

Novel Targets and Phase I/II Agents in Non-Small Cell Lung Cancer

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Novel Targeted Agents

Why

- To circumvent intrinsic and acquired resistance to existing targeted agents
- Probably higher degree of redundancy / crosstalk of pathways in advanced cancer

How

- Maximal inhibition of a target
- Maximal inhibition of a pathway
- Inhibition of parallel pathways

Novel Targeted Agents

Membrane tyrosine kinase

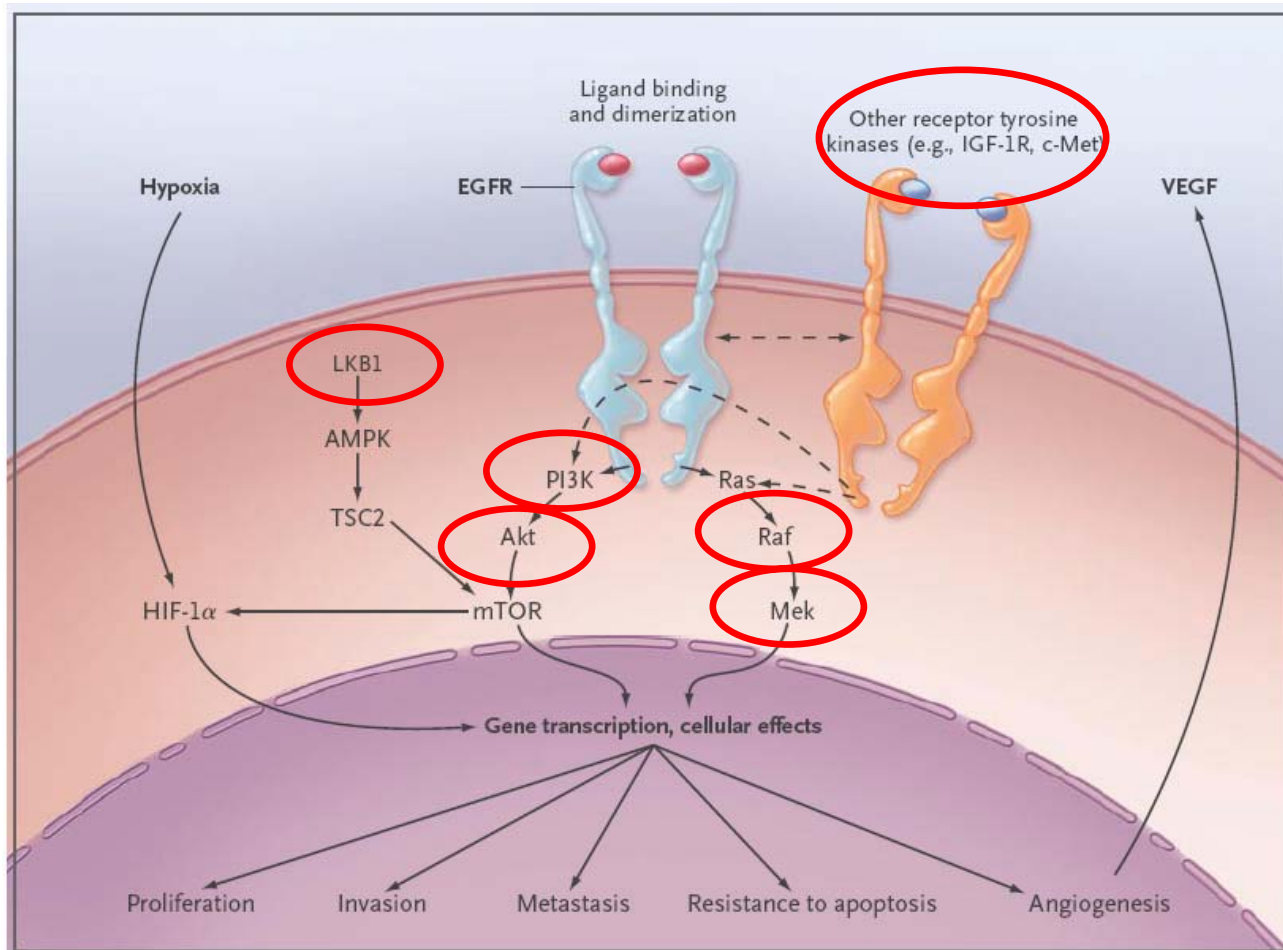
- EGFR family: HER2 inhibitor
- HGFR family: MET inhibitor
- INGR family: IGF1R inhibitor
- ALK family: ALK inhibitor

