10os ENCONTROS 2014 DA PRIMAVERA ONCOLOGIA
ONCOLOGY SPRING MEETING

New modalities and new drugs in the NSCLC treatment

centro hospitalar do Porto

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Disclosure slide

I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd and Pfizer, for which I received appropriate honoraria.

Targeted and biologic therapies for NSCLC

EGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Merrimack Pharmaceuticals	NA NA MM111	Bispecific antibody fusion protien	HER2-HER3 heterodimer	Phase I/II Phase I for lung cancer	
	Genmab	Zalutumumab NA HuMax-EGFr	Human MoAB	EGFR	No longer in clinical development	Rash, fatigue, and pyrexia
	Pfizer	Canertinib NA CI-1033	Irreversible small-molecule TKI	Pan-HER	No longer in clinical development	Rash, diarrhea, asthenia, and stomatitis
	Merck KGaA/EMD Serono	Matuzumab NA EMD 72000	Humanized MoAB	EGFR	No longer in clinical development	Rash and diarrhea
	AVEO Pharmaceuticals	NA NA AV-412	Irreversible small-molecule TKI	EGFR/HER2	No longer in clinical development	Diarrhea, nausea, and fatigue

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

VEGF and VEGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Exelixis/ GlaxoSmith-Kline	Foretinib NA GSK1363089/XL880	Small-molecule TKI	VEGFR-2, MET, Ron	Phase II	Hypertension, fatigue, nausea, diarrhea, and night blindness
	Novartis	NA NA AEE 788	Irreversible small-molecule TKI	VEGFR-2, EGFR, HER2	Phase I/II	Fatigue, diarrhea, nausea, and rash
	Exelixis	NA NA XL820	Small-molecule TKI	VEGFR-2, PDGFR β, KIT	Phase II No active lung trials	Nausea, fatigue, and rash
	Exelixis	NA NA XL999	Small-molecule TKI	VEGFR, PDGFR, FLT-3, Src, FGFR	Phase II (terminated due to safety concerns)	Cardiac toxicity, diarrhea, asthenia, and hypersensitivity
	Bayor	Telatinib NA BAY57-9352	Small-molecule TKI	VEGFR-2,3, PDGFR-β and KIT	Phase I (completed)	Hypertension, hoarseness, anorexia, and diarrhea
	Sanofi-Aventis	Ombrabulin NA AVE8062	Combretastatin A-4 derivative	Tubulin-binding agent that targets the immature neovasculature of tumors	Phase II	
	Genentech	NA NA MEGF0444A/RG7414	Humanized antibody against EGFL7	Targets EGFL7. A vascular-restricted secreted protein present in the tracks that surround tumor blood vessels	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

ALK inhibitors / BRAF / ROS

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
ALK inhibitors/ braf/ros	Pfizer	Crizotinib Xalkori PF-02341066	Dual small-molecule ATP competitive inhibitor	ALK, c-Met, ROS	FDA approved for ALK+ locally advanced or metastatic NSCLC	Nausea, diarrhea, visual disturbances, alanine aminotransferase elevation, and fatigue
	Xcovery	NA NA X-396	Small-molecule inhibitor	ALK	Phase I	
	Novartis	NA NA LDK378	Small-molecule inhibitor	ALK translocations	Phase I lung	
	Ariad Pharmeceuticals	NA NA AP26113	Small-molecule inhibitor	ALK/EGFR	Phase I/II	
	Chugai Pharmaceuticals	NA NA CHS424802/AF802	Small-molecule inhibitor	ALK	Phase I/II	
BRAF inhibitors	Plexxikon/Roche	Vemurafenib Zelboraf PLX4032/ RG7204	Small-molecule inhibitor	BRAF (V600E) mutation)	FDA approved for metastatic melanoma Phase I for NSCLC	Diarrhea, rash, fatigue, and skin squamous cell carcinoma
	GlaxoSmithKline	Dabrafenib NA GSK2118436	Small-molecule inhibitor	Mutant BRAF kinase	Phase III for melanoma Phase II for NSCLC	Pyrexia, rash, skin squamous cell carcinoma, and diarrhea
	Novartis	NA NA LGX818	Small-molecule inhibitor	BRAF kinase inhibitor	Phase I/II	
	ArQule	NA NA ArQ736	Small-molecule inhibotor	Pan-Raf inhibitor	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

BCL-2 inhibitors / BCR-ABL / STAT inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
BCL-2 inhibitors	Abbott & Genentech	Navitoclax NA ABT-263/ ABT-737	Small-molecule inhibitor (ABT-263 is orally bio-available)	Bad-like BH3 mimetic	Phase II for SCLC	Diarrhea, back pain, and throm-bocytopenia
	Genta	Oblimerson Genasense G3139	Antisense oligo-deoxyribo-nucleotide	Bcl-2	Phase II/III	Fever and elevated liver enzymes
	GeminX	Obatoclax NA GX15-070	Small-molecule inhibitor	Pan Bcl-2	Phase I/II	Neurotoxicity, cytopenias
	Ascenta	NA NA AT101	Negative enantiomer of gossypol	Pan Bcl-2	Phase II (NSCLC studies ter-minated, SCLC ongoing)	Gastrointestinal side effects
BCR-ABL/SRC tyrosine kinase / STAT inhibitors	Bristol-myers squibb	Dasatinib sprycel BMS-354825	Small-molecule TKI of SRC-family	Src, BCR-ABL, KIT, PDGFR, FMS or colony-stimulating factor 1 receptor CSF1R	FDA approved for chronic myelogenous leukemia Phase II for NSCLC	Fluid retention, pleural effusion, diarrhea, prolonged QTc, my-elosuppression, and rash
	Novartis	Imatinib gleevec STI-571	Small-molecule TKI	KIT, PDGFR, BCR-ABL fusion protein	FDA approved forGastrointes-tinal stromal tumorDermato-fibrosarcoma protuberans-Philadelphia chromosome positive chronic myelog-enous leukemia Phase II for NSCLC	Fluid retention, diarrhea, my-elosuppression, and rash
	AstraZeneca	Saracatinib NA AZD 0530	Small-molecule TKI of SRC-family binds the active conformation of the ATP binding pocket	Src, BCR-ABL(Inhibits Src kinase mediated osteoclast resorp-tion)	Phase II	Leukopenia, febrile neutrope-nia, and asthenia
	Pfizer (Wyeth)	Bosutinib NA SKI-606	4-anilino-3-quinolinecarbo-nitrile dual Src/Abl kinase inhibitor	Src, ABL	Phase II Phase I for lung cancer	Diarrhea, anorexia, and nausea
	Kinex Pharmaceuticals	NA NA KX2-391	Small-molecule TKI target-ing the substrate binding site	c-Src	Phase II Phase I for lung cancer	Hypokalemia, anemia, elevated AST, fatigue, dyspnea, fever, vomiting, constipation, he-maturia, and lymphopenia
	Exelixis	NA NA XL228	Multitargeted TKI	Src, ABL, IGF-1R, AURORA, FGFR1-3	Phase I	Nausea, neutropenia, fatigue, and hypoglycemia
	Otsuka Beijing Re-searchInstitute	NA NA OPB 51602	inhibitor of signal transducer and activator of transcrip-tion 3	STAT 3	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Epigenetic modulators of gene expression

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
		Valproic acid depakote	Aliphatic acid	Class I and IIa specific	Phase II	Anemia, neurological toxicity, nausea, and hepatic toxicity
		Sodium phenylbutyrate	Aliphatic acid	Class I and IIa specific	Phase II	Neuro-cortical toxicity, hypokalemia, hyponatremia, hyperuricemia, and nausea
	Novartis	Panobinostat Faridak LBH589	Hydroxamic acid-type	Pan-HDAC (all isoforms)	Phase II Phase I for lung cancer	Rash, QT interval prolongation, nausea, diarrhea, hypokalemia, and thrombocytopenia
	S*BIO	NA NA SB939	Small-molecule HDAC inhibitor	HDAC	Phase II Phase I for lung (no ongoing trials)	Fatigue, troponin elevation, and QTc prolongation
	Curis	NA NA CUDC-101	Hydroxamic acid	HDAC, HER2, EGFR	Phase Ib	Fatigue, increased creatinine, and increased hepatic enzymes
	Pharmacyclics	NA NA PCI-24781	Cyclic tetrapeptide	Class I and II	Phase I/II	
	Gloucestor Pharmaceuticals	NA NA FK-228	Cyclic tetrapeptide(depsipeptide)	Class I	Phase IIb Phase I for lung	
	Chroma therapeutics	NA NA CHR-3996	Small-molecule inhibitor	Class I HDAC isoforms	Phase I	Fatigue, nausea, and vomiting
	Novartis	Dacinostat NA NVP-LAQ824	Hydroxamic acid derivative	Class I and II	Drug dropped from further development after phase I	
	Italformaco	Givinostat NA ITF2357	Hydroxamic acid derivative	Class I and II	Currently being studied in hematologic malignancies in phase II	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Proteasome and FGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Proteasome inhibitors	Millennium Pharmaceuticals (takeda oncology)	Bortezomib velcade PS-341	Reversible inhibitor	26S proteasome and client proteins (i.e., p27, p53, NFkB, Bcl-2, Bax)	FDA approved forMultiple myelomaMantle cell lymphoma Phase II for NSCLC	Asthenia, nausea, diarrhea, constipation, peripheral neuropathy, hypotension, and thrombocytopenia
	Onyx Pharmaceuticals	Carfilzomib NA PR-171	Irreversible inhibitor	20S proteasome subunit	Phase II Phase I for lung cancer	Pancytopenia, peripheral neuropathy
	Millennium Pharmaceuticals (takeda oncology)	NA NA MLN9708	Reversible inhibitor	20S proteasome subunit	Phase I/II Phase I for lung cancer	Anorexia, dehydration, fatigue, nausea, peripheral sensory neuropathy, macular rash, renal failure and thrombocytopenia
	Nereus Pharmaceuticals	Salinosporamide A NA NPI-0052	Irreversible inhibitor	20S catalytic core subunit of the proteasome	Phase I	Fatigue, nausea, and neurological toxicity
	Cephalon and ethical oncology science	NA NA CEP-18770	Slowly reversible	Inhibits chymotrypsin-like activity of proteasome	Phase I	
FGFR inhibitors	Bristol-Myers Squibb	Brivanib NA BMS-582664	Small-molecule TKI	FGFR and VEGFR-2	Phase III Phase II for NSCLC	Hypertension, and fatigue
	Novartis	Dovitinib NA TKI-258	Small-molecule inhibitor	FGFR-1,2,3, PDGFR, VEGFR-2	Phase II Phase I for lung cancer	Hypertension, anorexia, nausea, vomiting, fatigue, and headache
	Five prime therapeutics	FP-1039	Soluble fusion protein consisting of a portion of the FGFR1 linked to Fc portion of IgG1	FGF ligand trap (multiple FGF's)	Phase II Phase I including lung (completed)	Neutropenia, bowel perforation, urticaria, and atrial fibrillation
	AstraZeneca	NA NA AZD4547	Small-molecule inhibitor	FGFR1,2,3	Phase I/II Phase I for lung cancer	
	ARIAD	Ponatinib NA AP24534	Small-molecule inhibitor	Pan-FGFR inhibitorPan-BCR ABL inhibitor	Phase II CMLCurrently no clinical trials in solid tumors initiated yer	Low platelet counts, headache, nausea, joint pain, fatigue, anemia, increased lipase, muscle spasms, rash, and pancreatitis
	Taiho Pharmaceutical	TSU-68	Small-molecule inhibitor	FGFR, PDGFR, VEGFR	Phase I/IINo active trials for lung	Fatigue, AST/ALT elevation, and diarrhea
	Novartis	NA NA BGJ398	Small-molecule inhibitor	FGFR1,2,3	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Hedgehog antagonists and hormone therapy

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Hedgehog antagonists	Genentech	Vismodegib NA GDC-0449	Small-molecule inhibitor	Smoothened receptor in the sonic hedgehog pathway	Phase II	Dysgeusia, hyponatremia, fatigue, and muscle spasms
	Novartis	NA NA LDE 225	Small-molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase II Phase I for lung cancer	Fatigue, nausea, anorexia, muscle cramps, and dysgeusia
	Infinity	NA NA IPI-926	Small-molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase II Phase I for lung	Fatigue, nausea, and transaminitis
	Bristol-Myers Squibb/ exelixis	NA NA BMS-33923/ XL-1395	Small-molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase I	Dysgeusia, hypophosphatemia, muscle spasms, and increase in lipase
	Pfizer	NA NA PF04449913	Small-molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase I	
	Eli Lilly	NA NA LY2940680	Small-molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase I	
Hormone therapy	AstraZeneca	Fulvestrant Faslodex ICI 182780	Blocks estrogen activity through receptor	Estrogen receptor	FDA approved for hormone receptor positive breast cancer Phase II for postmenopausal women with NSCLC	Hot flashes, injection-site reaction, headache, gastrointestinal disturbances, and back pain
	AstraZeneca	Anastrazole Arimidex	Decreases estrogen in postmenopausal women	Aromatase inhibitor	FDA approved for hormone receptor positive breast cancer Phase II for postmenopausal women with NSCLC	Hot flashes, joint disorders, osteoporosis, nausea, mood changes, and hypertension
	GTx Inc	Enobosarm Osterine GTx-024	A selective androgen receptor modulator	aryl propionamides	Phase III	Hair growth/virilization, prostatic hyperplasia, elevated red blood cell counts, decrease in HDL cholesterol, and liver function abnormalities

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Hypoxia activated prodrug

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Hypoxia activated prodrug	Threshold Pharmaceuticals	NA NA TH-302	Tumor-selective hypoxia activated prodrug	2-Nitroimidazole moiety is triggered by hypoxic conditions to release DNA-alkylating dibromo isophosphoramide mustard	Phase II Phase I/II for NSCLC	Skin lesions, mucositis, fatigue, and nausea,
	Proacta	NA NA PR-104	Tumor selective hypoxia activated preprodrug	Converted to a prodrug that is reduced under hypoxic conditions to a hydroxylaminemetabolite, PR-104H, which is a cytotoxic nitrogen mustard alkylating agent.	Phase II (phase II in NSCLC and SCLC terminated)	Cytopenias, nausea, vomiting, and fatigue
	Novacea	Banoxatrone NA AQ4N	Tumor-selective hypoxia-activated prodrug	Converted selectively under hypoxic conditions to the drug's active form, AQ4, a potent topoisomerase II inhibitor	Phase I/II No active trials for lung	
	SRI International	Tirapazamine NA SR-4233	Benzotriazine di-N-oxide, which acts as a hypoxia-activated cytotoxin	Forms free radicals in hypoxic cells that cause DNA damage. Also sensitizes hypoxic cells to ionizing radiation and inhibits the repair via inhibition of topoisomerase II	Phase III completed No longer underdevelopment for lung or other cancers	Ototoxicity, muscle cramps, nausea, and vomiting

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

HIF-1 inhibitor and immunomodelatory agents

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
HIF-1 inhibitor	Oncothyreon	PX-478	Small-molecule inhibitor	HIF-1α	Phase I	Anemia, fatigue, nausea, elevated AST/ALT
	Eon Pharmaceuticals	EZN-2968	**HIF-1α mRNA antagonist**	HIF-1α	Phase I	Vomiting and fatigue
Immunomodulatory agents	Celgene	Lenalidomide revlimid CC-5013		Immunomodulatory, anti-inflammatory, and antiangiogenic	FDA approved for Multiple myeloma,Myelodysplastic syndrome. Phase II completed for NSCLC	Myelosuppression, rash, and thrombosis
	Celgene	Thalidomide thalomid		Immunomodulatory, anti-inflammatory, and antiangiogenic	FDA approved for -multiple myeloma Phase II for NSCLC	Somnolence, peripheral neuropathy, dizziness, neutropenia, thrombosis, and rash
	Agennix	Talactoferrin NA rhLF	Recombinant human lactoferrin	Dendritic cell recruiter and activator	Phase III randomized trial vs. placebo negative for OS in previously treated NSCLC	Diarrhea
Immunomodulatory antibodies	Bristol-Myers Squibb	Ipilimumab Yervoy MDX 010	IgG1 Human MoAB	CTLA-4	FDA approved for metastatic melanoma Phase II for lung cancer.	Rash, diarrhea (autoimmune colitis), hypothyroidism,hypophisitis, and hepatitis
	MedImmune	Tremelimumab/ ticilimumab NA CP675,206	IgG2 monoclonal antibody	CTLA-4	Phase II (malignant mesothelioma)	
	Bristol-Meyers Squibb	NA NA MDX-1105	Human IgG4 MoAB	Inhibitor of PD-L1	Phase I	Rash, diarrhea, fatigue, hypothyroidism,hypophisitis, and hepatitis
	Bristol-Meyers Squibb	NA NA MDX- 1106/ BMS936558/ ONO4538	Human IgG4 MoAB	Inhibitor of PD1(a receptor expressed on activated T cells, and may suppress antitumor immunity)	Phase I	Rash,lymphopeni, arthralgia, and myalgia
	GlaxoSmithKline / Amplimmune	NA NA AMP-224	Fc-fusion protein	Targets PD-L2, which binds to PD-1	Phase I	
	Bristol-Myers Squibb	BMS-663513	Humanized MoAB	Agonist of CD-137, a TNF receptor	Phase II (terminated) Phase I in combination with chemoradiation in NSCLC (terminated)	Neutropenia, elevated liver enzymes, rash, pruritus, diarrhea

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

IAP antagonist and IGF-1R inhibitor

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
IAPs antagonist	Human Genome Sciences/Aegera	NA NA HGS 1029/ AEG 40826	Small-molecule Smac mimetic	IAPs antagonist	Phase I	Nausea, anorexia, diarrhea, fatigue, elevated amylase and lipase, and supraventricular tachycardia
	Tetralogic	NA NA TL32711	Small-molecule Smac mimetic	IAPs antagonist	Phase I/II	
	Ascenta Therapeutics	NA NA AT-406	Small-molecule Smac mimetic	Multi-IAP antagonist (XIAP, c-IAP1, c-IAP2, and ML-IAP)	Phase I	
	Genentech	NA NA GDC0917	Small-molecule peptide Smac mimetic	IAPs antagonist	Phase I	
	Novartis	NA NA LCL161	Small-molecule Smac mimetic	IAPs antagonist	Phase I	
IGF-1R inhibitor	Pfizer	Figitumumab CP-751871	IgG2 type human MoAB	IGF-1R	Phase III terminated (further development halted)	Cardiac toxicity, hyperglycemia, asthenia, anorexia, pneumonia, dehydration, and early death.
	OSI Pharmaceuticals/ Astellas	NA NA	Small-molecule inhibitor	IGF-1R and IR	Phase III Phase II for NSCLC	Nausea, vomiting, fatigue, hyperglycemia, and elevated liver enzymes
	Amgen	NA NA AM	IgG1-type human MoAB	IGF-1R	Phase III Phase I/II for lung was terminated based on results from similar study	Thrombocytopenia, neutropenia, hyperglycemia, fatigue, rash, elevated LFTs, and asymptomatic TSH increase
	ImClone	Cixutumumab NA IMC-A12	IgG1-type human MoAB	IGF-1R	Phase II	Pruritus, rash, anemia, hyperglycemia, and infusion-related reaction
	Merck	Dalotuzumab NA MK-0646	IgG1-type humanized MoAB	IGF-1R	Phase II	Fatigue, hyperglycemia, nausea, constipation, and diarrhea
	Biogen idec	BIIB022	Human nonglycosylated IgG4 MoAB	IGF-1R	Phase II Phase I for NSCLC	Hypertension, fatigue, dyspnea, and QTc prolongation
	Bristol-Myers Squibb	NA NA BMS-754807	Small-molecule reversible inhibitor	IGF-1R and IR	Phase I	Fatigue and hyperglycemia
	Sanofi-Aventis	NA NA AVE1642	Humanized MoAB	IGF-1R	Phase I/II(no active trials. Company discontinued development)	Hyperglycemia, asthenia and hypersensitivity
	Genmab & Roche	Robatumumab NA R1507	IgG1-type human MoAB	IGF-1R	Phase II (development is halted)	Fatigue, anorexia, and weight loss
	Schering-Plough	Robatumumab NA SCH717454	IgG1-type human MoAB	IGF-1R	Phase II (development halted)	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Integrins and mTOR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Integrins	Merck Serono	Cilengitide NA EMD121974	Cyclic peptide	$\alpha_v\beta_3$, and $\alpha_v\beta_5$ integrin	Phase III Phase I/II for NSCLC	Lymphopenia, thrombocytopenia, neutropenia, fatigue, nausea,anorexia
	PDL BioPharma and Biogen Idec	Volociximab NA M200	Chimeric MoAB	$\alpha 5\beta 1$ integrin	Phase II	Fatigue, nausea, constipation, diarrhea, and arthralgia
	Pfizer	NA NA PF-04605412	Human IgG1 MoAB	$\alpha 5\beta 1$ integrin	Phase I	
	MedImmune	Vitaxin NA MEDI-522	Humanized IgG1 MoAB	$\alpha 5\beta 1$ integrin	Phase I	Chills, fever, and nausea
mTOR inhibitors	Pfizer (Wyeth)	Temsirolimus Torisel CCI-779	Ester analog of rapamycin	mTORC1	FDA approved foradvanced renal cell carcinoma Phase II for NSCLC	Fatigue, rash, asthenia, hyperglycemia, hyperlipemia, hypophosphatemia, myelosuppression, nausea, and diarrhea
	Novartis	Everolimus Afinitor RAD001	Derivative of the natural macrocyclic lactone sirolimus	mTORC1	FDA approved for advanced renal cell carcinoma Phase II for NSCLC closed (Gefitinib +Everolimus)	Stomatitis, asthenia, pneumonitis, fatigue, infections, diarrhea, and neutropenia
	Merck/Ariad	Ridaforolimus Taltorvic (proposed) AP-23573	Small-moleculeserine/threonine kinase inhibitor	mTOR	Phase III Phase II for NSCLC	Fatigue, anorexia, and mucositis
	Generic drug with multiple manufacturers	Sirolimus Rapamune Rapamycin	A macrolide derived from *Streptomyces hygroscopicus*	mTORC1	Phase I/II	Cytopenias, hypoalbuminemia, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia
	AstraZeneca	NA NA AZD 8055	ATP competitive small-molecule inhibitor	mTOR C1,2	Phase I/II	Transaminitis,
	OSI Pharmaceuticals	NA NA OSI 027	Small-molecule inhibitor	mTORC1,2	Phase II	
	Novartis	NA NA BEZ 235	Small-molecule inhibitor	PI3K/mTORC1	Phase I/II	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

c-MET/HGFR pathway inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
c-MET/HGFR pathway inhibitors	ArQule	Tivantinib NA ARQ197	Small-molecule inhibitor	c-MET/ HGFR	Phase III	Hepatotoxicity
	Roche/Genentech	Onartuzumab NA MetMab/RG3638	Humanized monovalent MoAB	c-MET	Phase III	Peripheral edema
	Amgen	Rilotumumab NA AMG 102	Human IgG2 MoAB	HGF (ligand)	Phase I/II	Fatigue, constipation, anorexia, nausea, and dyspnea
	AVEO Pharmaceuticals	Ficlatuzumab NA AV-299/SCH900105	Humanized IgG1 MoAB	HGF (ligand)	Randomized phase II	Fatigue, peripheral edema, headache, and diarrhea
	Astex Pharmaceuticals//	Amuvatinib NA MP-470	Small-molecule inhibitor	KIT, c-MET, RET, PDGFR, FLT3	Phase II (SCLC)	
	MethylGene	NA NA MGCD265	Small-molecule inhibitor	c-MET, VEGFR1,2,3, Ron, Tie-2	Phase I/II	
	Merck	NA NA MK2461	Small-molecule inhibitor	c-MET	Phase I/II	
	Bristol-Myers Squibb	NA NA BMS777607	Small-molecule inhibitor	c-MET	Phase I/II	
	Incyte	NA NA INCB28060	Small-molecule inhibitor	c-MET	Phase I	
	Amgen	NA NA AMG 208	Small-molecule inhibitor	c-MET	Phase I	
	Eli Lilly	NA NA LY2875358	Humanized IgG4 MoAB	c-MET	Phase I	
	Pfizer	NA NA PF-4217903	Small-molecule inhibitor	c-MET/ HGFR	Phase I (terminated)	
	Johnson & Johnson	NA NA JNJ38877605	Small-molecule inhibitor	c-MET	Phase I (terminated)	Elevation in Creatinine
	SGX Pharmaceuticals	NA NA SGX523	Selective small-molecule inhibitor	Met	Phase I (terminated)	Nephrotoxicity, fatigue, pyrexia, nausea, and vomiting

