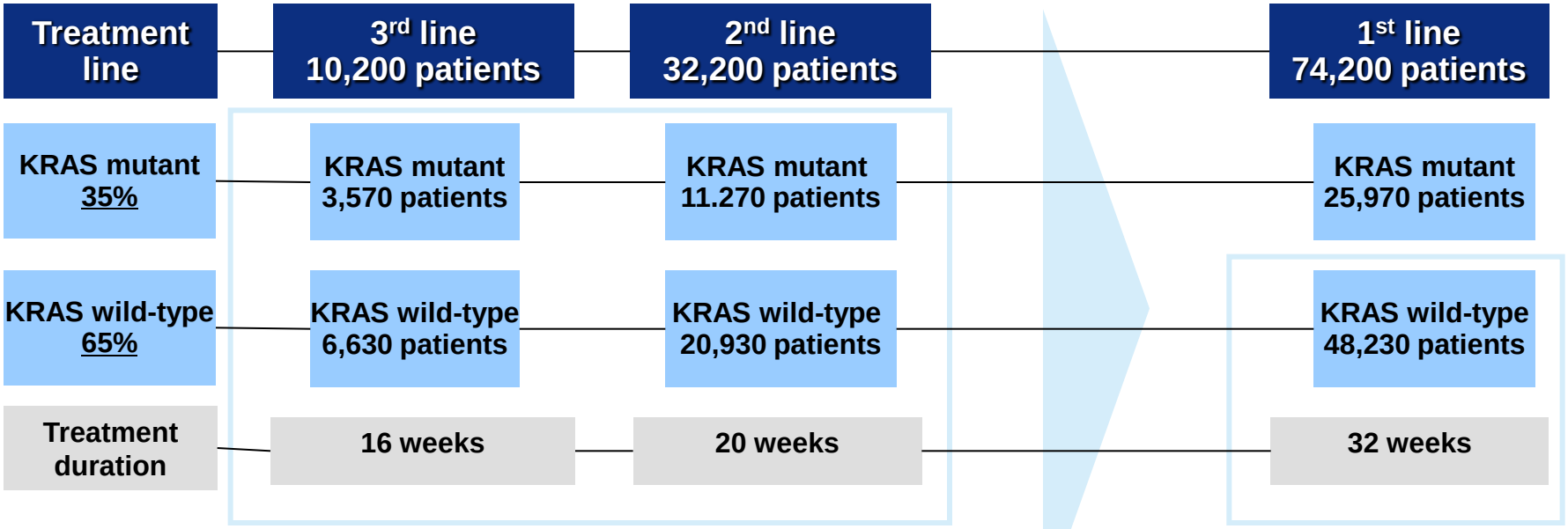
Reference	ITT population	Assessable tumor samples	Analyzed samples		
			EGFR GCN	EGFR genotype	KRAS genotype
Hirsch 2006 ISEL	1692 (100%)	460 (27%)	370 (22%)	215 (13%)	152 (9%)
Zhu 2008 BR.21	731 (100%)	230 (31%) 240 (33%)	159(22%)	204 (28%)	206 (28%)
Bell 2005 IDEAL 1/2 INTACT ½	2555 (100%)	643 (25%)	543 (21%)	391 (15%)	–
Eberhard 2005, Hirsch 2006 TRIBUTE	1059 (100%)	274 (26%)	245 (23%)	228 (22%)	264 (25%)
Mok 2008 IPASS	1217 (100%)	?	406 (33%)	437 (36%)	–
Pirker 2009 FLEX	**1125 (100%)**	**580 (52%)**	**279 (25%)**	**436 (39%)**	**395 (35%)**
Pirker 2009 FLEX	**1125 (100%)**	**1123 (99.8%)**	**EGFR expression by IHC**		

Availability of specimens is the limiting factor for biomarker research !

Erbitux® (Cetuximab) FDA Approved Indications

		Clinical Setting	Tumor Selection Criteria
Colorectal Cancer			
Erbitux with Irinotecan	2004	Patients refractory to irinotecan containing therapy	EGFR-expressing
Erbitux as Single agent	2004	Patients intolerant of irinotecan containing therapy	EGFR-expressing
Erbitux as Single agent	2007	After failure of both irinotecan and oxaliplatin containing therapy	EGFR-expressing
Head & Neck Cancer			
Erbitux with Radiation Therapy	2006	Locally or regionally advanced SCCHN	None
Erbitux as Single agent	2006	Recurrent / metastatic SCCHN after failure of platinum based therapy	None

Extension of mCRC Indication to 1st Line with KRAS Stratification



Treating 2nd and 3rd line, both KRAS wild-type and mutant: Market = 807,200 weeks treatment

Treating 1st line, KRAS wild-type only: Market = 1,543,360 weeks treatment

Bigger market enabled by stratification
Higher penetration due to improved efficacy

Vemurafenib for advanced melanoma
The regulatory path

- At an end-of-phase 1 meeting in 5/09, the sponsor proposed to develop the drug in patients with advanced melanoma with the BRAFV600E mutation and to use a response rate of ≥30% or PFS (HR 0.5 and an improvement in medial PFS of 2 months) as regulatory endpoints for accelerated approval.
- The proposal was based on tumor responses in 11 of 16 patients (69%) with advanced melanoma positive for the BRAFV600E mutation in the phase 1 trial.
- At that meeting the FDA recommended that the sponsor conduct a randomized phase 3 trial with overall survival as the primary endpoint but expressed willingness to discuss use of their single-arm phase 1 and 2 trials to support accelerated approval once they had more data suggesting impressive activity.
- At that meeting issues regarding the development of a companion diagnostic to detect the BRAFV600E mutation were discussed.