Cytoplasmic serine / threonine kinase

- KRAS / BRAF / MEK inhibitor
- PI3K / AKT / mTOR inhibitor

Others

Novel Targeted Agents

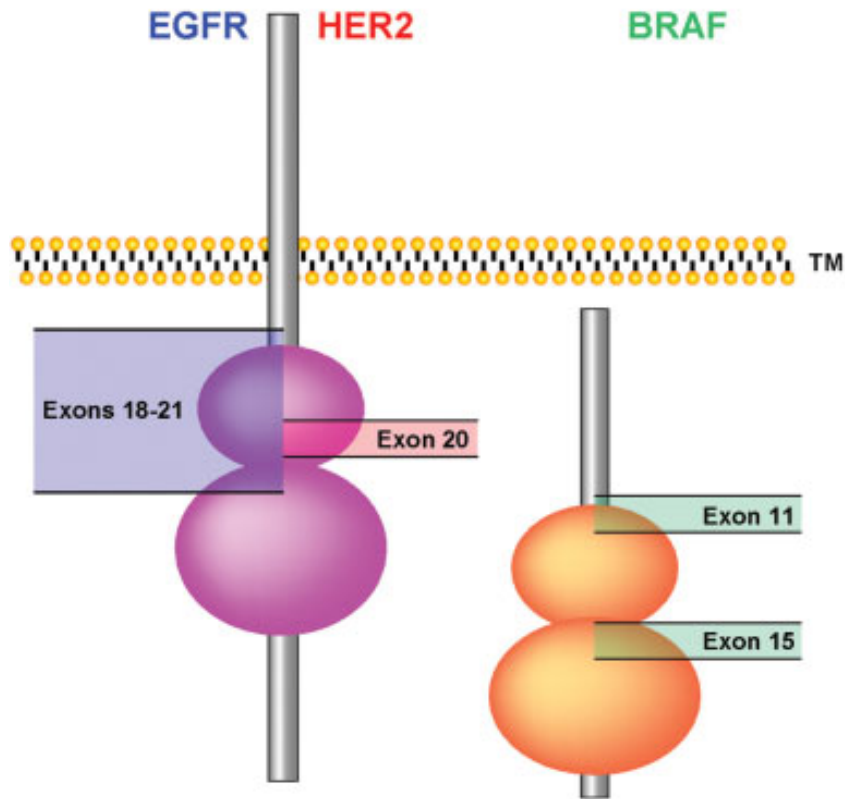


HER2 Inhibitors

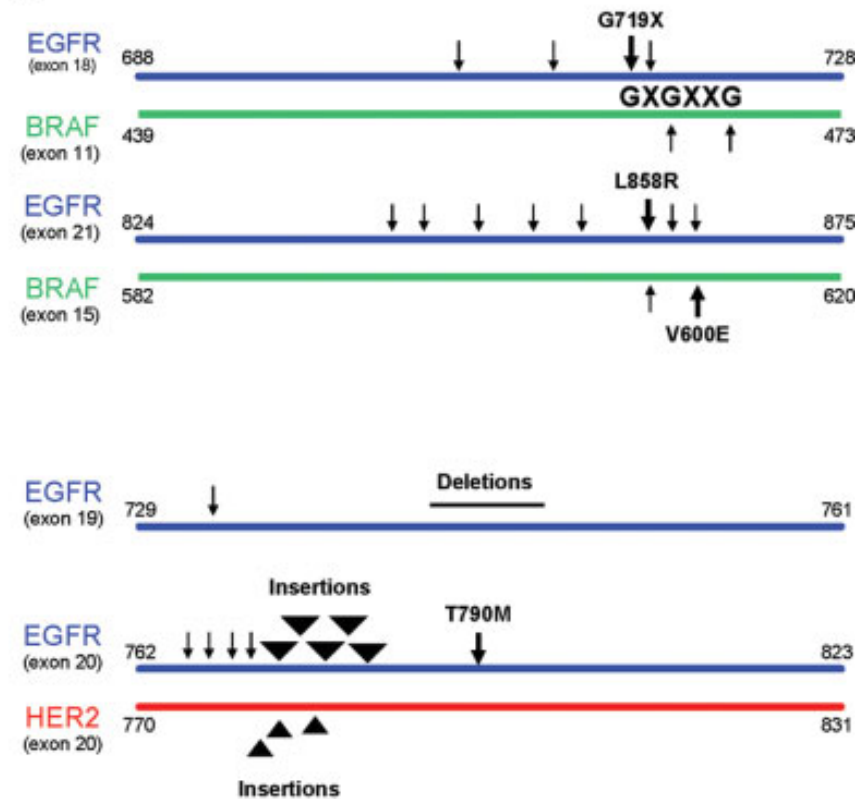
- HER2 mutation (insertion 774 [AYVM] of exon 20) occurs in ~5 - 10% of NSCLC.
- EGFR / HER2 tyrosine kinase inhibitor
- Reversible
 - GW786034 (lapatinib): PR in 1 of 75 NSCLCs
- Irreversible
 - BIBW2992: PR in 29 of 55 EGFR mut NSCLCs
 - HKI272 (neratinib): PR in 3 of 167 NSCLCs
 - EKB569 (pelitinib)
 - CI1030 (canertinib)
 - PF00299804
 - Stephens P, et al. Nature 2004;432:525-6
 - Ross HJ, et al. Clin Cancer Res 2010;16:1938-49
 - Shih JY, et al. J Clin Oncol 2009;27 (Suppl 15) Abstr 8013
 - Sequist LV, et al. EORTC-NCI-AACR 2008

HER2 Mutation

a Mutations in kinase domains of EGFR, HER2 and BRAF genes.

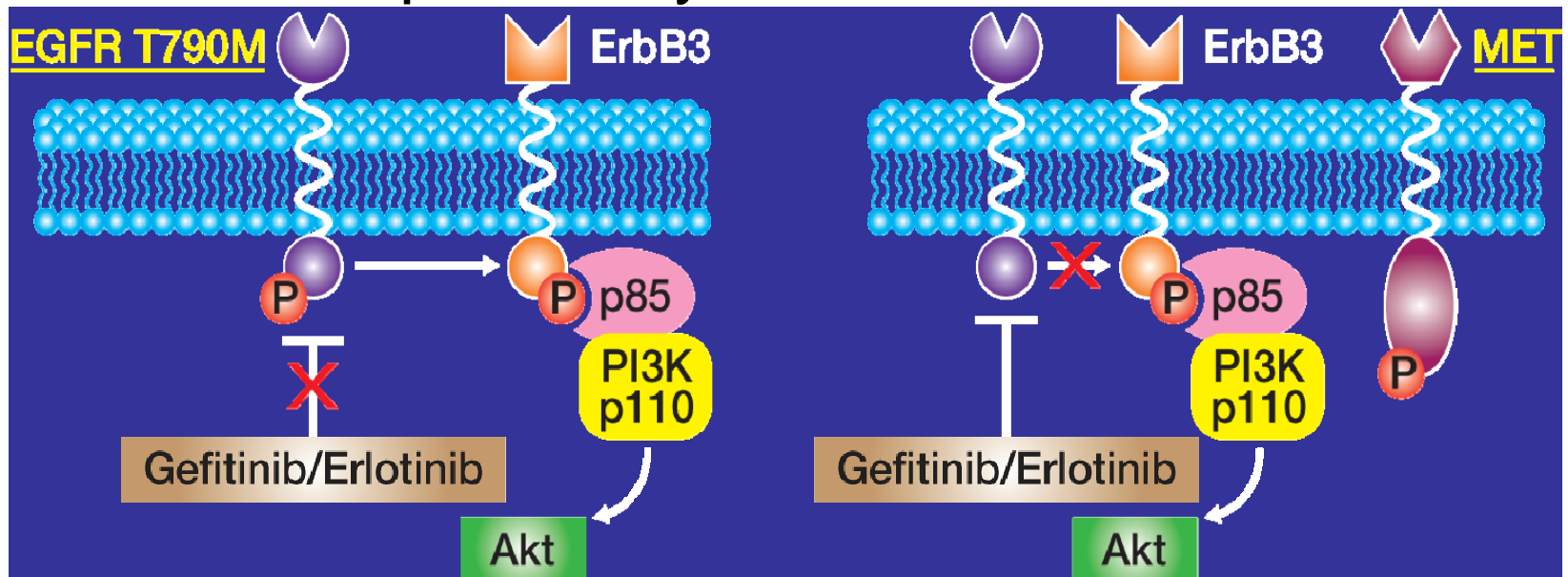


b Location of mutations in EGFR, HER2 and BRAF genes.



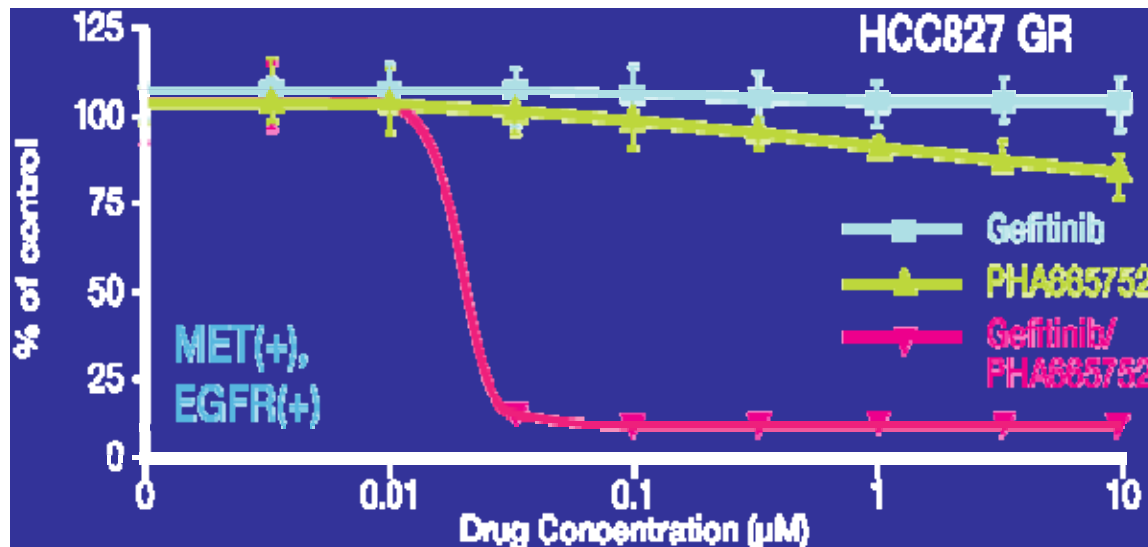
MET Amplification

- In tumors with T790M mutation, erlotinib / gefitinib is unable to inhibit EGFR phosphorylation.
- In tumors with MET amplification, MET activates erbB3 independently of EGFR.



MET Amplification

- MET amplification occurs in ~20% of erlotinib / gefitinib-treated NSCLC.
- MET amplification occurs in ~5% of erlotinib / gefitinib-naïve NSCLC.
- Both EGFR inhibition and MET inhibition are needed to induce apoptosis in gefitinib-resistant HCC827 cells.



