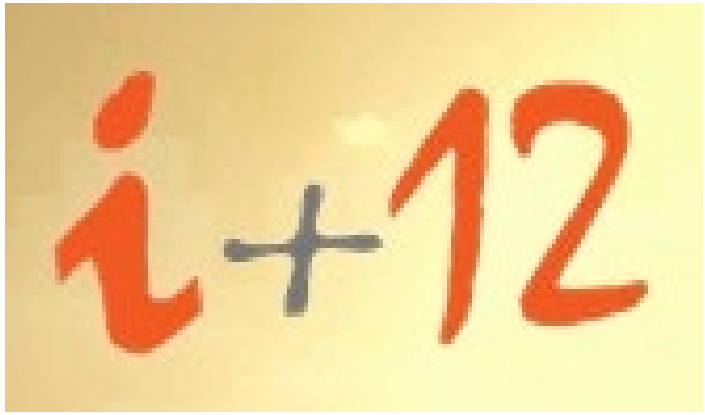

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UNIVERSIDAD COMPLUTENSE MADRID

Medicina Personalizada en Oncología Perspectivas Futuras

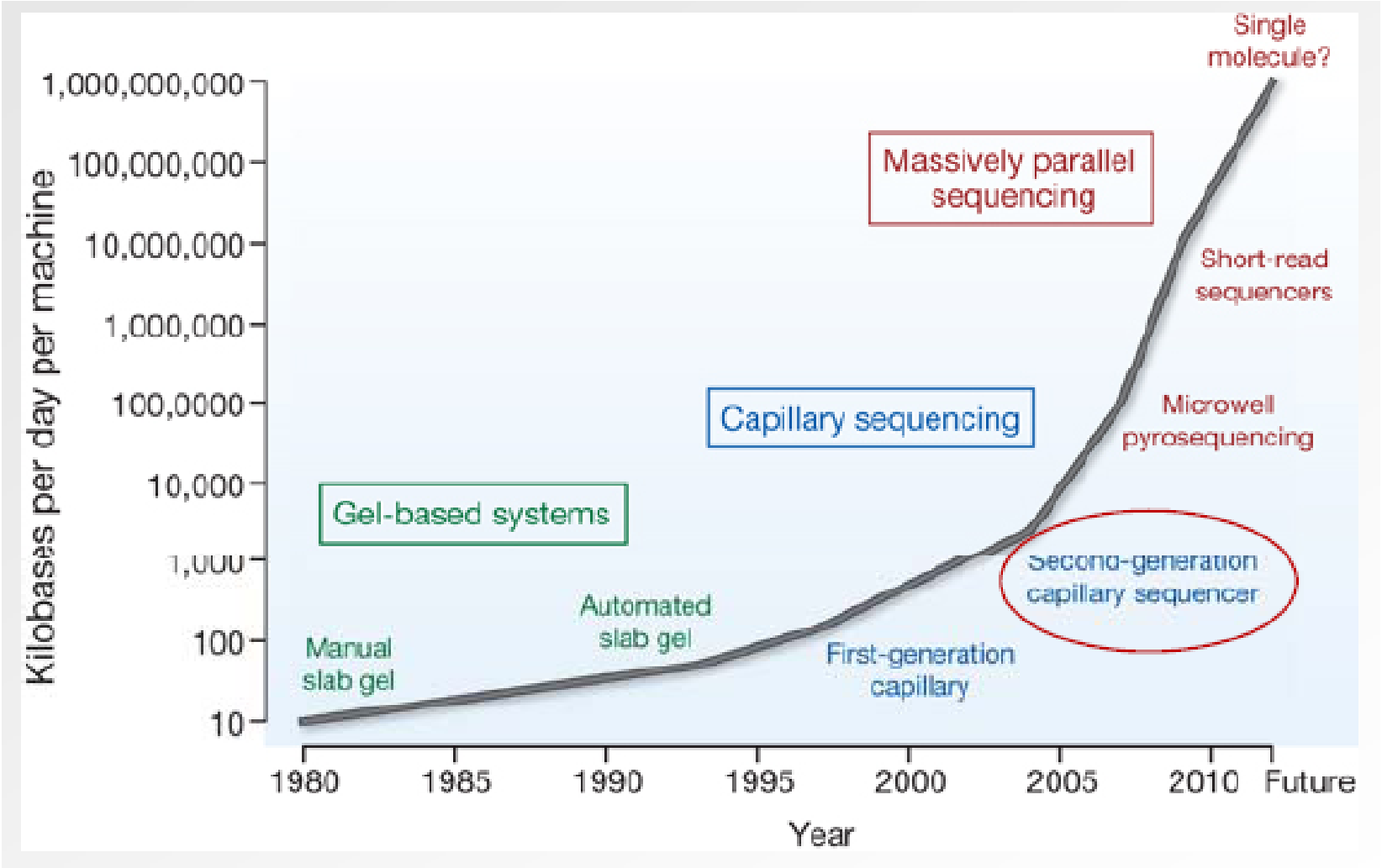
Luis Paz-Ares

Hospital Universitario Doce de Octubre, Madrid, Spain

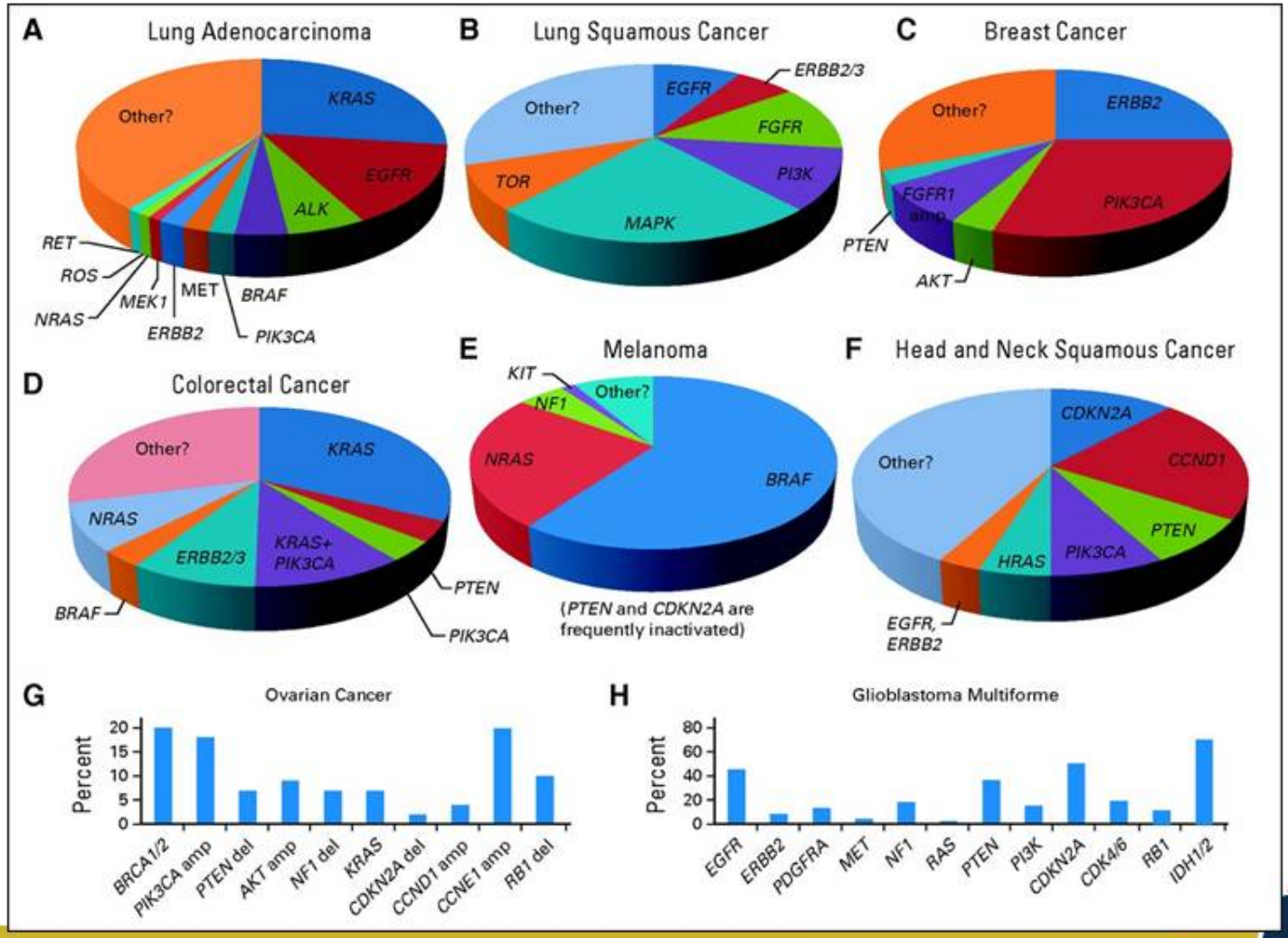
Drivers of Cancer treatment Evolution

- **Multidisciplinary teams**
- **Uncovering of molecular aberrations**
  - Novel targets
  - Predictive biomarkers
- **Technology acquisition**
  - Tumor profiling
  - Effective targeting

Tumor Profiling Evolution
The Example of NGS



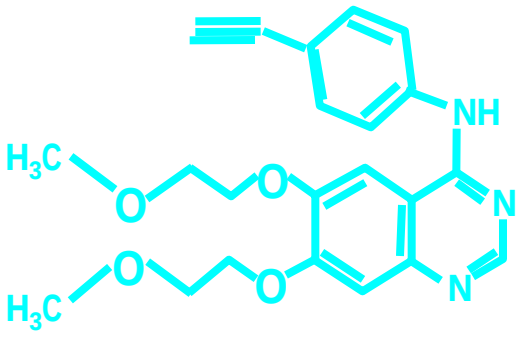
Genomic Aberrations in Common Solid Tumors



Garraway L A JCO 2013;31:1806-1814

Major classes of molecular-targeted agents

Oral molecules

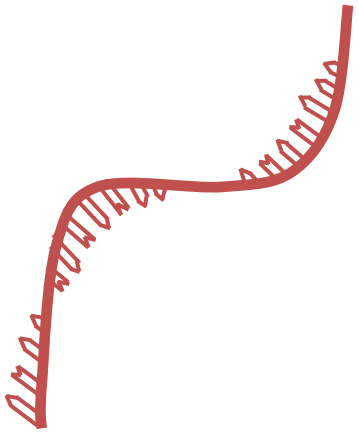


Intracellular action
c 0.5–2kDa
Orally available

Monoclonal antibodies

Extracellular action
c 150kDa
i.v. infusion

Antisense oligonucleotides



Intracellular action
c 10kDa
i.v. infusion

Temas

- **Agentes dirigidos a Dianas moleculares específicas**
- **Inmunoterapia**
- **Desarrollo de nuevos fármacos y EECC**
- **Implementación**

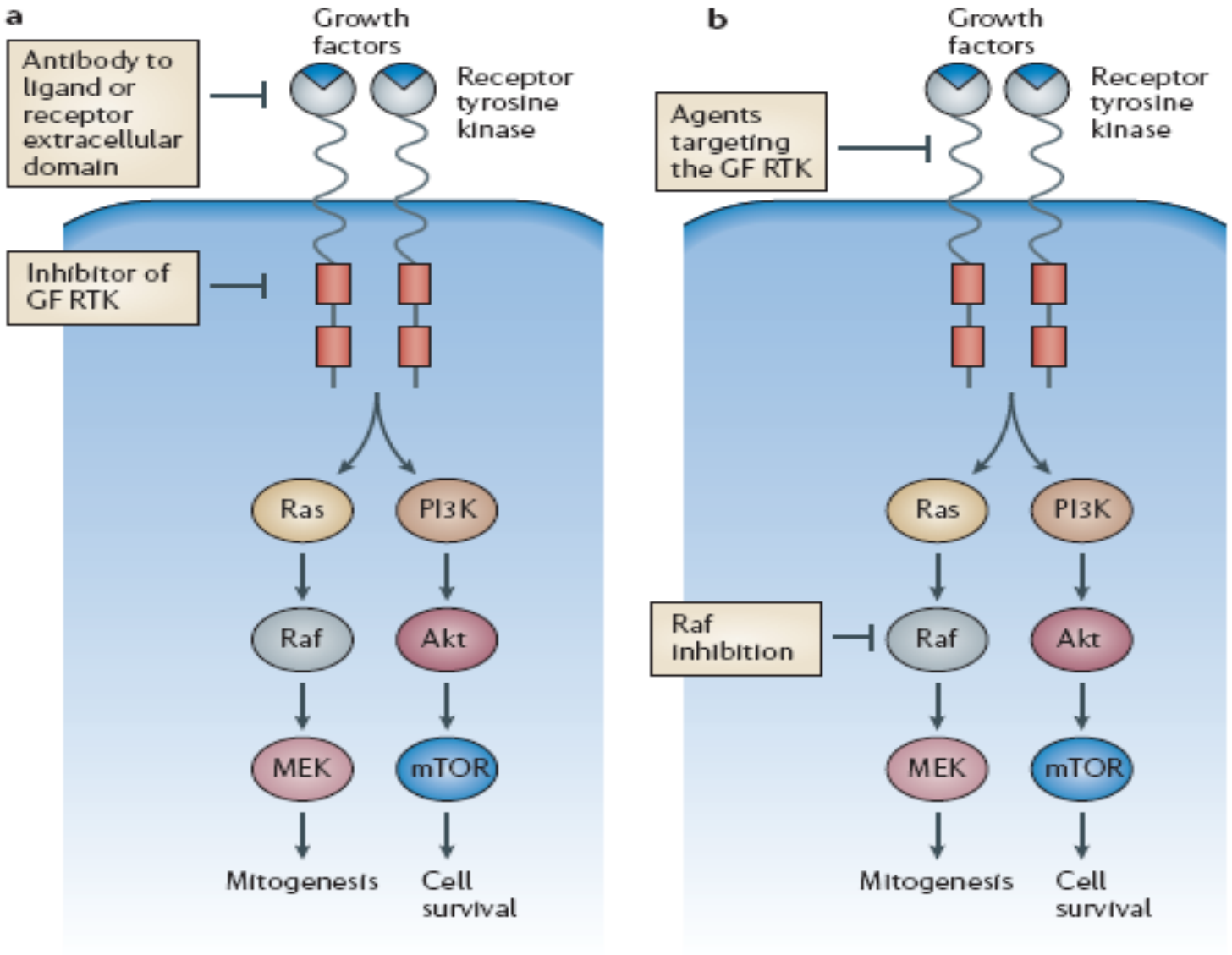
Temas

- **Agentes dirigidos a Dianas moleculares específicas**
- **Inmunoterapia**
- **Desarrollo de nuevos fármacos y EECC**
- **Implementación**

