What is the feature of an optimal new agent?
Selective target versus multi-targeted versus combination

Jan Schellens MD PhD & Serena Marchetti MD PhD

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NKI-AVL
The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Disclosure

- Research grants to NKI from:
  - Roche, Novartis, GSK, Eisai
- Investigator on ~30 phase I, II studies
- Member Dutch Medicines Evaluation Board
- Member SAG-Oncology EMA

Targeted Therapies since EMA registration of rituximab in 1998

Selective agents

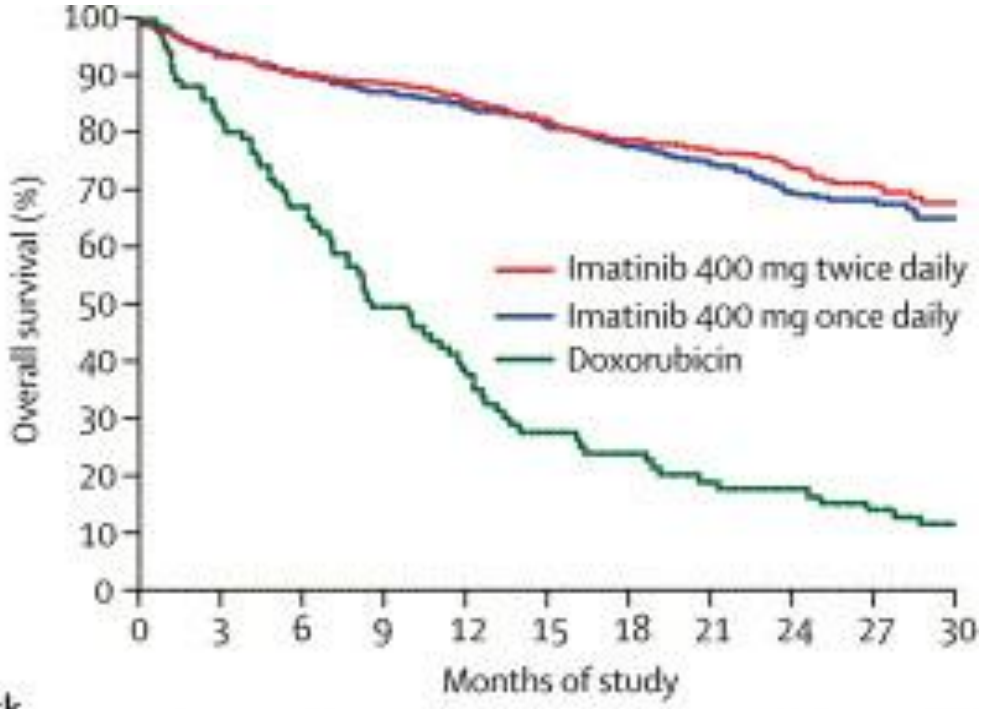
Drug	Main target
Rituximab	CD20
Trastuzumab	Her2
Alemtuzumab	CD52
Cetuximab	EGFR
Bevacizumab	VEGF
Panitumumab	EGFR
Ofatumumab	CD20
Brentuzumab vedotin	CD30-Ab drug conjugate
Erlotinib, gefitinib	EGFR
Vemurafenib	BRAF V600E
Crizotinib	ALK

Multi-targeted agents

Drug	Main target
Imatinib	BCR-ABL, CD117, PDGFR
Sunitinib	VEGFR1-3, PDGFR, CD117
Sorafenib	VEGFR2-3, C-, BRAF, CD117, FLT-3, PDGFR
Dasatinib	BCR-ABL, SRC
Temsirolimus	mTOR, immunosuppressive
Nilotinib	BCR-ABL, PDGFR
Lapatinib	EGFR, Her2
Everolimus	mTOR, immunosuppressive
Pazopanib	VEGFR1-3, multikinase,
Vandetanib	RET, VEGFR2, EGFR
Axitinib	VEGFR1-3, PDGFR, CD117

GIST survival: imatinib vs doxorubicin

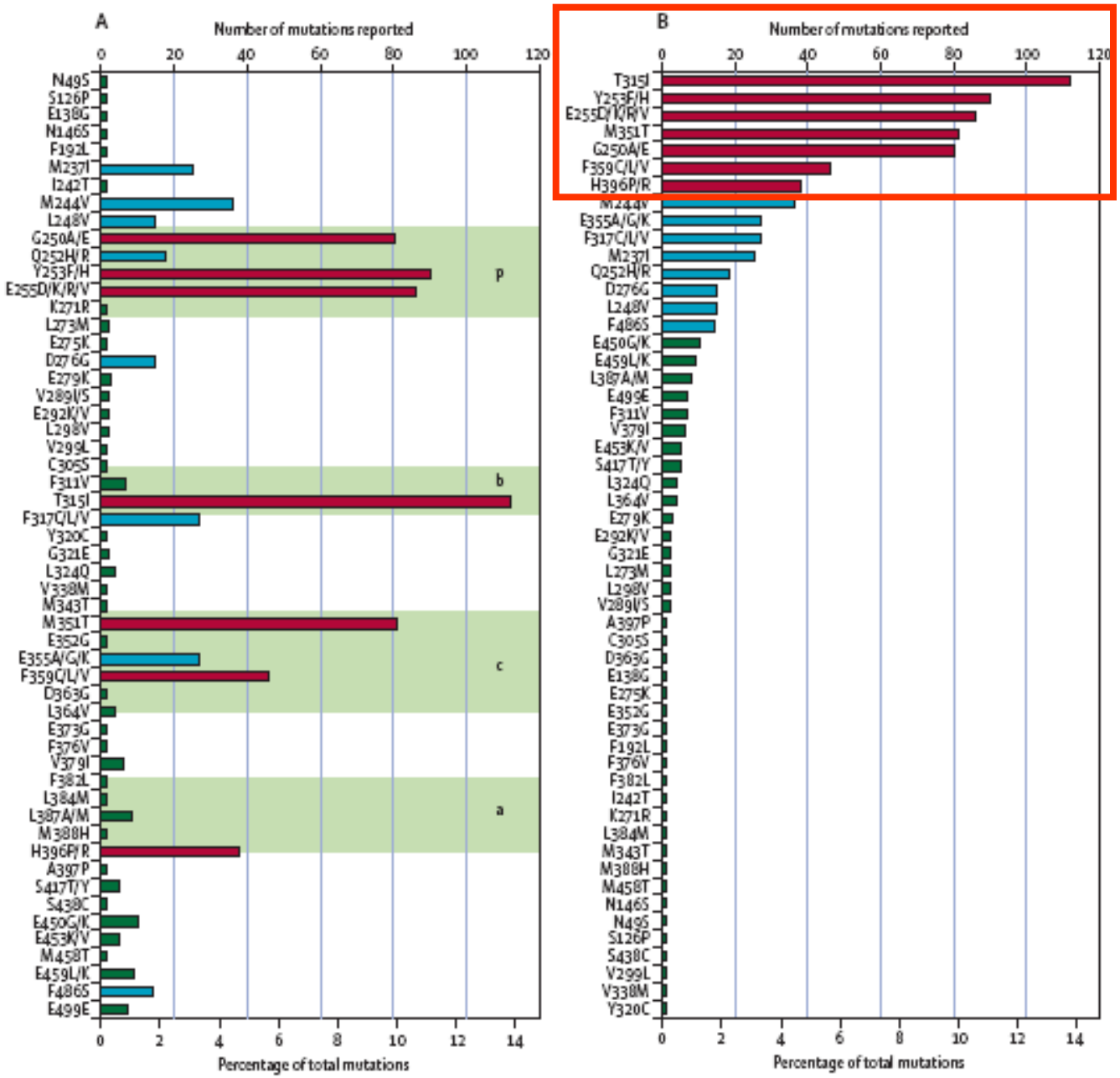
historical controls EORTC database



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij et al., The Lancet 2004; 364: 1127 - 1134