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

MEK inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
MEK inhibitors	AstraZeneca/Array BioPharma	Selumetinib NA AZD6244/ARRY142880	Allosteric inhibitor	MEK ½	Phase III Phase II completed in NSCLC (phase I ongoing in KRAS & BRAF mutants)	Rash, diarrhea, nausea, and emesis
	Merck KGaA/EMD Serono	NA NA AS 703026/ MSC1936369B	Noncompetitive small-molecule inhibitor	MEK 1/2	Phase I/II	Asthenia, diarrhea, constipation, rash, nausea, and vomiting
	Ardea Biosciences	NA NA RDEA119/ BAY 869766	Allosteric inhibitor	MEK 1/2	Phase I/II	Rash, diarrhea, nausea, vomiting, fatigue, and peripheral edema
	GlaxoSmithKline	Trametinib NA GSK1120212	Allosteric small-molecule inhibitor	MEK 1/2	Phase I/ II	Rash, diarrhea, and central serous retinopathy
	Novartis	NA NA MEK162	Small-molecule inhibitor	MEK	Phase IIPhase I in lung cancer	
	Pfizer	NA NA PD325901	Small-molecule inhibitor	MEK 1/2	Phase I	Ocular toxicity, neurological toxicity
	AstraZeneca/Array BioPharma	NA NA AZD8330	Small-molecule inhibitor	MEK 1	Phase I	
	Genentech	NA NA GDC-0973/ XL518	Small-molecule inhibitor	MEK 1	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Inhibitors of mitosis

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Polo-like kinase inhibitor	Boehringer ingelheim	NA NA BI-2536	ATP competitive small-molecule inhibitor	Plk1 (serine threonine kinase)	Phase II	Neutropenia, fatigue, and nausea
	Boehringer ingelheim	Volasertib NA BI-6727	Dihydropteridinone derivative (binds to ATP-binding pocket)	Plk1 (serine threonine kinase)	Phase II	Anemia, neutropenia, thrombocytopenia, and fatigue
	GlaxoSmithKline	NA NA GSK461364	ATP competitive inhibitor	Plk1 (serine threonine kinase)	Phase I	Fatigue, anemia, abdominal pain
	Nerviano Medical Sciences	NA NA NMS1286937	Small-molecule inhibitor	Plk1 (serine threonine kinase)	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Notch pathway inhibitors and osteoclast function modifiers

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Notch pathway inhibitors	Roche	NA NA RO 4929097	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase II	Asthenia, nausea, diarrhea, hypophosphatemia, and pruritus.
	Merck	NA NA MK0752	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch	Phase I/II Phase I in lung cancer	Abdominal cramps, diarrhea, nausea, and fatigue
	Pfizer	NA NA PF03084014	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase I	Gastrointestinal toxicity (reduced with steroids)
	Regeneron	NA NA REGN421	Human MoAB	Delta-4 ligand	Phase I	
Osteoclast function modifiers (important in bone metastasis)	Novartis	Zoledronate zometa NA	Farnesyl pyrophosphate	Osteoclast inhibitor	FDA approved for OsteoporosisCancer-related bone metastases (multiple myeloma and solid tumors)	Hypocalcemia, osteonecrosis of jaw, and renal toxicity
	Amgen	Denosumab Xgeva/Prolia AMG-162	Fully human monoclonal antibody	RANK ligand inhibitor (transmembrane protein important for osteoclast activity and survival)	FDA approved for Osteoporosis **Prevention of skeletal-related events in patients with bone metastases from solid tumors**	Hypocalcemia, osteonecrosis of jaw, serious infections, and skin reactions
	Procter & Gamble Pharmaceuticals	Etidronate Didronel	Bisphosphonate-ATP requiring small molecule	Osteoclast inhibitor	FDA approved for symptomatic Paget's disease, and hypercalcemia from cancer Phase III for bone metastasis	Esophagitis, arthralgias, and hypersensitivity reactions
	Novartis	Alendronate Fosamax	Nitrogen containing bisphosphonate targets farnesyl pyrophosphate synthase	Osteoclast inhibitor	FDA approved for osteoporosis Phase III for bone metastasis	Esophagitis, osteonecrosis of jaw, delayed healing, hypersensitivity reaction, and bone/muscle pains
	Merck	NA NA L-000845704	Integrin antagonist- decreases bone resorption	αvβ3	Phase III for osteoporosis. (not being pursued further)	
	Merck	Odanacatib NA MK-0822	Anti-cathepsin K, (decreases bone resorption)	Cathepsin K (osteoclast specific enzyme)	Phase III for osteoporosisNo open cancer-specific trials	
	Novartis	Balicatib NA AAE-581	Anticathepsin K		Phase II for osteoporosisNo open cancer trials	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

PI-3K/AKT inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
PI-3K/AKT inhibitors: AKT inhibitors	Merck	NA NA MK2206	Non-ATP competitive allosteric Akt	Akt	Phase II	Rash, mucositis, and gastrointestinal toxicity
	Agouron Pharmaceuticals	Nelfinavir Viracept AG 1343	Protease inhibitor	Akt	Phase II (Phase II for lung terminated due to poor accrual)	Diarrhea, rash, fatigue, leukopenia
	Keryx/AOI Pharmaceuticals	Perifosine NA KRX-0401	Alkylphospholipid	Akt	Phase I/II (NSCLC trial suspended)	Nausea, vomiting, diarrhea, and fatigue
PI-3K inhibitors	Novartis	NA NA BEZ235	Small-molecule inhibitor	PI-3K (pan-class 1), mTOR complexes 1/2	Phase I/II	Nausea, emesis, diarrhea, fatigue, and anemia
	Novartis	NA NA BKM120	Small-molecule ATP competitive inhibitor	PI-3K (pan-class 1)	Phase II	Rash, hyperglycemia, altered mood, and pruritus
	Onconova Therapeutics	Rigosertib estybon ON01910	Non-ATP competitive small-molecule inhibitor	PI-3K inhibitordown-regulates Cyclin D1, induces NOXA, BIM and JNK	Phase III Phase I in solid tumors including lung cancer	Fatigue and anorexia
	Exelixis	NA NA XL147	Small-molecule inhibitor	PI-3K (class 1 isoforms)	Phase II Phase I for lung cancer	Rash, arterial thrombosis, transaminitis, and hyperglycemia
	Novartis	NA NA NVP-BGT226	Dual small-molecule inhibitor	PI-3K and mTOR	Phase I/II (completed)	
	Oncothyreon	NA NA PX-866	Irreversible small-molecule inhibitor (Wortmanin analog)	PI-3K, lowers p-mTOR, p-S6 ribosomal protein	Phase I/II	Diarrhea, nausea, and vomiting
	Genentech	NA NA GDC-0941	Small-molecule inhibitor	PI-3K (class 1 isoforms)	Phase I	Nausea, fatigue, diarrhea, dysgeusia, headache, and pleural effusion
	Pfizer	NA NA PF-04691502	Dual molecule inhibitor	PI-3K and mTOR	Phase I	
	Exelixis	NA NA XL765	Dual selective oral inhibitor	PI-3K (Class 1) and mTOR	Phase I	Nausea, diarrhea, transaminitis, rash, anorexia, and fatigue
	Bayor	BAY80-6946	Highly selective reversible inhibitor	Pan-class I PI-3K	Phase I	Fatigue, nausea, diarrhea, mucositis, dysgeusia, and anemia

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

PDGFRα and PARP inhibitors, SMAC mimetics, SURVIVIN and telomerase inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
PDGFRα inhibitors	Imclone LLC	Ramucirumab NA IMC-3G3	Human IgG1 MoAB	PDGFRα	Phase II	Fatigue
	MedImmune	NA NA MEDI-575	MoAB	PDGFRα	Phase II	
PARP inhibitors	Sanofi-Aventis(BiPar Sciences)	Iniparib NA BSI-201	Small lipophilic molecule inhibitor	PARP-1	Phase III (squamous)	Nausea and fatigue
	Pfizer	Rucaparib NA AG014699/PF-01367338	Small-molecule inhibitor	PARP-1	Phase II Phase I for NSCLC	Fatigue, thrombocytopenia, hypophosphatemia, and lymphopenia
	Abbott	Veliparib NA ABT 888	Small-molecule inhibitor	PARP-1, 2	Phase II	Fatigue, neutropenia (with chemotherapy)
	AstraZeneca	Olaparib NA AZD2281	Small-molecule inhibitor	PARP	Phase II Phase I/II for lung cancer	Nausea, fatigue, and anemia
	Merck	NA NA MK4827	Small-molecule inhibitor	PARP -1. 2	Phase I	Fatigue, nausea, myelosuppression
SMAC mimetics	Tetralogic	Birinapant NA TL32711	Small-molecule Smac mimetic	Antagonizes IAPs	Phase I	
	Ascenta Therapeutics	NA NA AT-406	Small-molecule Smac mimetic	Antagonizes IAPs	Phase I	
SURVIVIN inhibitors	Isis Pharmaceuticals and Eli Lilly	NA NA LY2181308	Antisense oligonucleotide	Blocks survivin	Phase II	PTT prolongation, headache, lymphopenia, fever, fatigue, and nausea
	Astellas	NA NA YM155	Small-molecule inhibitor	Suppresses survivin	Phase II	Hypertension, neutropenia, fatigue, nausea, stomatitis, and fever.
TELOMERASE inhibitors	Geron Corporation	Imetelstat NA GRN163L	Competitive telomerase RNA template antagonist	Telomerase	Phase II	PTT prolongation, gastrointestinal side effects, fatigue, anemia, GGT elevation, and peripheral neuropathy
	University of Maryland	Sodium metaarsenite NA KML001	Oral arsenic agent	Telomerase	Phase I	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

TRAIL receptor agonists and vascular disrupting agents

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	MediciNova	NA NA MN-029	Binds reversibly to the colchicine-binding site on tubulin.	Disrupts the endothelial tubulin cytoskeleton	Phase I (completed)	Nausea, vomiting, hypotension, fatigue, diarrhea
	AstraZeneca	NA NA ZD6126	Small-molecule VDA	Disrupts the endothelial tubulin cytoskeleton	Phase I (completed)	Anorexia, constipation, dyspnea, and fatigue

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Vaccines

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	University of Miami, Sylvester Cancer Center	NA NA Ad100-gp96Ig-HLA A1	Irradiated NSCLC cells, manipulated to express and secrete heat shock protein gp96-Ig fusion protein	CTL response against NSCLC cells	Phase I	
	NCI	MAGE-12 peptide vaccine (emulsified in Montanide ISA-51) NA	Peptide vaccine	MAGE-12 Antigen-positive tumors	Phase I(all solid tumors-completed)	
	Corixa Corporation	pVAX/L523S and Ad/L523S NA	Recombinant DNA and adenovirus expressing L523S protein		Phase I (no updates available)	
	University of Pittsburgh	Semiallogeneic human fibroblasts (MRC-5) transfected NA	Fibroblasts transfected with DNA from autologous tumor	Autologous tumor cells	Phase I (suspended due to funding)	
	Memorial Sloan Kettering Cancer Center	WT-1 analog peptide vaccine NA	Peptide vaccine	WT-1 gene-expressing tumors	Phase II for mesothelioma	

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

Targeted and biologic therapies for NSCLC

Anti-sense oligonucleotides and anti-body engineering

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Anti-Sense Oligonucleotides	Genta	Oblimerson Genasense G3139	Antisense oligo-deoxyribo-nucleotide	Bcl-2	Phase II/III	Fever and elevated liver enzymes
	OncGenex	Custirsen NA OGX 011	ASO	Clusterin	Phase III (prostate) Phase I/II for NSCLC	
	Isis pharmaceuticals & Eli Lilly	NA NA LY2181308	ASO	Blocks survivin	Phase II	PTT prolongation, headache, lymphopenia, fever, fatigue, and nausea
	Isis pharmaceuticals	NA NA ISIS 2503	ASO	H-ras	Phase II (completed)	
	Isispharmeceuticals	NA NA ISIS 5132	ASOagainst c-Raf kinase mRNA expression	Raf-1	Phase II	Mild hematologic toxicity, asthenia, fever
	Eli lilly Isis Pharmaceu-ticals	Affinitac NA LY900003 /ISIS 3521	ASO	Protein kinase C alpha	Phase III completed. Further development discontinued.	
Therapeutic anti-body engineering (novel targets, antibody-drug conjugates, anti-body fragments)	Trion Pharma	Catumaxomab Removab	Rat-murine hybrid mono-clonal antibody binding to EpCAM and CD3 antibody	EpCAM/CD3	Phase III(phase I/II for lung cancer)Approved in Europe for malignant ascitis	Fever,Nausea,Vomiting
	Genzyme	NA NA	Human IgG4 MoAB	Pan-neutralizing TGF- β	Phase II (mesothelioma)	
	Peregrine Pharmaceu-ticals	Bavituximab Tarvacin UNII-Q16CT95N25 3G4	Chimeric IgG1 MoAB	Membrane phosphati-dylserine complexed with β2-glycoprotein I on tumor vasculature	Phase II	Nausea, fatigue, headache, alopecia, anemia, and hyper-tension
	Alder Pharmaceuticals	ALD518	Anti-IL-6 antibody	To treat anemia, ca-chexia, and fatigue	Phase II	
	Acceleron and Celgene	Sotatercept NA ACE-011	Fully human soluble activin receptor type 2A IgG-Fc fusion protein	Activin antagonist(increases hemoglobin and also increases bone mineral density)	Phase II	Headache, paresthesia, dizzi-ness, fatigue, and hyperten-sion
	Lpath/Merck-Sereno	Sonepcizumab/ASONEP	Humanized MoAB	Shingosine-1-phos-phate	Phase I	Infusion reaction
	Micromet AG	MT110	EpCAM/CD3 bispecific anti-body construct (BiTE)	EpCAM/CD3	Phase I	Fever and elevated liver enzymes
	Pfizer	CVX-045	Human MoAB	Thrombospondin-1 Mimetic	Phase I	Fatigue, gastrointestinal upset, dyspnea, headache, dizziness and anemia

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

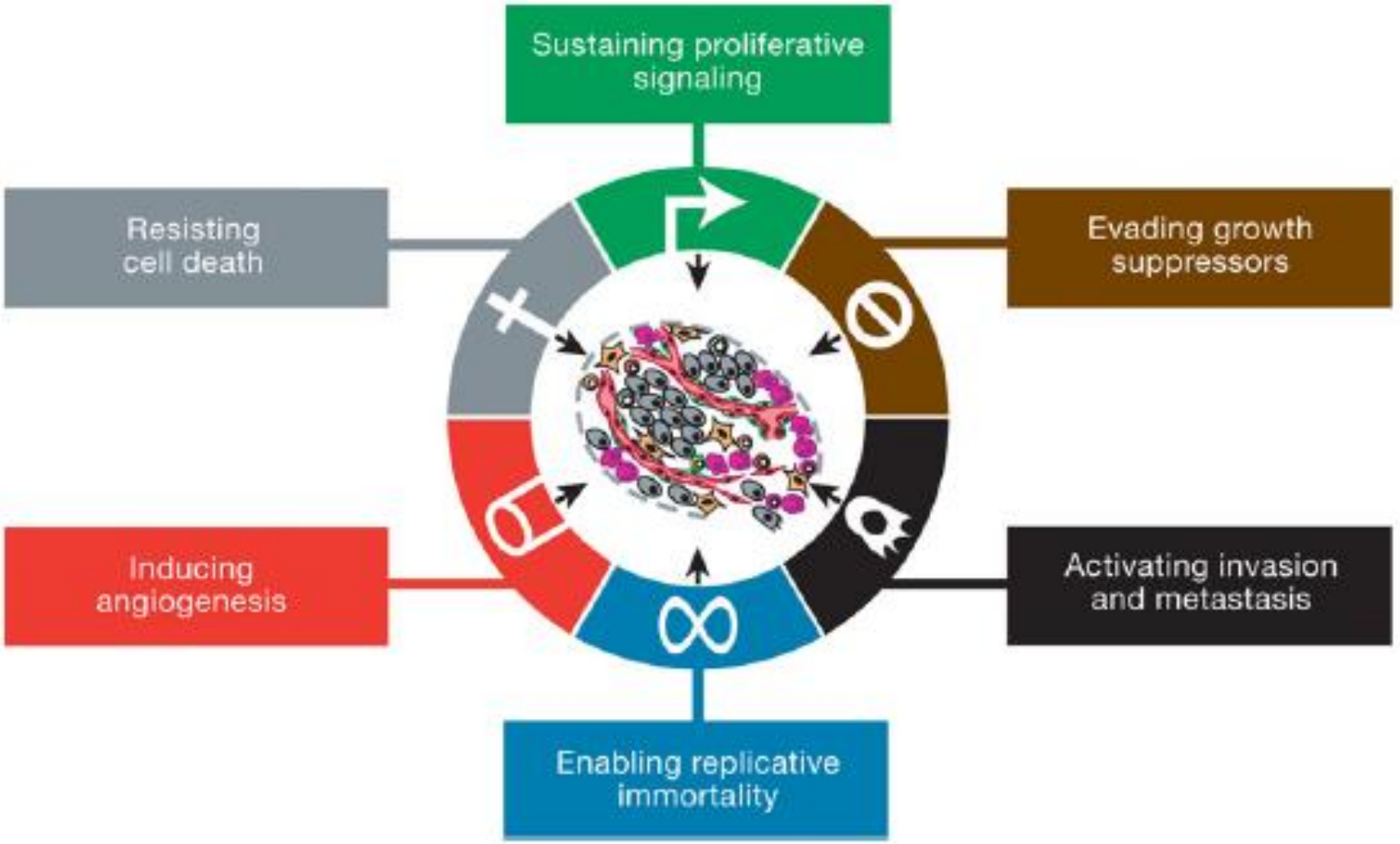
Targeted and biologic therapies for NSCLC

Therapeutic viruses and others

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Pfizer	PF-00562271	Reversible FAK inhibitor	FAK	Phase I	Headache, nausea, and peripheral neuropathy, diarrhea, fatigue, edema
	AstraZeneca	ZD4054	ETAR antagonist	ETAR	Phase II	
	AstraZeneca	AZD 6918	Small-molecule inhibitor	Tropomyosin-related kinases	Phase I (development discontinued)	
	Eisai Inc.	Eribulin mesylate E7389	Non-taxane microtubule dynamics inhibitor		Phase II	Fatigue and cytopenias
	Vion Pharmaceuticals,NCI	Triapine	Ribonucleotide reductase inhibitor(enhancing the activity of gemcitabine)		Phase II	
	Bristol-Meyers Squibb	Epofolate BMS-753493	Folate conjugate of epothilone analog BMS-748265		Phase I	Fatigue, nausea, elevated liver enzymes, and diarrhea
	Daiichi Sankyo	Efatutazone NA CS 7017/ RS5444	PPARγ agonist	PPAR- γ	Phase II	Fluid retention
	Pfizer/Onyx	NA NA PD 0332991	Small-molecule inhibitor	CDK 4/6 inhibitor	Phase II	
	Pfizer	Celecoxib celebrex or celebra for arthritis; Onsenal for polyps	Eicosanoid	Cyclooxygenase-2 inhibitor	Phase II	
	Tragara Pharmaceuticals	Aprecoxib CS-706. TG01 Capoxigem	A benzenesulfonamide nonsteroidal anti-inflammatory drug	Small-molecule selective Cox-2 inhibitor	Phase II	
	Quintessence Biosciences	QBI-139	Variant of human pancreatic ribonuclease 1	Causes destruction of RNA	Phase I	
	Pfizer	CVX-060	Anti-Angiogenic COVX-Body	A selective angiopoietin-2 binding	Phase I	Fatigue and proteinuria
	AstraZeneca	NA NA AZD1480	Small-molecule inhibitor	JAK2 kinase	Phase I	
	NCI	4-(N-(S-glutathionylacetylamino) phenylarsonous acid	Synthetic tripeptide trivalent arsenical	Angiogenesis inhibitor that targets the mitcohondria o actively dividing but not quiescent endothelial cells arresting their proliferation and causing apoptosis	Phase I	
	Introgen Therapeutics	DOTAP: chol-FUS1	Lipid-based nanoparticles	Fus1 tumor suppressor gene	Phase I	Fever and hypophosphatemia