MET Inhibitors

- Monoclonal antibody
 - HGF: AMG102, SCH900805
 - MET: MetMAb
- Small molecule inhibitor
 - ATP-competitive: PF02341066, XL184, XL880, MGCD265, JNJ38877605
 - Non-ATP-competitive: ARQ197

MET Inhibitors

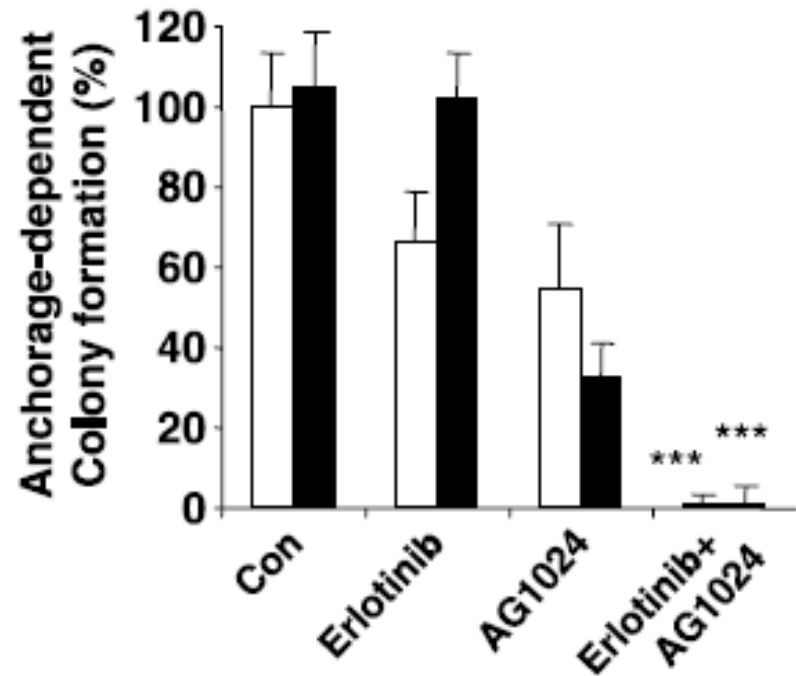
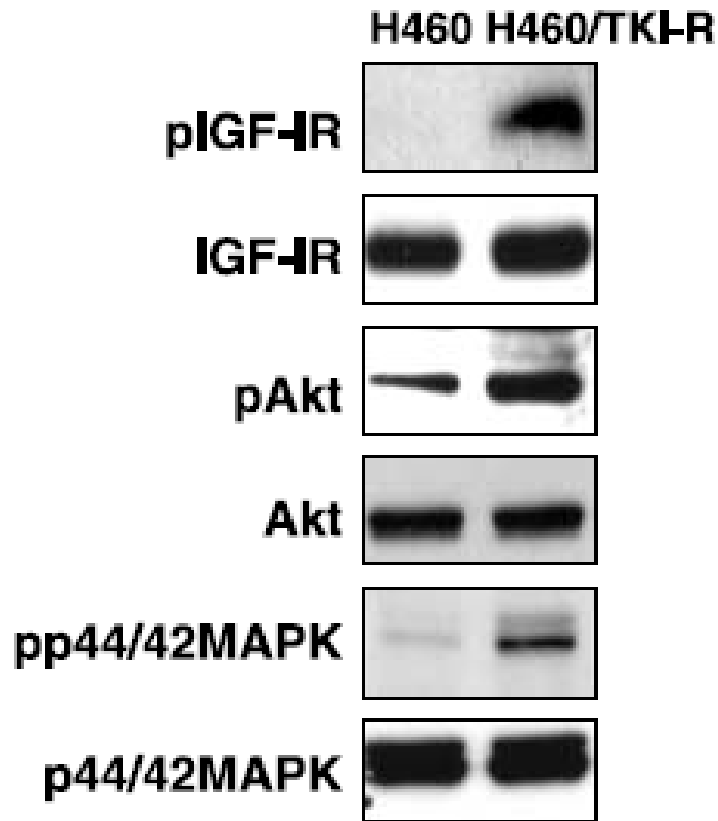
- ARQ197 (non-ATP-competitive MET inhibitor) plus erlotinib (150 mg QD)
- 120 - 360 mg BID
- DLT: Neutropenia, sinus bradycardia
- No MTD indentified, RP2D: 360 mg BID
- Sinus bradycardia, fatigue, rash, pruritus, diarrhea
- All 3 evaluable NSCLC patients achieved SD of 14 - 32 weeks.
- Ongoing randomized phase II trial of erlotinib plus ARQ197 vs. erlotinib in second- or third-line NSCLC

MET Inhibitors

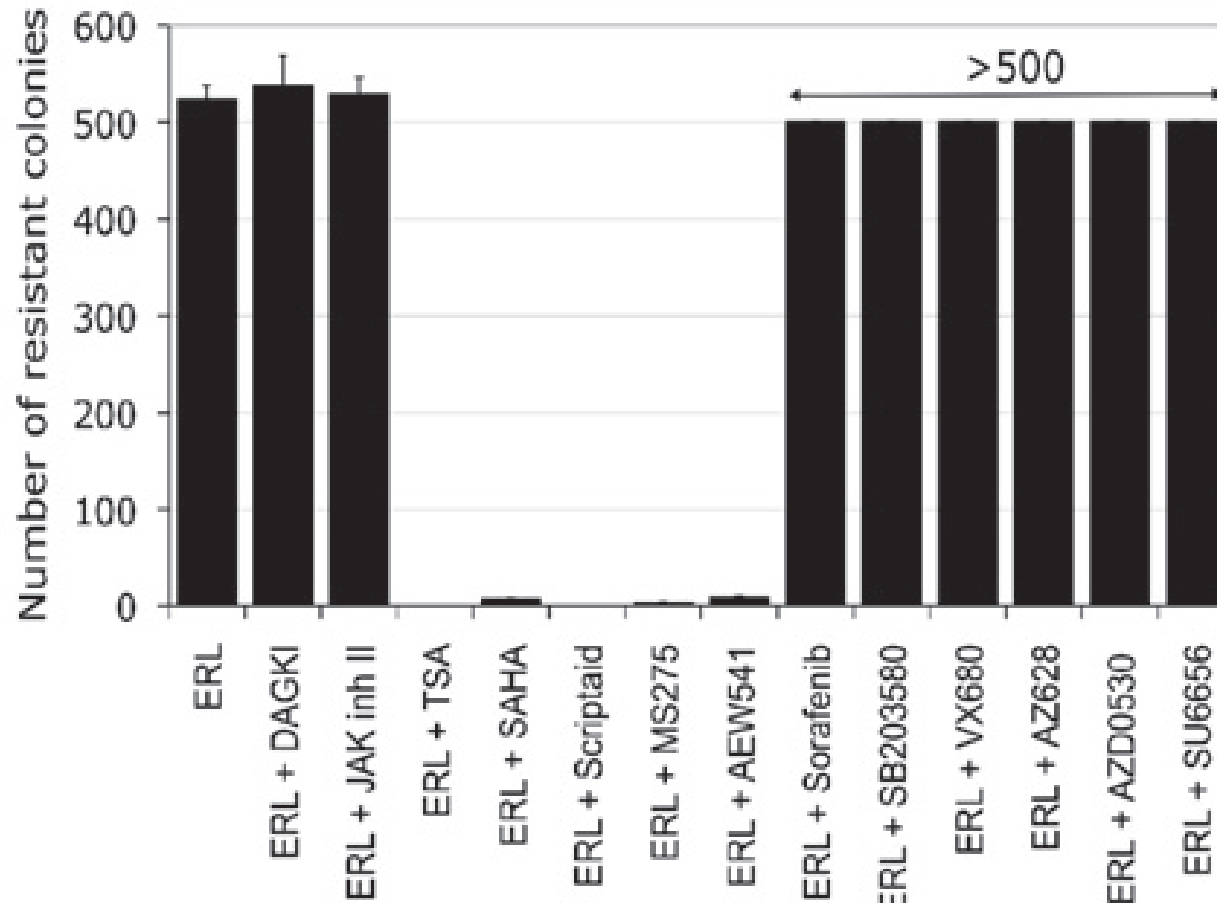
- Response

Patient ID	Number of prior biologic/hormonal / chemo drug regimens	Prior erlotinib (Y/N)	Past RECIST response	Time on treatment	Patient status
01	1	No	SD	26.3	Off-study (clinical PD)
03	4	Yes	SD	31.9	Off-study (PD)
04	6	Yes	SD	14.6	Off-study (PD)
05	1	No	NE	1.9	Off-study (AEs)
18	3	Yes	SD	33.6+	Active as of 5/15/09
21	2	Yes	SD	32.7+	Active as of 5/15/09
27	2	Yes	NE	7.7	Off-study (clinical PD)
32	4	Yes	SD	17.6+	Active as of 5/15/09