Imatinib resistance induced by mutations in BCR ABL



T315I
'gatekeeper'

Apperley JF
Lancet Oncol
2007; 8: 2018

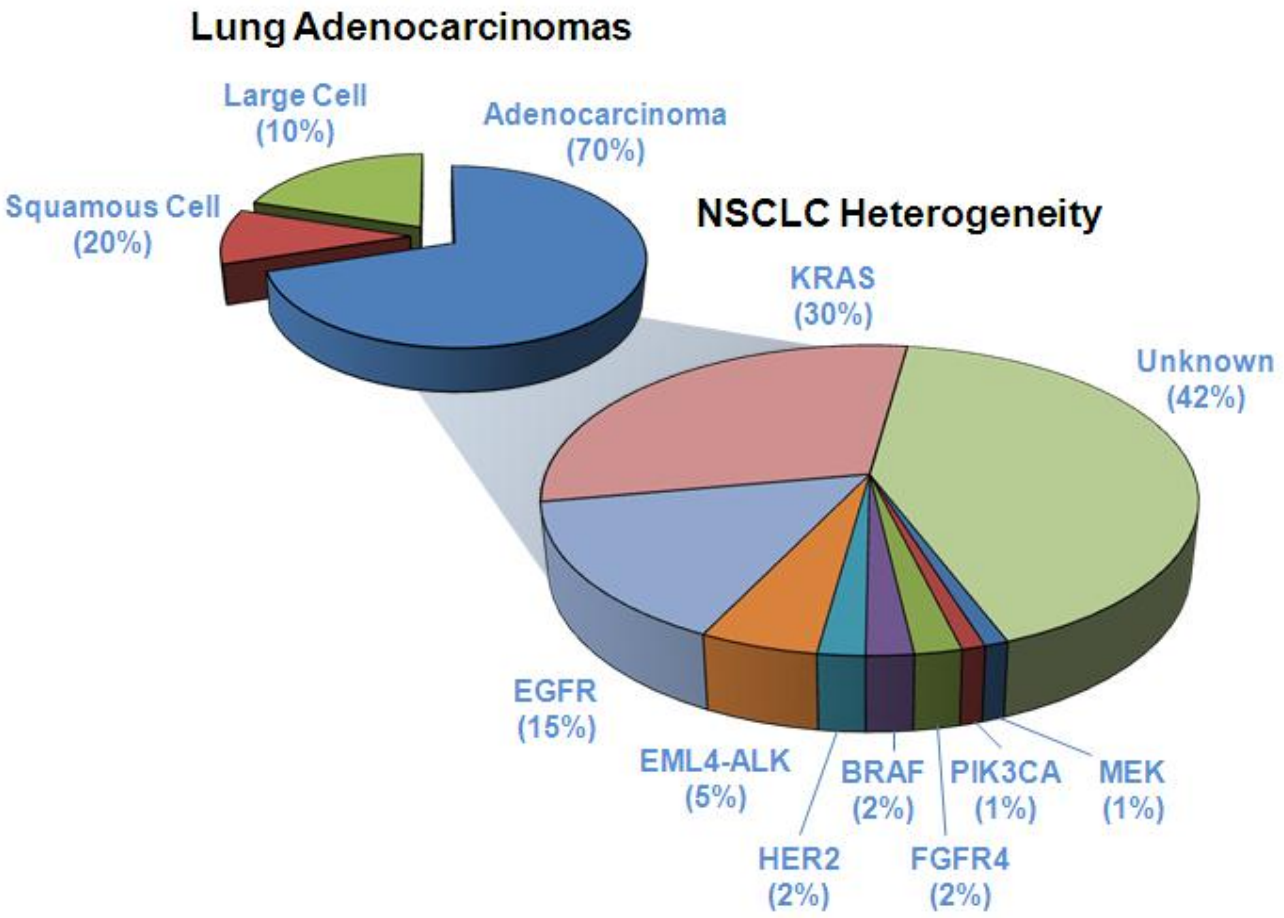
Reversal of imatinib resistance in KIT^{T6701} gatekeeper mutation

Mutations	Imatinib	Dasatinib	Sorafenib	Nilotinib
560Vdel/V654A	3,927	585	1,074	192
557-8WKdel/T670I	>10,000	>10,000	1,063	>10,000
V559D/D820Y	3,202	432	944	297
V560delN822K*	NA	NA	NA	NA
V559D †	63	27	66	44
557-8WKdel †	460	58	211	83
502-503AY †	509	74	400	671
T670I	>10,000	7,543	918	>10,000
D820Y*	NA	NA	NA	NA
N822K	>10,000	868	3,550	3,083

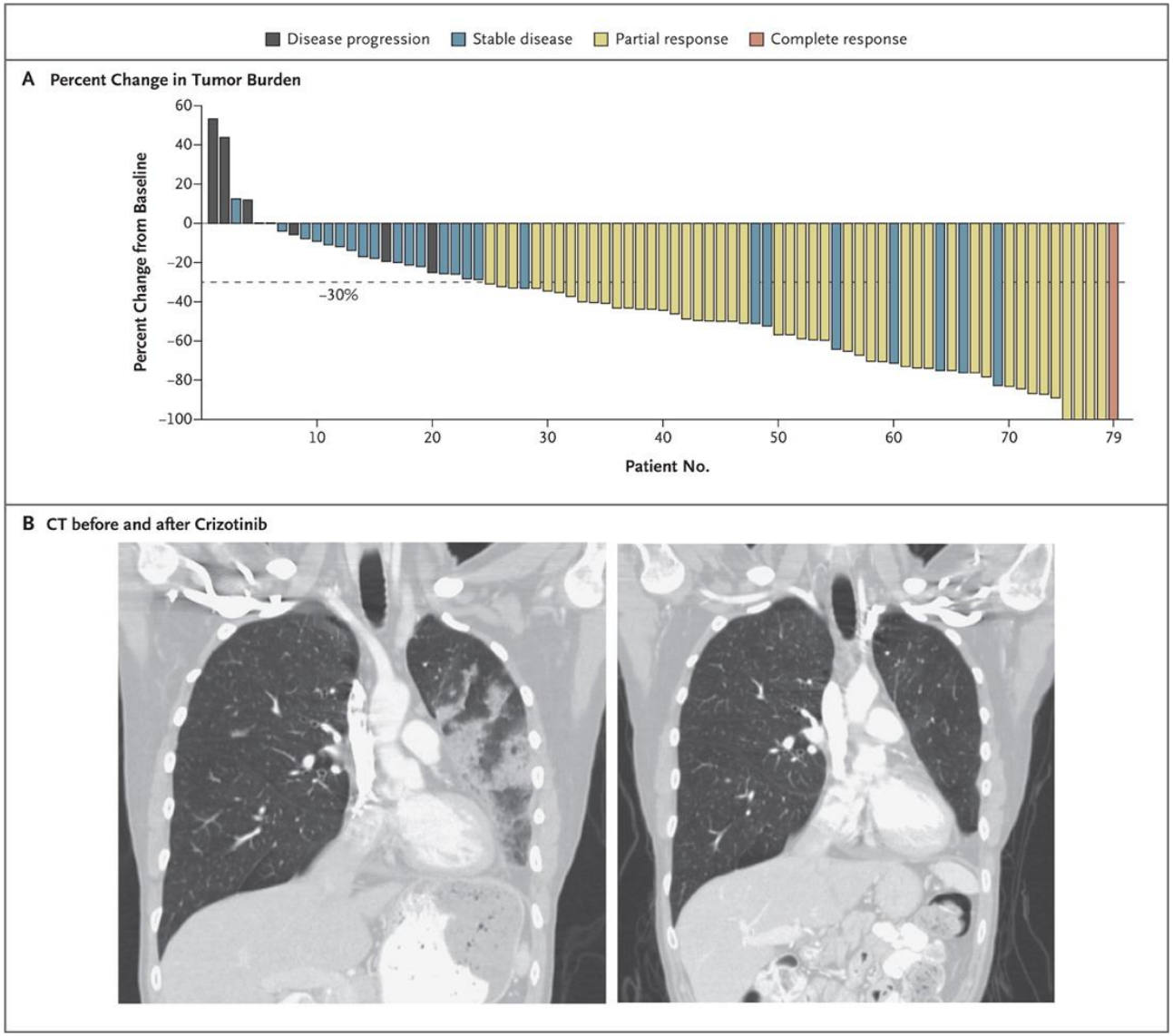
Values are given in IC_{50} (nmol/L)