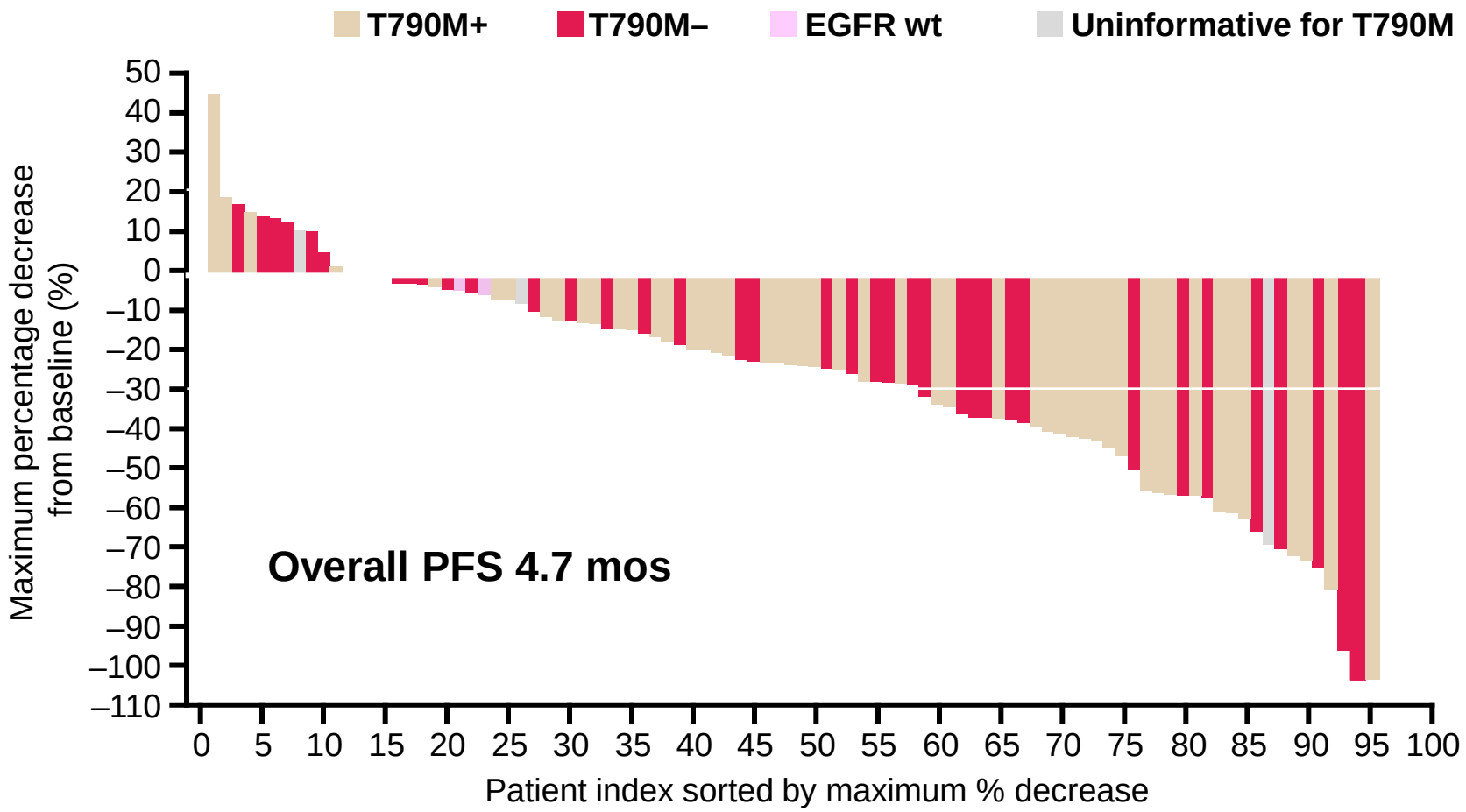
Dianas Moleculares

- **Combinaciones**
- **Prevención y tratamiento de Resistencias**
- **Co-mutaciones**

Strategic combinations

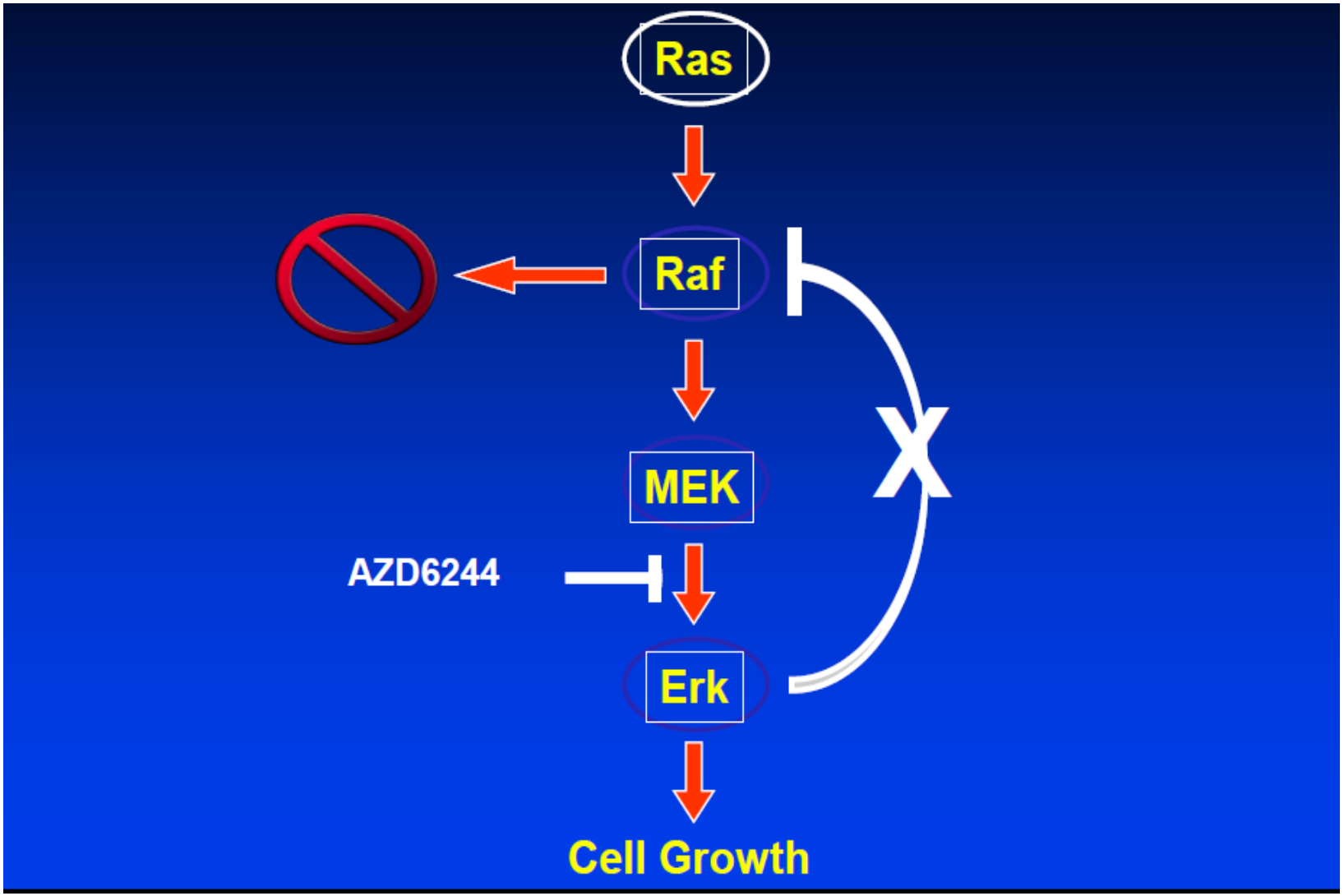


Afatinib plus cetuximab at MTD: responses by T790M mutation



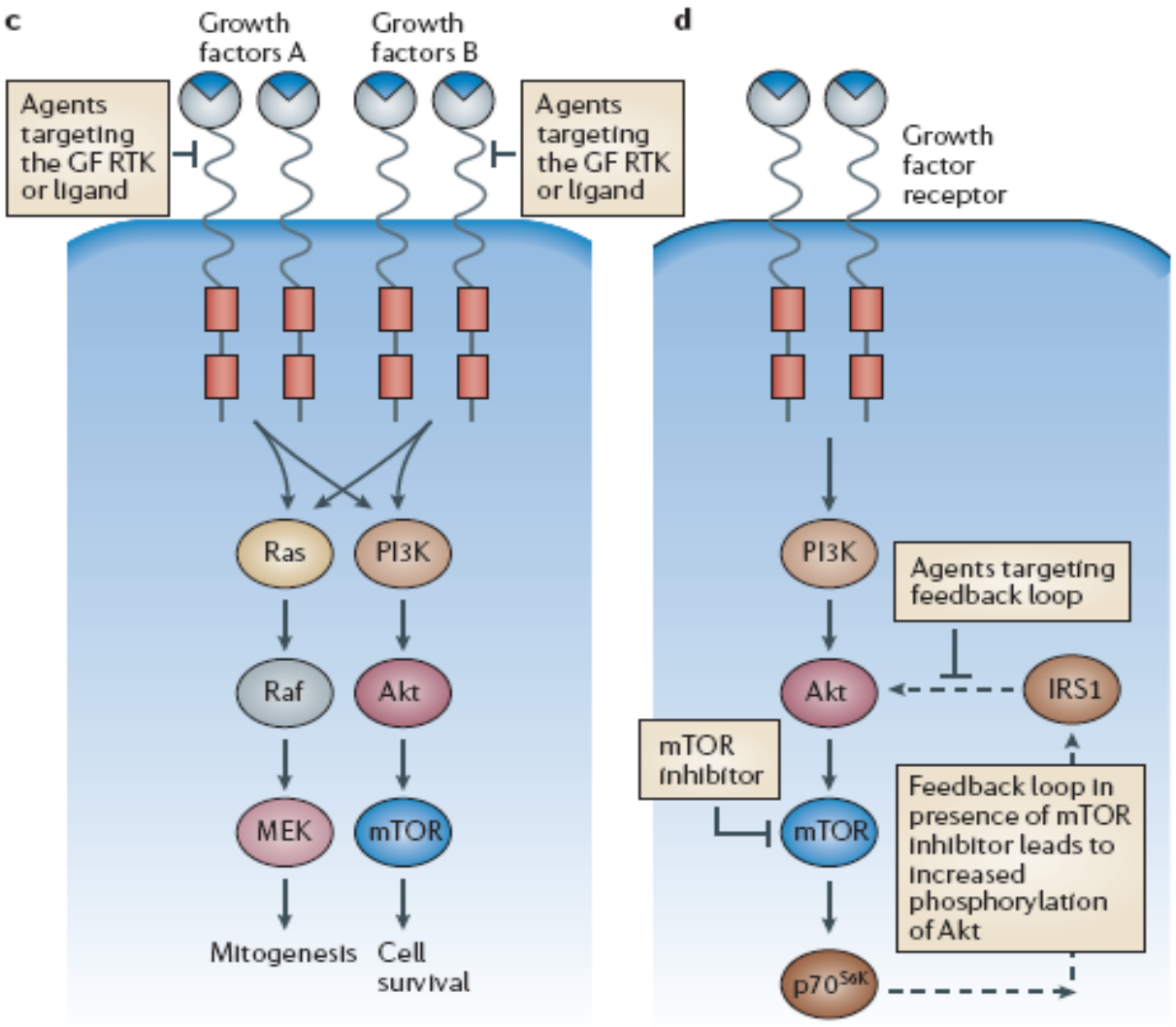
Janjigian YY, et al. Ann Oncol 2012;23(9S):abstract 1227O