IGF1R Overexpression



IGF1R Overexpression



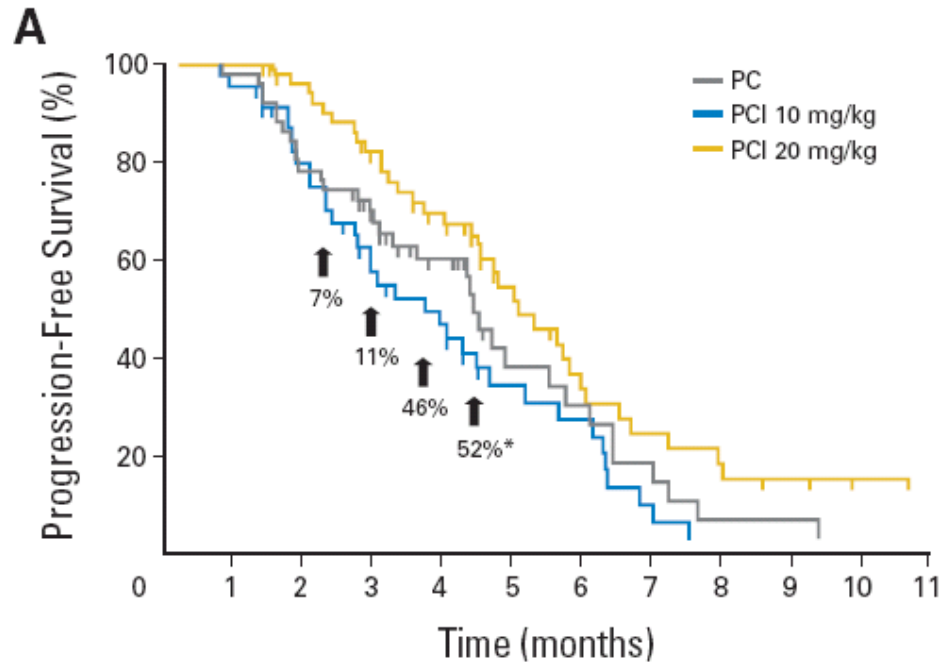
IGF1R Inhibitors

- Monoclonal antibody
 - CP751871 (figitumumab)
 - IMC-A12
 - AMG479
 - MK0646 (Dalotuzumab)
 - BIIB022
- Small molecule inhibitor
 - IMSM18 (EM1421)
 - OSI906
 - XL228
 - BMS536924
 - BMS554417

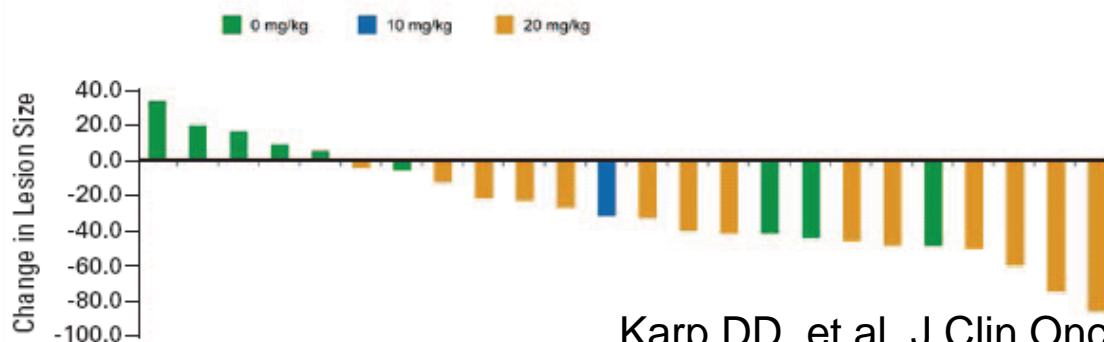
IGF1R Inhibitors

- Figitumumab (CP751871) (IGF1R inhibitor) plus paclitaxel / carboplatin
- 10 mg/kg or 20 mg/kg (n = 98)
- RR: 62 vs. 43 vs. 33% (p = 0.478)
- PFS: 5.0 vs. 3.6 vs. 4.3 months (p = 0.7)
- Ongoing randomized phase III trial of CP751871 plus paclitaxel / carboplatin vs. paclitaxel / carboplatin in first-line non-adenocarcinoma NSCLC (n = 820)
- Ongoing randomized phase III trial of CP751871 plus erlotinib vs. erlotinib in second-line non-adenocarcinoma NSCLC (n = 600)