Guo et al. CCR 2007; 13:2007

Biological subtypes non-small cell lung cancer (NSCLC)

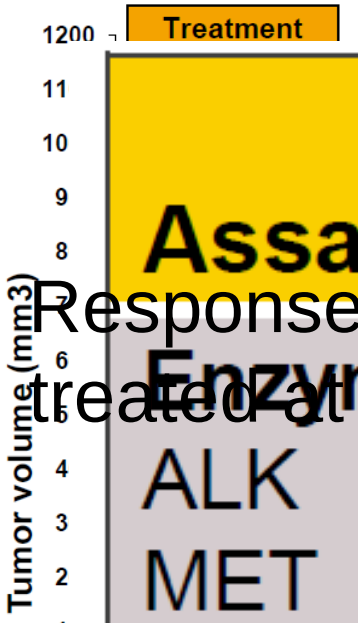


Anti-tumor activity of crizotinib in EML4-ALK+ NSCLC



Kwak EL et al.
NEJM 2010;363:1693

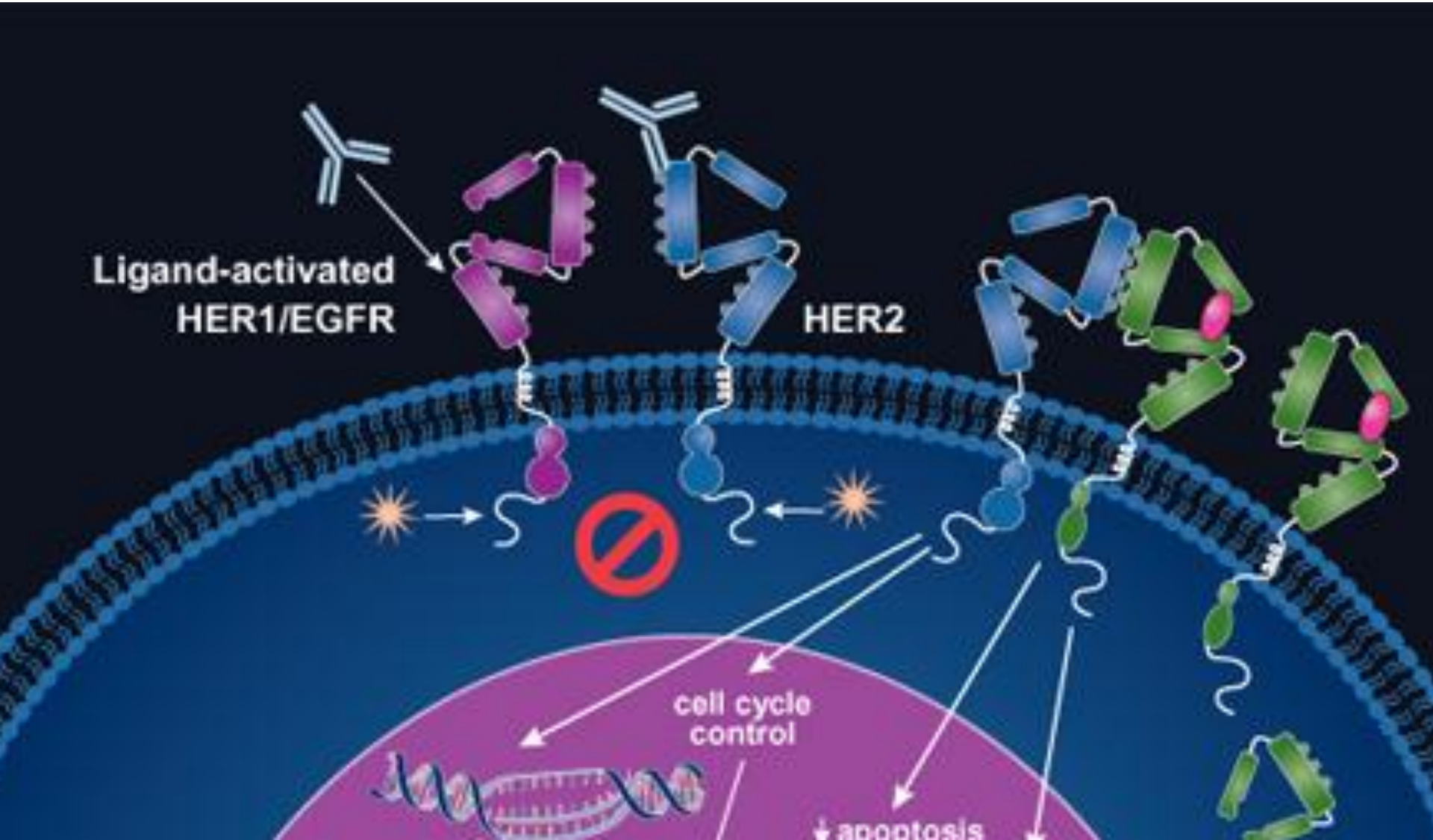
LDK378 is active in EML4-ALK xenografts & in crizotinib-resistant mutations (C1156Y)