Somaiah N et al. J Thorac Oncol 7(Suppl 5):S342-S368, 2012

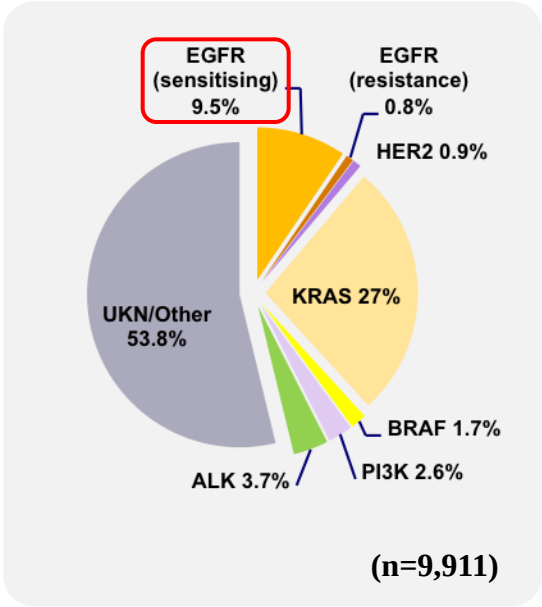
Characteristics of cancer cells



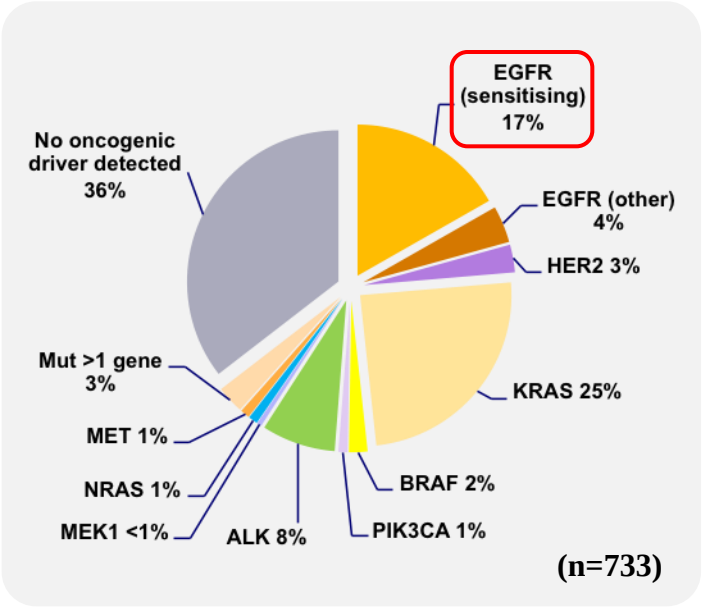
Hanahan D et al, Cell 144:646-674, 2011

Molecular alterations in lung cancer

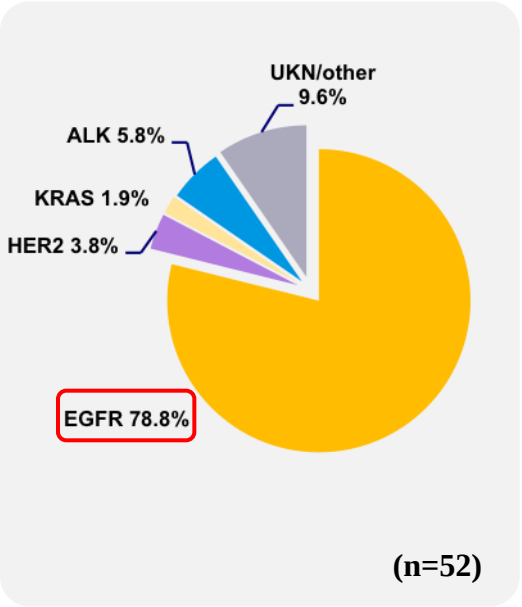
Europe
All histology



US
Adenocarcinoma

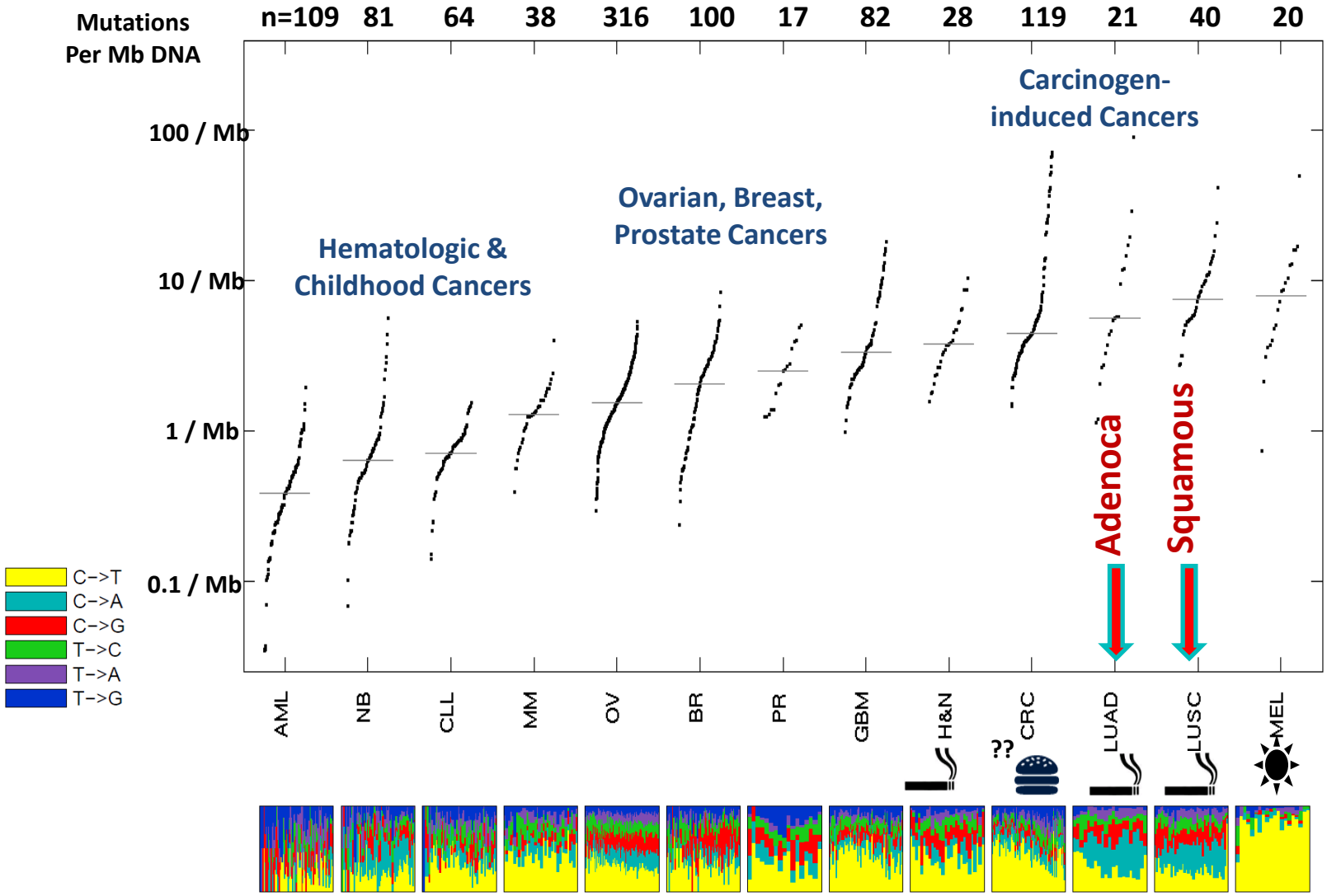


East Asia
Adenocarcinoma, never smokers



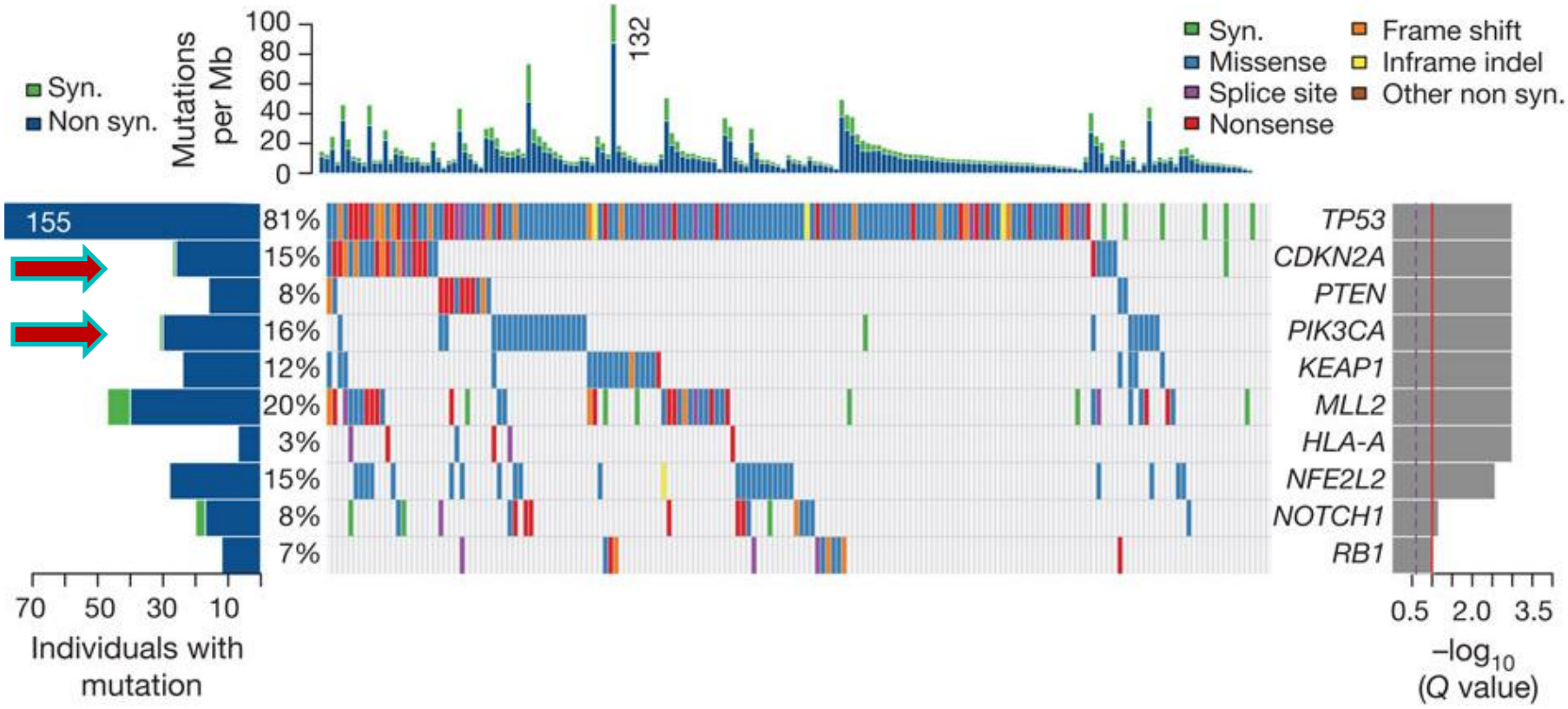
Johnson, et al. ASCO 2013
Sun, et al. J Clin Oncol 2010; Barlesi, et al. ASCO 2013

Magnitude of genomic derangement



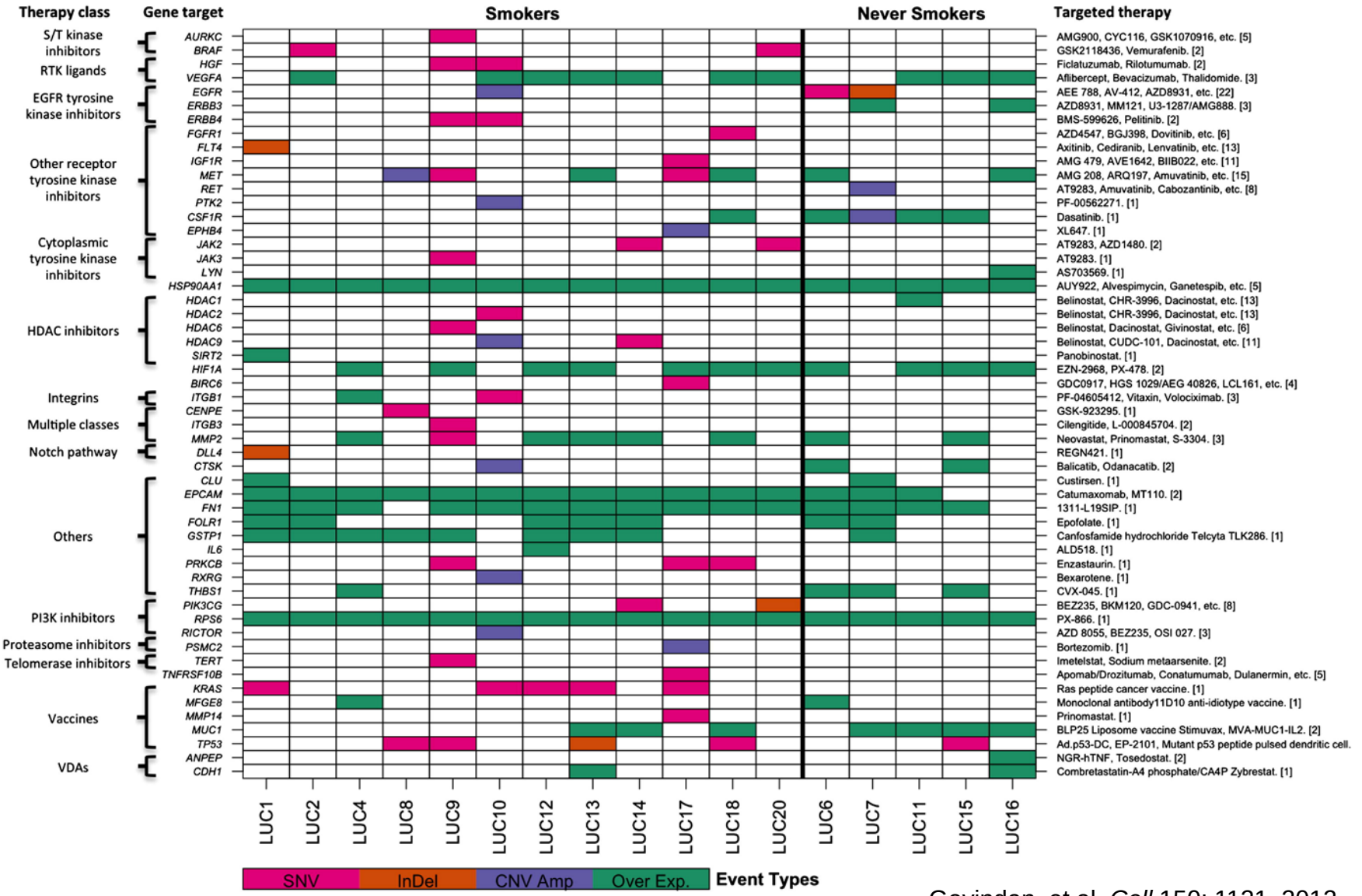
From The Cancer Genome Atlas Project: Govindan R. J Clin Oncol. 2012 (Proc ASCO Annual Meeting);30 (suppl): abstr 7006.

Significantly mutated genes in squamous NSCLC



Nature 489:519-525, 2012

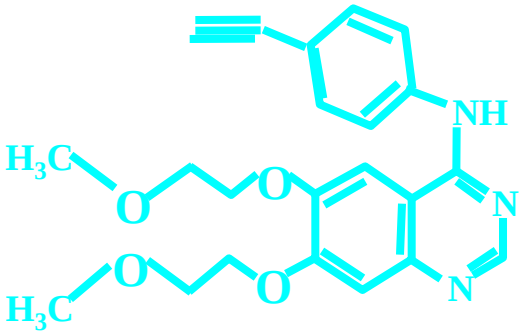
Drugable targets in smokers and never smokers



Govindan ,et al. *Cell* 150: 1121, 2012

Major classes of molecular-targeted agents

Oral molecules

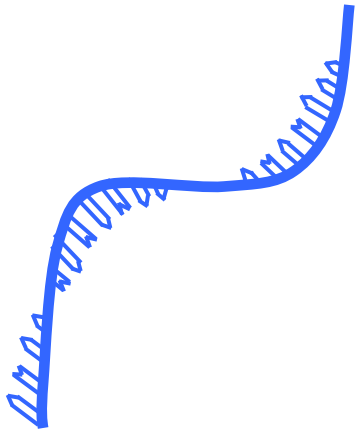


Intracellular action
c 0.5–2kDa
Orally available

Monoclonal antibodies

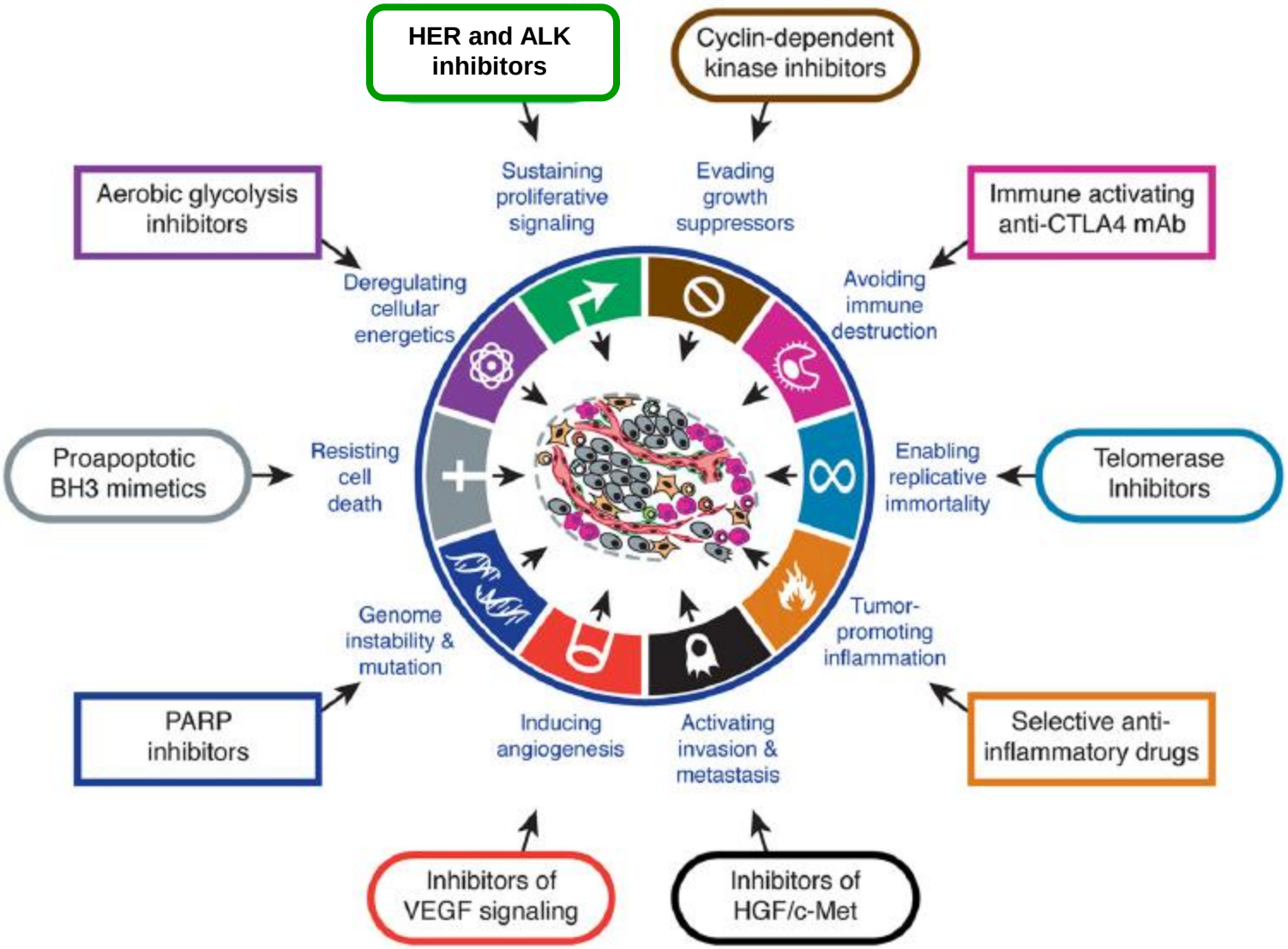
Extracellular action
c 150kDa
i.v. infusion

Antisense oligonucleotides



Intracellular action
c 10kDa
i.v. infusion

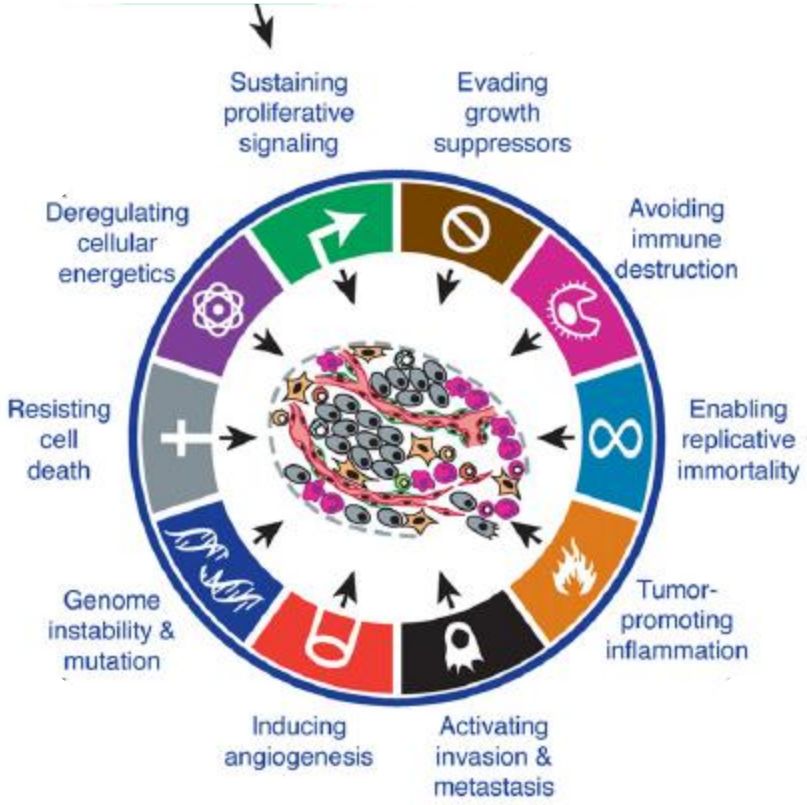
Characteristics of cancer cells



Hanahan D et al, Cell 144:646-674, 2011

Characteristics of cancer cells

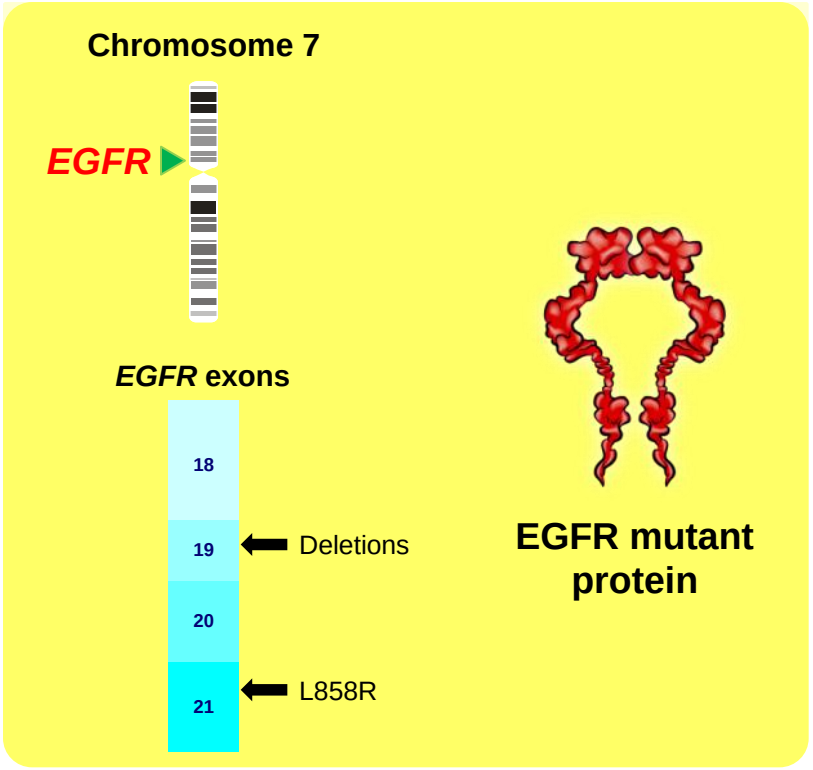
HER and ALK inhibitors



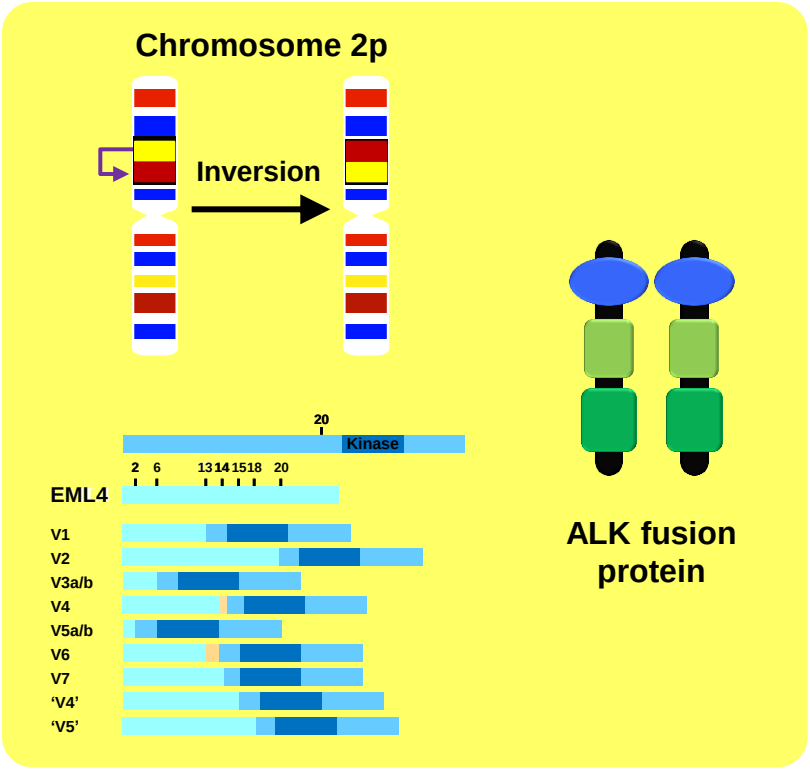
Hanahan D et al, Cell 144:646-674, 2011

EGFR mutations and *ALK* translocations: "actionable" genetic alterations

EGFR Mut+



EML4-ALK



- Potent oncogenic drivers
- Most common in adenocarcinoma; mutually exclusive

Shaw & Solomon. Clin Cancer Res 2011
Horn & Pao. J Clin Oncol 2009; Riely, et al. Clin Cancer Res 2006

Use of TKI's of EGFR

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 23 (Supplement 7): vii56–vii64, 2012
doi:10.1093/annonc/mds226

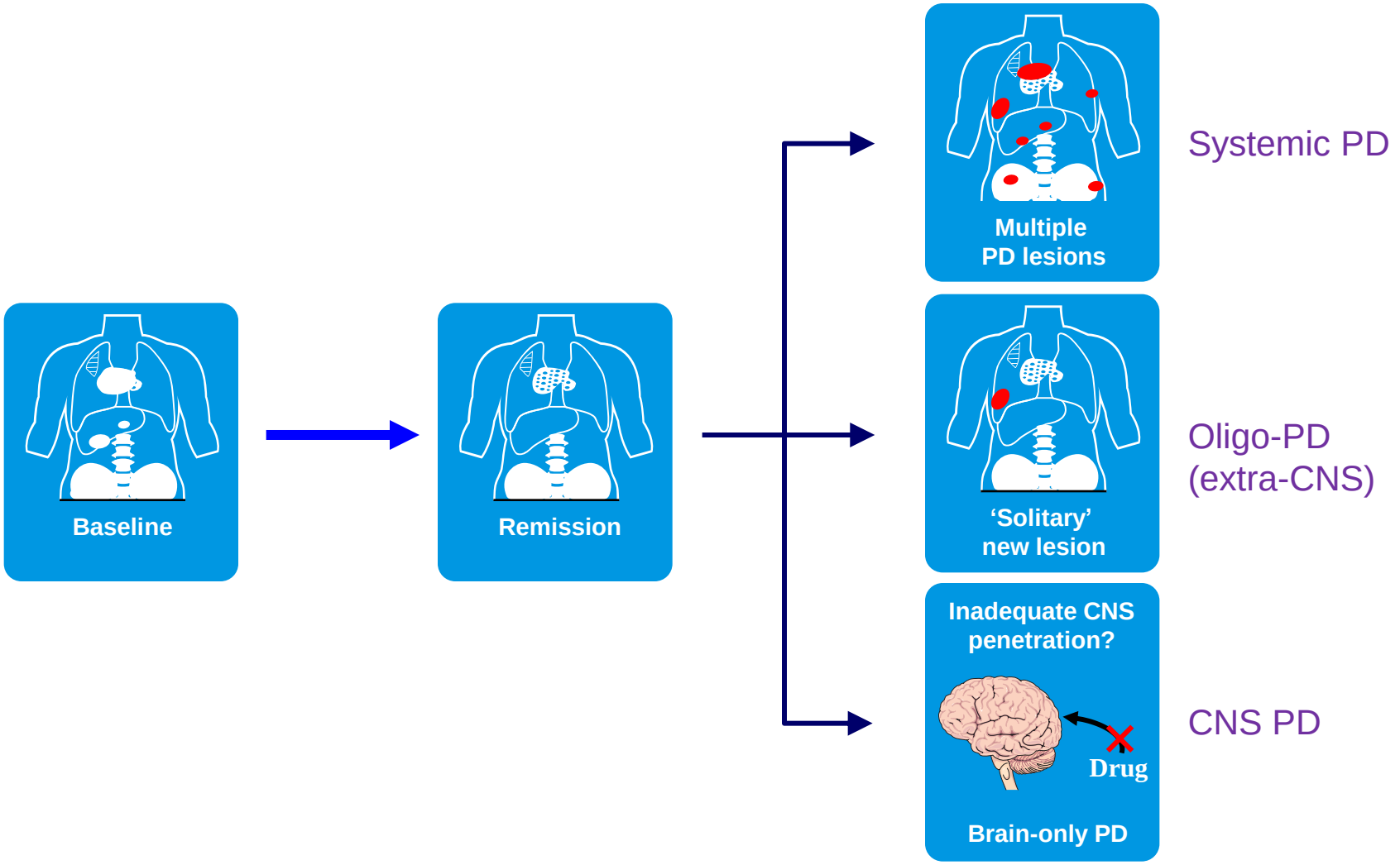
clinical practice guidelines

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

First-line treatment with a TKI (erlotinib or gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation because of significantly higher RR, longer PFS, and better QoL when compared with first-line chemotherapy [32, 33] [I, A].