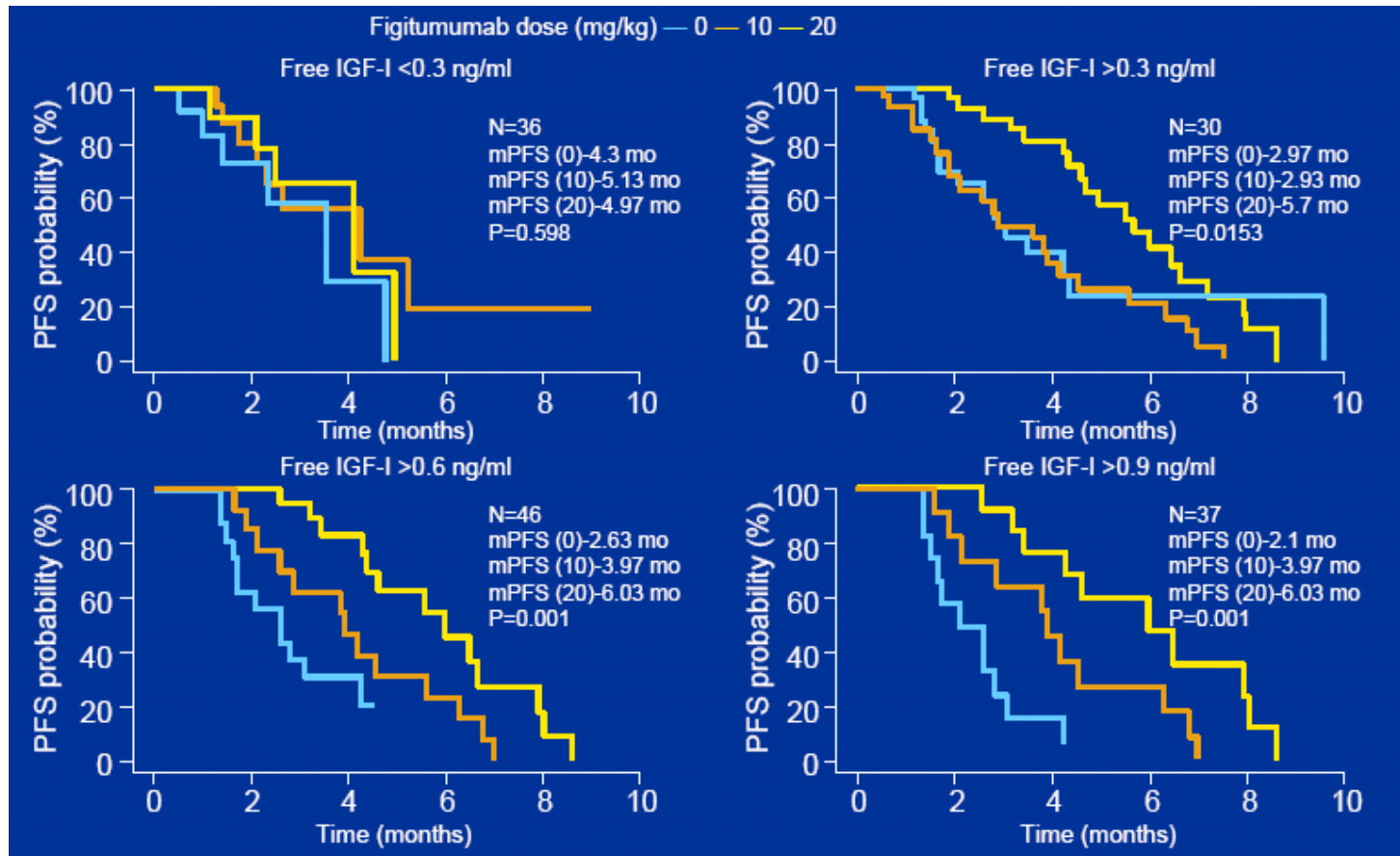
IGF1R Inhibitors



Treatment Responses in Bulky (> 5 cm) Squamous Tumor Lesions n = 24/ 28

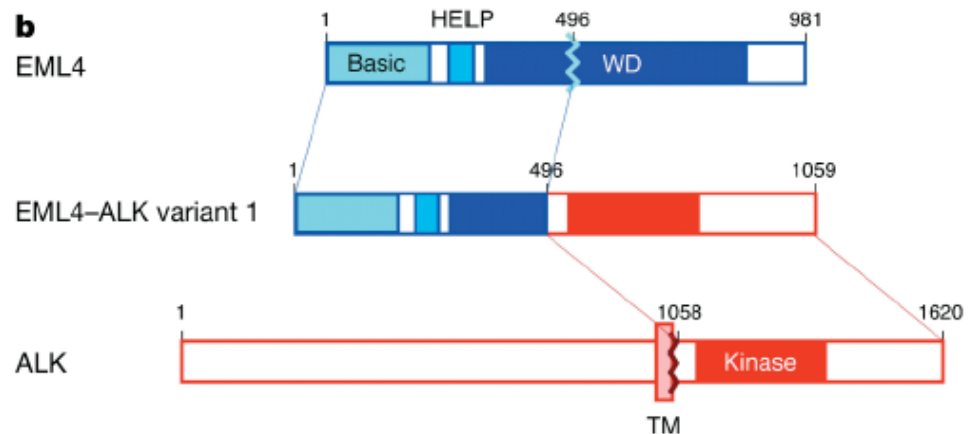


IGF1R Inhibitors



ALK Fusion

- Chromosome 2p inversion results in a fusion gene comprising of portions of the EML4 and ALK genes.
- Transgenic mice expressing EML4-ALK in lung alveolar epithelial cells develop adenocarcinoma nodules, treatable with a small-molecule ALK inhibitor.
- Occurs in ~4% of NSCLC.
 - Younger
 - Male
 - Light / never smokers
 - Adenocarcinoma, signet ring cell type
 - EGFR TKI-resistant



Soda M, et al. Nature 2007;448:561-6

Soda M, et al. Proc Natl Acad Sci 2008;105:19893-7

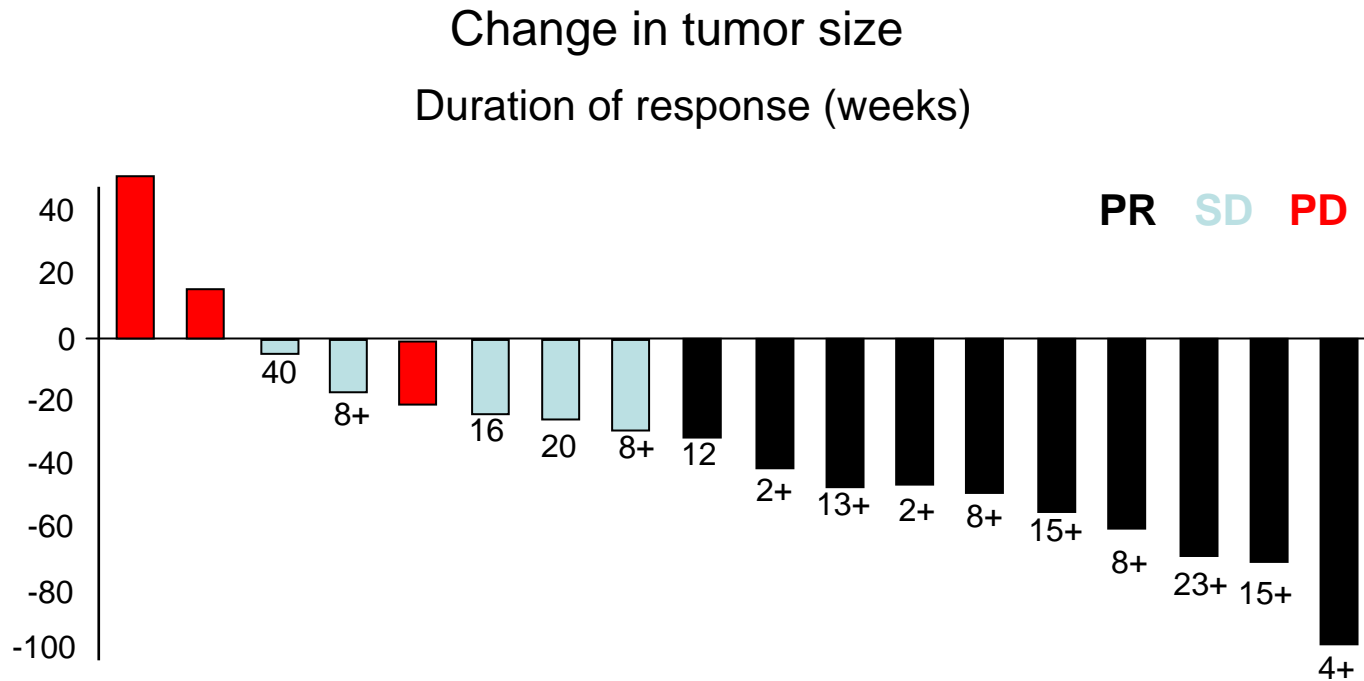
Shaw AT, et al. J Clin Oncol 2009;26:4247-53

ALK Inhibitors

- PF02341066: MET / ALK inhibitor
- 50 mg QD - 300 mg BID (n = 37)
- DLT: Grade 3 transaminitis (n = 1) at 200 mg QD, grade 3 fatigue (n = 2) at 300 mg BID
- MTD: 250 mg BID
- Nausea, vomiting, fatigue, diarrhea
- 1 pt (STS [inflammatory myofibroblastic tumor] harboring ALK rearrangement) PR
- 19 NSCLC harboring EML4-ALK rearrangement
 - 10 PR, 5 SD
- Ongoing randomized phase III trial of PF02341066 vs. pemetrexed or docetaxel in second-line NSCLC with ALK fusion (n = 318)

ALK Inhibitors

- Response



One patient had clinical progression and discontinued without radiographic confirmation.

BRAF Inhibitors

- BRAF mutation ~2%
- MSKCC (n = 17 / 916)
 - Exon 15 V600E (n = 11)
 - Exon 15 non-V600E (n = 2)
 - Exon 11 (n = 4)
- DFCI (n = 2 / 127)
 - Exon 15 non-V600E (n = 1)
 - Exon 11 (n = 1)
- U Penn (n = 5 / 179)
 - Exon 15 V600E (n = 1)
 - Exon 15 non-V600E (n = 1)
 - Exon 11 (n = 3)