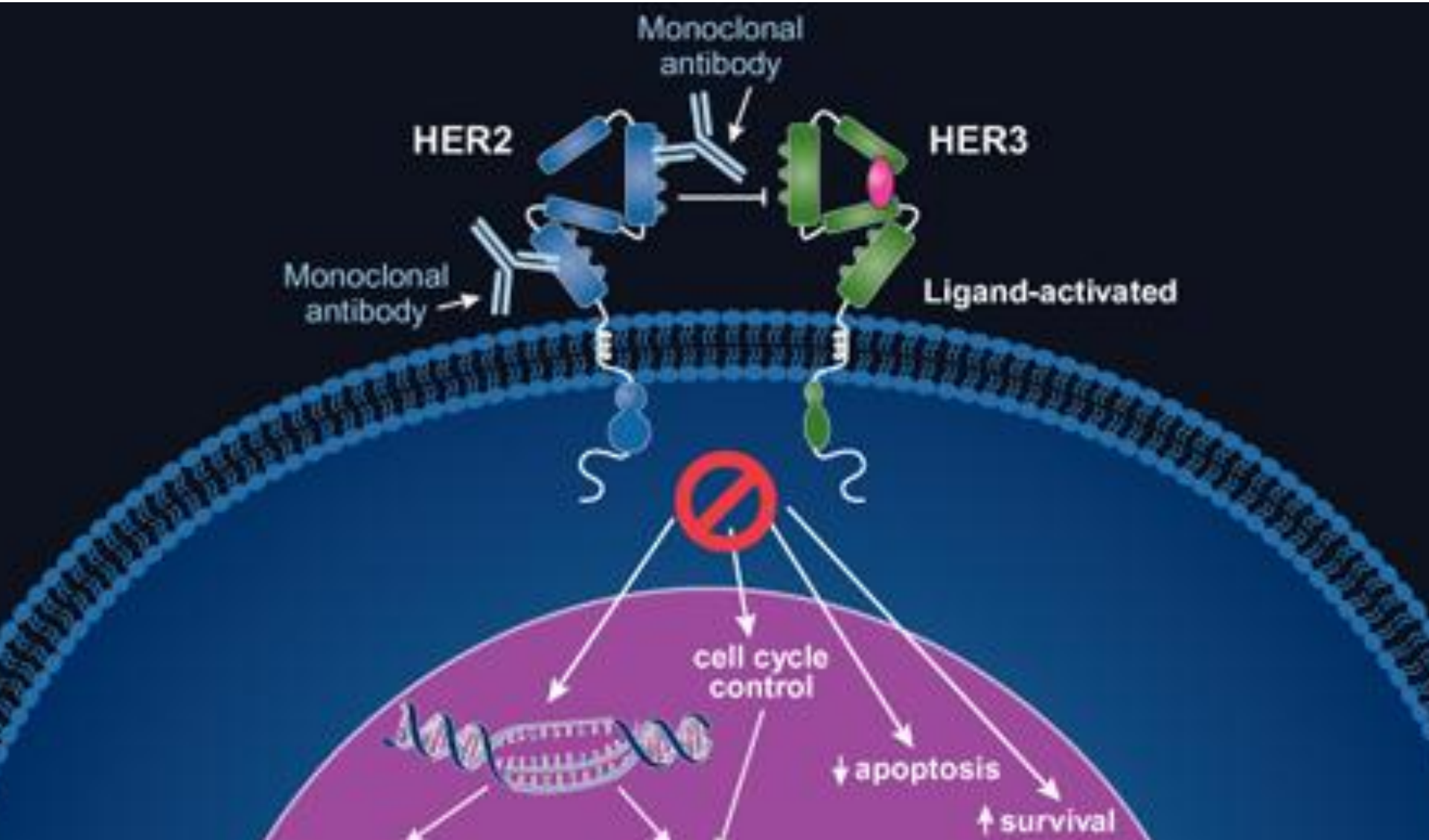
Assay	LDK378 IC_{50} (μM)	Crizotinib IC_{50} (μM)
Enzymatic		
ALK	0.00015	0.003
MET	3.2	0.008
Cell-based		
ALK	0.027	0.11
MET	1.3	0.028

Response rate 81% (21/26) in patients with NSCLC treated at ≥ 400 mg/day who progressed on crizotinib

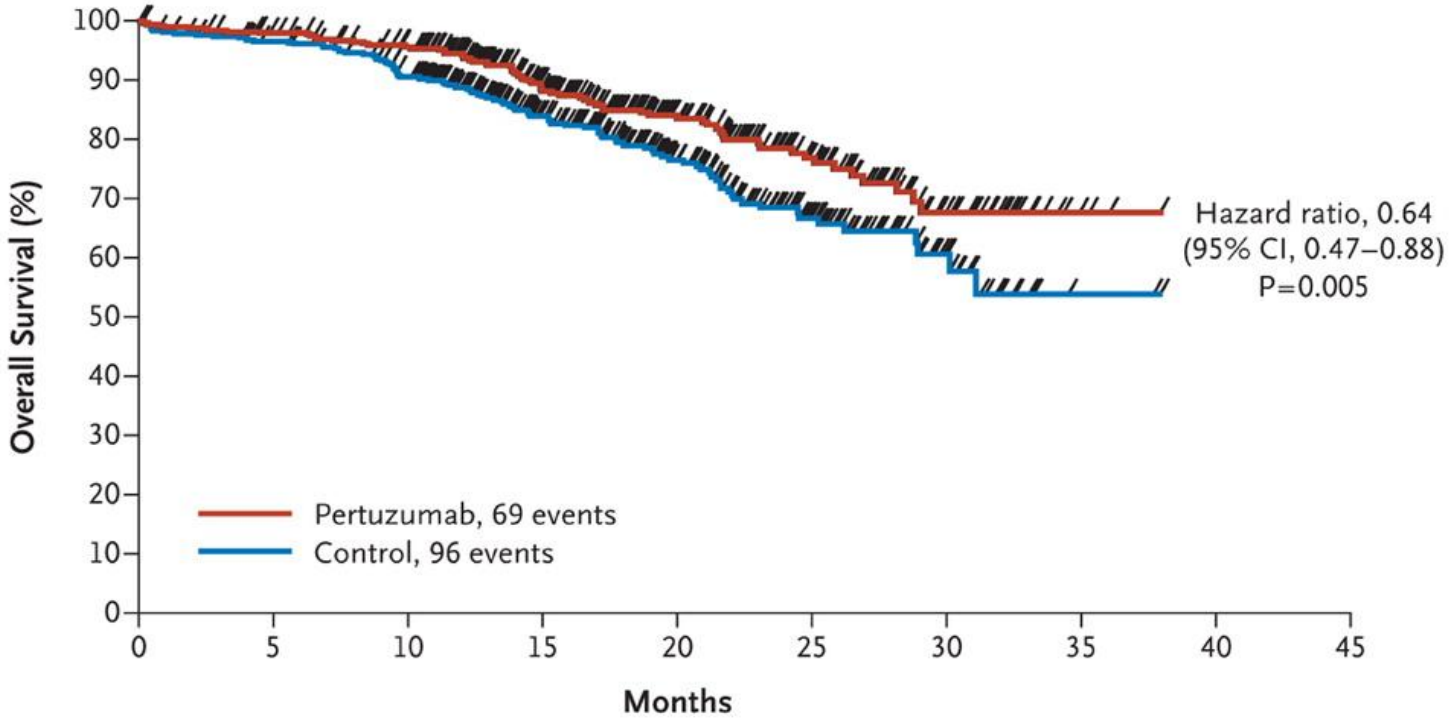
Trastuzumab effectively inhibits Her2 signaling



Unresponsiveness due to Her2-Her3 heterodimerization

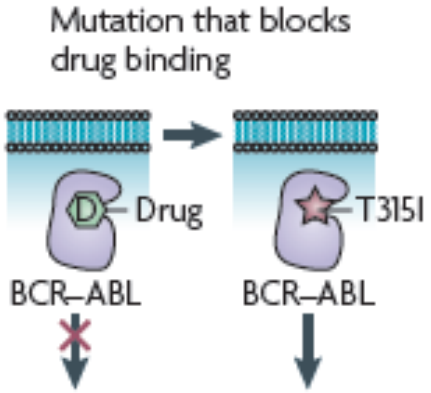


Inactivation of Her2 and Her2-Her3
trastuzumab + pertuzumab



No. at Risk										
Pertuzumab	402	387	367	251	161	87	31	4	0	0
Control	406	383	347	228	143	67	24	2	0	0

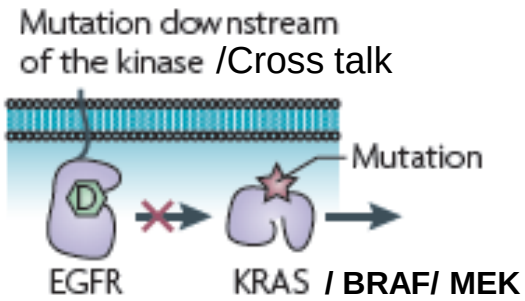
Resistance to TKIs & MoAbs



Imatinib Sorafenib/ Nilotinib/ Dasatinib/....