Abrogation of feedback loop of Raf by Erk

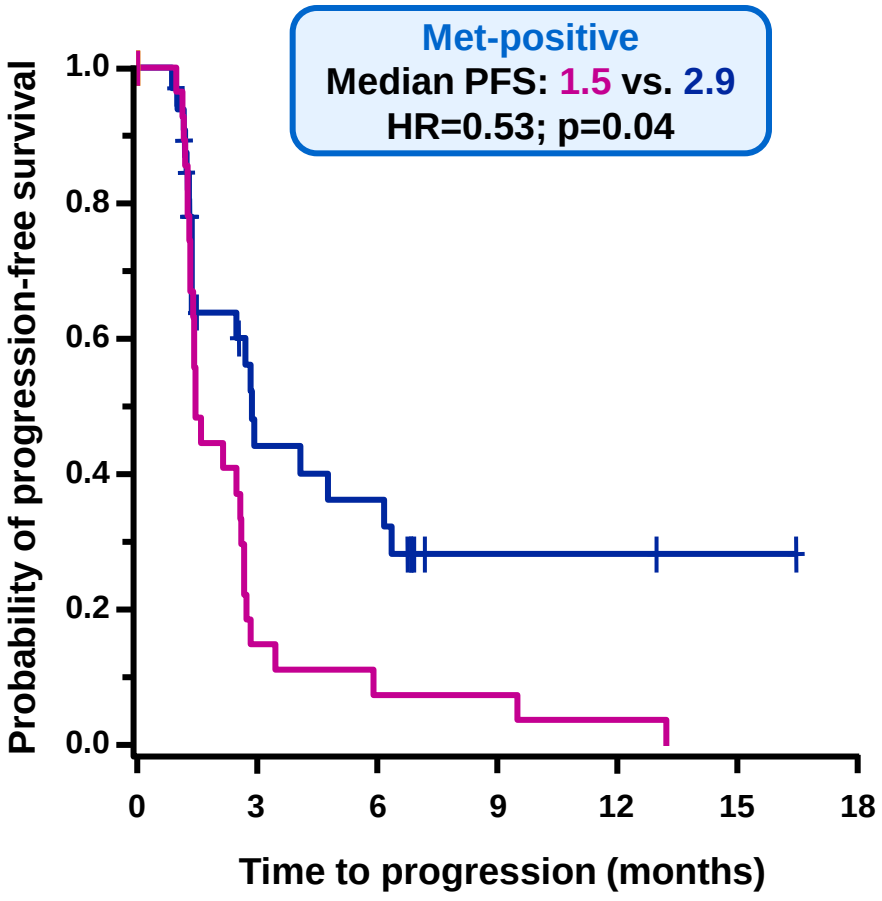


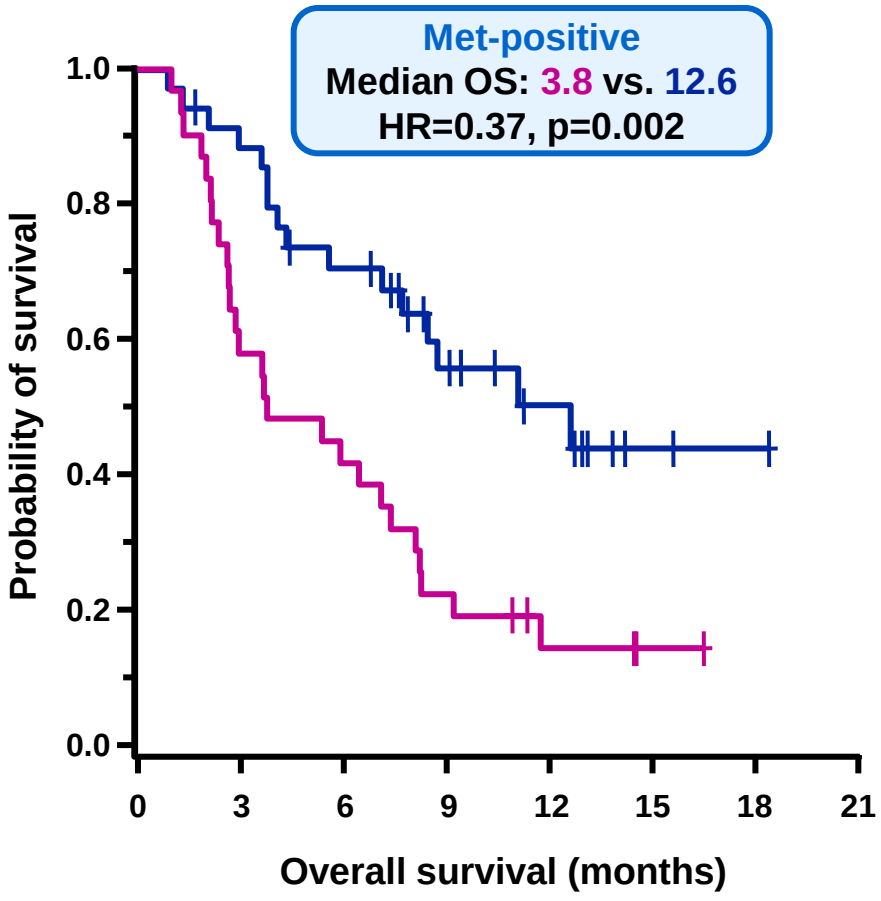
Zhao Y, Adjei AA. Nat Res Clin Oncol 2014;11:385–400

Strategic combinations



METMAB: PFS and OS in patients with Met-positive disease



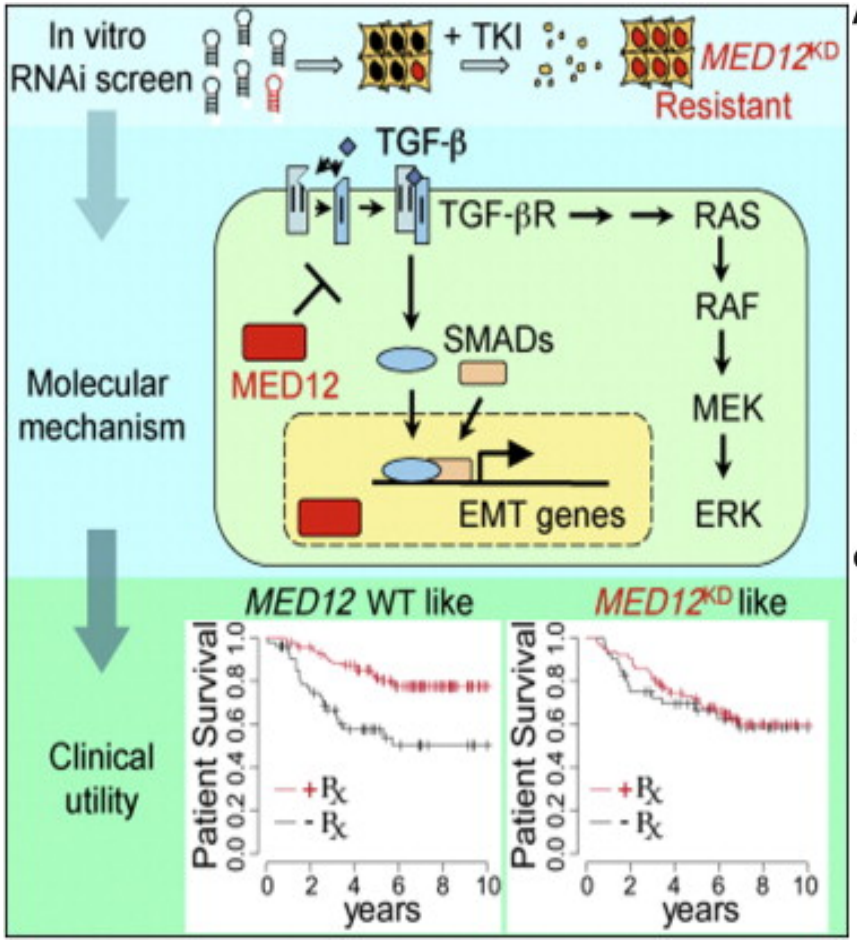


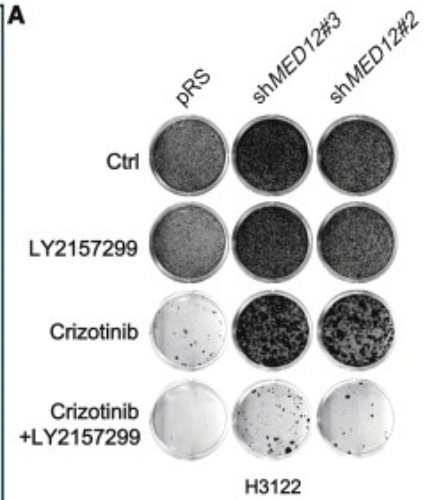
Placebo + erlotinib

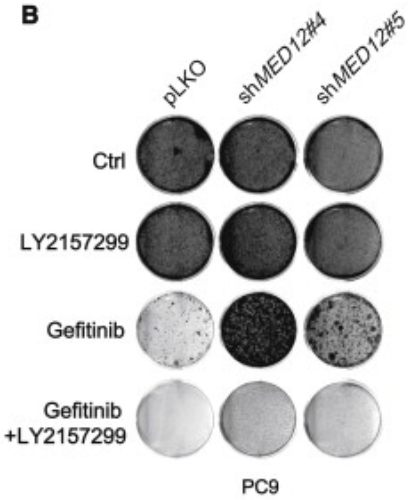
Onartuzumab + erlotinib

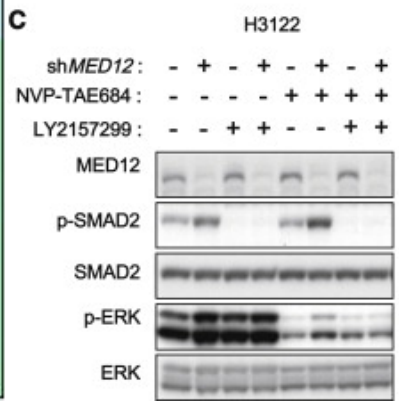
Spigel DR, et al. J Clin Oncol 2011;29(suppl):abstract 7505

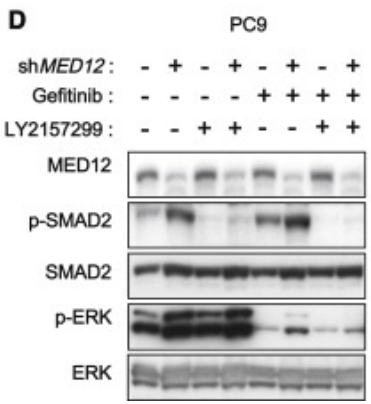
MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signalling