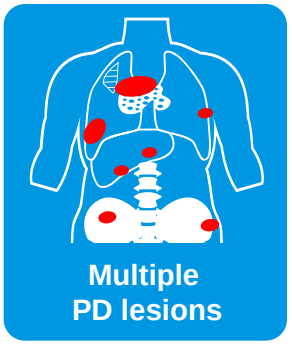
Level of evidence: I **Strenght of recommendation: A**

Scenarios for progression on TKI therapy



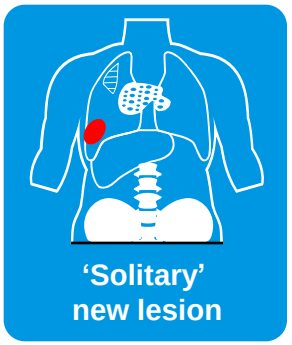
Adapted from Gandara. ASCO 2013

Scenarios for progression on TKI therapy



Multiple PD lesions

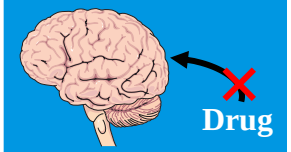
Systemic PD → ?



'Solitary' new lesion

Oligo-PD (extra-CNS)

Inadequate CNS penetration?



Brain-only PD

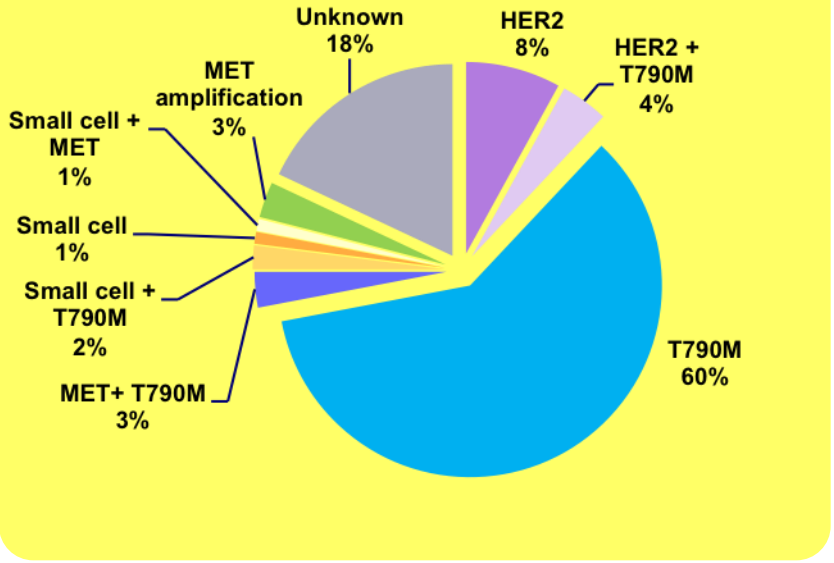
CNS PD

→ Local therapy for relapse + Continue targeted therapy

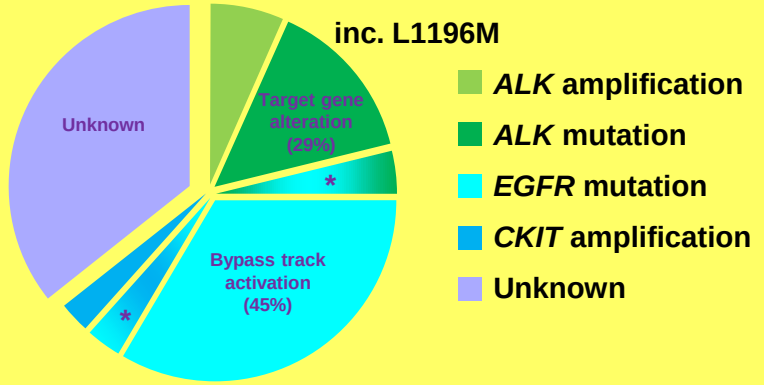
Adapted from Gandara. ASCO 2013

Acquired resistance in EGFR Mut+ and ALK+ NSCLC

EGFR Mut+



EML4-ALK+



*more than one resistance mechanism

Common themes

Second site mutations in target (e.g., T790M / L1196M)

Use of alternative signalling pathways (e.g., MET / EGFR)

Yu, et al. Clin Cancer Res 2013; Shaw & Engelman, J Clin Oncol 2013

How can we target the EGFR or ALK TKI resistant cells?

Reversible TKI ?

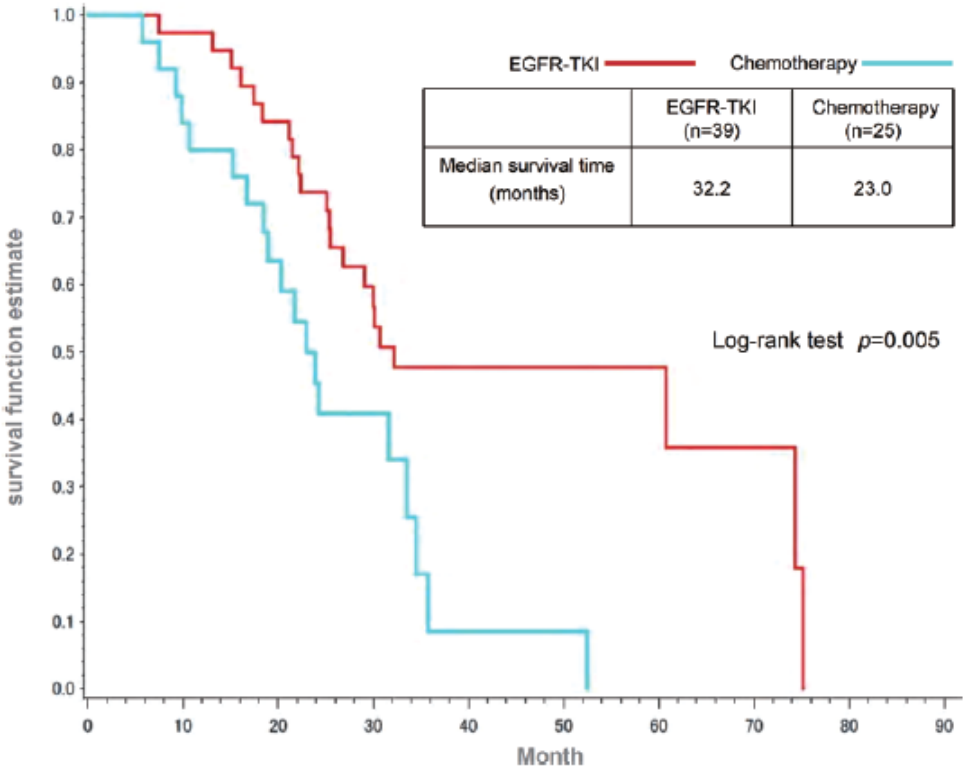
Irreversible TKI ?

TKI + Chemotherapy ?

Chemotherapy ?

EGFR TKI beyond progressive disease

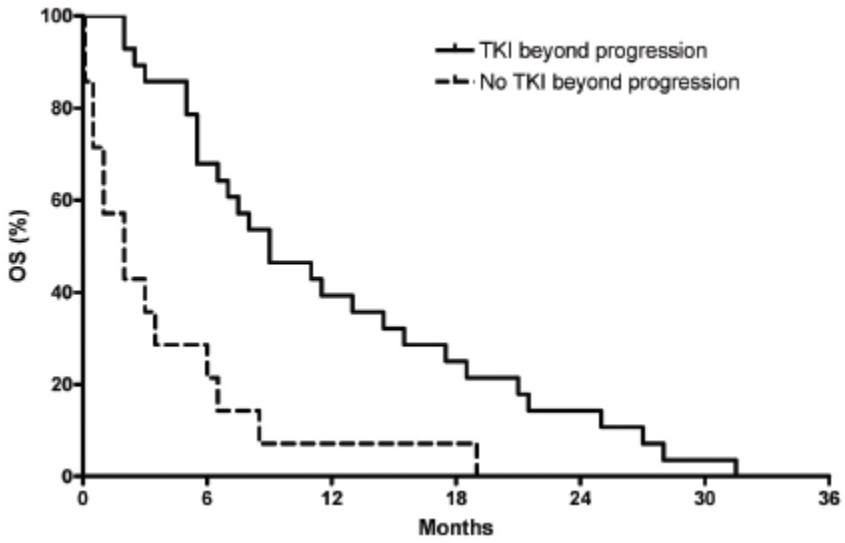
A retrospective analysis for Japanese patients with activating *EGFR* mutations



	EGFR-TKI (n=39)	Chemotherapy (n=25)
Median survival time (months)	32.2	23.0

Nishie K et al. JTO, 2012

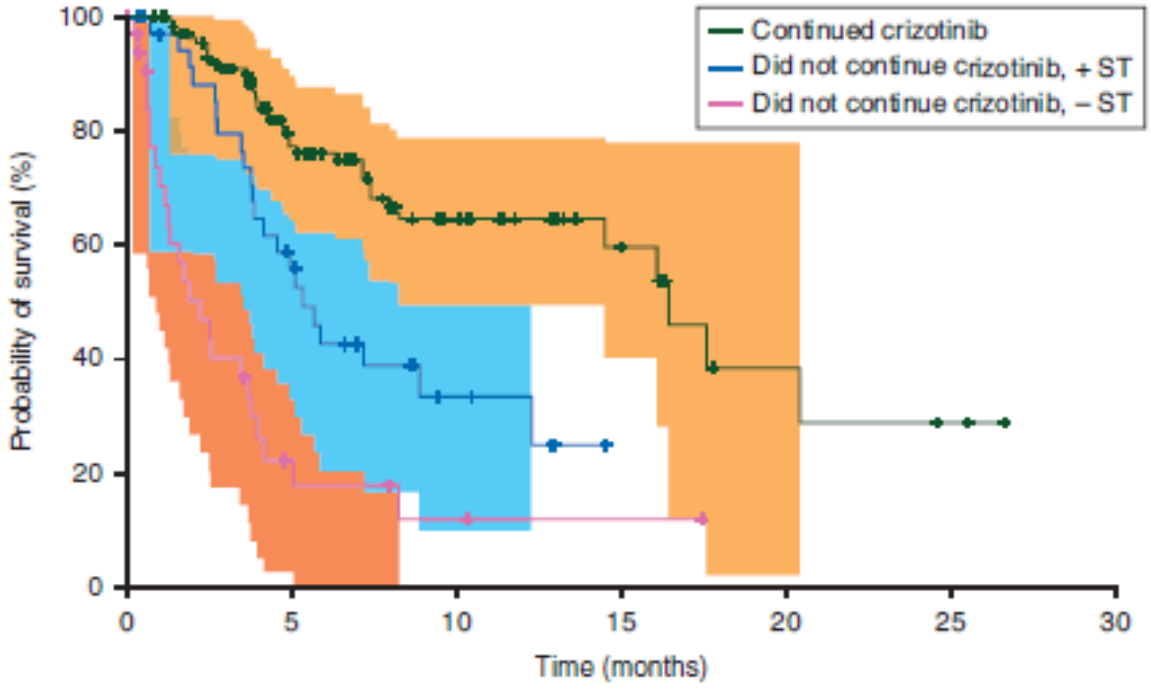
Treatment with TKI beyond progression in long term responders to erlotinib in advanced NSCLC



	TKI beyond progression	No TKI beyond progression	Significance (p)
n	28	15	-
OS after progression on TKI (months)	9	2	0.0002
OS from start of TKI therapy (months)	25.5	14.5	0.019
PFS from start of TKI therapy (months)	13	11.75	n.s. (0.49)
Age at progression	65.1	67.8	n.s. (0.37)
Patients receiving Chemotherapy after progression	18 (64.3%)	8 (53.3%)	
Patients receiving Radiotherapy after progression	7 (25%)	3 (20%)	
Patients receiving BSC after progression	3 (10.7%)	5 (33.3%)	

Faehling M et al. JTO, 2011

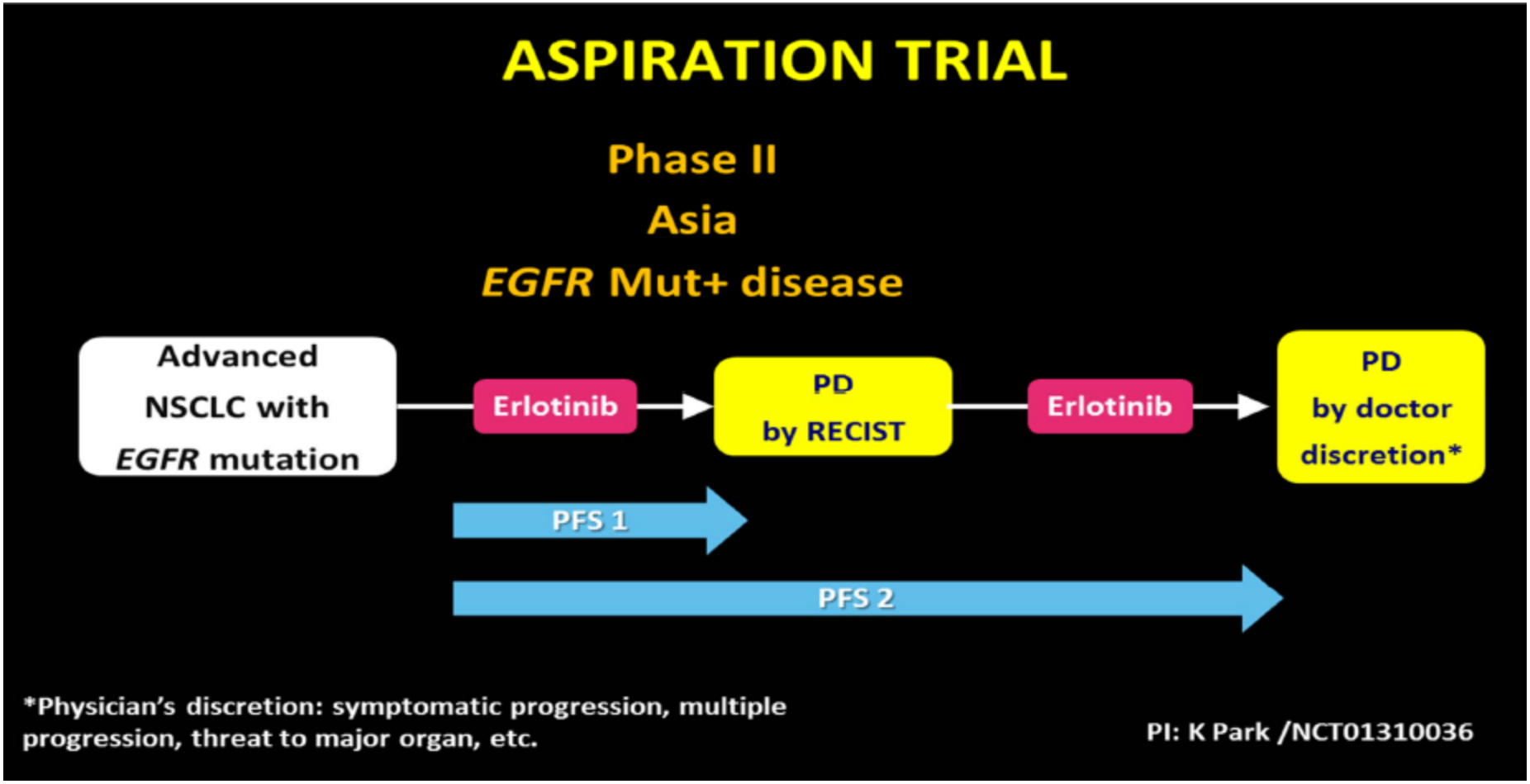
ALK TKI beyond progressive disease - OS



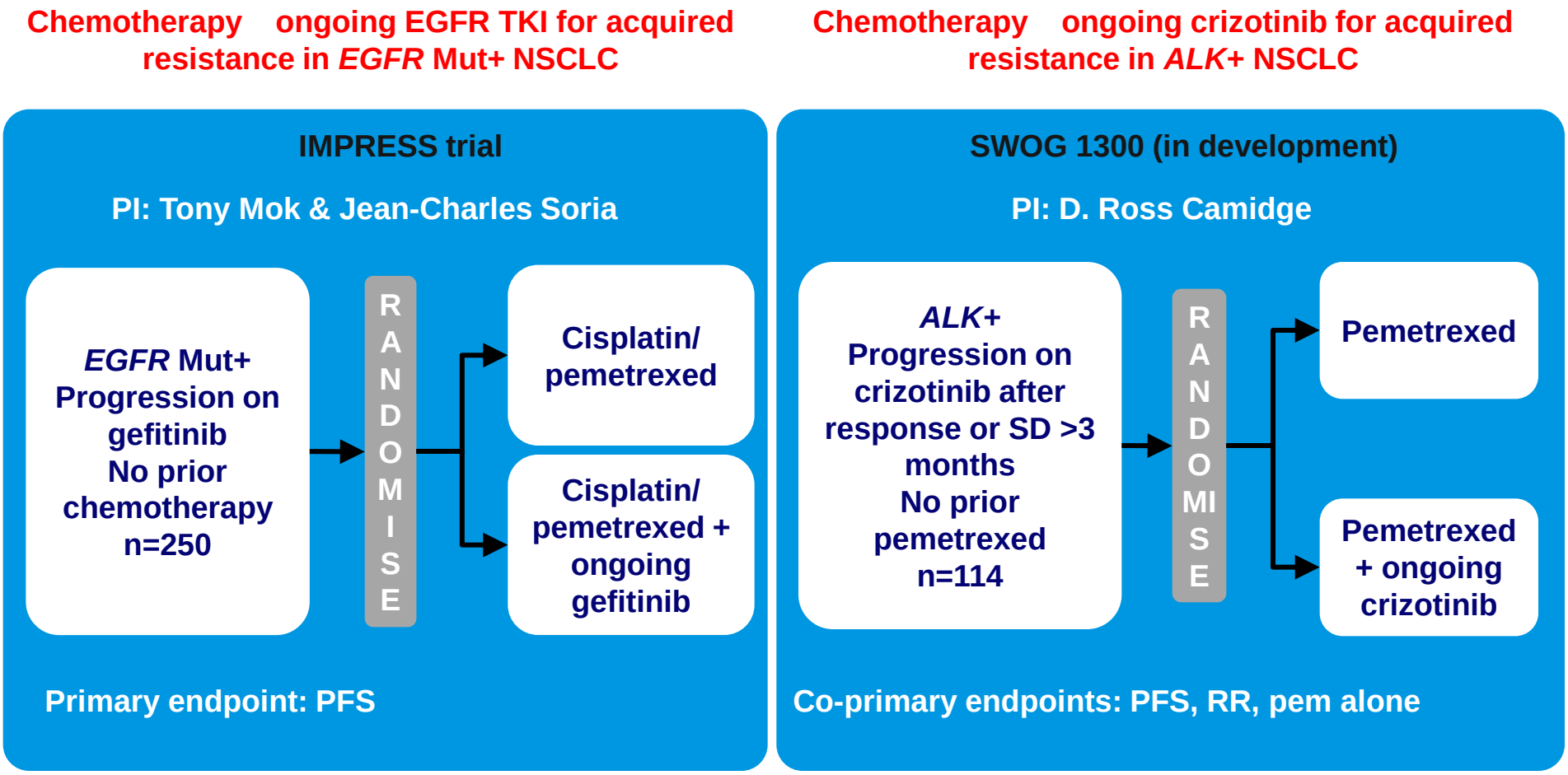
Number at risk				
Continued	120	29	4	0
Did not continue, + ST	37	5	0	
Did not continue, – ST	37	2	0	

Ou S-HI et al. Annals of Oncology, 2014

EGFR TKI beyond RECIST PD in acquired resistance



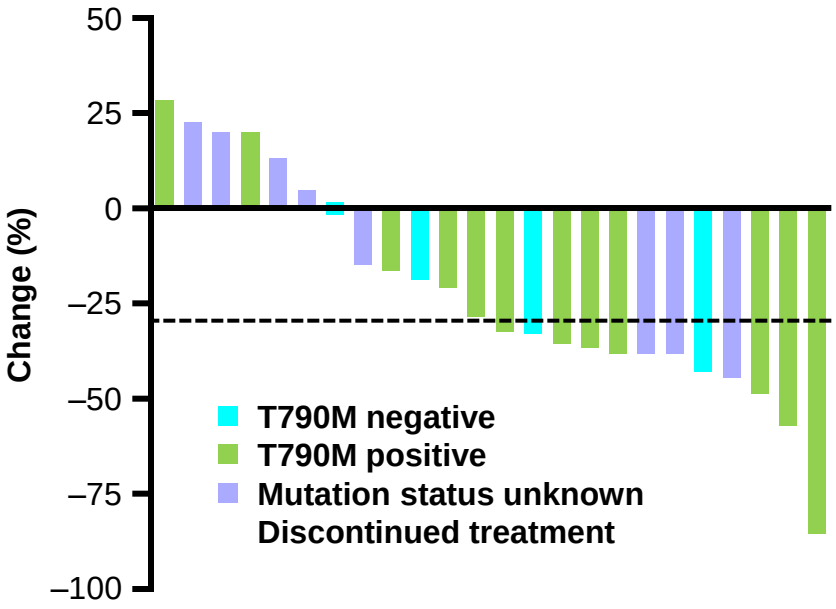
EGFR TKI beyond RECIST PD in acquired resistance



Systemic PD: switch to 2nd/3rd generation TKI

EGFR Mut+

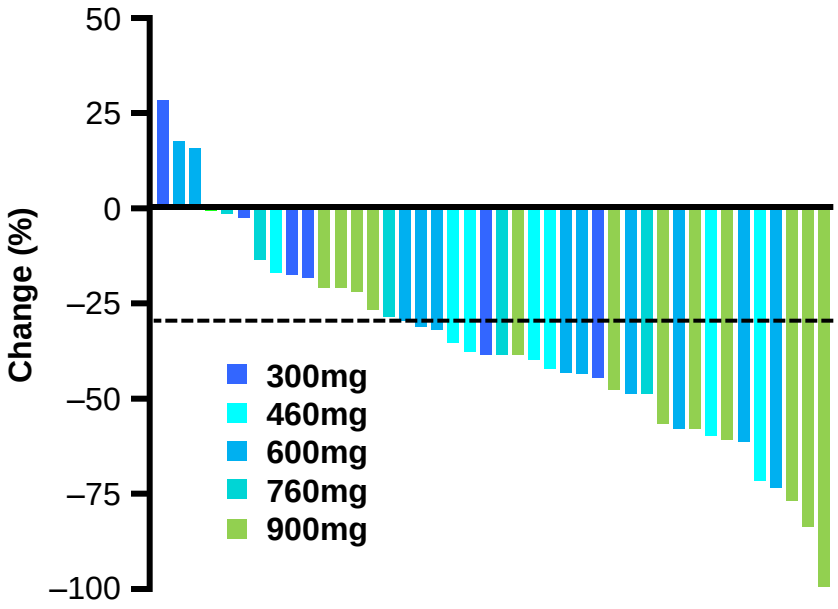
AZ9291 (n=24)



ORR in T790M+ (n=12)
58%

EML4-ALK+

Alectinib (CH5424802)