EML4-ALK C1156Y mut

Crizotinib LDK378



BRAF V600 Melanoma

BRAFi BRAFi + MEKi

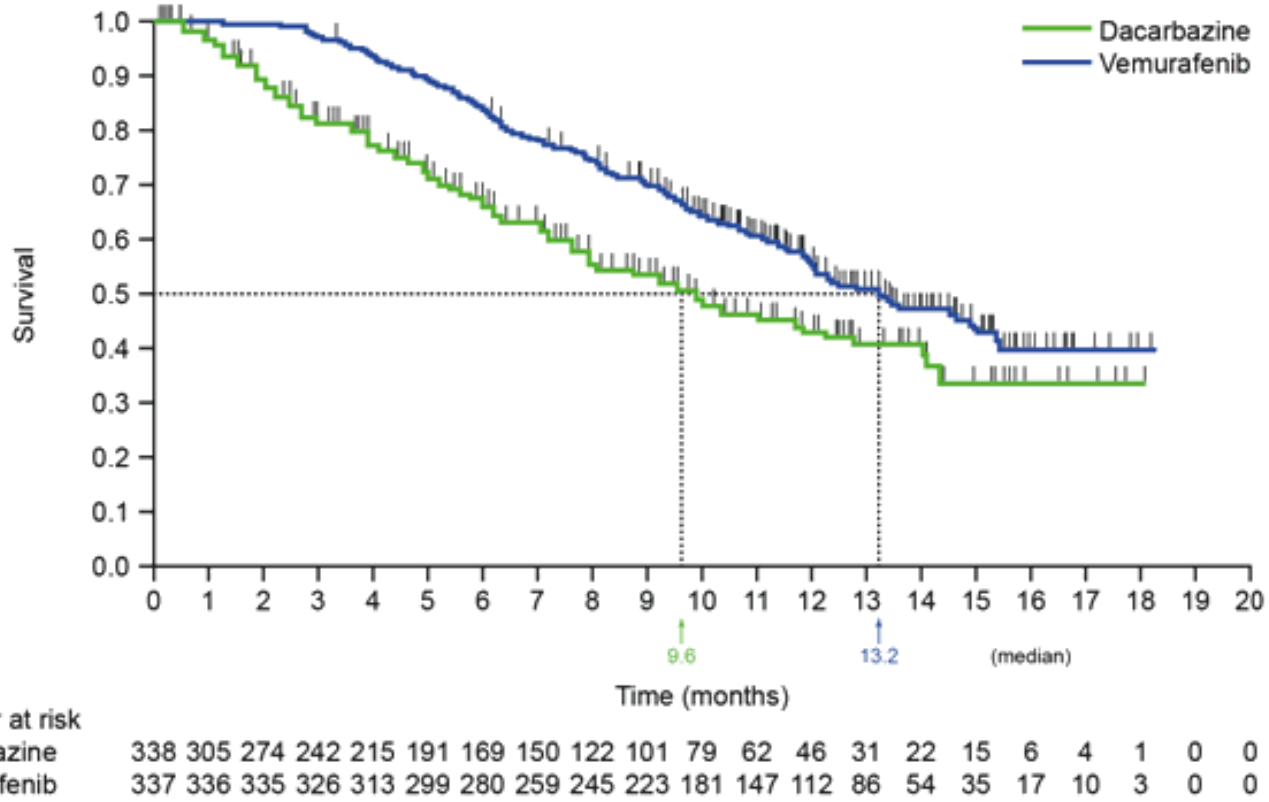
BRAF V600 CRC

BRAFi BRAFi + EGFRi

Knight & Shokat Nat Rev Cancer 2010; 10: 130-7; Prahallad et al., Nature 2012
LDK378 Proc ASCO 2012; BRIM7 study ESMO 2012; Weber et al., Proc ASCO 2012

Vemurafenib in BRAF V600 melanoma

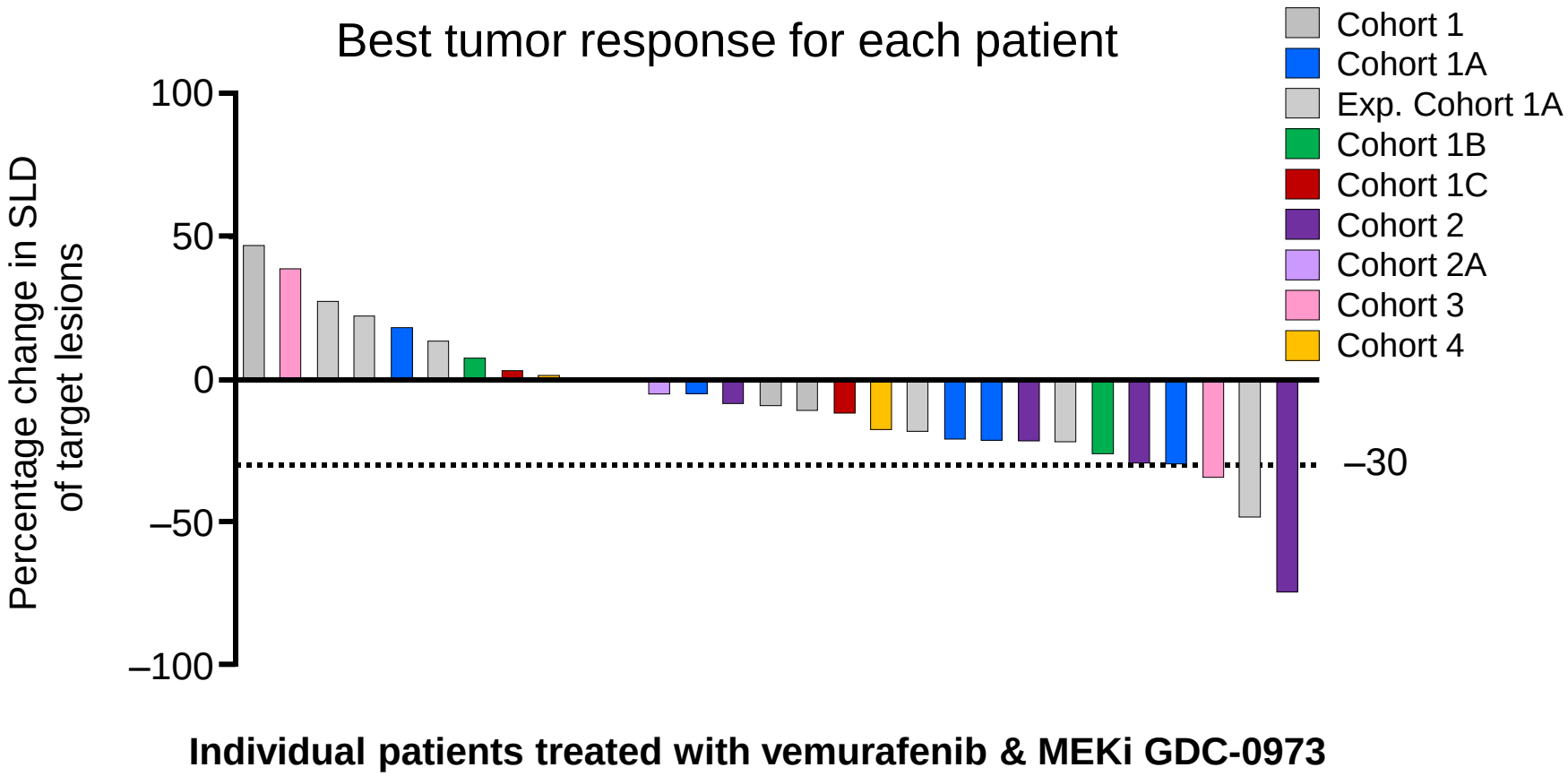
Kaplan-Meier curves of Overall Survival – previously untreated patients [October 3, 2011 cut-off; HR 0.62 (0.49, 0.77)*]