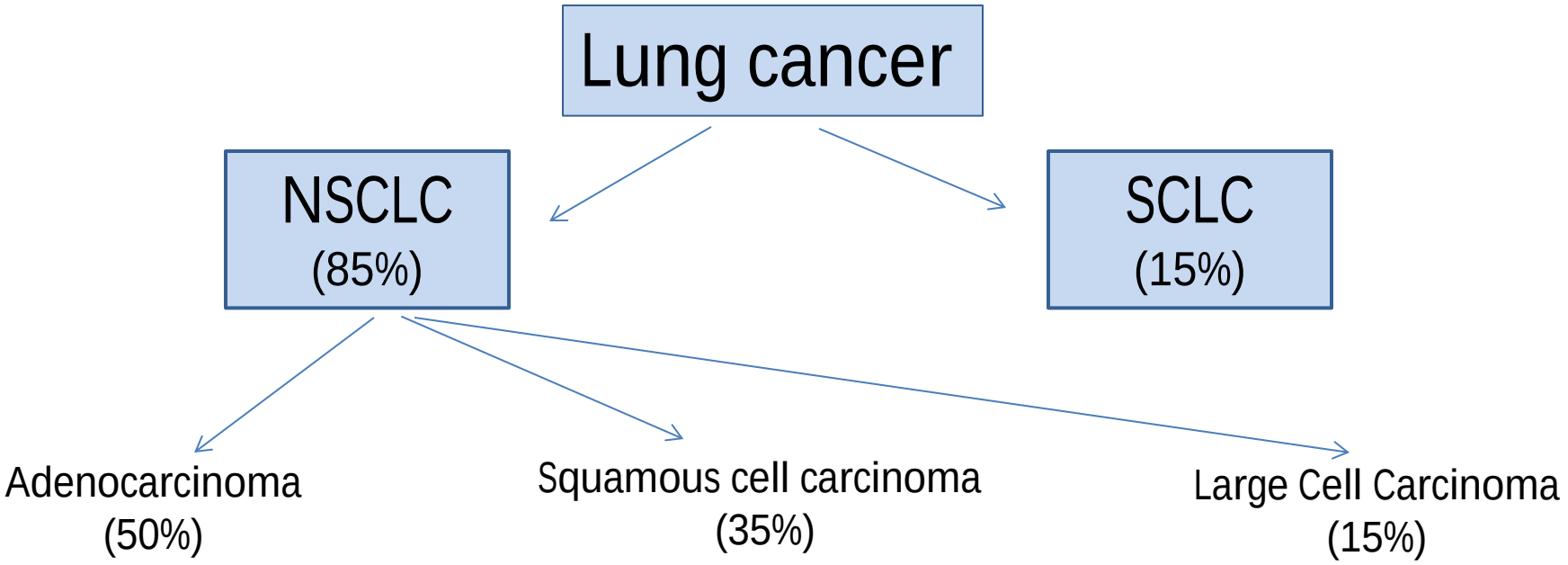


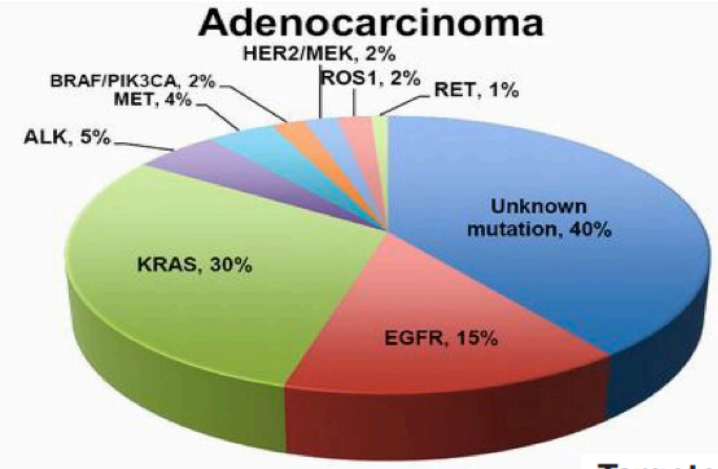


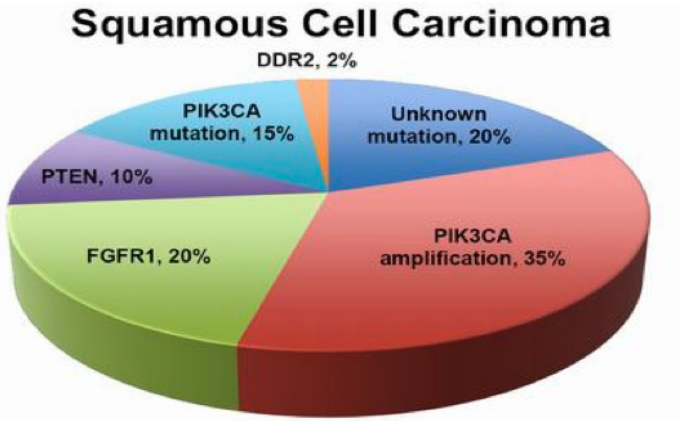


Huang S, et al. Cell 2012;151:937–50

SCC – FGFR1 amplification







Targeted therapy for non-small cell lung cancer: current standards and the promise of the future

Bryan A. Chan[1,2], Brett G.M. Hughes[1,2,3]

Transl Lung Cancer Res 2015;4(1):36-54

Efecto de FGFR1/4 en la tumorigénesis *in vitro*

SCC

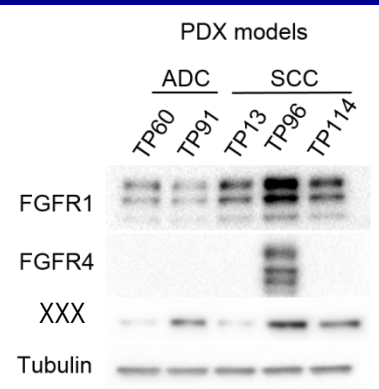
Cell line	Driver	Action	Proliferation (10%FBS)	Proliferation (0,5%FBS)	Clonability	Soft Agar
H520	TN	FGFR1 or FGFR4 silencing	↓	↓	↓	↓
H226	TN	FGFR4 overexpression	↑	↑	↑	↑
Calu-1	KRAS		↑	↑	↑	↑

ADC

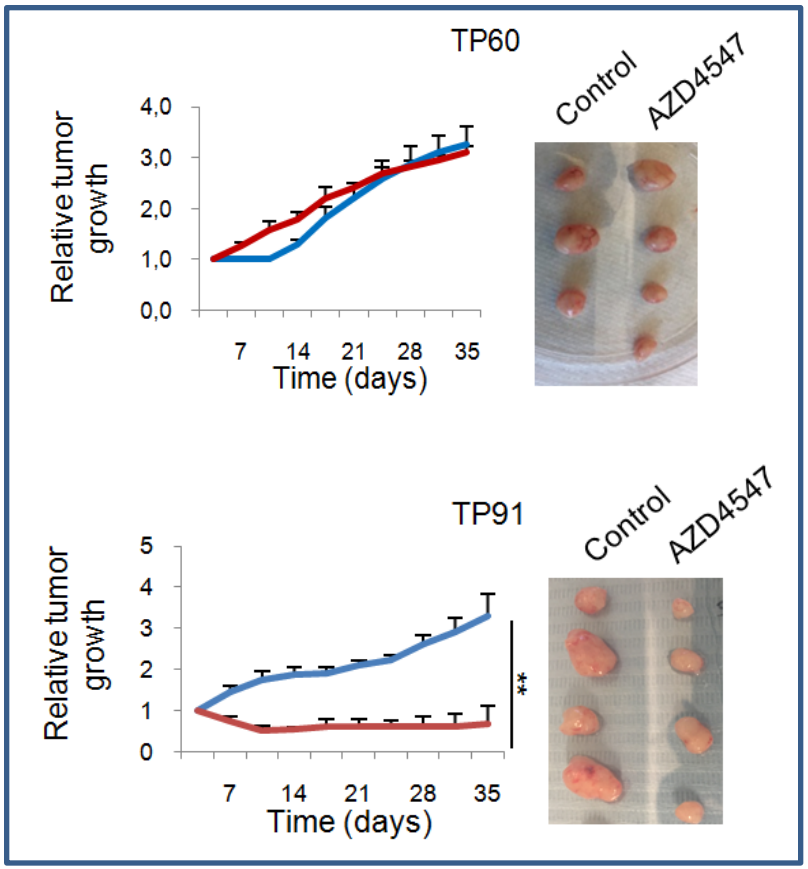
Cell line	Driver	Action	Proliferation (10%FBS)	Proliferation (0,5%FBS)	Clonability	Soft Agar
H2009	KRAS	FGFR1 or FGFR4 overexpression	↓	↓	↓	↓
H3122	ALK		↓	↓	↓	↓
H1437	TN		=	↓	=	=
A549	KRAS	FGFR1 or FGFR4 silencing	↑	↑	↑	↑

Correlación entre los efectos observados y activación de AKT, MAPK y STAT3

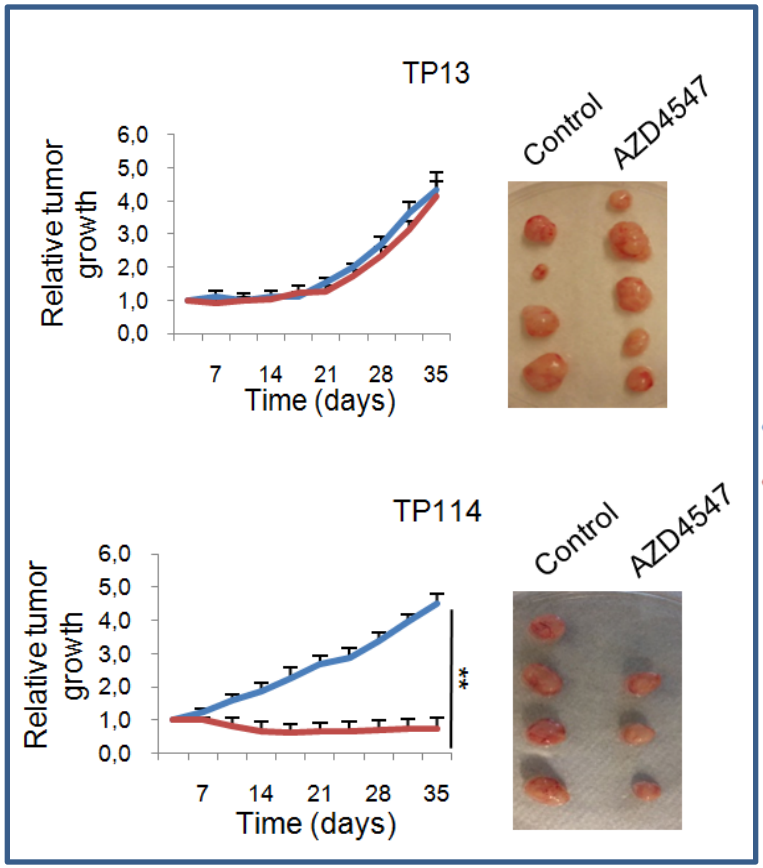
XXX predice la sensibilidad a inhibidores de FGFR en PDXs