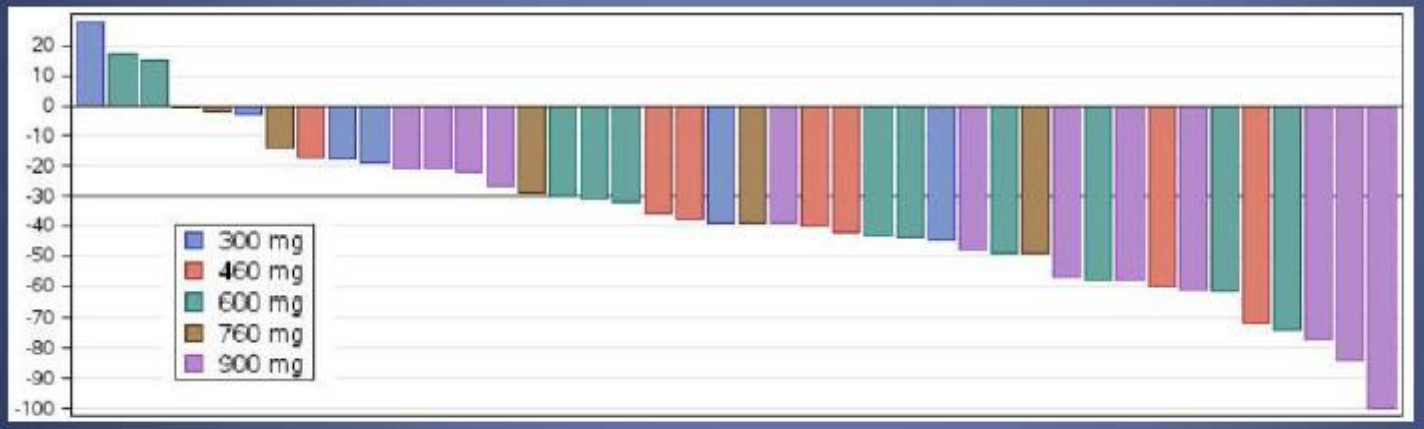
ORR in crizotinib failure
54.5%

Ranson, et al. ECC 2013; Ou, et al. ECC 2013

Alectinib: Crizotinib resistant NSCLC – Phase I trial

- N=47 patients
- 70% received ≥ 2 prior regimens

RP 2D: 600 mg BID

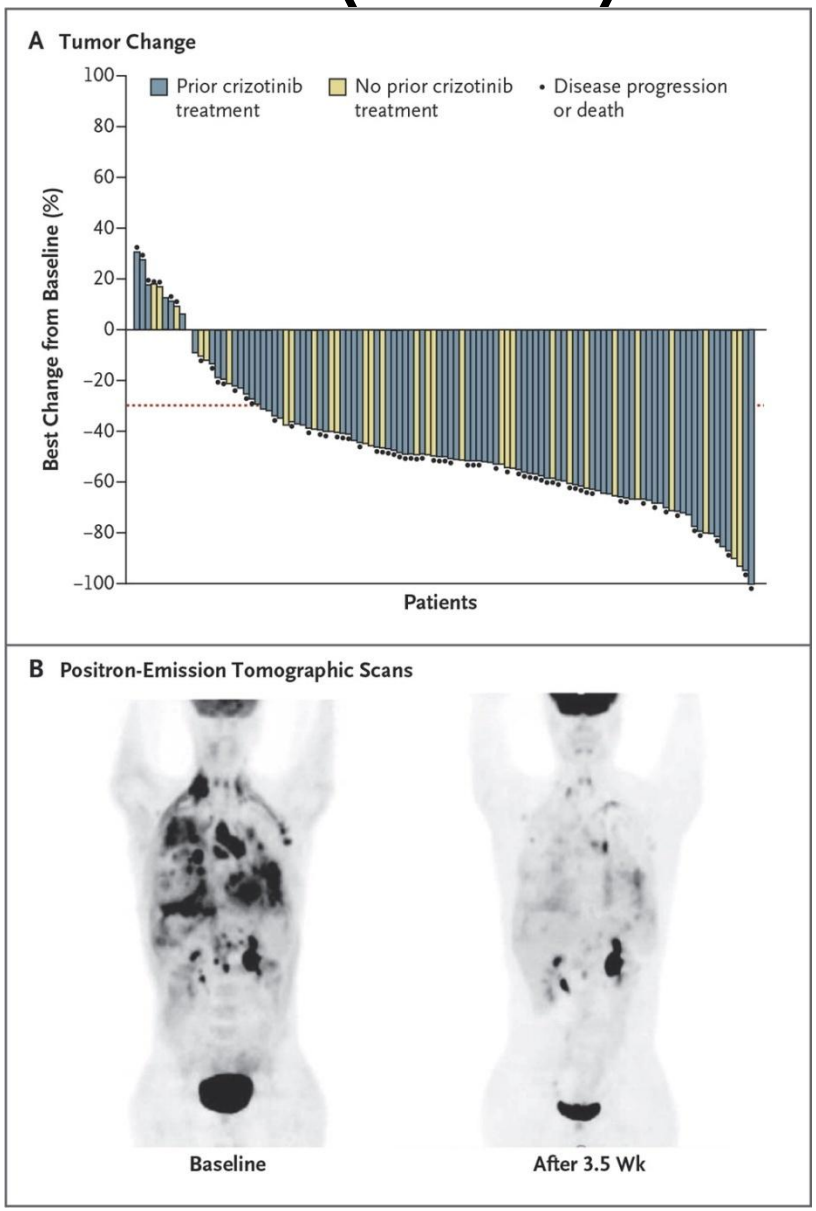


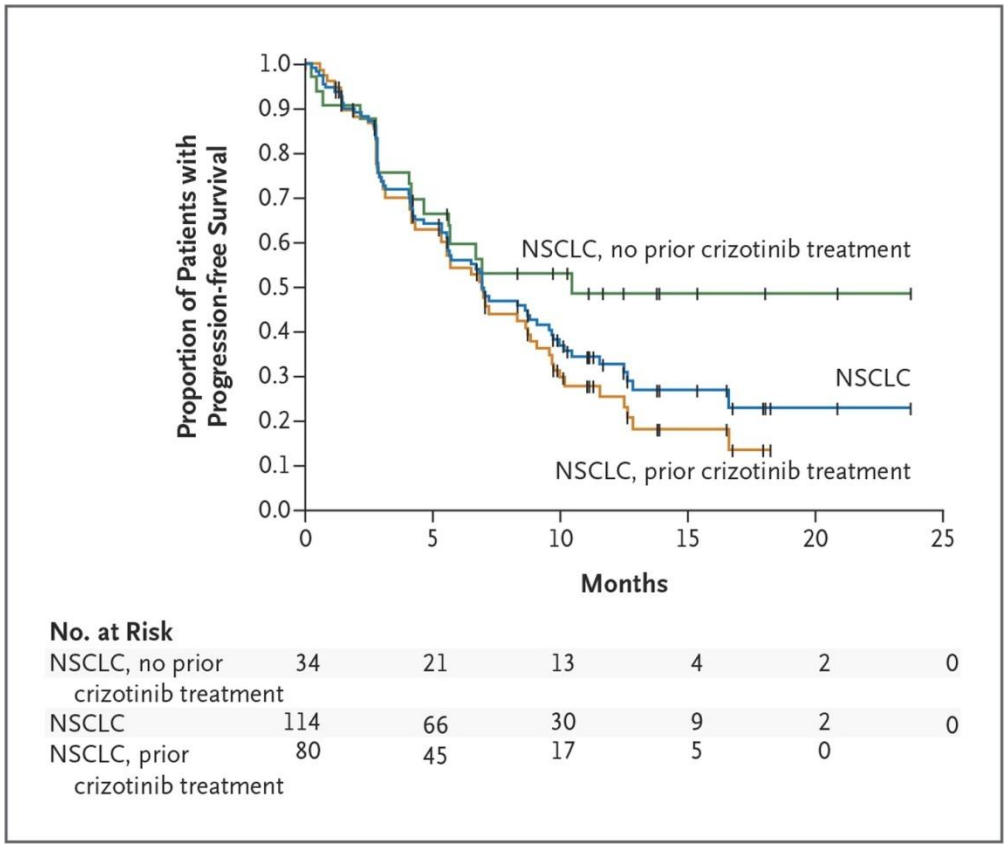
Objective response rate 60%

Adverse events: Myalgia, fatigue, peripheral edema, elevated CPK, nausea and Photosensitivity (Grades 1/2)

Gadgeel et al., Abstract #O16.06

Ceritinib (LDK378): Crizotinib resistant NSCLC – Phase I





CR – 1%
PR – 57%
SD – 22%
ORR – 58%
OSR at 12 months – 65%

Shaw AT et al. N Engl J Med 370:1189-1197., 2014

HER2 mutations among lung adenocarcinomas

Study group	Total (No.)	HER2 mutation (No.)	%
Tomizawa K *et al.* (*Lung Cancer* 2011)	504	13	2.58
Li C *et al.* (*J Thor Oncol* 2012)	224	8	3.57
Sun Y *et al.* (*J Clin Oncol* 2010)	52[‡]	2	3.85
Arcila M *et al.* (*Clin Cancer Res* 2012)	560	25	4.46
Zhang Y *et al.* (*Clin Cancer Res* 2012)	349[‡]	16	4.58
Cardarella S *et al.* (*J Thor Oncol* 2012)	276	13	4.71
Li C *et al.* (*PLos One* 2011)	202[‡]	12	5.94

[‡]Inclusion of adenocarcinoma samples of never-smokers only; [ǂ]Inclusion of adenocarcinoma samples of female never-smokers only

Garrido-Castro AC, et al. Trans Lung Cancer Res, 2013

HER2 mutated NSCLC treated with anti-HER2 therapies

	First-Line Treatment		Second-Line Treatment		Third-Line Treatment		Fourth-Line Treatment	
Patient	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response
11	VIN-HER	PR						
15	CAR-PAC-TRAS	SD						
19	TXT-MASA	PD						
24	VIN-TRAS	PR						
26	CAR-PAC-TRAS	PR						
27	VIN-TRAS	PR						
28	VIN-TRAS	SD						
30	LAP	PD						
31	NVB-HER	PR						
32	LAP	PD	TRAS-VIN	PR	AFA	SD	CAR-TRAS	SD
37	VIN-TRAS	PD						
41	DOC-TRAS	PR						
43	VIN-TRAS	PR	AFA	PR				
44	VIN-TRAS	PR	AFA	SD				
45	VIN-TRAS	SD	PAC-TRAS	SD				
47	TRAS	PR						

RR: 50%

NOTE. Conventional treatment: CAR, PAC, VIN, and DOC. HER2-specific treatments: TRAS, LAP, AFA, and MASA.

Abbreviations: AFA, afatinib; CAR, carboplatin; DOC, docetaxel; HER2, human epidermal growth factor receptor 2; LAP, lapatinib; MASA, masatinib; NE, not evaluated; NVB, Navelbine (VIN; Pierre Fabre, Castres, France); PAC, paclitaxel; PD, progressive disease; PR, partial response; SD, stable disease; TRAS, trastuzumab; TXT, Taxotere (DOC; sanofi-aventis, Paris, France); VIN, vinorelbine.

Mazières J, et al. J Clin Oncol, 2013

EGFR antibody – Necitumumab (IMC-11F8)

CP11-0805 (INSPIRE)
14X-IE-JFCB

Appr 947 pts,
NSCLC non-scc
Stage-IV
PS 0-2

RANDOMIZE 1 : 1

Arm A: IMC-11F8 + CIS + PEM q3w
- IMC-11F8 800 mg, D1, 8
- Cisplatin 75 mg/m², D1
- Pemetrexed 500 mg/m², D1

PR / CR / SD → IMC-11F8 → PD
PD

maximum of 6 cycles

Arm B: CIS + PEM q3w
- Cisplatin 75 mg/m², D1
- Pemetrexed 500 mg/m², D1

→ PD

Following IDMC recommendation, enrollment stopped after 634 patients (02FEB2011)because of unexpected safety signal

CP11-0806 (SQUIRE)
14X-IE-JFCC

1080 pts,
NSCLC scc
Stage-IV
PS 0-2

RANDOMIZE 1 : 1

Arm A: IMC-11F8 + CIS + GEM q3w
- IMC-11F8 800 mg, D1, 8
- Cisplatin 75 mg/m², D1
- Gemcitabine 1250 mg/m², D1, 8

PR / CR / SD → IMC-11F8 → PD
PD

maximum of 6 cycles

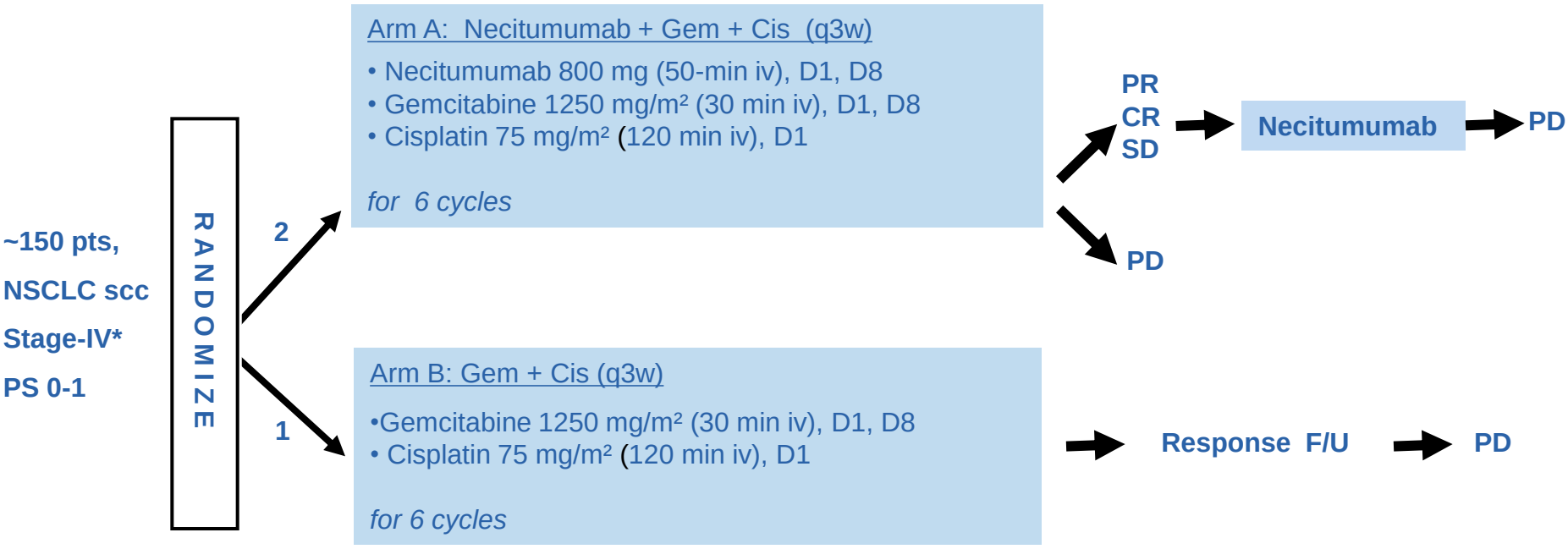
Arm B: CIS + GEM q3w
- Cisplatin 75 mg/m², D1
- Gemcitabine 1250 mg/m², D1, 8

→ PD

Trial ongoing, as per IDMC recommendation to continue without modification

EGFR antibody – Necitumumab (IMC-11F8)

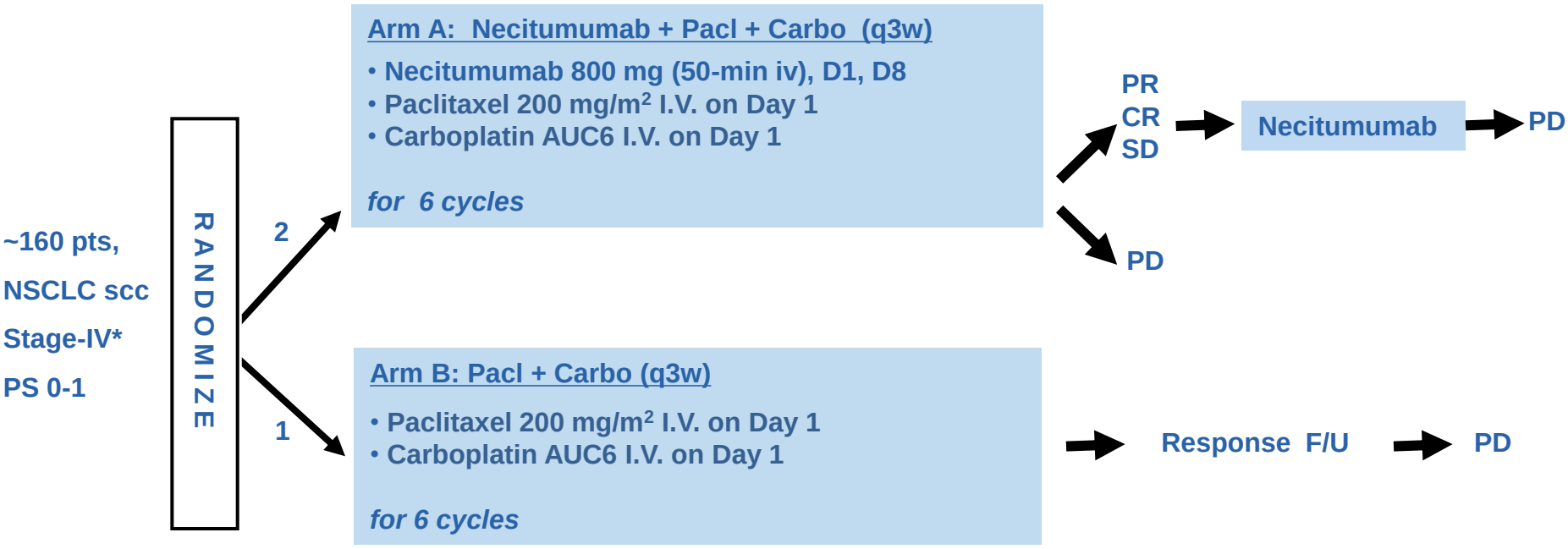
I4X-IE-JFCK - Phase II 1st-line squamous cell NSCLC



US NIH, ClinicalTrials.gov; http://clinicaltrials.gov/.

EGFR antibody – Necitumumab (IMC-11F8)

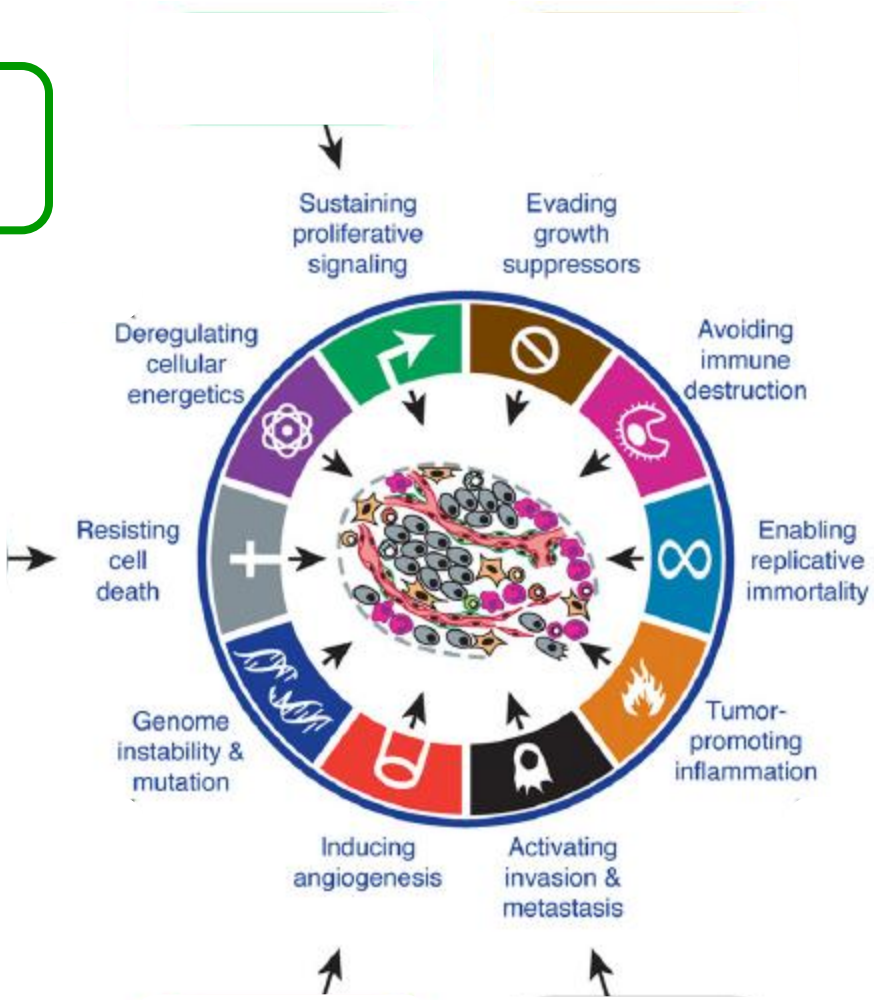
I4X-IE-JFCL - Phase II 1st-line squamous cell NSCLC



US NIH, ClinicalTrials.gov; http://clinicaltrials.gov/.

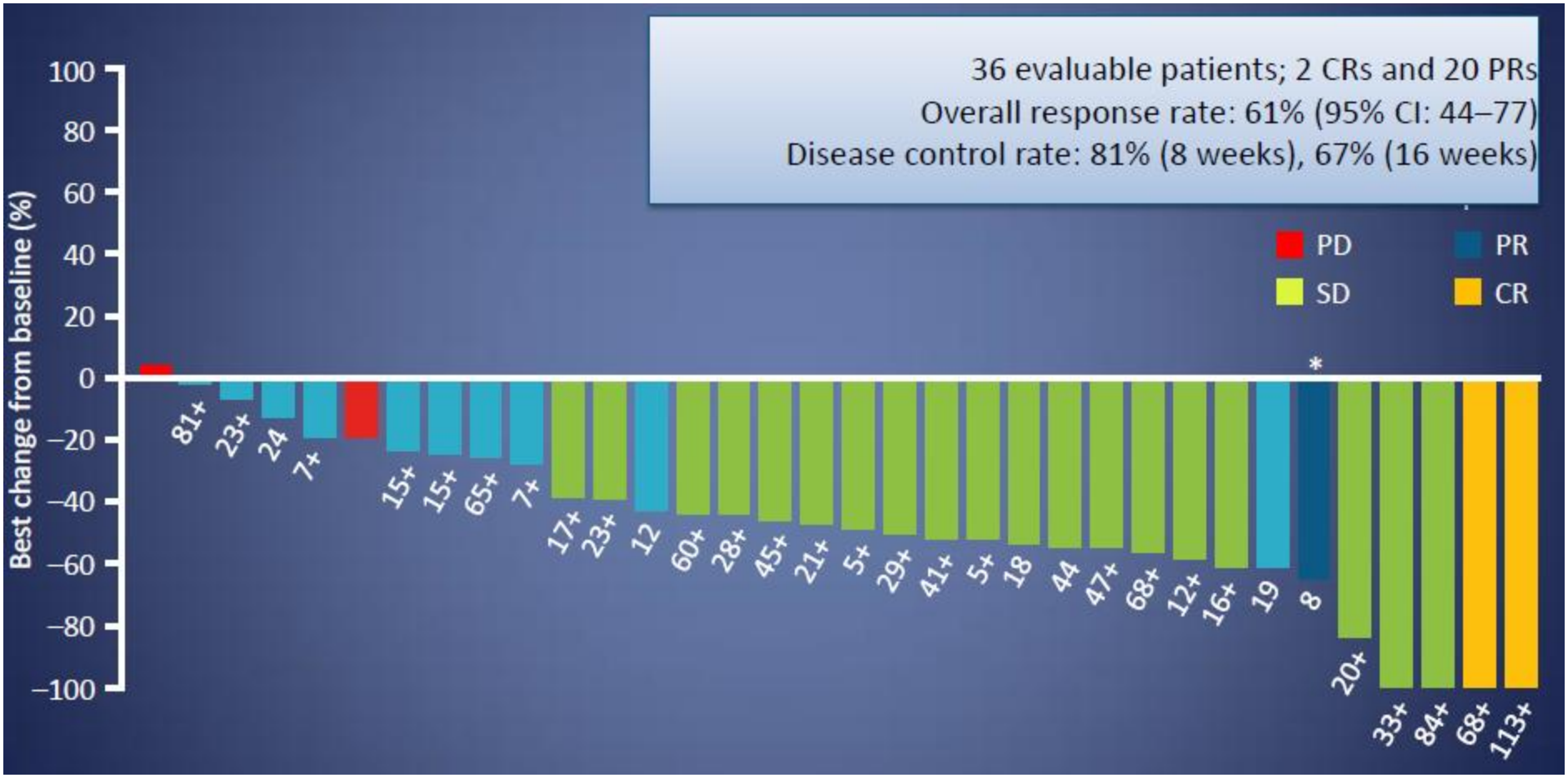
Characteristics of cancer cells

ROS1 inhibitor



Hanahan D et al, Cell 144:646-674, 2011

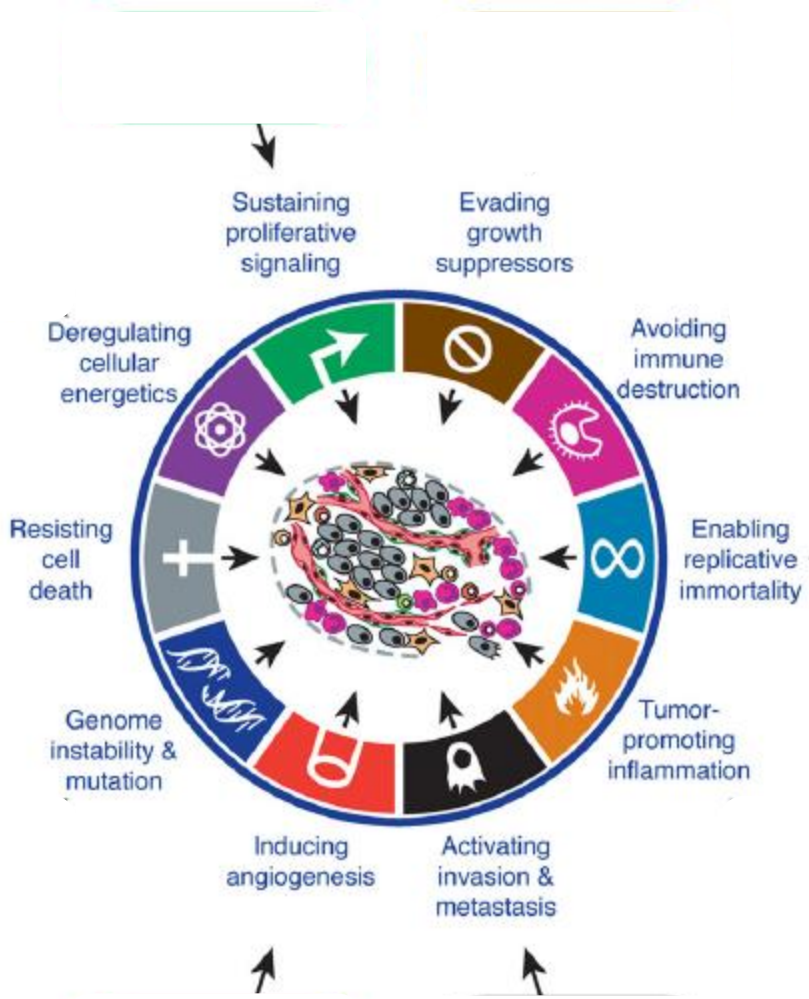
Crizotinib phase II trial in ROS1+ NSCLC patients