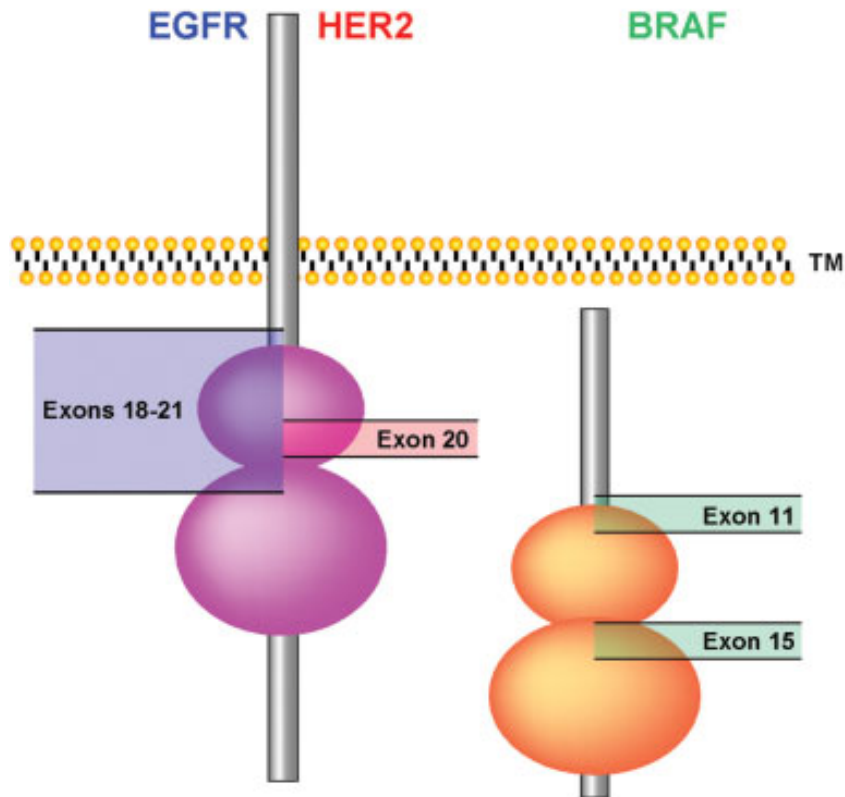
BRAF Inhibitors

- PLX4720
- GDC0879
- RAF265
- XL281

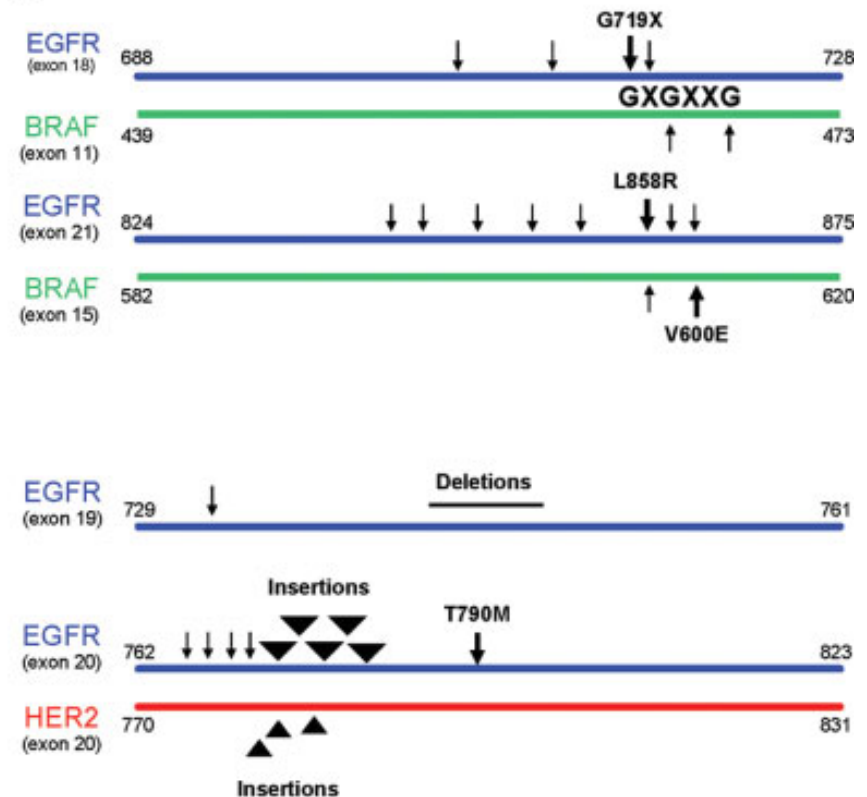
Practilas CA, et al. Cancer Res 2008;68:9375-83
Naoki K, et al. Cancer Res 2002;62:7001-3
Shaw AT, et al. Cancer Res 2002;62:6997-700

BRAF Mutation

a Mutations in kinase domains of EGFR, HER2 and BRAF genes.



b Location of mutations in EGFR, HER2 and BRAF genes.



MEK1 Mutation / Inhibitors

MEK1 Mutation

- K57N mutation in 2 of 207 NSCLC and 1 of 280 NSCLC

MEK inhibitors

- AZD6244
- RDEA119
- PD0325901

PIK3CA Mutation

	Percentage of tumors with mutation / number of samples			
	PIK3CA		PTEN	
Primary tumor tissues	%	#	%	#
Prostate	29	7	14	371
Breast	27	987	6	561
Endometrium	23	199	38	1467
Colon	15	1128	9	344
Central nervous system	5	808	20	2758
Skin	3	149	17	555
Lung	3	537	8	548

PI3K Inhibitors

PI3K inhibitors

- GDC0941
- XL147
- GSK1059615
- PX866
- BKM120

PI3K + mTOR inhibitors

- XL765
- SF1126
- BEZ235

AKT1 Mutations

- E17K mutation in breast (8%), colorectal (6%), and ovarian (2%)
- E17K mutation in 0 (n = 157) - 2 (n = 89) % (squamous cell 6%, adeno 0%) of NSCLC

AKT Inhibitors

- XL418
- MK2206
- GSK690693

Carpten JD, et al. Nature 2007;448:439-44
Kim MS, et al. Br J Cancer 2008;98:1533-5
Malanga D, et al. Cell Cycle 2008;5:665-9

LKB1 Mutation

- LKB1-AMPK-mTOR rather than PI3K-AKT-mTOR
- LKB1 inactivating mutation occurs in 10 - 38% of lung cancer.
 - Nonsense mutations
 - Indel frame shift mutations
 - Large deletions
 - Intronic mutations in splicing-conserved sites
- Biomarkers of mTOR inhibitors?
 - Temsirolimus
 - Everolimus
 - Deforolimus
 - AZD8055
 - PP242
 - WYE132
 - WYE354

Protein Folding and Degradation

- EGFR activating mutation: Exons 19 and 21
- Mutated EGFR with primary resistance: Exon 20
- Mutated EGFR with acquired resistance T790M
- Other mutated or activated kinase: c-Met, HER2, B-Raf
- HSP90 inhibitor
 - 17AAG (tanespimycin)
 - IPI504
 - 17DMAG (alvespimycin)
 - BIIB021 (CNF2024)
 - SNX5422
 - AUY922
 - CUDC305

Protein Folding and Degradation

- IPI504 400 → 225 mg/m² IV D1, 4, 8, 11, Q21D

	EGFR mutant	EGFR wild type	EGFR Pending	Overall
N	19	28	10	57
RR	0	4	0	4
SD >3 months	6	6	1	13
Clinical benefit	6	10	1	17
PFS	3.0 mo	3.9 mo		

Cell Cycle

- p53 mutation 50 to 70%
- Cyclin dependent kinase (CDK) inhibitor
- Checkpoint kinase (CHK) inhibitor
- Wee1 inhibitor
- Mitotic kinase inhibitors
- Kinesin spindle protein (KSP) inhibitor
- Aurora kinase inhibitor
- Polo-like kinase (PLK) inhibitor