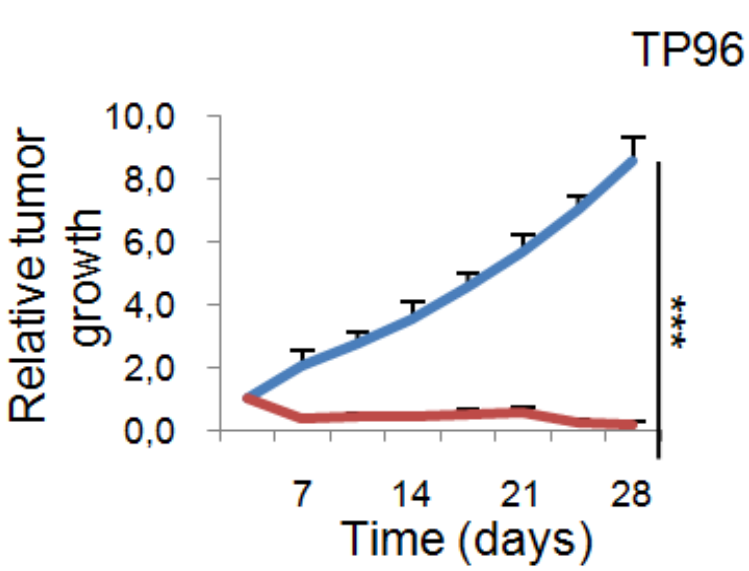
ADC PDXs

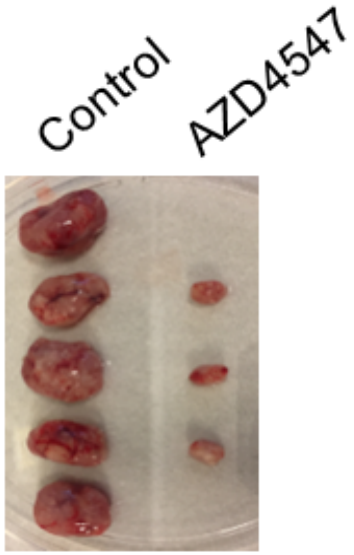


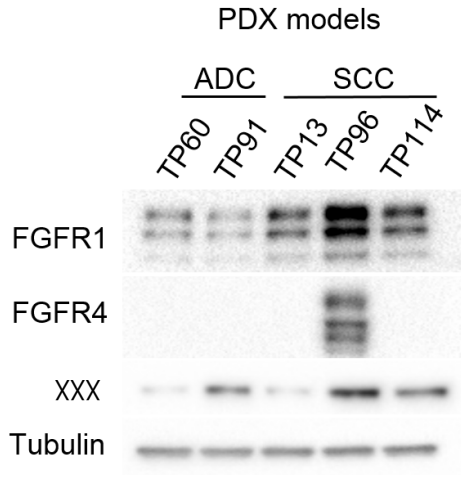
SCC PDXs



XXX predice la sensibilidad a inhibidores de FGFR en PDXs







Control

AZD4547

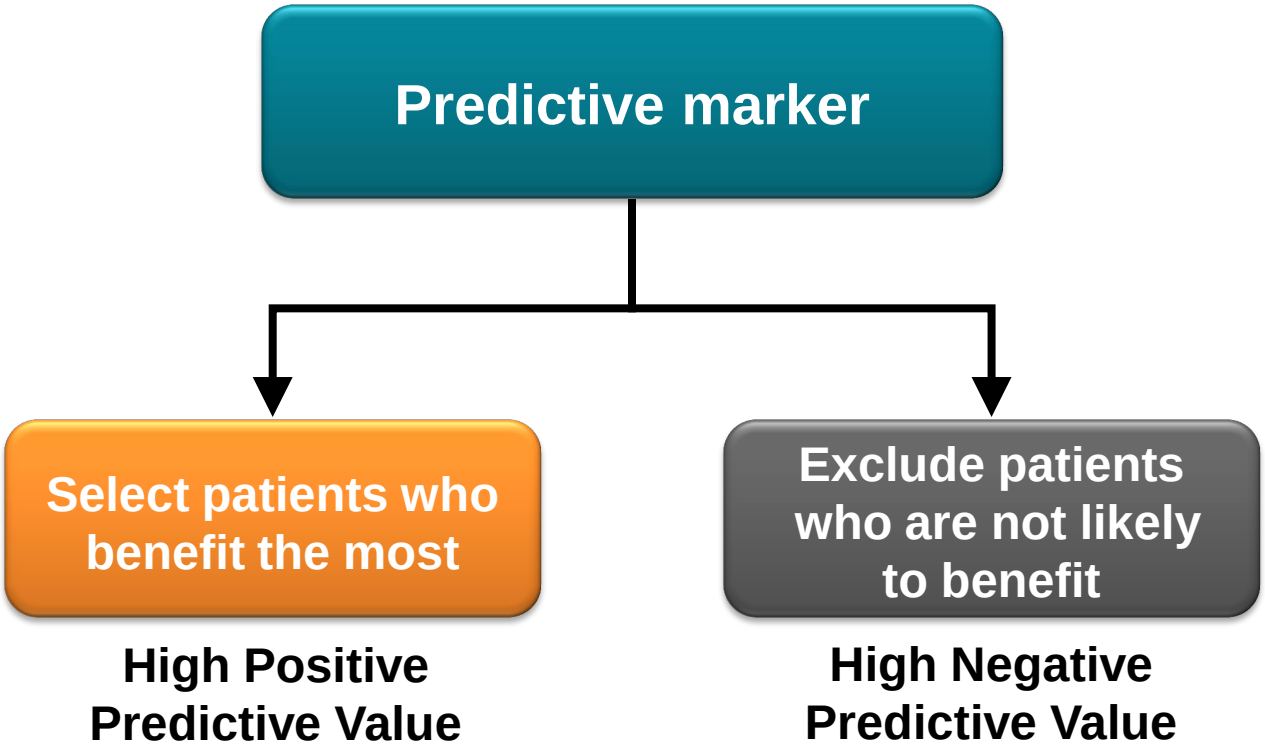
Temas

- Agentes dirigidos a Dianas moleculares específicas
- **Inmunoterapia**
- Desarrollo de nuevos fármacos y EECC
- Implementación

Inmunoterapia

- **Biomarcadores**
- **Nuevas estrategias**
- **Combinaciones**

How Can Predictive Markers Guide Clinical Practice?



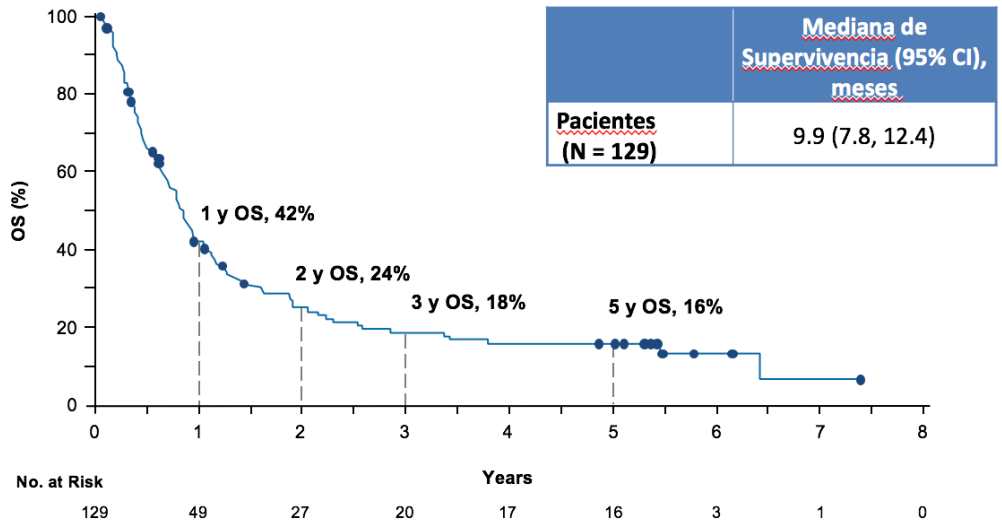
NPV, negative predictive value; PPV, positive predictive value.
Richard Simon. *J Natl Cancer Inst.* 2015;107(8):1-3.

Most patients are not benefitting from PD-1/L1 Agents

	CheckMate 017 phase 3[129]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel	Durvalumab	Avelumab
Patients (n)	135	137	292	290	345	346	343	144	143	198	184
Response rate (%)											
All patients	20	9	19	12	18	19	9	15	15	16	14
PD-L1 positive	21	8	36	13	30	29	8	38	13	27	16
PD-L								8	10	5	10
Media											
All p								2·7	3·0	NA	2·9
PD-L								2·8	3·0	NA	3·0
PD-L								1·7	4·1	NA	1·4
Media											
All p								2·6	9·7	NA	8·9
PD-L								5·5	9·2	NA	8·4
PD-L								9·7	9·7	NA	4·6
Histol								comers	All comers	All comers	All comers
Settin								cond line	Second line	Pre-treated	Pre-treated
PD-L1											
Posi								mour cell 1–3 or tumour-iltrating immune cells 1–3		≥25%	≥1%
Neg								mour cell 0 and tumour-iltrating immune cells 0		<25%	<1%
Percenta											

Table 4:

Nivolumab NSCLC Phase I Cohort 5 Year Survival

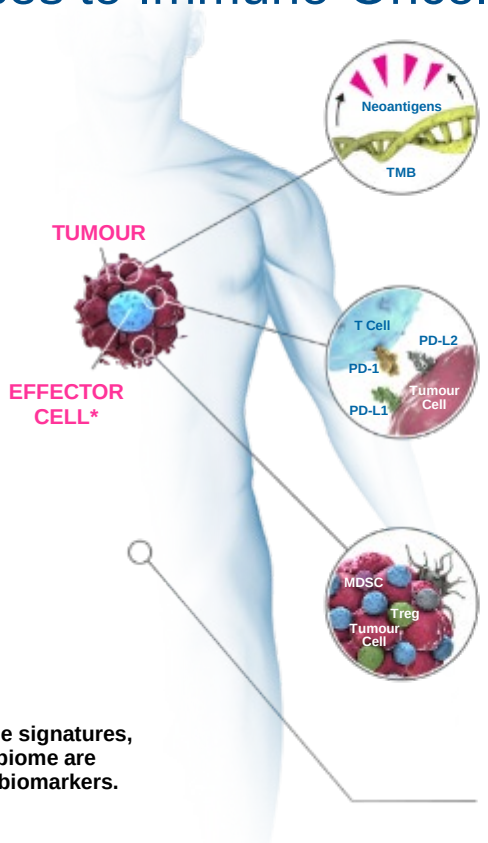


	Mediana de Supervivencia (95% CI), meses
Pacientes (N = 129)	9.9 (7.8, 12.4)

Brahmer et al. AACR 2017

Hirsch et al. Lancet 2016

Tumour and Immune Biomarkers Under Investigation to Better Predict Potential Responses to Immuno-Oncology Therapy



TUMOUR ANTIGENS[1,2]

- Tumour mutation burden (TMB)
- High microsatellite instability/ deficient mismatch repair (MSI-H/dMMR)
- Neoantigens

INFLAMED TUMOURS[1,2]

- Programmed death ligand 1 (PD-L1)
- Programmed death ligand 2 (PD-L2)
- Tumour-infiltrating lymphocytes (TILs)
- Inflammation gene signatures

IMMUNE SUPPRESSION[1-3]

- Lymphocyte-activation gene 3 (LAG-3)
- Indoleamine 2,3-dioxygenase (IDO)
- Regulatory T cells (Tregs)
- Myeloid-derived suppressor cells (MDSCs)

HOST ENVIRONMENT[2]

- Microbiome
- Germline Mutations

TMB, neoantigens, TILs, inflammation gene signatures, LAG-3, IDO, Tregs, MDSCs, and the microbiome are currently under investigation as potential biomarkers.

*Effector T cell or NK cell.

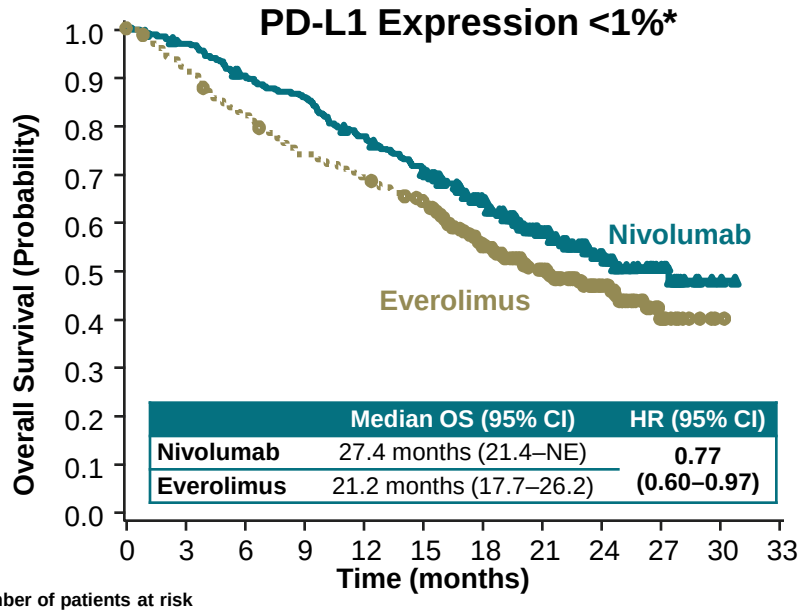
PD-1, programmed death receptor-1.

1. Ma W et al. *J Hematol Oncol*. 2016;9:47. 2. Sharma P, Allison JP. *Science.* 2015;348(6230):56-61. 3. Yuan J et al. *J Immunother Cancer.* 2016;4:3.

CheckMate 025: Overall Survival in ITT and PD-L1 Subgroups

RCC

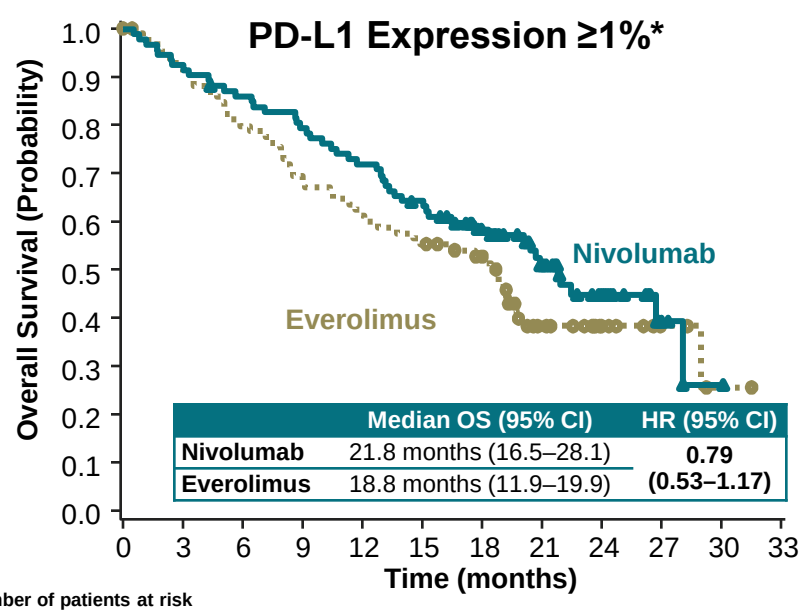
- Median OS in the ITT population was 25.0 months and 19.6 months in the nivolumab and everolimus arms, respectively



	Median OS (95% CI)	HR (95% CI)
Nivolumab	27.4 months (21.4–NE)	0.77 (0.60–0.97)
Everolimus	21.2 months (17.7–26.2)	

Number of patients at risk

Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	192	137	92	51	16	1	0



	Median OS (95% CI)	HR (95% CI)
Nivolumab	21.8 months (16.5–28.1)	0.79 (0.53–1.17)
Everolimus	18.8 months (11.9–19.9)	

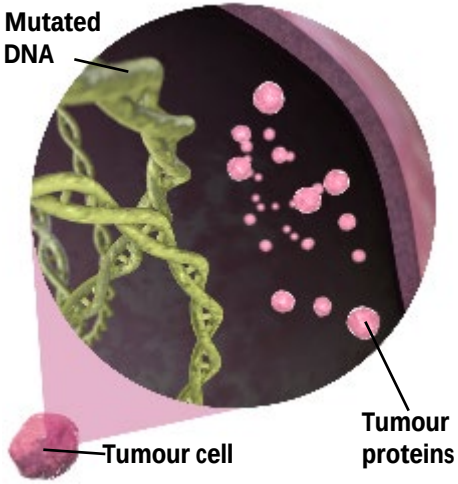
Number of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	97	77	68	59	52	47	40	19	9	4	1	0

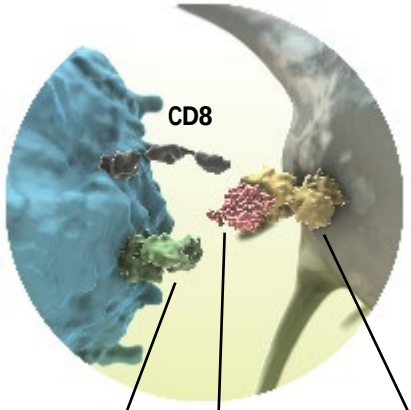
*PD-L1 expression was assessed using Dako 28-8 pharmDx.
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma.
Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813.