Number of cross-over patients 81 (24%)

http://www.medicines.org.uk/EMC/medicine/26056/SPC/Zelboraf+240+mg+Film-coated+Tablets/

BRAFi + MEKi in BRAF V600 melanoma in vemurafenib progressors

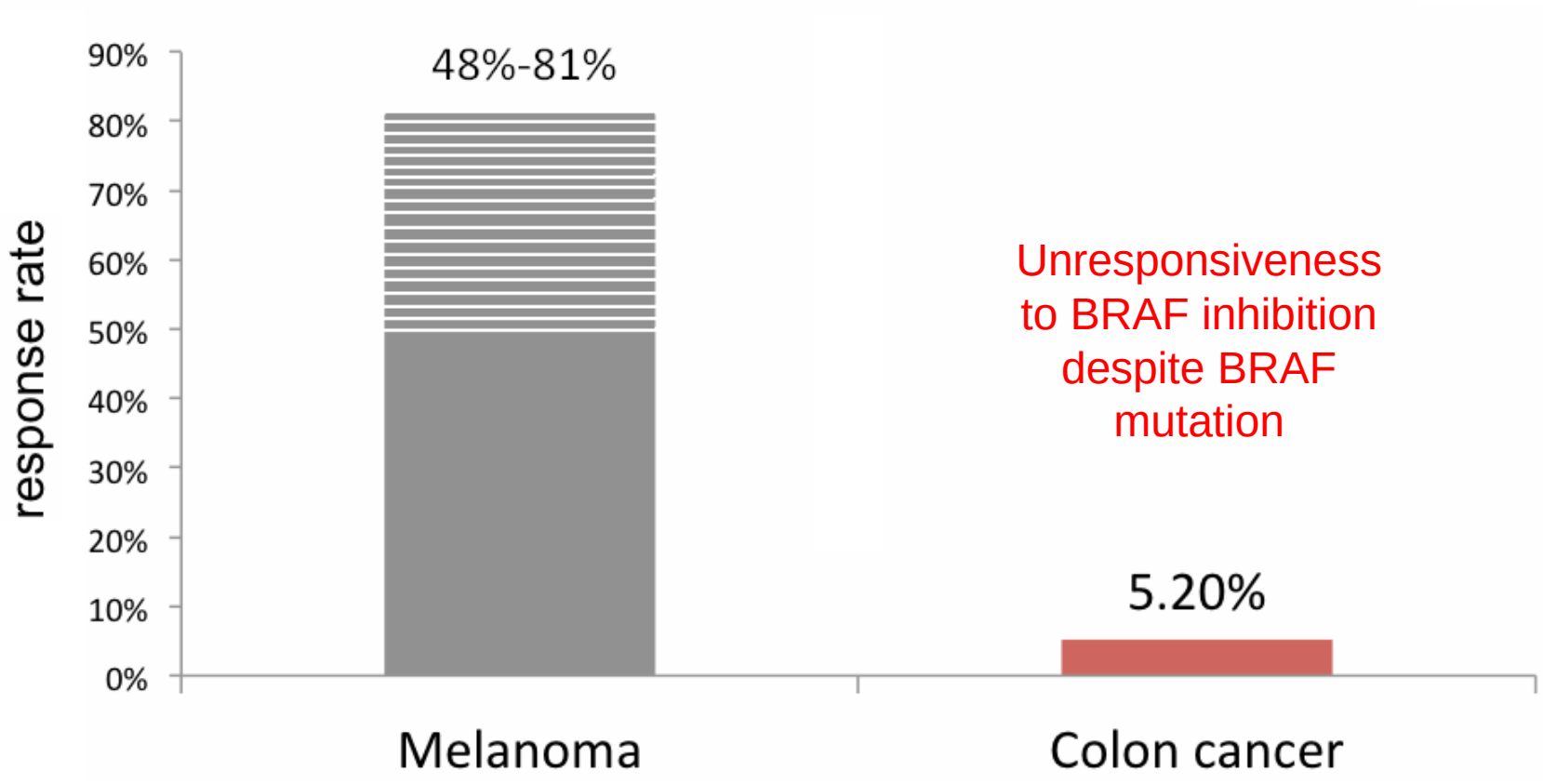


Individual patients treated with vemurafenib & MEKi GDC-0973

Gonzalez et al. BRIM-7 study Proc. ESMO 2012;

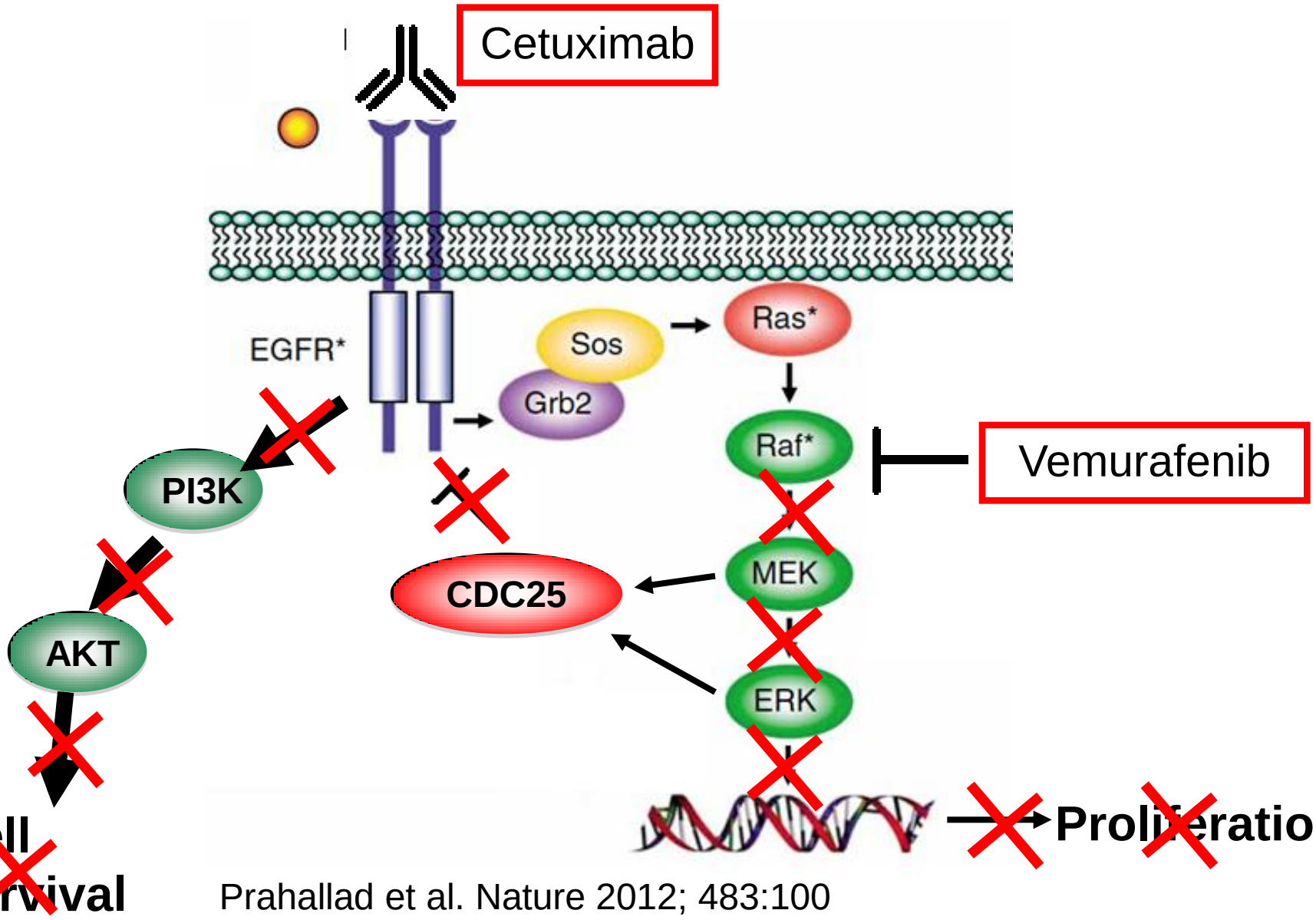
Also strong indication of synergy with Dabrafenib + Trametinib [Weber et al. Proc ASCO 2012]