Cell Cycle

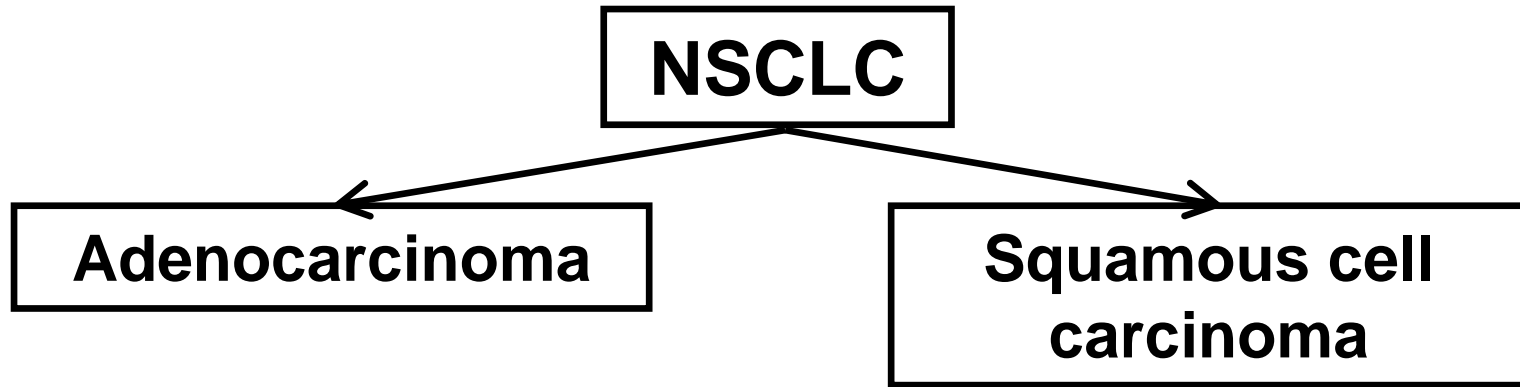
- Preclinical studies
 - BI6727 in the NCI-H460 xenograft model
 - GSK461364 in the MV522 and A549 xenograft models
- PLK inhibitors
 - BI2536
 - BI6727
 - GSK461364

 - ON01910
 - HMN214

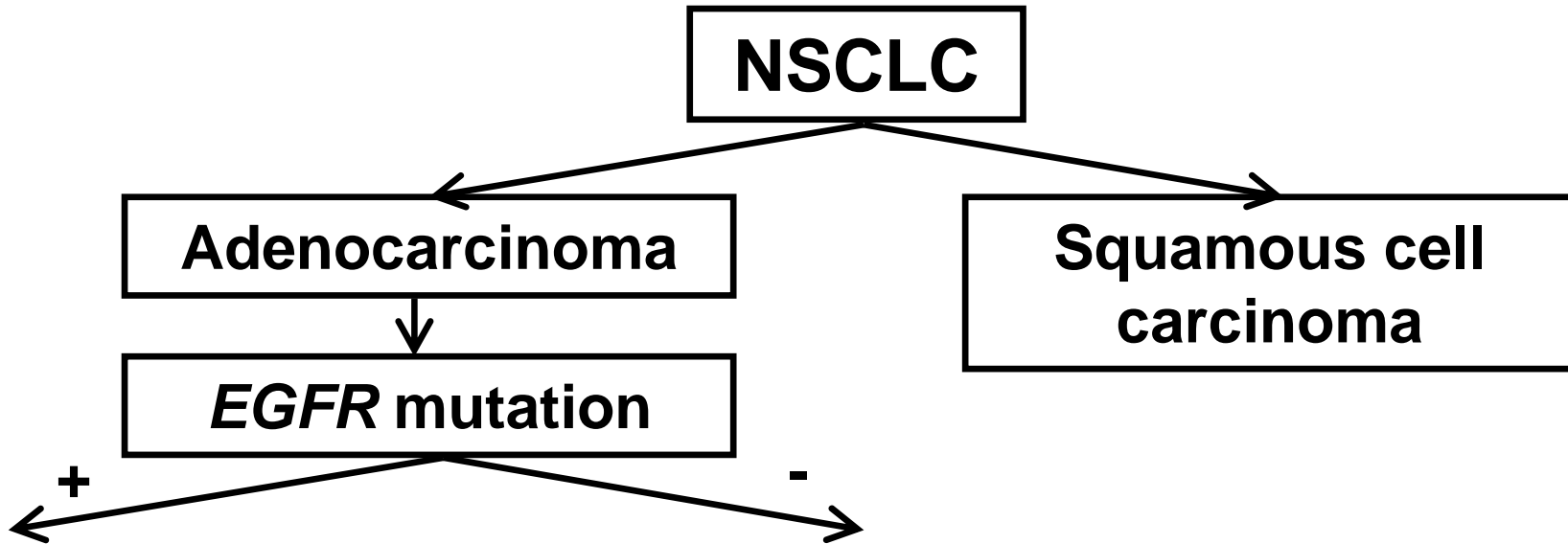
Cell Cycle

- BI2536: Polo-like kinase inhibitor
- Randomized phase II trial 200 mg on day 1 vs. 50 - 60 mg on days 1 - 3) in second- or third-line NSCLC (n = 95)
- PR: 4 of 95 patients
- Grade 4 adverse events were chiefly neutropenia, mostly transient.
- Grade 3 or 4 neutropenia (n = 12), including
 - Sepsis (n = 1)
 - Febrile neutropenia (n = 1)
 - Fever or infection associated with low neutrophil count (n = 10)
- Ongoing randomized phase II trial of BI6727 vs. BI6727 + pemetrexed vs. pemetrexed in second- or third-line NSCLC (n = 135)