Rationale for Tumour Mutation Burden (TMB) As a Biomarker for I-O

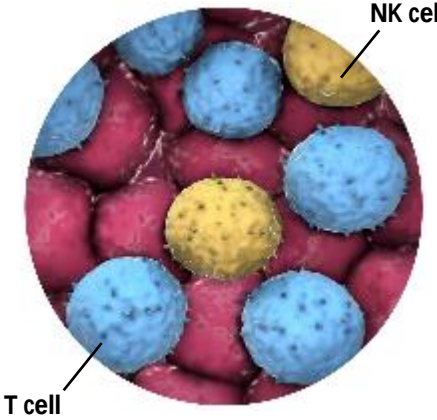
Tumour cells with high TMB…[1,2]



…may have high neoantigen load…[1,2]



…which can lead to increased immune and anti-tumour response[2-5]



The hypothesis that high TMB increases the immunogenicity of tumours makes them a rational target for treatment with I-O therapies[1,2]

DNA, deoxyribonucleic acid; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

1. Schumacher TN, Schreiber RD. *Science.* 2015;348(6230):69-74. 2. Kim JM, Chen DS. *Ann Oncol*. 2016;27(8):1492-1504. 3. Liontos M et al. *Ann Transl Med*. 2016;4(14):264. 4. Sharma P, Allison JP. *Science*. 2015;348(6230):56-61. 5. Giannakis M et al. *Cell Rep*. 2016;15:857-865.

TMB Can Be Assessed Using Next-Generation Sequencing

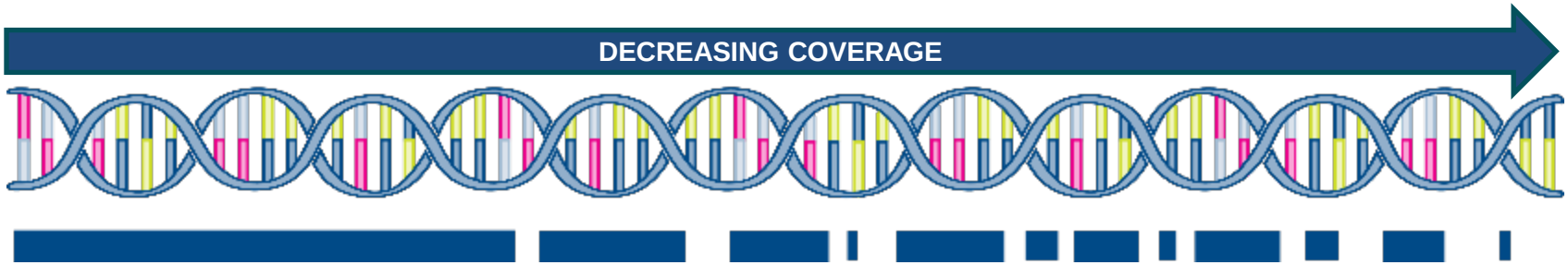
- TMB can be assessed by comparing somatic mutations to germline DNA using next-generation sequencing (NGS)[1]

Whole-genome/Whole-exome sequencing

- Allows for full complement of genomic analyses or coding regions
- All coding regions making up ~1% of the genome[1]
  - 85% of mutations contributing to disease are found in the coding region[2]
- Typically used in concert with RNA sequencing

Targeted gene panel

- Predefined set of genes[3,4]
- Validated tests are commercially available[5-7]



TMB, tumour mutation burden.

1. Ng SB et al. *Nature*. 2009;461(7261):272-276. 2. Choi M et al. *Proc Natl Acad Sci USA*. 2009;106(45):19096-19101. 3. Roszik J et al. *BMC Med*. 2016;14(1):168. 4. Warner JL et al. *Genome Med*. 2016;8(1):113. 5. Frampton GM et al. *Nat Biotechnol*. 2013;31(11):1023-1031. 6. Veloso ZA et al. Presentation at AACR 2016. Abstract 854. 7. Kowanetz M et al. Oral presentation at WCLC 2016.

CheckMate 026 (nivolumab)

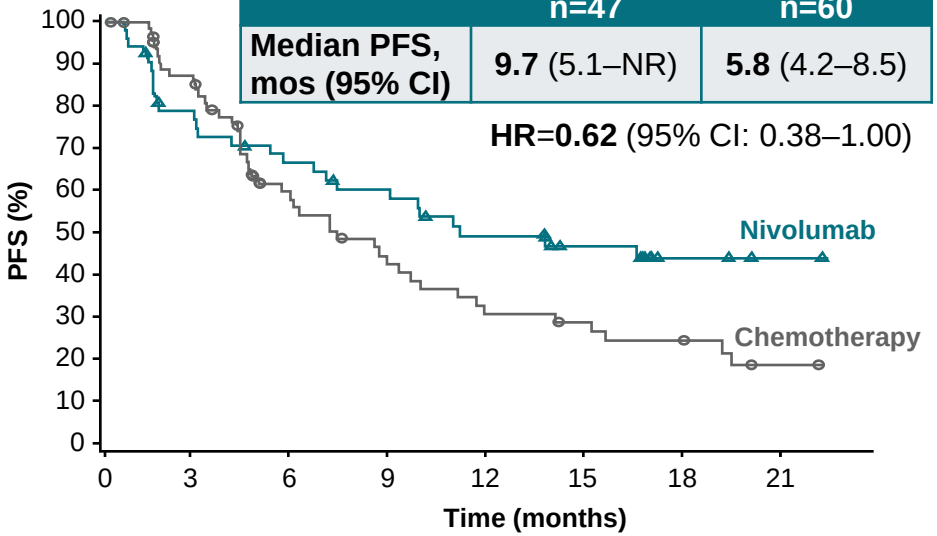
Progression-Free Survival in the TMB Subgroup

- Individual patient TMB levels were assessed from tissue biopsy samples using **WES on the Illumina HiSeq 2500**; blood samples were used for germline control

High TMB*†

	Nivolumab n=47	Chemotherapy n=60
Median PFS, mos (95% CI)	**9.7** (5.1–NR)	**5.8** (4.2–8.5)

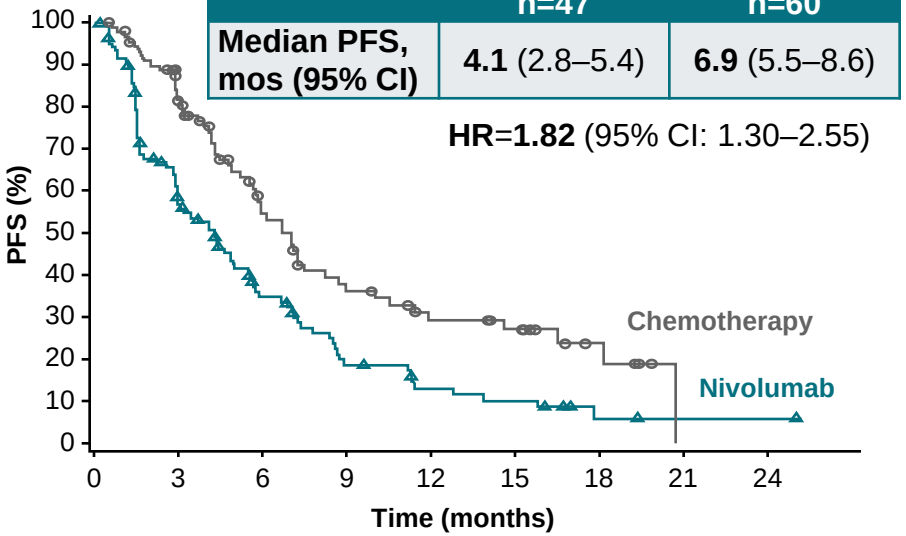
HR=0.62 (95% CI: 0.38–1.00)



Low/medium TMB*†

	Nivolumab n=47	Chemotherapy n=60
Median PFS, mos (95% CI)	**4.1** (2.8–5.4)	**6.9** (5.5–8.6)

HR=1.82 (95% CI: 1.30–2.55)



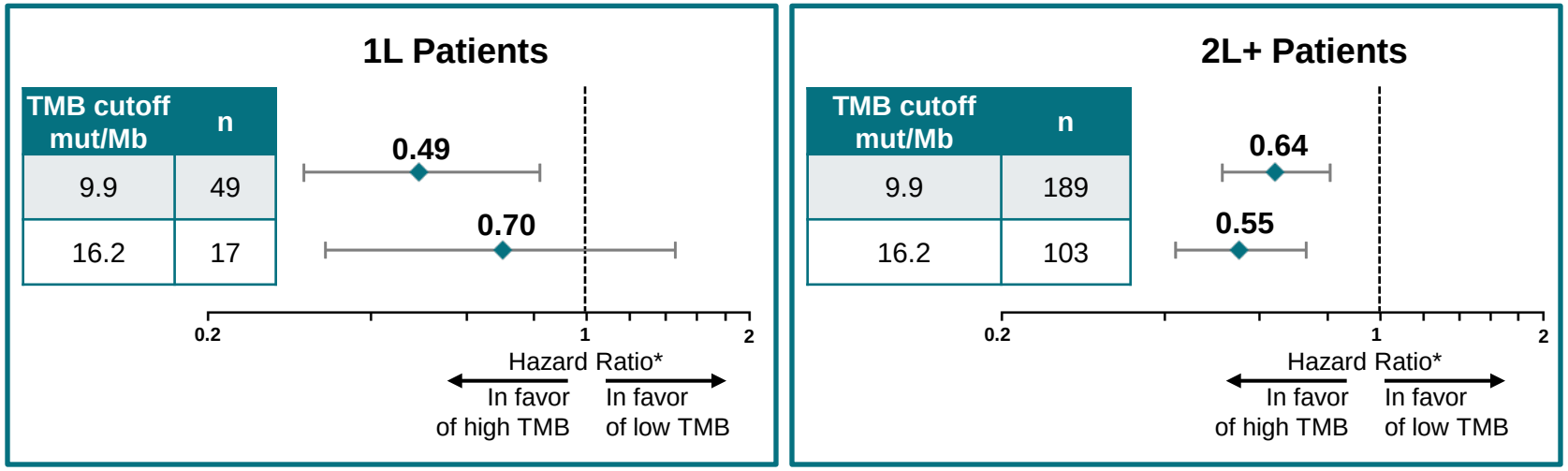
*TMB threshold was split into tertiles defined as total number of missense mutations: high ≥243, medium 100 to 242, and low 0 to <100. †DNA was sequenced on the Illumina HiSeq 2500 using 2×100-bp paired-end reads; an average of 45 and 50 million reads were sequenced per tumour and germline sample, respectively (average 84.6× and 93× the mean target coverage, respectively).
CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TMB, tumour mutation burden; WES, whole-exome sequencing.

Carbone DP et al. *N Engl J Med* 2017;376:2415-2426.