Vemurafenib response rate in BRAF mutant melanoma versus colon cancer



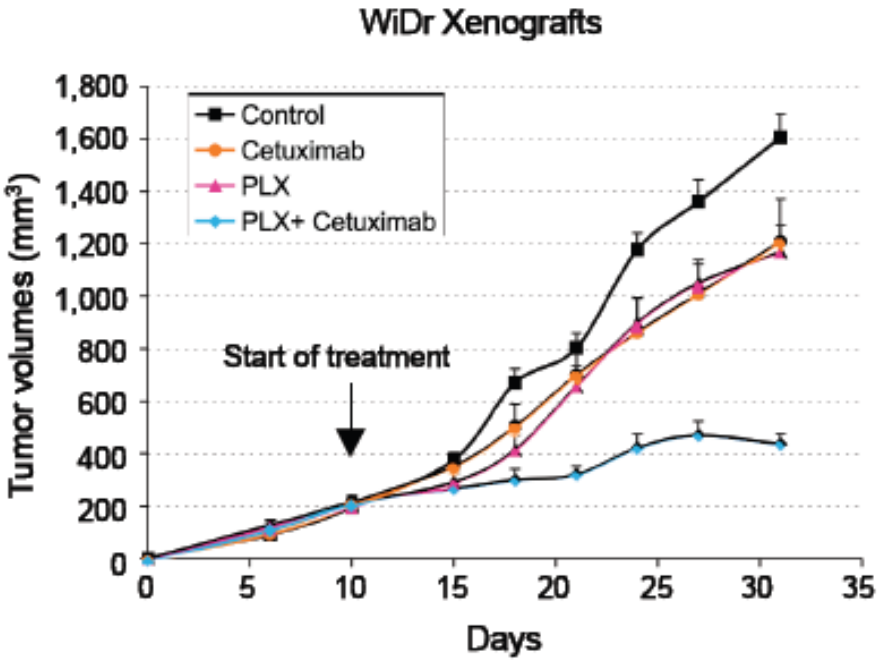
Flaherty et al. NEJM 2010 Chapman et al. NEJM 2011
Kopetz et al. ASCO 2010

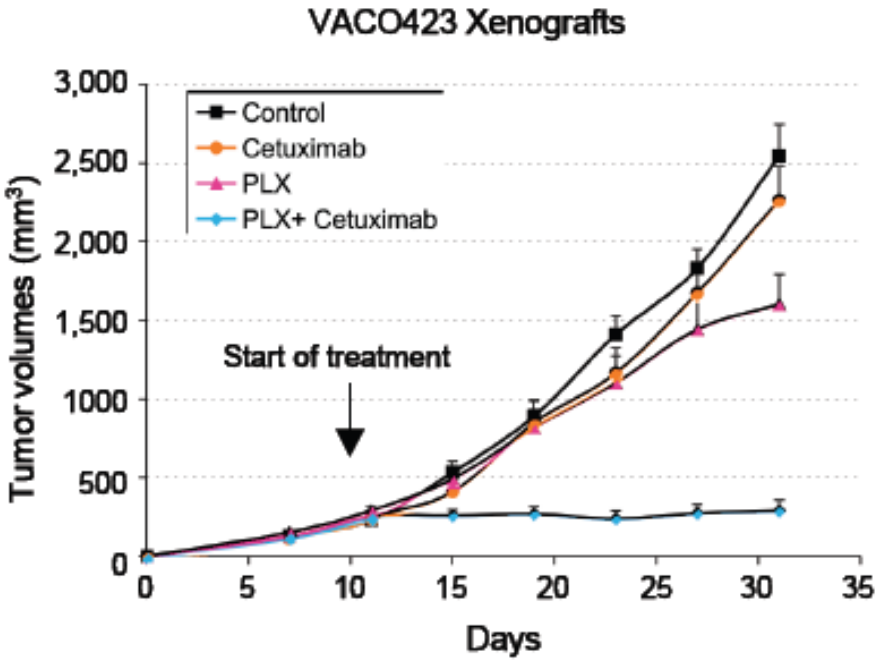
Feedback regulation of EGFR by BRAF inhibition



Prahallad et al. Nature 2012; 483:100
Corcoran et al. Cancer Discovery 2012; 2: 227

In vivo proof of the principle

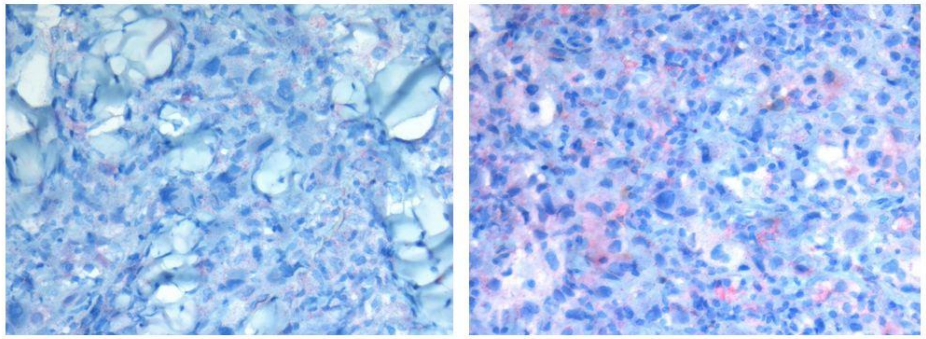




Two colon cancer models with BRAF mutation (and no KRAS mutation)

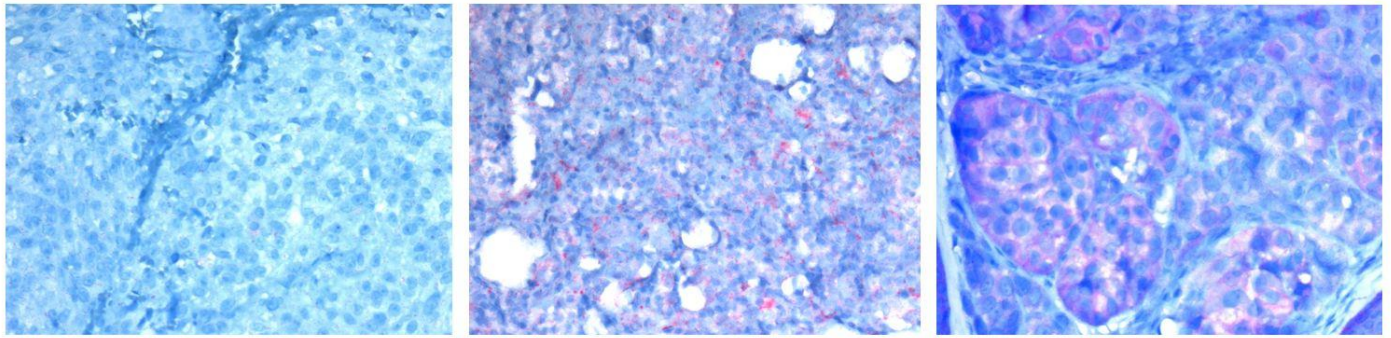
BRAF mutant melanomas upregulate EGFR during development of drug resistance