Ou et al., Abstract # O16.07

Characteristics of cancer cells

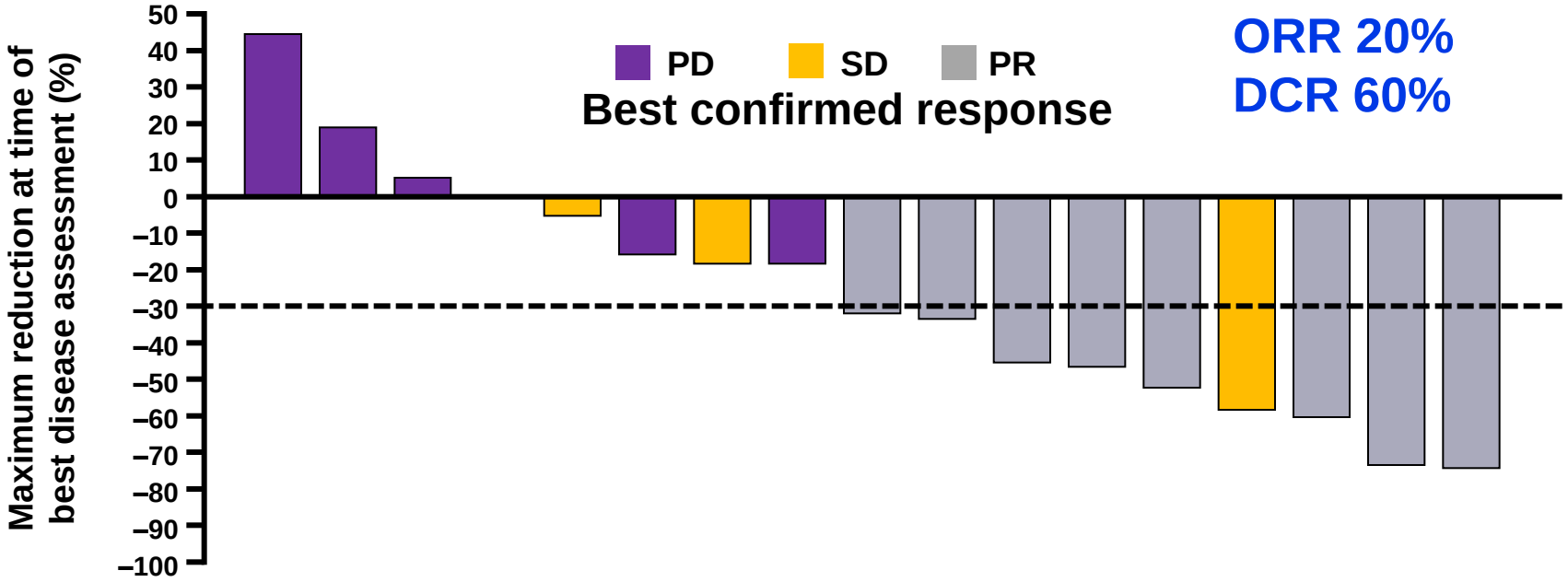
BRAF



Hanahan D et al, Cell 144:646-674, 2011

Dabrafenib phase II trial in BRAF V600E Mut+ NSCLC

- Single arm; dabrafenib 150mg bid
- Preliminary efficacy data among 20 patients



Most common toxicities: arthralgia, back pain, headache, fatigue, PPES, pyrexia

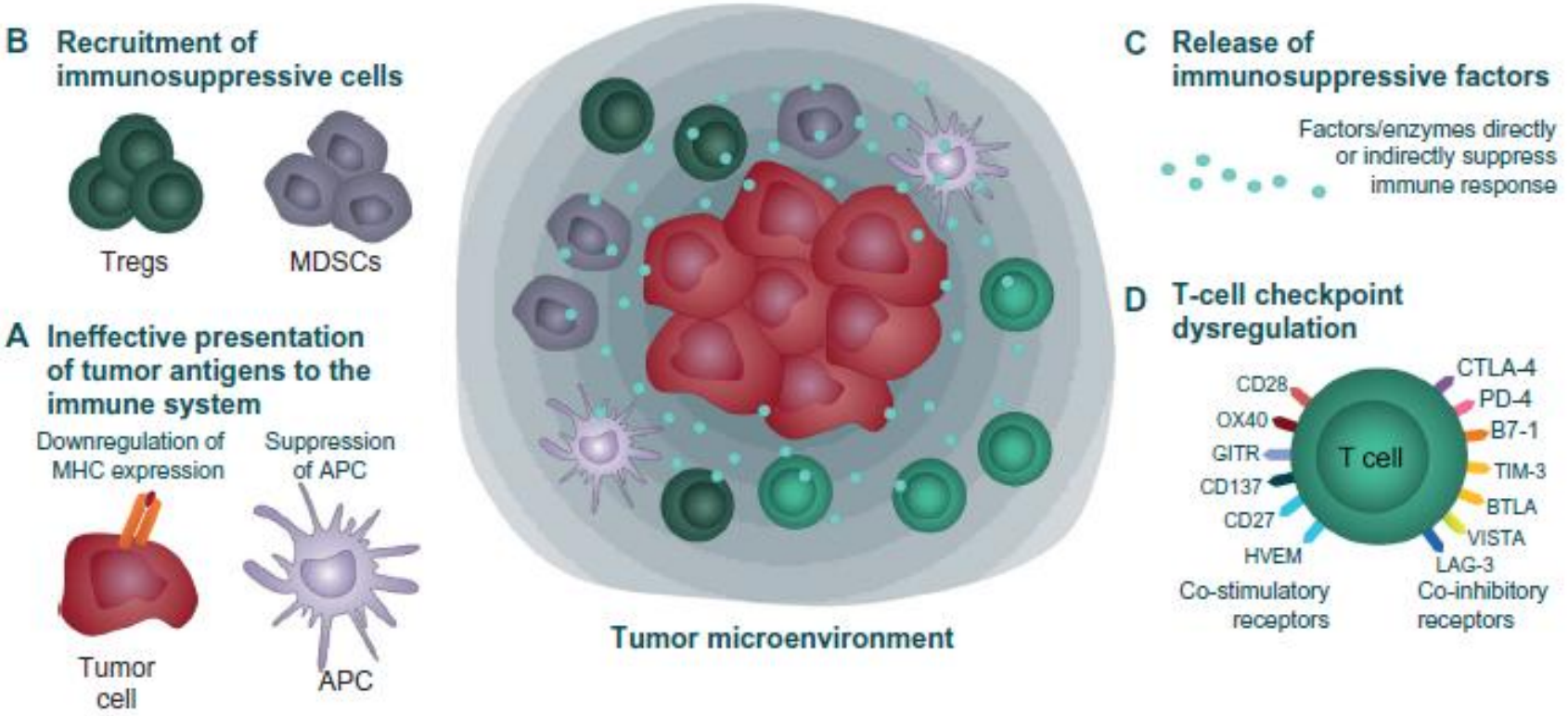
Planchard, et al. ASCO 2013

Characteristics of cancer cells

PD1 & PDL1

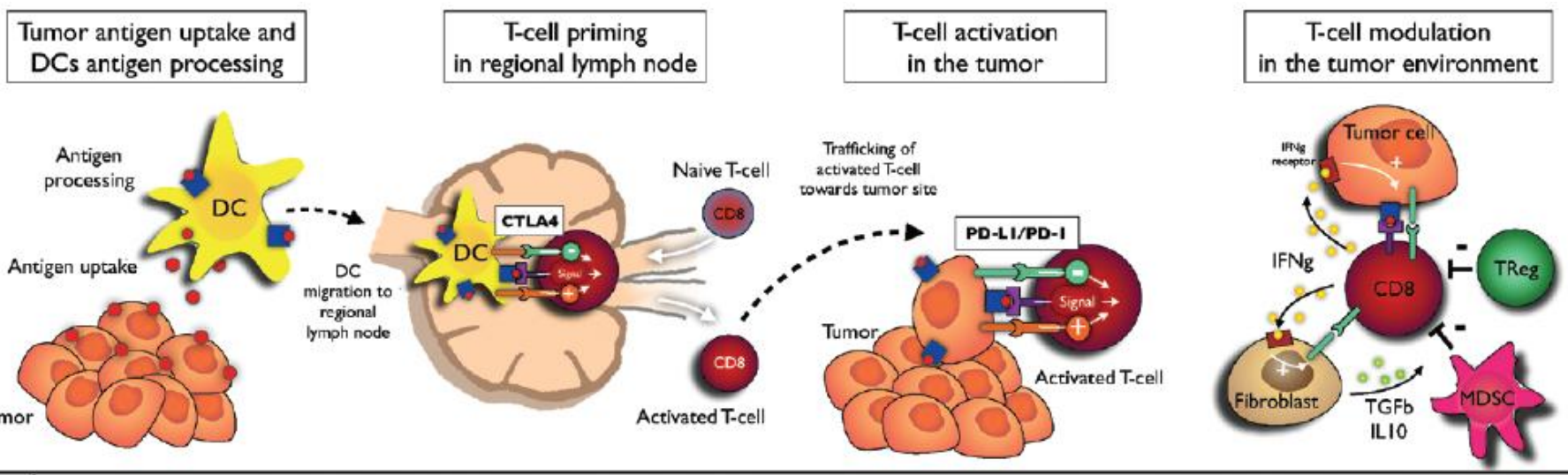
Hanahan D et al, Cell 144:646-674, 2011

Immune evasion or immunosuppressive strategies used by tumor cells



Davies M, Cancer Management and Research 6:63-75, 2014

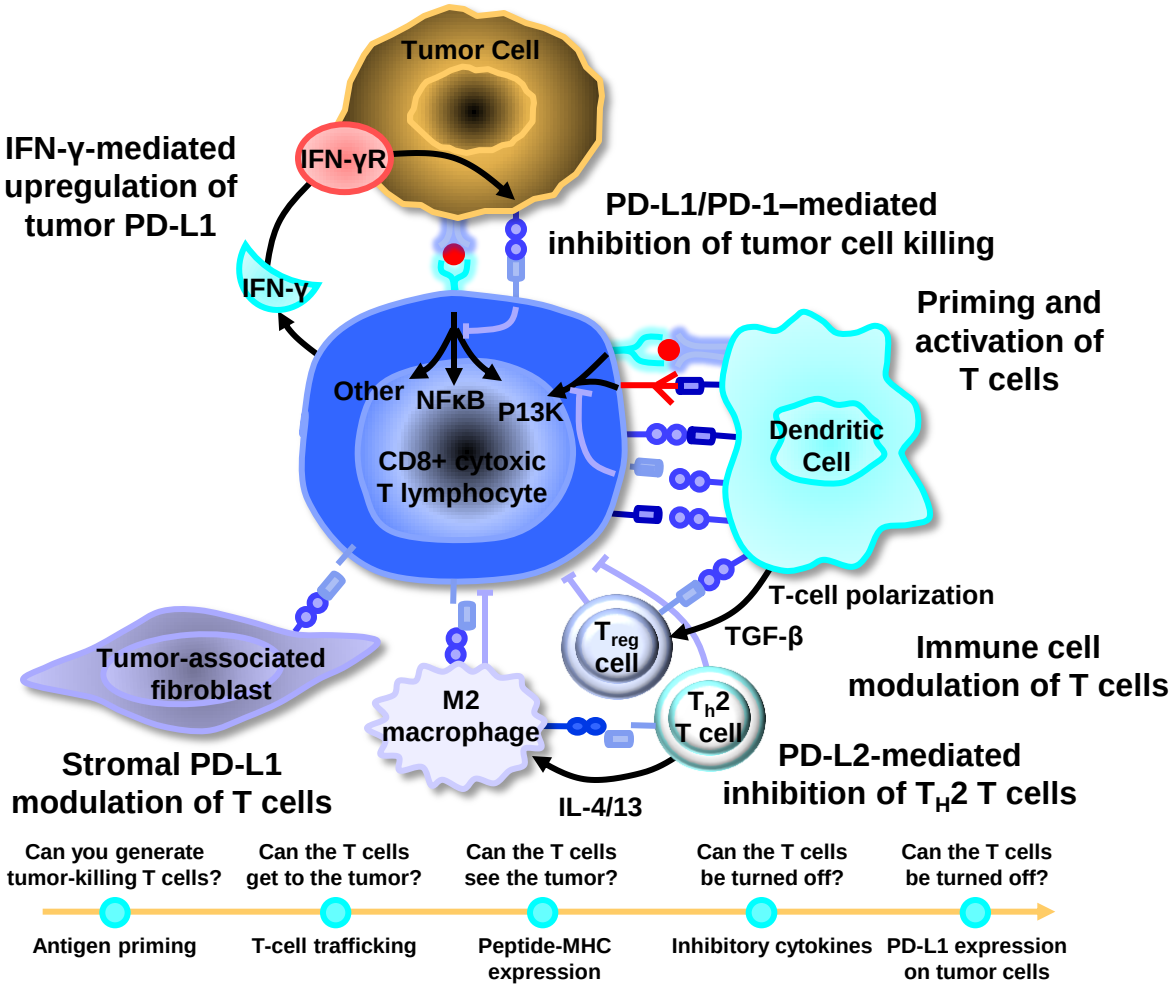
NSCLC tumor immunology and modulation by conventional therapies



immune system modulation in NSCLC	> down-regulation of MHC-I	> up-regulation of PD-L1 through activation of PI3K/Akt ? MAPK ? Alk ?	> up-regulation of TRegs > up-regulation of MDSCs	> IL-10 and TGFß increased concentration by tumor environment > up-regulation of PD-L1 by IFNg secreted by activated T-cell
immuno modulation by NSCLC drugs	**immunogenic cell death** irradiation **vaccination strategies** MAGE-A3, MUC-1, rHU EGF	**up-regulation of MHC-I** paclitaxel, gemcitabine, erlotinib **DC maturation** paclitaxel, docetaxel, bevacizumab **anti-CTLA4** Ipilimumab, Tremelimumab	**anti-PD-1** MDX-1106, CT-011, MK-3475 **anti-PD-L1** MPDL-3280A, MDX-1105 **up-regulation of PD-L1** paclitaxel, etoposide	**TReg inhibition** cisplatin, paclitaxel, bevacizumab **MDSC inhibition** cisplatin, docetaxel, gemcitabine **down-regulation of PD-L1** by PI3Ki ? MEKi ? Crizotinib ?

Champiat S et al, J Thorac Oncol 9:144-153, 2014

Blockade of PD-1 binding to PDL1 (B7-H1) and PDL-2 (B7-DC) revives T cells



- PD-L1 expression on tumor cells is induced by γ-interferon
- In other words, activated T cells that could kill tumors are specifically disabled by those tumors

- PD-1
- PD-L1
- PD-L2
- T-cell receptor
- MHC-1
- CD28
- Shp-2
- B7.1

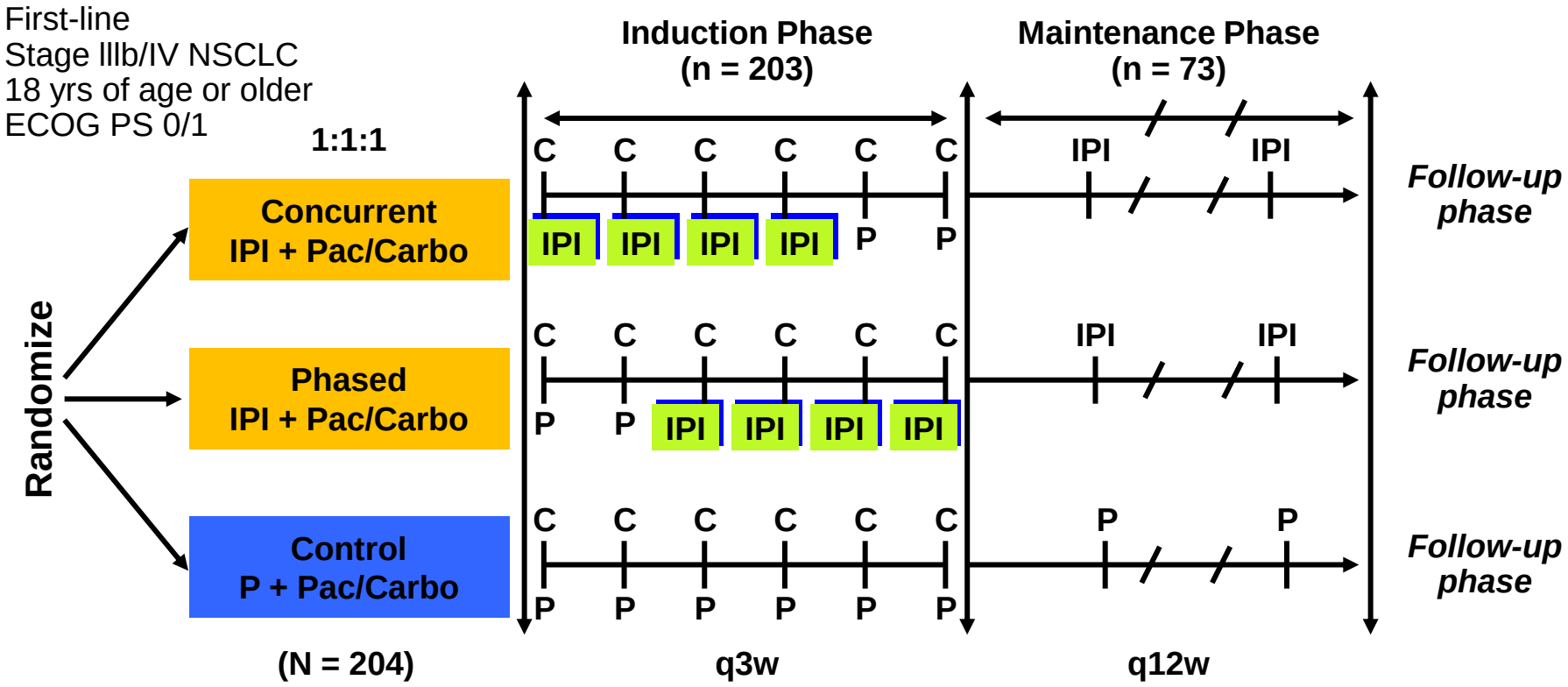
Sznol M, et al. Clin Cancer Res. 19:1021-1034, 2013

Immune checkpoint inhibitors in NSCLC

Compound	Company	Target	Development Stage in NSCLC
Ipilimumab	Bristol-Myers Squibb	CTLA4	Phase III
Tremelimumab	MedImmune	CTLA4	Phase I
Nivolumab (BMS-936558)	Bristol-Myers Squibb	PD-1	Phase III
Lambrolizumab (MK-3475)	Merck	PD-1	Phase III
BMS-936559	Bristol-Myers Squibb	PD-L1	Phase I
Medi-4736	MedImmune	PD-L1	Phase I
MPDL-3280A	Genentech	PD-L1	Phase III

Champiat S et al, J Thorac Oncol 9:144-153, 2014

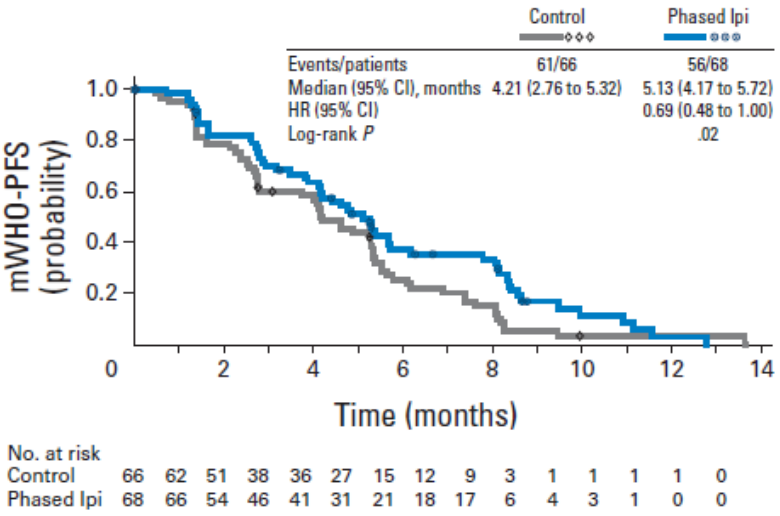
Randomized phase II study of Ipilimumab and CT in advanced NSCLC

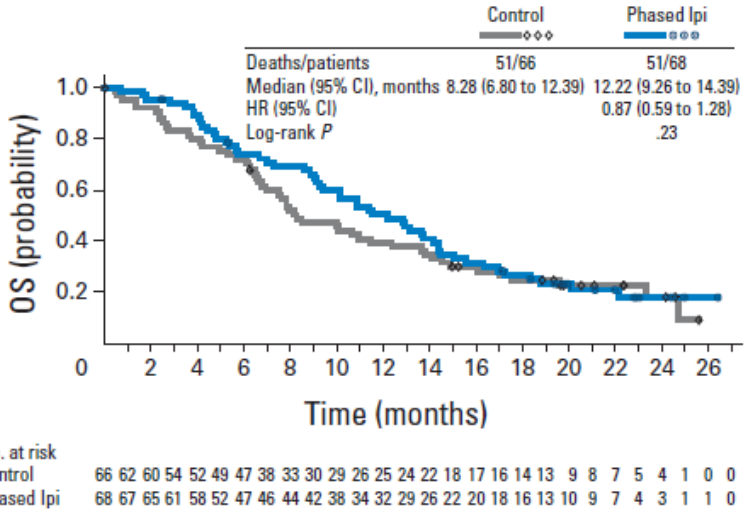


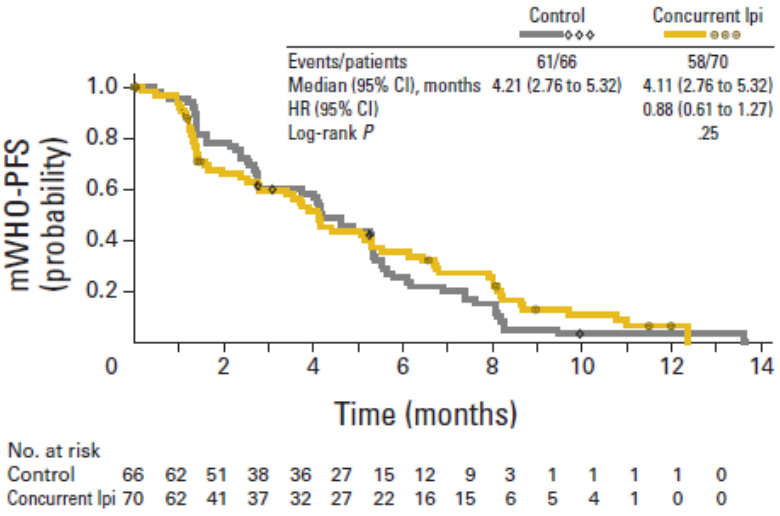
- Primary endpoint: irPFS
- Cx regimen: Pac 175 mg/m^2/carbo AUC 6 prior to start of ipilimumab (10 mg/kg)

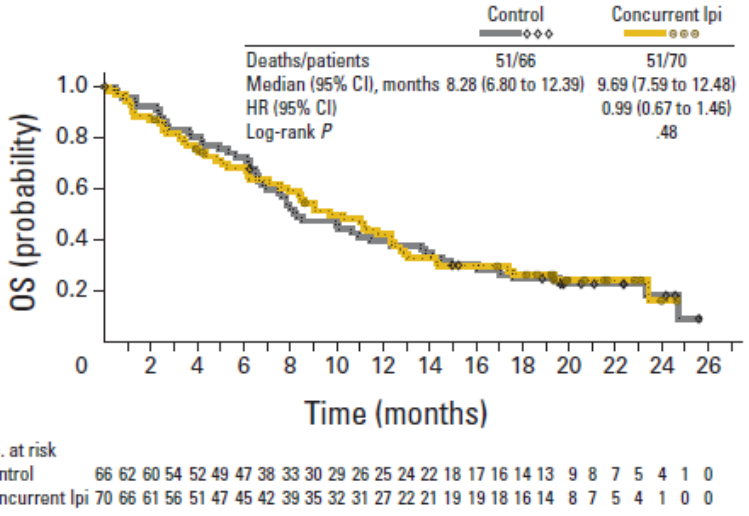
Lynch TJ et al, J Clin Oncol 30:2046-2054, 2012