Assessment of TMB and Clinical Benefit in PD-L1–Selected Patients

Methods/Design	
• FIR and BIRCH: phase 2, single-arm, open-label studies of atezolizumab at 1200 mg q3w in PD-L1–selected patients[1,2]	
• **FoundationOne® sequencing panel** for TMB (300+ genes) in archival tumour samples[3]	• TMB cutoffs defined at 9.9 mutations/MB (median) or 16.2 mutations/MB (75% quantile)[3]

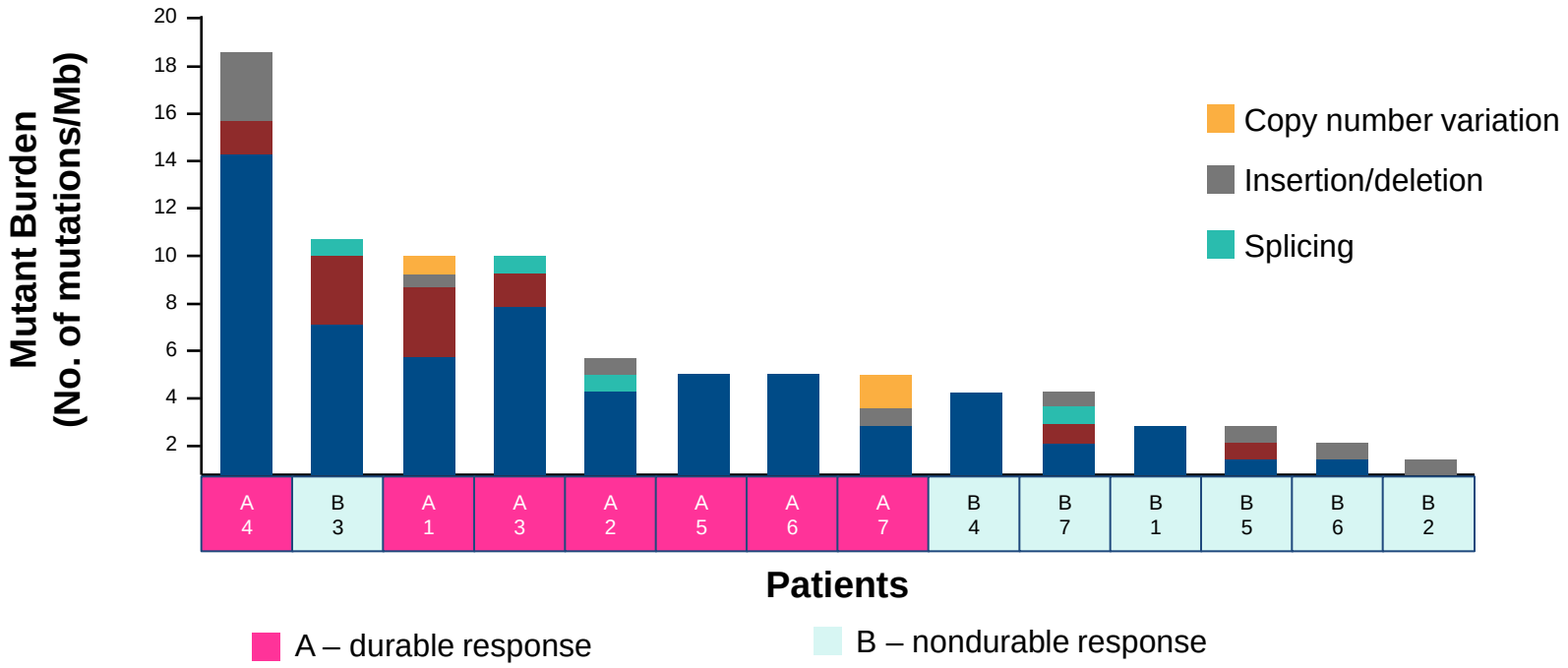
PFS in Patients from FIR and BIRCH



*Unadjusted and unstratified HRs for above vs below TMB cutoffs.
mut, mutation; MB, megabase; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; PFS, progression-free survival; q3w, every 3 weeks; TMB, tumour mutation burden.
1. Clinicaltrials.gov. NCT01846416. Accessed February 22, 2017. 2. Clinicaltrials.gov. NCT02031458. Accessed February 22, 2017. 3. Kowanetz M et al. Oral presentation at WCLC 2016.

Liquid Biopsies May Eventually Be Used for Assessing TMB

- ctDNA is being investigated as a surrogate to measure TMB in the absence of tissue biopsy



TMB has been measured in ctDNA using WES and a consolidated gene panel; ctDNA, circulating tumour DNA; Mb, megabase; No, number; TMB, tumour mutation burden; WES, whole-exome sequencing.

Cai W et al. Oral presentation at WCLC 2016.

Nivolumab

MSI-H/dMMR Clinical Data in mCRC Patients

- CheckMate 142 was a multicentre, open-label, single-arm study conducted in patients with locally determined MSI-H or dMMR metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy[1]
- MSI status was assessed using IHC and/or PCR[2]
- US indication was based on the following efficacy data[1]:

	All Patients (n=74)	Prior Treatment With Fluoropyrimidine, Oxaliplatin, and Irinotecan (n=53)
IRC-Confirmed Objective Response Rate, n (%)	24 (32%)	15 (28%)
95% CI	22–44	17–42
Complete response (%)	2 (2.7%)	1 (1.9%)
Partial response (%)	22 (30%)	14 (26%)
Duration of Response		
Median in months (range)	NR (1.4+–26.5+)	NR (2.8+–22.1+)

CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair deficient; IHC, immunohistochemistry; IRC, independent review committee; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; NR, not reached; PCR, polymerase chain reaction.

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017. 2. Overman MJ et al. *Lancet Oncol* 2017; [Epub ahead of print].

Pembrolizumab

Pan-Tumour dMMR/MSI-H Clinical Data

Efficacy Results for Patients with dMMR/MSI-H Cancer

Tumour Type	Objective response rate % (95% CI)
All Patients (n=149)	39.6% (31.7–47.9)
Colorectal cancer (n=90)	36% (26–46)
Non-colorectal cancer (n=59)	46% (33–59)

Tumour Type	Objective response rate % (95% CI)
Endometrial cancer (n=14)	36% (13–65)
Biliary cancer (n=11)	27% (6–61)
Gastric or GE junction cancer (n=9)	56% (21–86)
Pancreatic cancer (n=6)	83% (36–100)
Small intestinal cancer (n=6)	38% (9–76)
Breast cancer (n=2)	PR, PR
Prostate cancer (n=2)	PR, SD

Tumour Type	Objective response rate % (95% CI)
Bladder cancer (n=1)	NE
Esophageal cancer (n=1)	PR
Sarcoma (n=1)	PD
Thyroid cancer (n=1)	NE
Retroperitoneal adenocarcinoma (n=1)	PR
Small cell lung cancer (n=1)	CR
Renal cell cancer (n=1)	PD

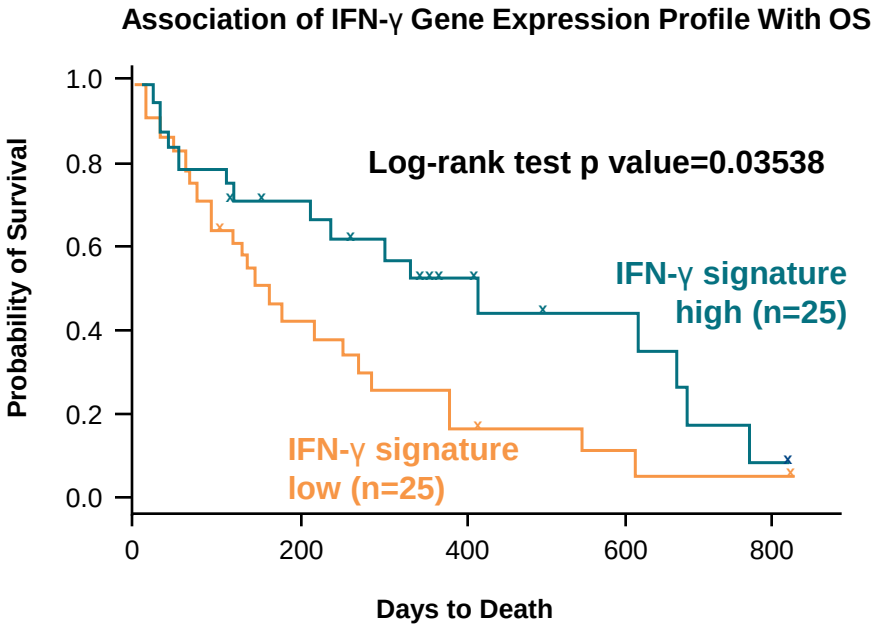
- **All patients received at least 1 prior therapy before clinical trial enrollment**
- **Data pooled from KEYNOTE-016, KEYNOTE-164, KEYNOTE-028, KEYNOTE-012, and KEYNOTE-158, with various dosing rates and schedules**

CI, confidence interval; CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; GE, gastroesophageal; MSI-H, microsatellite instability high; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

KEYTRUDA [package insert]. Whitehouse Station, NJ: Merck & Co; 2017.

Inflammation Gene Signatures in SCCHN

- A 6-gene IFN-γ panel was performed using NanoString nCounter® on 50 SCCHN patients treated with nivolumab or pembrolizumab[1]
  - NanoString nCounter® may show better gene expression quantification vs PCR in total RNA extracted from clinical, archival, FFPE samples[2]
- CD8 expression correlated with the IFN-γ gene expression profile, signifying the T cells' mediated inflammation in "hot" tumours
- Probability of survival was higher in patients categorised IFN-γ signature high



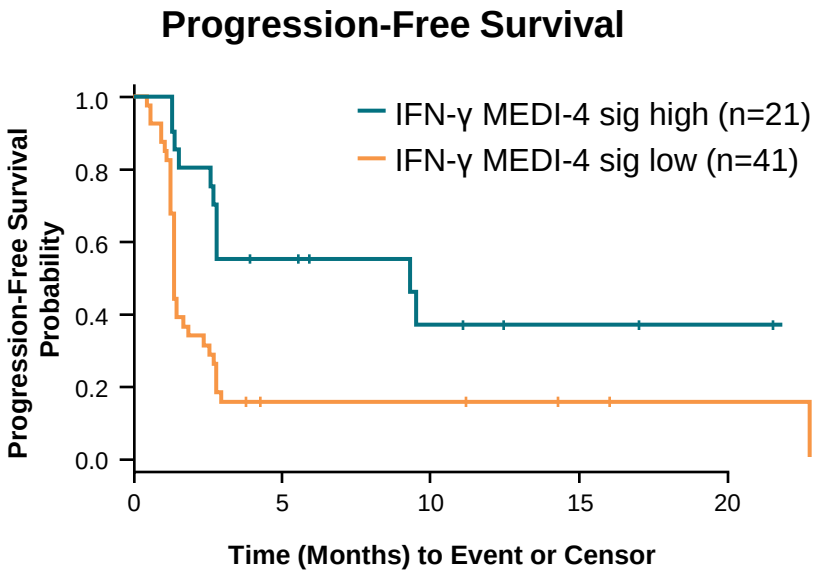
FFPE, formalin-fixed paraffin-embedded; IFN, interferon; OS, overall survival; PCR, polymerase chain reaction; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; SCCHN, squamous cell carcinoma of the head and neck.

1. Seiwert TY et al. Poster presentation at ASCO 2017. 6049. 2. Reis PP et al. *BMC Biotechnology* 2011;11:(46):1-10.

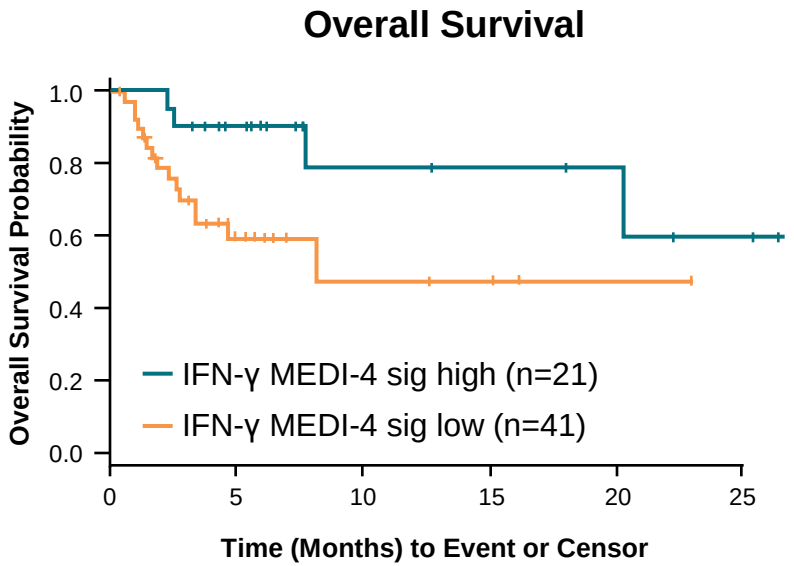
Study 1108 (durvalumab)

Inflammation Gene Signatures in Bladder Cancer

- IFN-γ MEDI-4 signature-high bladder cancer patients treated with durvalumab had improved outcomes



HR (adjusted)=0.3; *P*=0.005

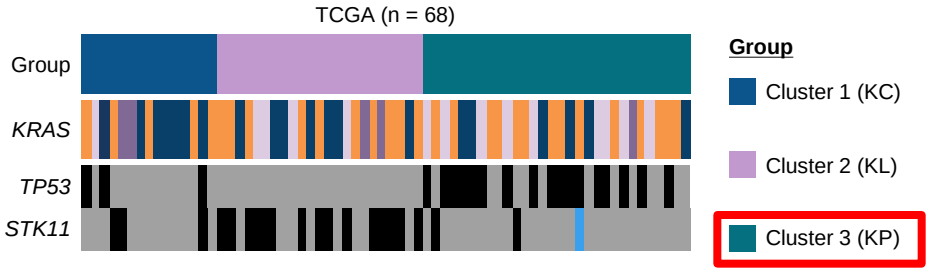


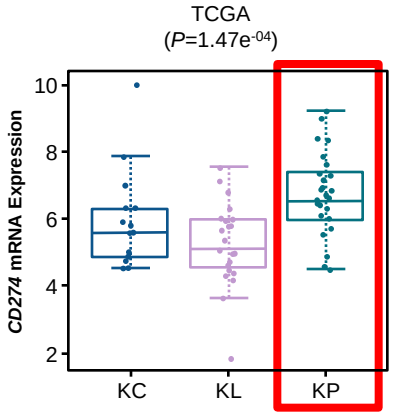
HR (adjusted)=0.18; *P*=0.016

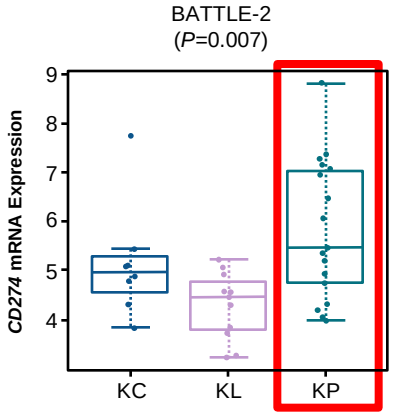
HR, hazard ratio; IFN, interferon; sig, signature.
Bais C et al. Poster presentation at ASCO 2017. 3037.