Patient #2



Before RAFi | After RAFi

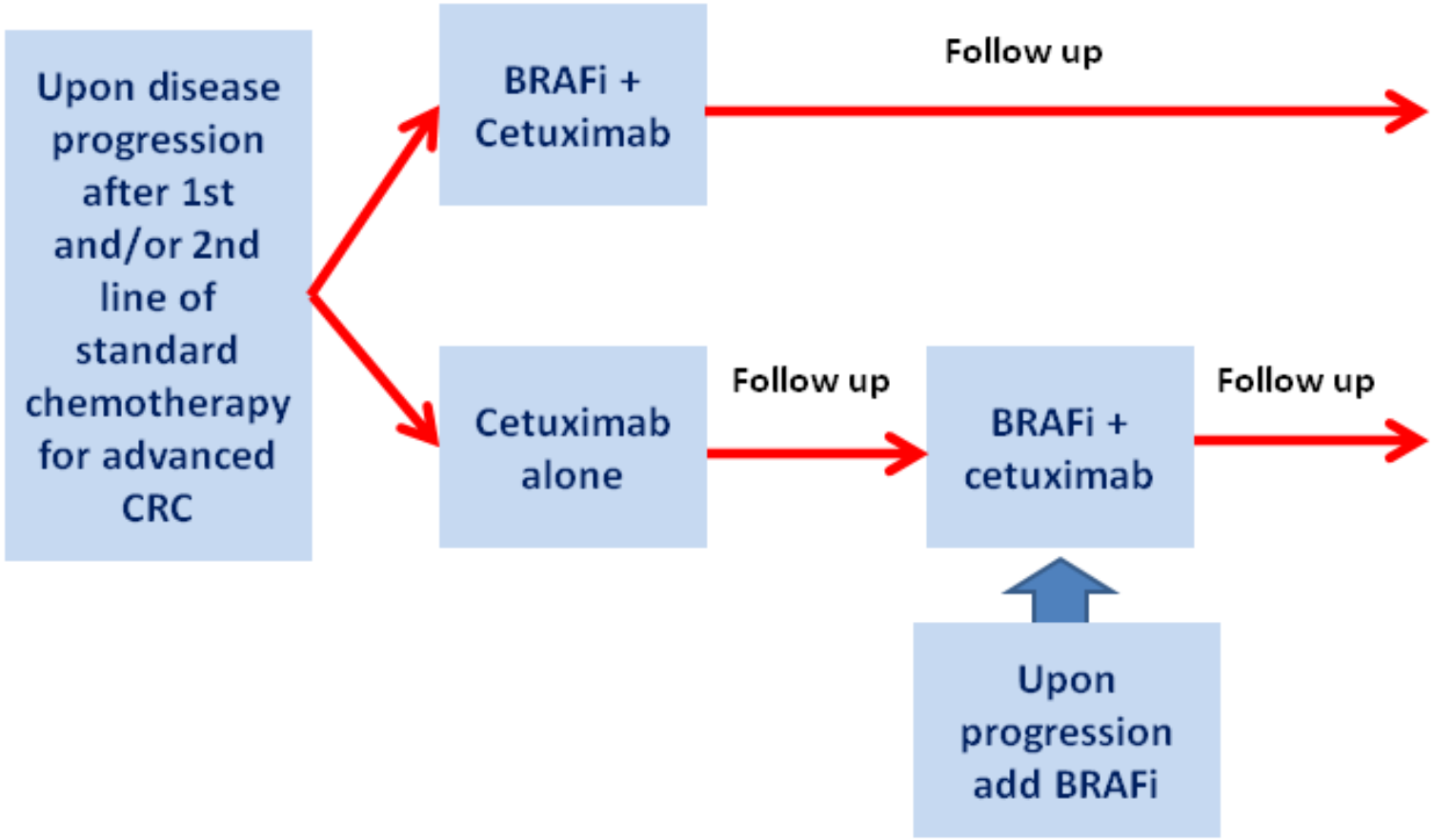
Patient #5



Before MEKi | After MEKi (T1) | After MEKi (T2)

EGFR IHC in red

Proposed phase II/III study design to demonstrate proof of concept

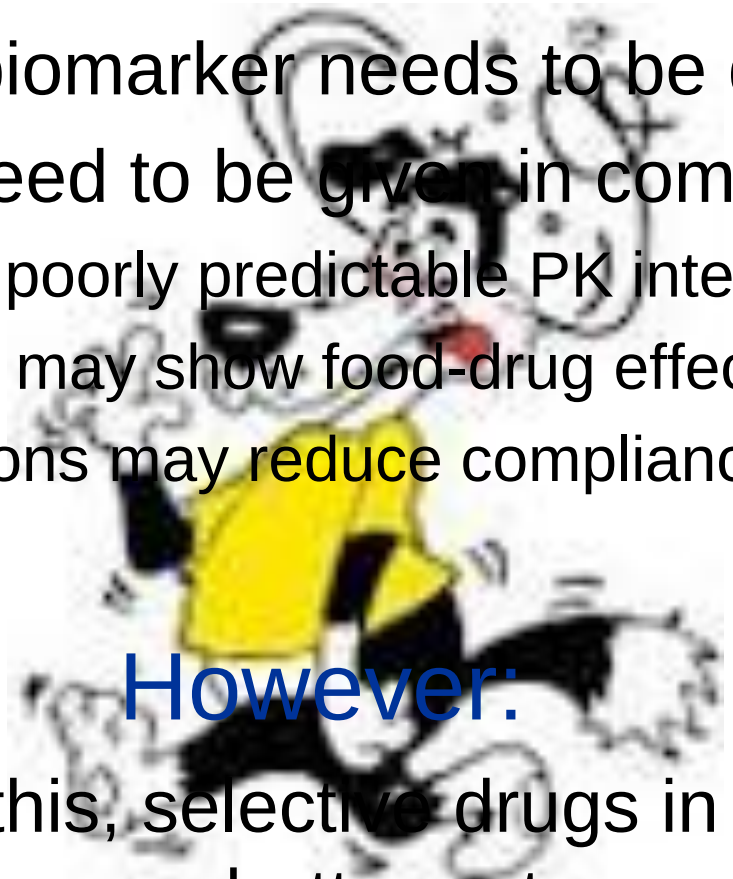


What is the feature of an optimal new agent?

- It selectively engages a unique and dominant target in cancer tissue
- It can easily be combined with partnering agents to overcome tumor unresponsiveness
- It is completely devoid of normal tissue interactions and thus has excellent safety
- It can be given orally continuously
- It has unremarkable ADME
- It is cost-effective

Sobering remarks about selective agents

- Predictive biomarker needs to be determined
- Will often need to be given in combinations:
  - May show poorly predictable PK interactions
  - Oral drugs may show food-drug effects as well
  - Combinations may reduce compliance



However:

- Despite all this, selective drugs in biomarker driven trials have proven better outcome than (unselective) drugs in unselected populations