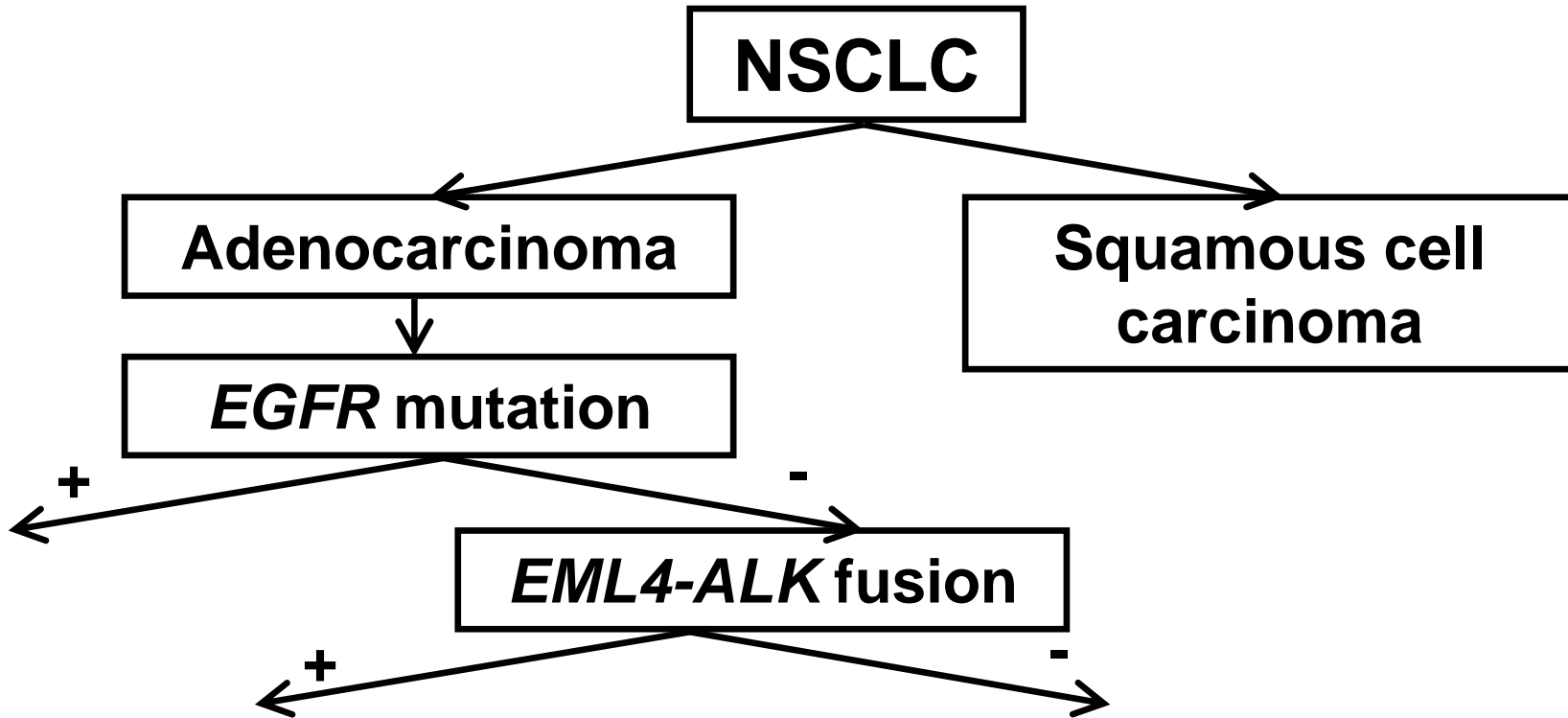
The Evolving World of NSCLC



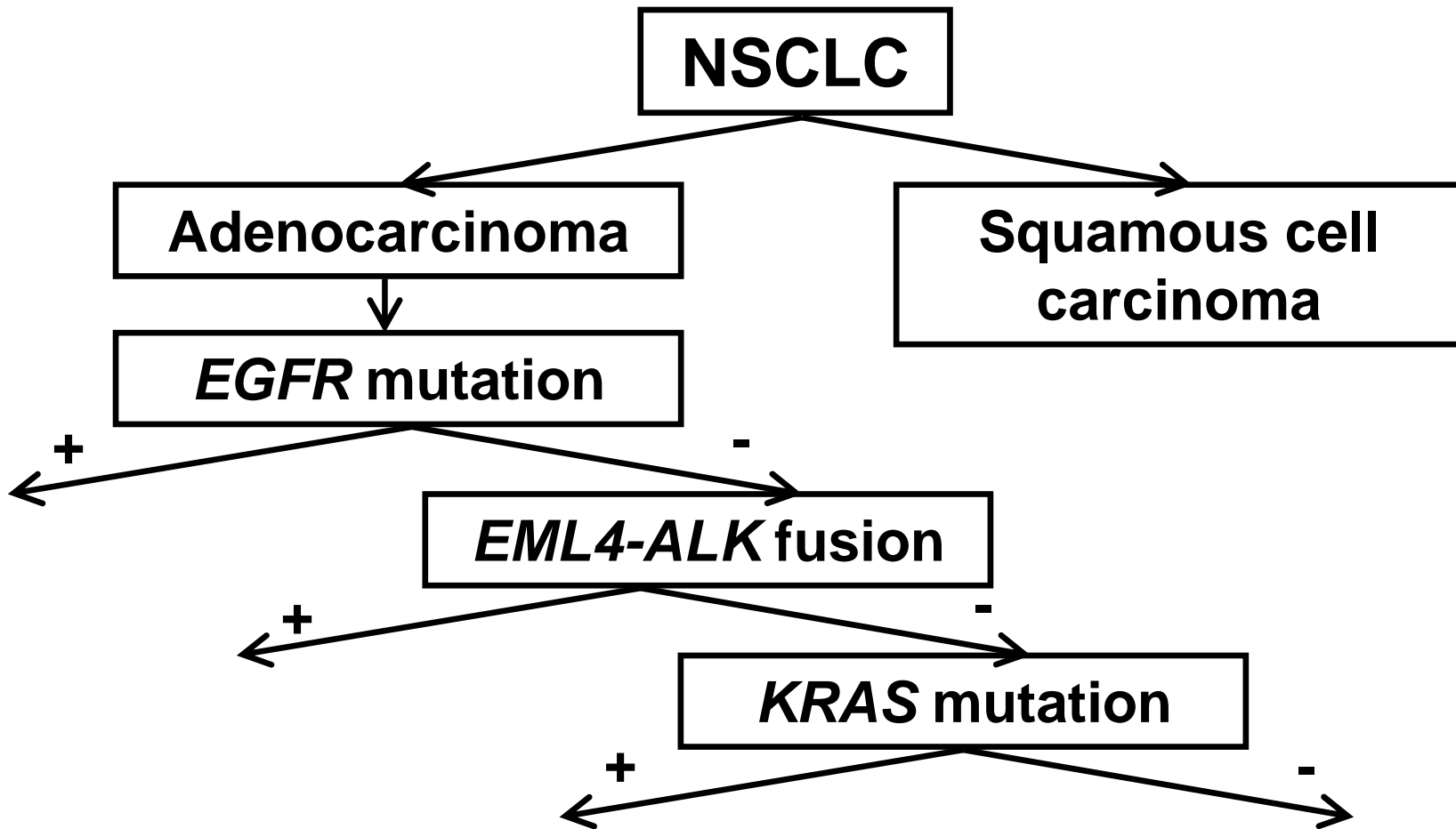
The Evolving World of NSCLC



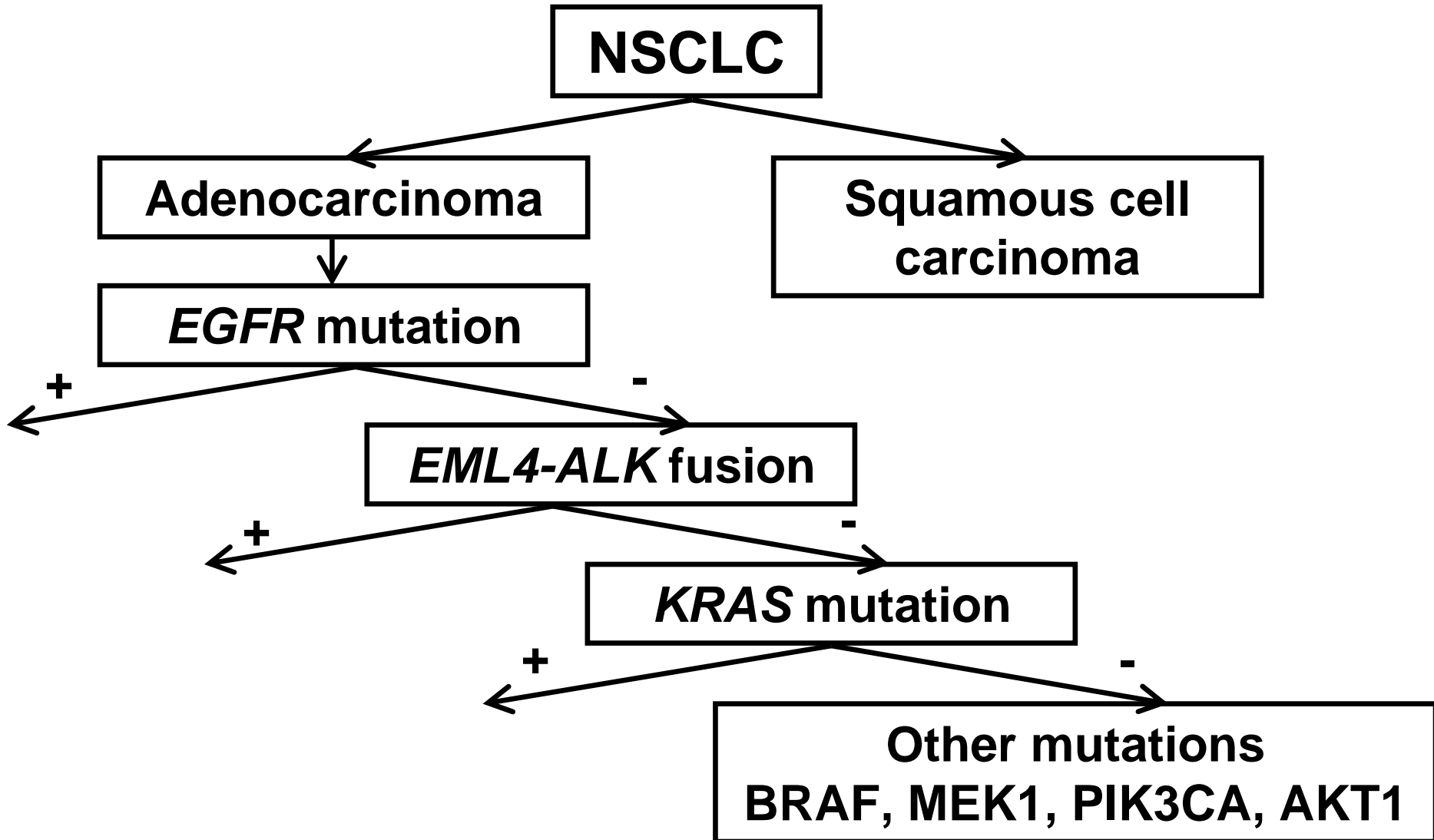
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