Randomized phase II study of Ipilimumab and CT in advanced NSCLC



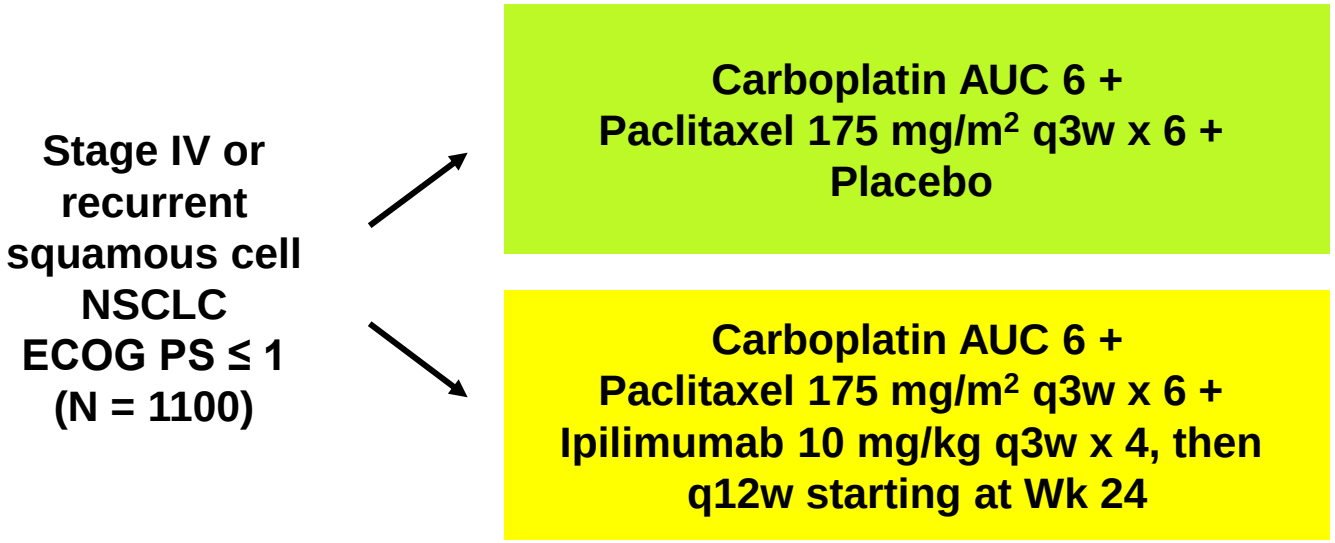






Lynch TJ et al, J Clin Oncol 30:2046-2054, 2012

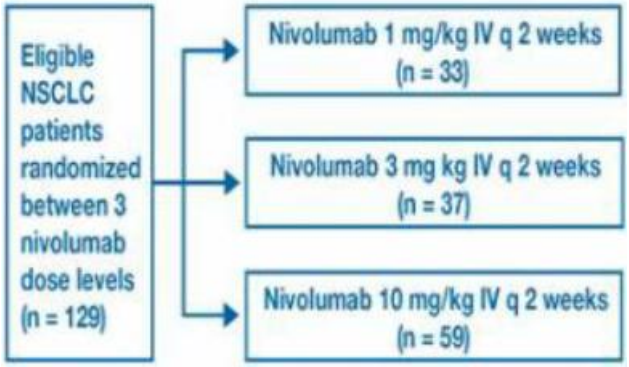
Ongoing phase III: Ipilimumab in squamous NSCLC

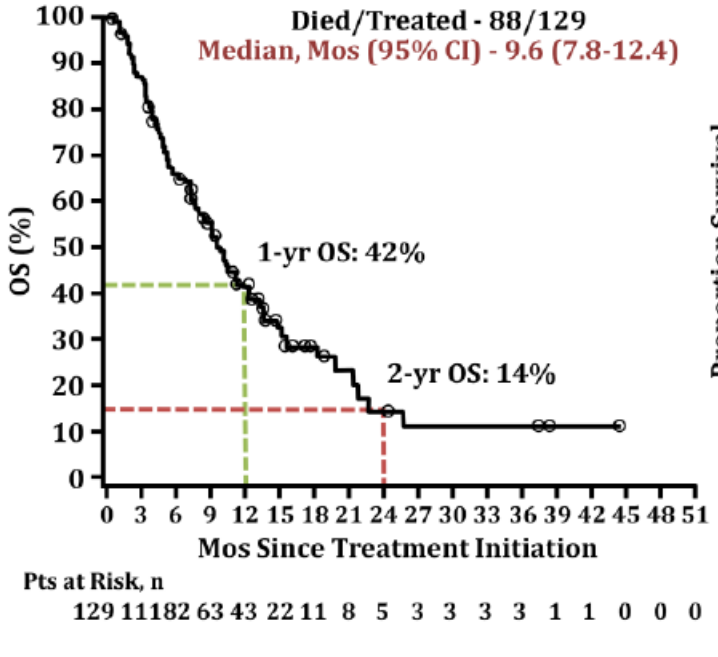


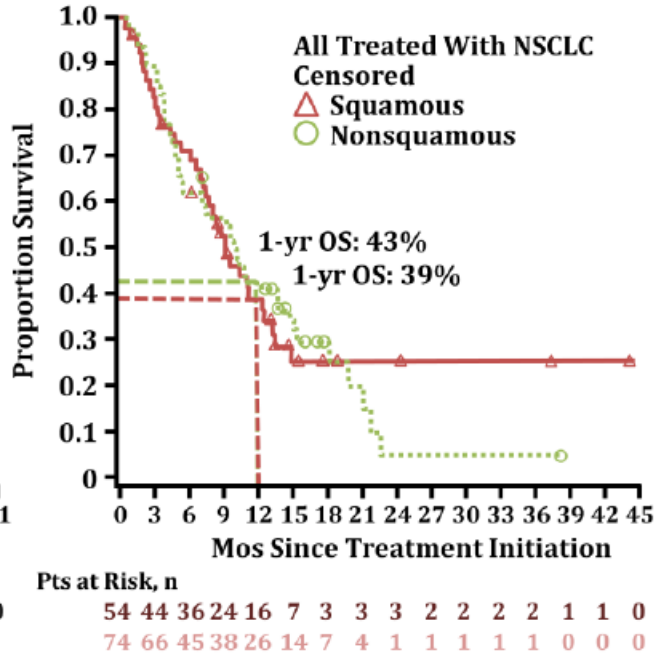
- Double-blind study
- Primary endpoint: OS
- Secondary endpoints: OS in patients who receive 1 dose of ipilimumab/ placebo, PFS, RR

ClinicalTrials.gov. NCT01285609

Nivolumab phase I trial in squamous/nonsquamous NSCLC



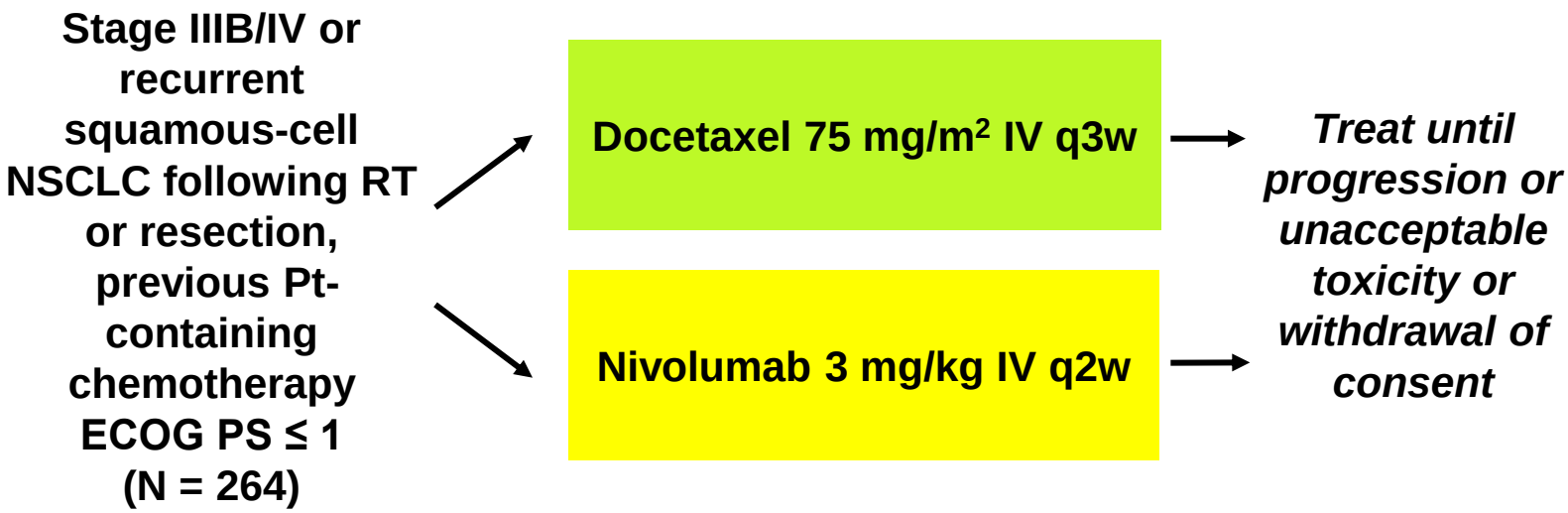




Open circles indicate censored events, denoting the time to the last known alive date before the date of data analysis, for patients without a death.

Brahmer JR et al. ASCO 2013. Abstract 8030

Ongoing phase III: Nivolumab in squamous NSCLC



- Primary endpoints: ORR, OS
- Secondary endpoints: PFS, ORR, and OS in PD-L1–positive vs PD-L1–negative subgroups, duration of OR, time to OR, proportion of patients exhibiting disease-related symptom progression as per Lung Cancer Symptom Scale

ClinicalTrials.gov. NCT01642004

Lambrolizumab (MK-3475) in 2nd line for NSCLC

Objectives of Protocol:

- Assess safety and efficacy in patients with previously treated NSCLC

Eligibility Criteria for Protocol:

- 2 prior systemic therapies
- ≥1 measurable lesion
- ECOG PS of 0-1
- Submission of a new tumor specimen for PD-L1 analysis

Treatment: 10 mg/kg IV Q3W until progression by irRC, intolerable toxicity, or consent withdrawal

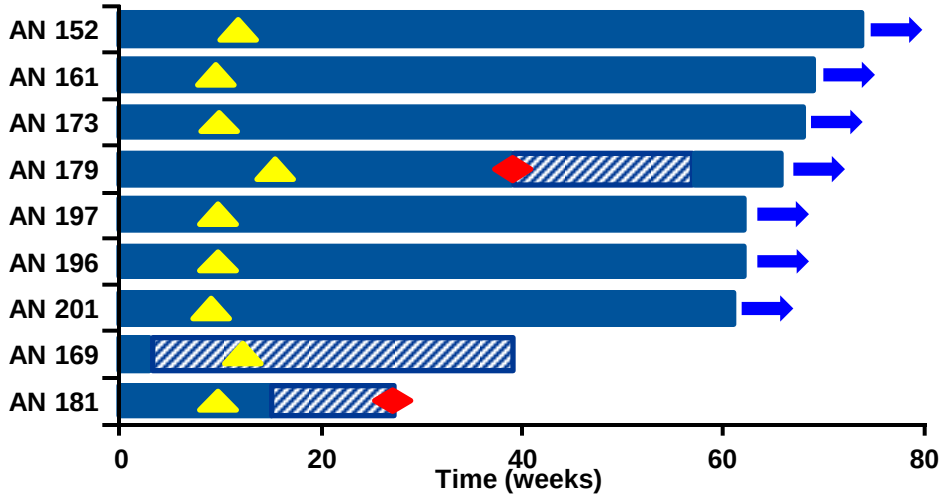
Patients: N = 38: 42% male, 45% aged ≥65 years, 58% with ECOG PS 1, 66% former/current smokers, 16% squamous, 11% treated brain metastases

PD-L1 Status: Assessed with a Merck proprietary IHC clinical trial assay; 61% positive (>0), 26% negative, 13% not evaluable; potential cut point determined by the Youden Index from a receiver operator characteristics curve

IASLC, 15th WCLC, abst 2416, 2013

Lambrolizumab (MK-3475) in 2nd line for NSCLC

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—



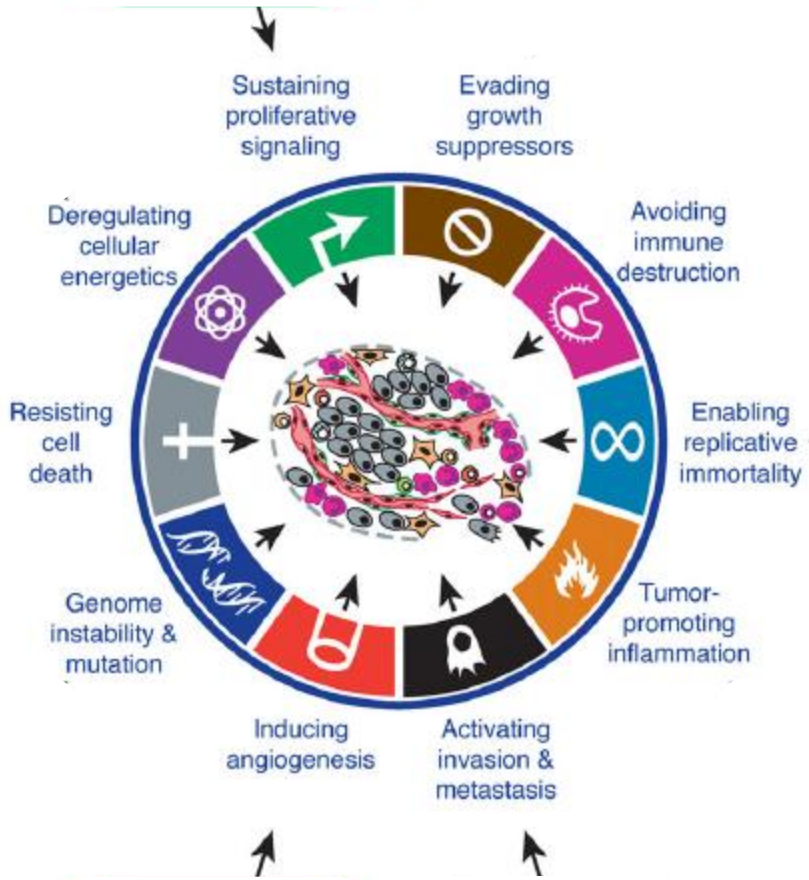
MK-3475 Responders Have Prolonged Duration of Response

On therapy
Confirmed response
Off therapy
Progression
Therapy continuing

IASLC, 15th WCLC, abst 2416, 2013

Characteristics of cancer cells

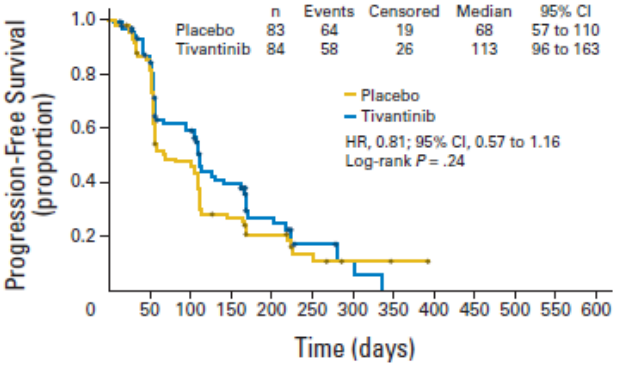
MET

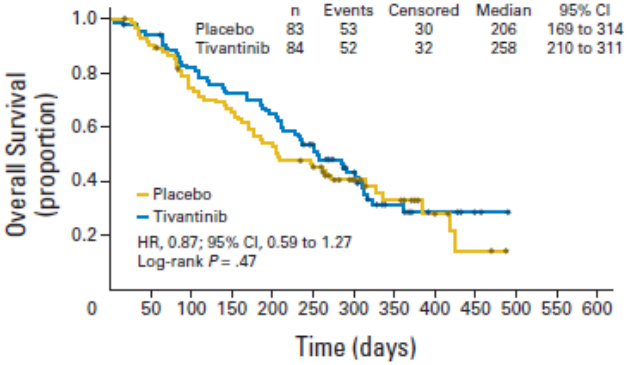


Hanahan D et al, Cell 144:646-674, 2011

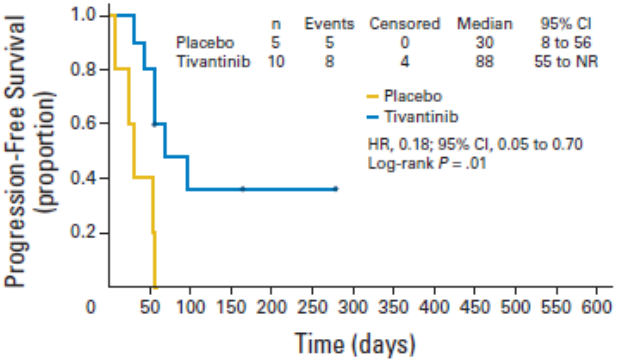
Tivantinib plus Erlotinib phase II trial

Intention-to-treat population





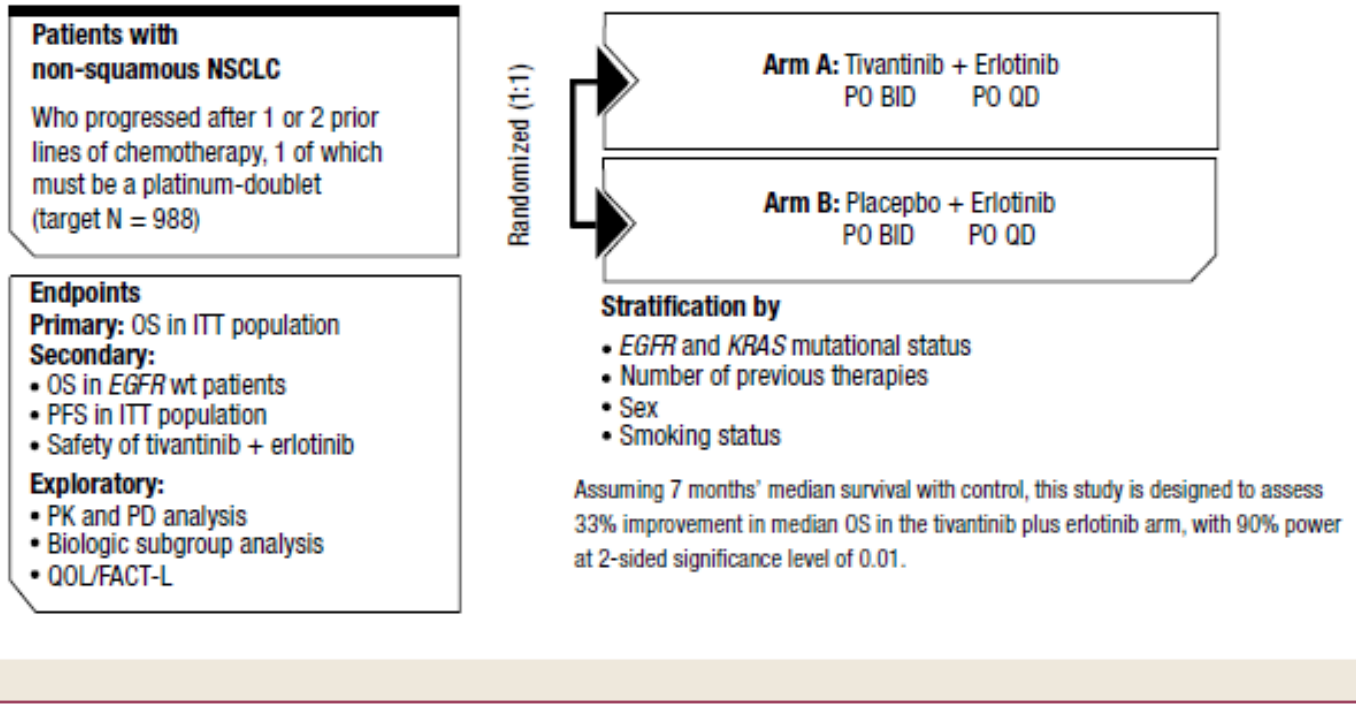
***KRAS* mutation positive population**



Sequist LV, et al. J Clin Oncol 29:3307-3315, 2011

Tivantinib plus Erlotinib phase III trial

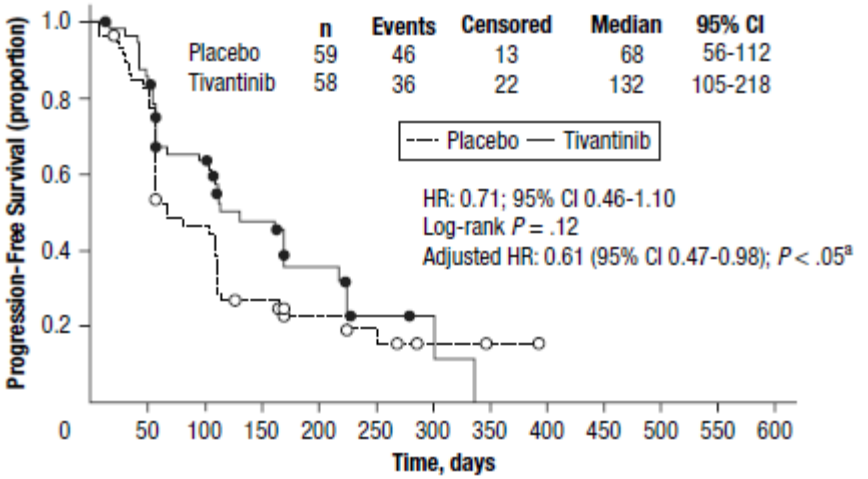
Schematic Diagram of the MARQUEE Study Design

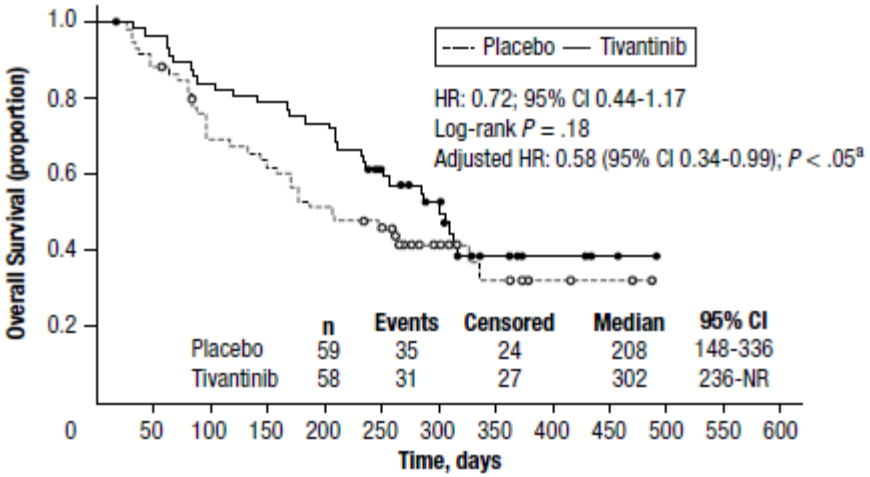


Abbreviations: BID = twice daily; EGFR = epidermal growth factor receptor; FACT-L = Functional Assessment of Cancer Therapy-Lung; ITT = intent-to-treat; NSCLC = non–small-cell lung cancer; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; PO = orally; QD = once daily; QOL = quality of life; TKI = tyrosine kinase inhibitor; wt = wild type.

Scagliotti GV, et al. Clin Lung Cancer 13:391-395, 2012

Tivantinib plus Erlotinib phase III trial



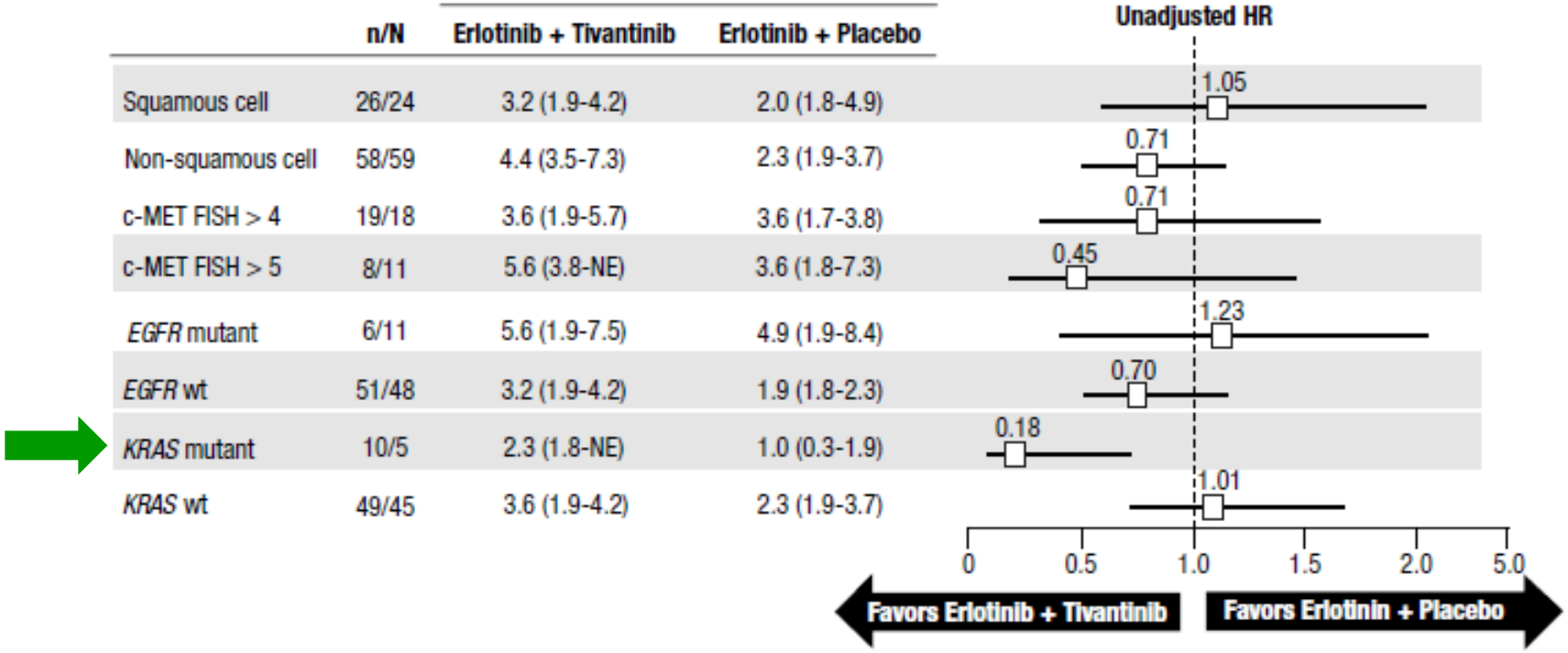


	Patients, n	Median PFS, months	Median OS, months
Erlotinib + Tivantinib	58	4.4	9.9
Erlotinib + Placebo	59	2.3	6.8

Scagliotti GV, et al. Clin Lung Cancer 13:391-395, 2012

Tivantinib plus Erlotinib phase III trial

	n/N	Median PFS (95% CI), months	
		Erlotinib + Tivantinib	Erlotinib + Placebo
Squamous cell	26/24	3.2 (1.9-4.2)	2.0 (1.8-4.9)
Non-squamous cell	58/59	4.4 (3.5-7.3)	2.3 (1.9-3.7)
c-MET FISH > 4	19/18	3.6 (1.9-5.7)	3.6 (1.7-3.8)
c-MET FISH > 5	8/11	5.6 (3.8-NE)	3.6 (1.8-7.3)
EGFR mutant	6/11	5.6 (1.9-7.5)	4.9 (1.9-8.4)
EGFR wt	51/48	3.2 (1.9-4.2)	1.9 (1.8-2.3)
KRAS mutant	10/5	2.3 (1.8-NE)	1.0 (0.3-1.9)
KRAS wt	49/45	3.6 (1.9-4.2)	2.3 (1.9-3.7)



Scagliotti GV, et al. Clin Lung Cancer 13:391-395, 2012

Onartuzumab plus Erlotinib phase II trial

- Second-/ third-line NSCLC
- ECOG PS 0–2
- Tissue required

(n=137)

R

1 → Erlotinib + onartuzumab → PD

1 → Erlotinib + placebo → PD → Add onartuzumab if eligible

Stratification

Smoking history

PS

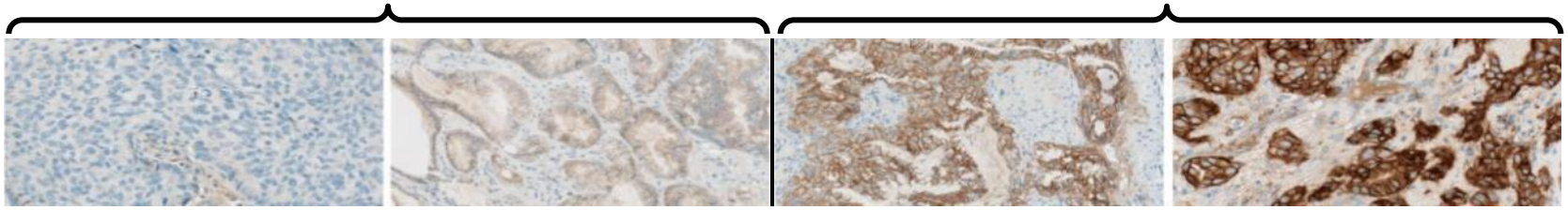
Histology

Co-primary objectives

- PFS in 'MET-positive' patients
- PFS in overall ITT population

MET IHC as a companion diagnostic

'MET-positive' = majority (≥50%) of tumour cells with moderate or strong staining intensity

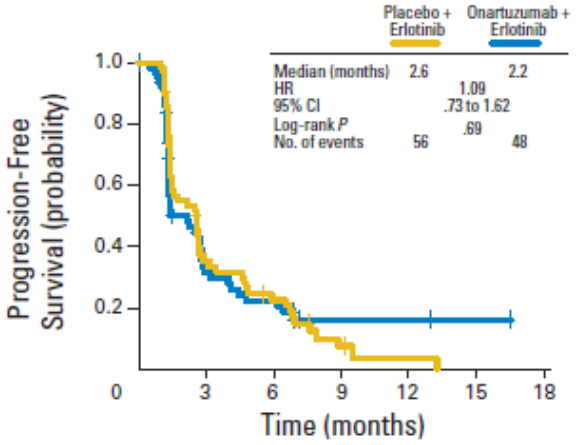


Erlotinib 150mg/day; Onartuzumab 15mg/kg i.v. q3w

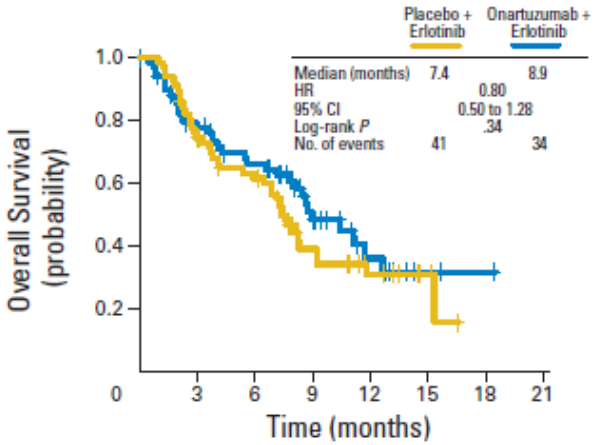
Spiguel DR, et al. J Clin Oncol 31:4105-4114, 2013

Onartuzumab plus Erlotinib phase II trial

Intention-to-treat population

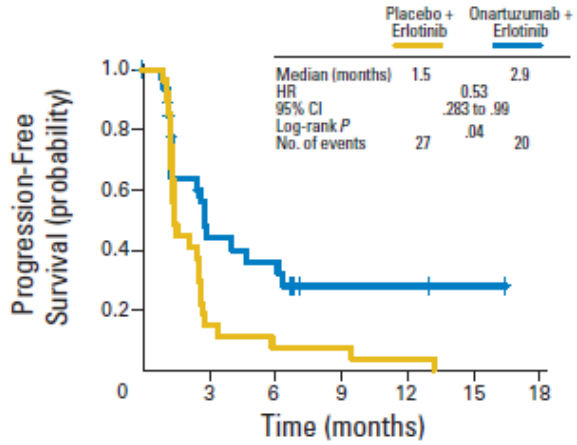


Placebo + erlotinib	68	20	12	3	1	0	0
Onartuzumab + erlotinib	69	17	12	2	2	1	0

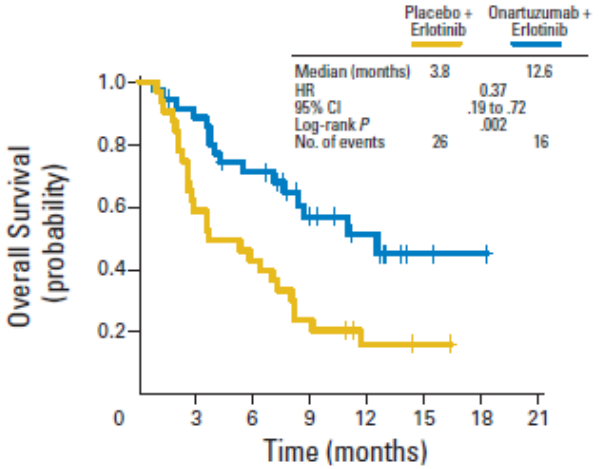


Placebo + erlotinib	68	49	38	16	9	3	0	0
Onartuzumab + erlotinib	69	50	39	19	8	2	1	0

MET positive population



Placebo + erlotinib	31	4	2	2	1	0	0
Onartuzumab + erlotinib	35	11	9	2	2	1	0

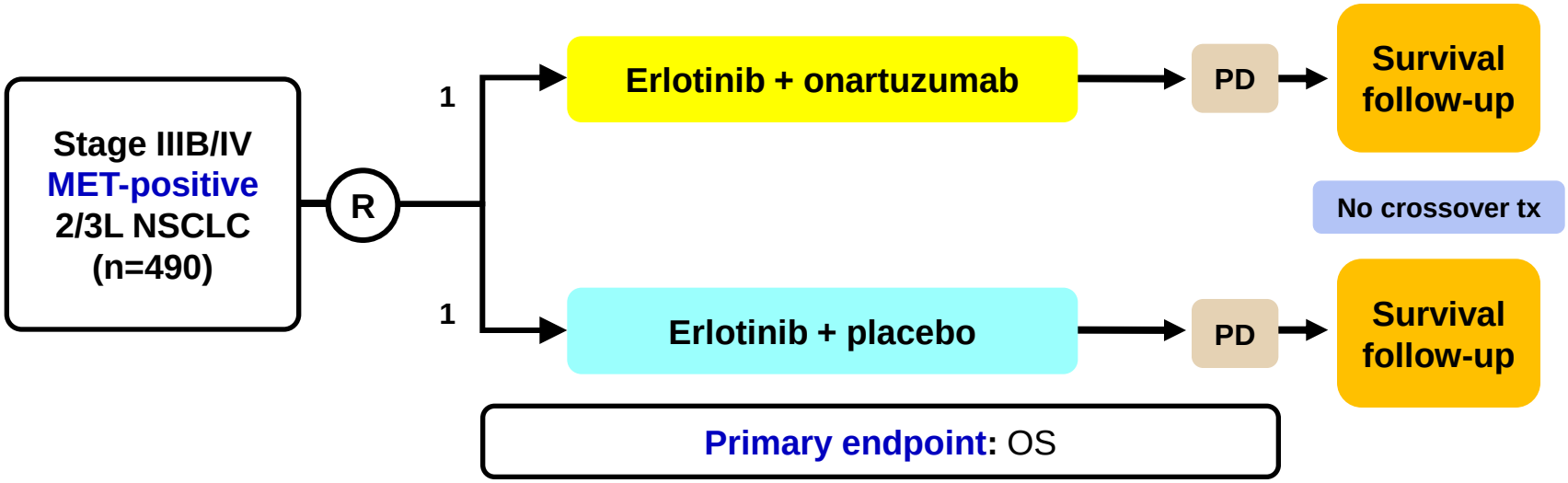


Placebo + erlotinib	31	18	13	7	3	1	0	0
Onartuzumab + erlotinib	35	30	23	14	8	2	1	0

Spiguel DR, et al. J Clin Oncol 31:4105-4114, 2013

Onartuzumab global phase III trial - METLung

Enrolment complete, data expected 2014



Stratification:

- *EGFR* Mut+ vs WT
- MET 2+ vs 3+
- Number of prior EGFR inhibitors
- Histology

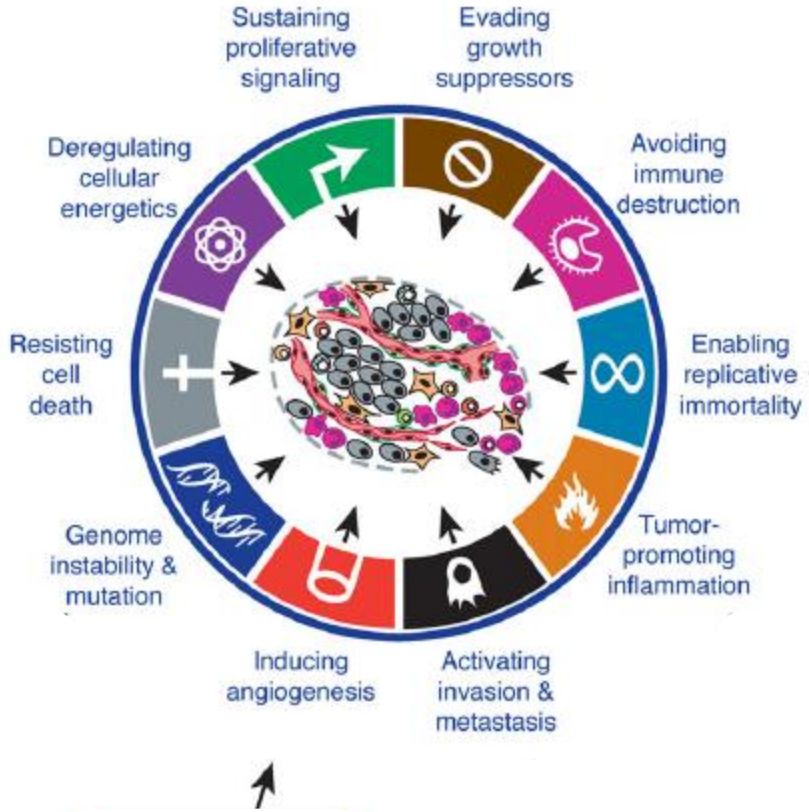
Key eligibility criteria:

- MET-positive (2+ or 3+)
- Central testing for MET IHC status
- 1 prior platinum-based line

MetLung (OAM4971g, NCT01456325)

Characteristics of cancer cells

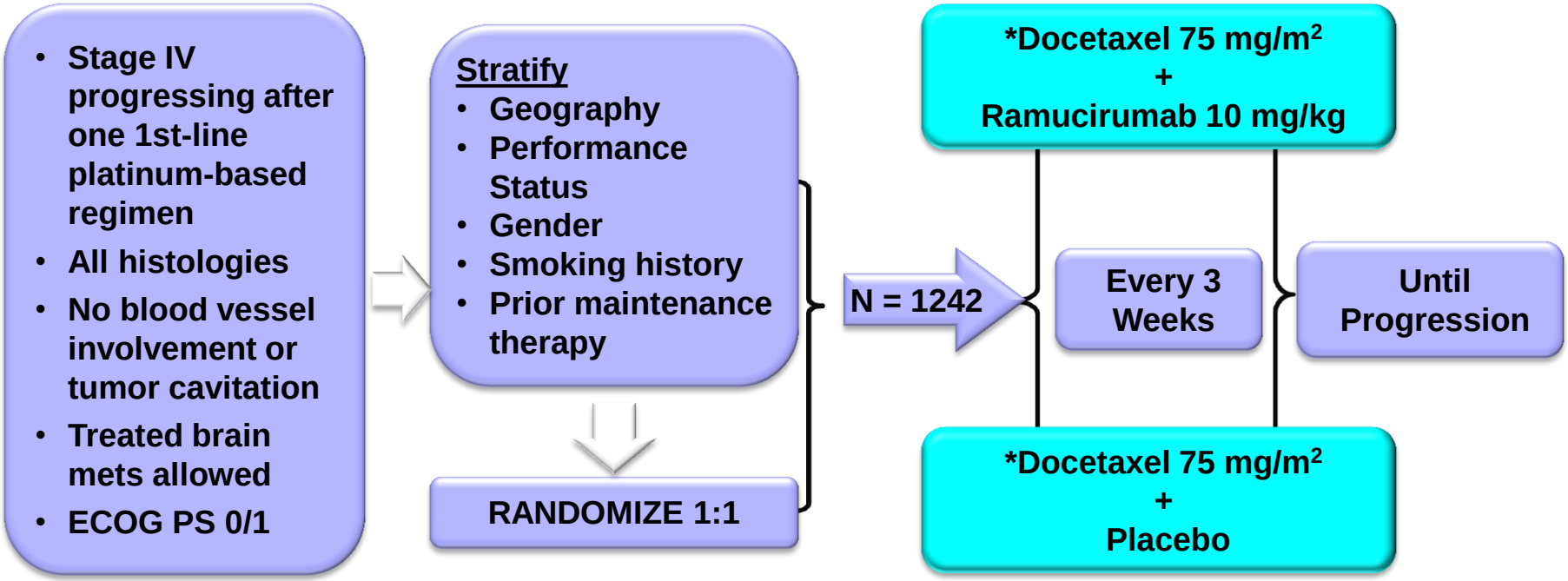
VEGFR2



Hanahan D et al, Cell 144:646-674, 2011

Ramucirumab (IMC-1121B) - fully human anti-VEGFR2

Phase 3 Randomized Study of Ramucirumab or Placebo plus Docetaxel as Second-Line Treatment of Patients With NSCLC



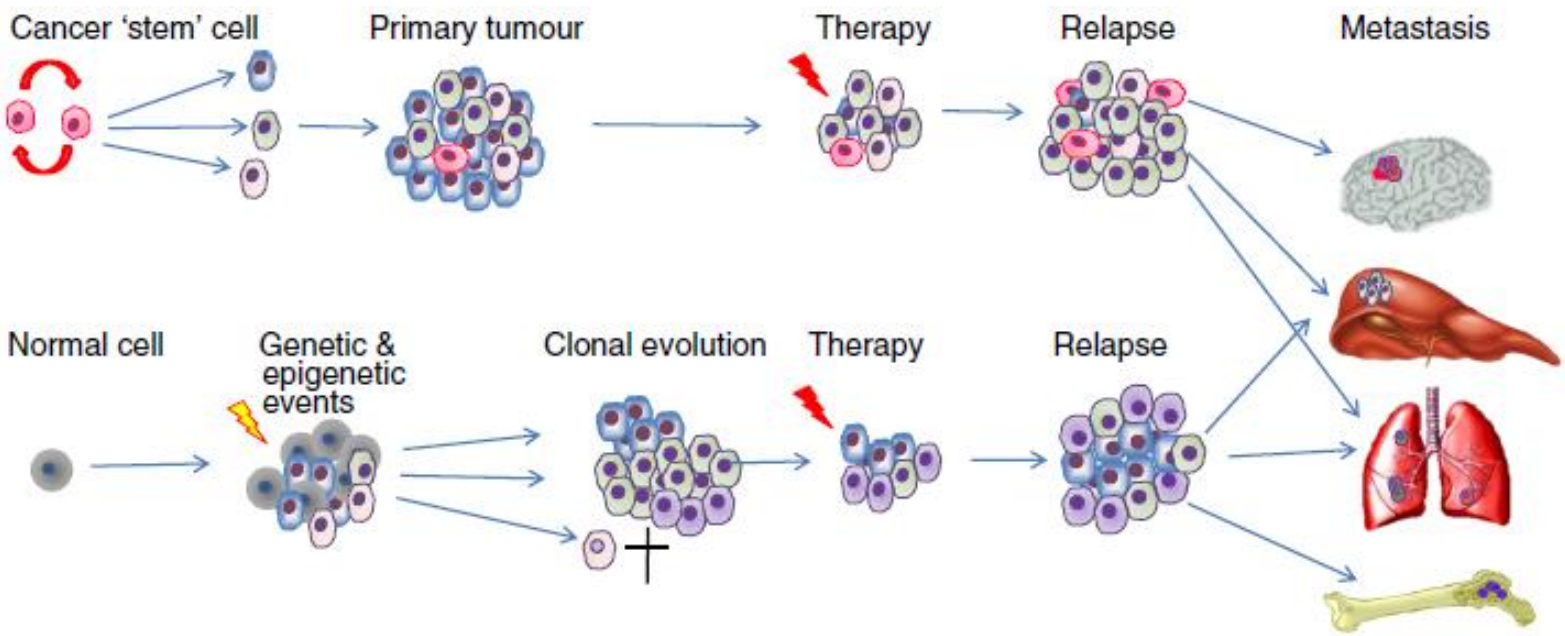
Primary end point: Overall survival
Secondary end points: Progression-free survival, overall response rate, safety, patient-reported outcomes

Study locations: North, South and Central America, Europe, Asia, Middle East, New Zealand

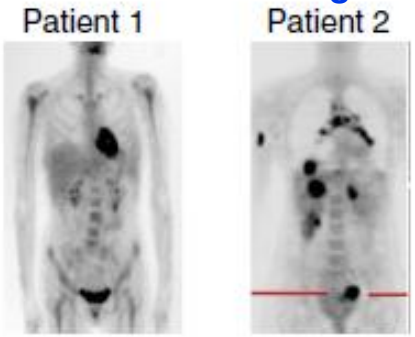
**Docetaxel 60 mg/m² in Korea and Taiwan*

US NIH, ClinicalTrials.gov; http://clinicaltrials.gov/.

Tumor heterogeneity

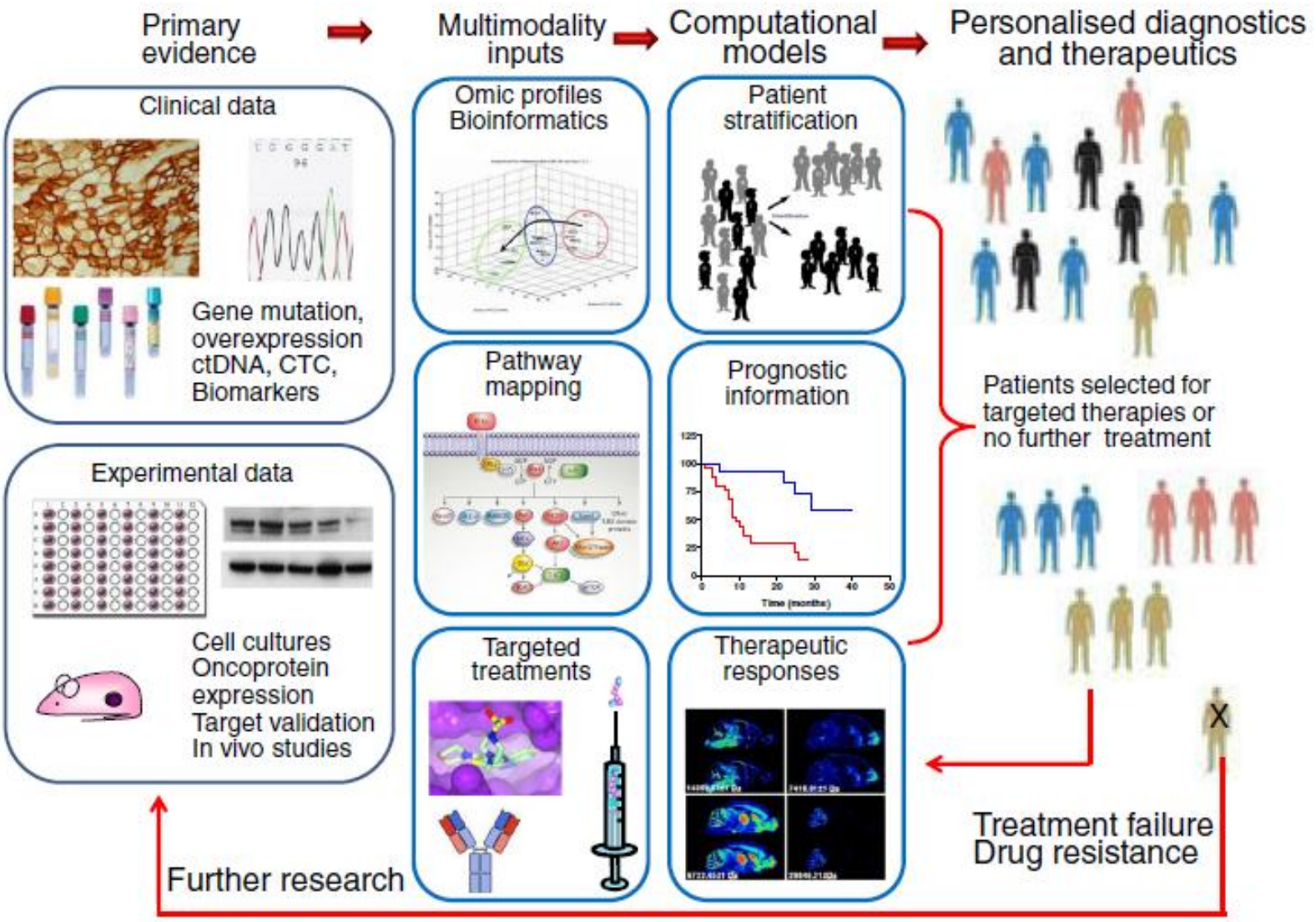


Tumors with identical histological type and biochemical parameters



Eccles S, et al. Breast Cancer Res 15:R92, 2013

Integrated vision of multidisciplinary research



Eccles S, et al. Breast Cancer Res 15:R92, 2013

Summary

→ Exciting clinical data with new targeted approaches - more effective therapy with more selective toxicity

→ Potential for biomarker-directed therapy to select patients most likely to benefit:

- *BRAF* mutation
- *ROS1* translocation
- PDL1 IHC
- MET IHC
- Other

→ Challenges for trials design, biomarker based selection and rational combinations development

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