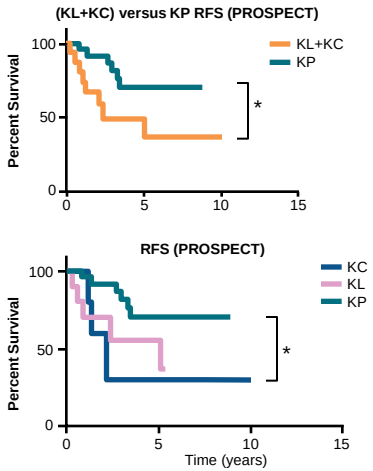
Mutation or Neoantigen Burden

- ***KRAS/P53* mutated tumours demonstrated higher mutation burden, higher PD-L1 expression, and improved relapse-free survival**









*Statistical significance at the *P* ≤0.05 level.
CD274, programmed cell death ligand 1 gene; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; KC, cluster including *CDKN2A/B* inactivation coupled with low expression of the NKX2-1 (TTF1) transcription factor; KL, cluster including *STK11/LKB1*; KP, cluster including STK11*; p53,* tumour protein 53 gene; RFS, relapse free survival; *STK11,* serine/threonine kinase11; TCGA, the cancer genome atlas.
Skoulidis F et al. *Cancer Discov.* 2015;5(8):860-877.

I-O in *KRAS*-Mutant NSCLC

- 162 *KRAS*-mutated NSCLC patients who received at least 1 round of anti–PD-1/PD-L1 therapy and who had molecular profiling data available

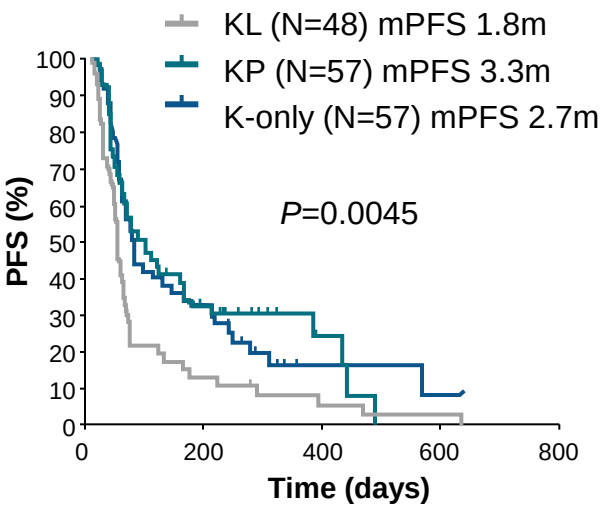
	ORR n/N (%)
KL	5/48 (10.4)
KP	22/56 (39.3)
K-only	13/56 (23.2)

KL=*KRAS;STK11* double mutant or *KRAS;TP53;STK11* triple mutant

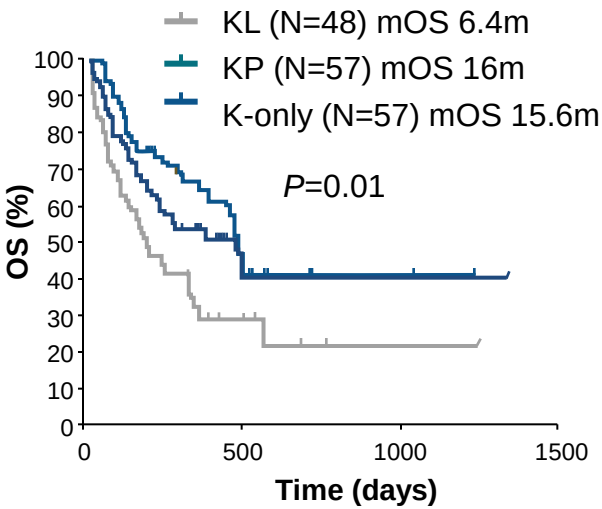
KP=*KRAS;TP53* double mutant

K only=*KRAS* single mutant

Progression-Free Survival (PFS)



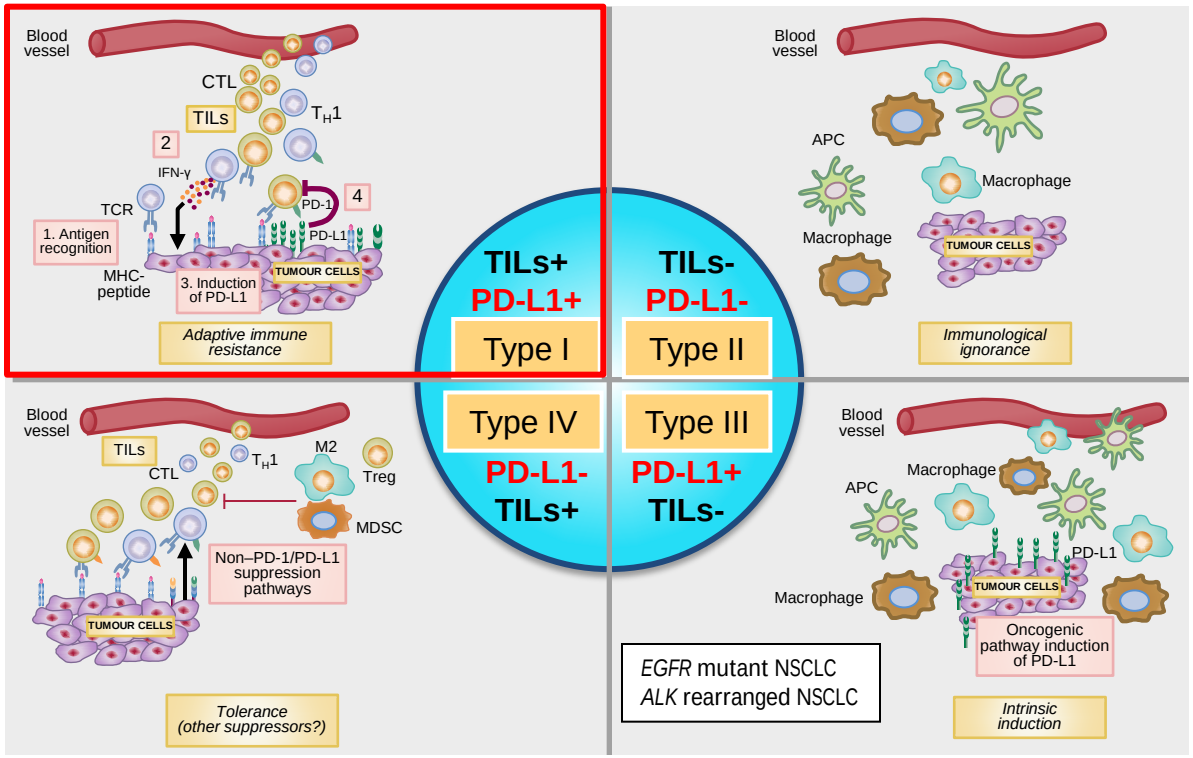
Overall Survival (OS)



mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1.

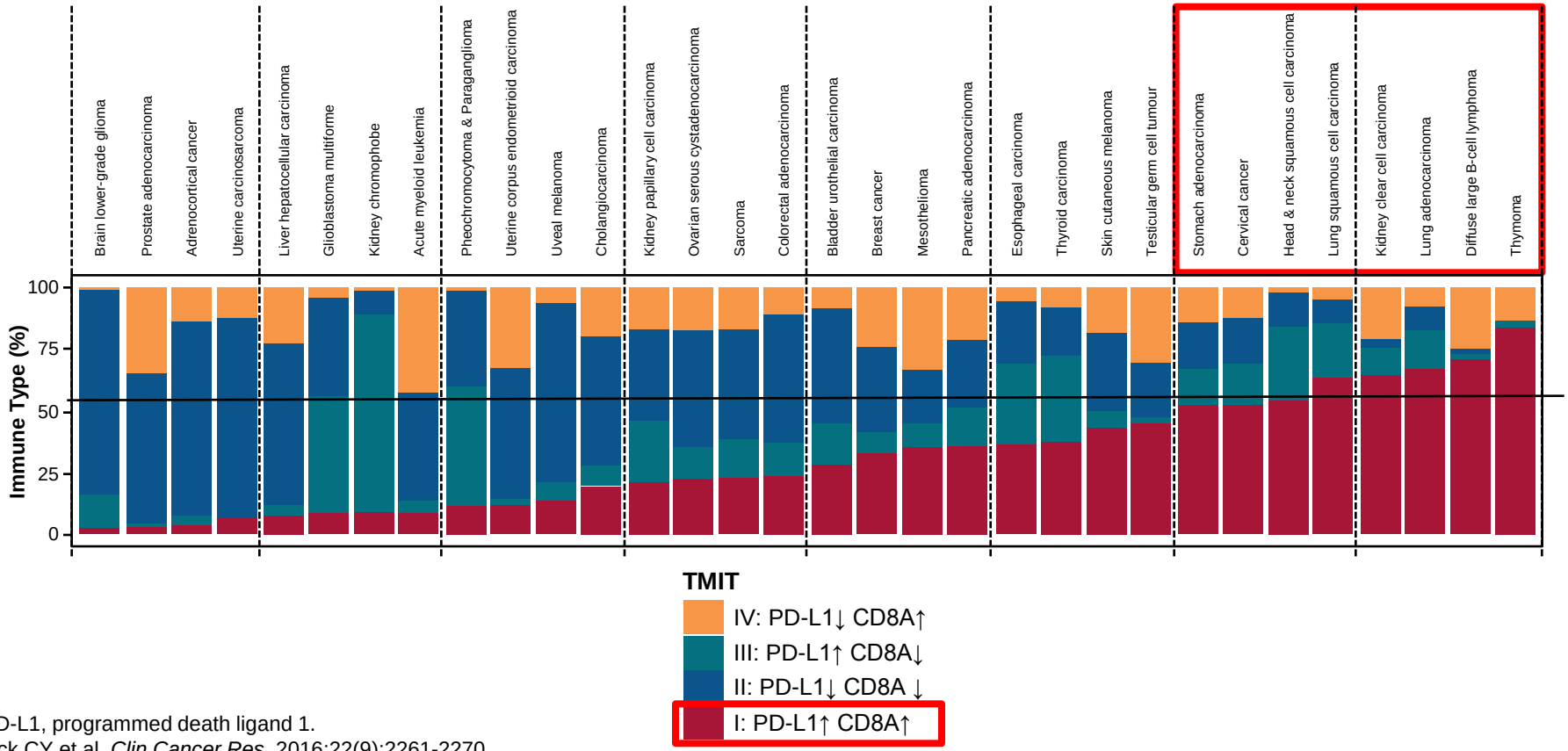
Skoulidis F et al. Poster presentation at ASCO 2017. 9016.

Tumour Microenvironment Types Based on TILs and PD-L1



APC, antigen-presenting cell; CTL, cytotoxic T cell; IFN-γ, interferon gamma; M2, M2 macrophage; MDSC, myeloid derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; TCR, T cell receptor; T_H1, T helper 1; TIL, tumour infiltrating lymphocyte; Treg, regulatory T cell.
Teng MWL et al. *Cancer Res.* 2015;75(11):2139-2145.

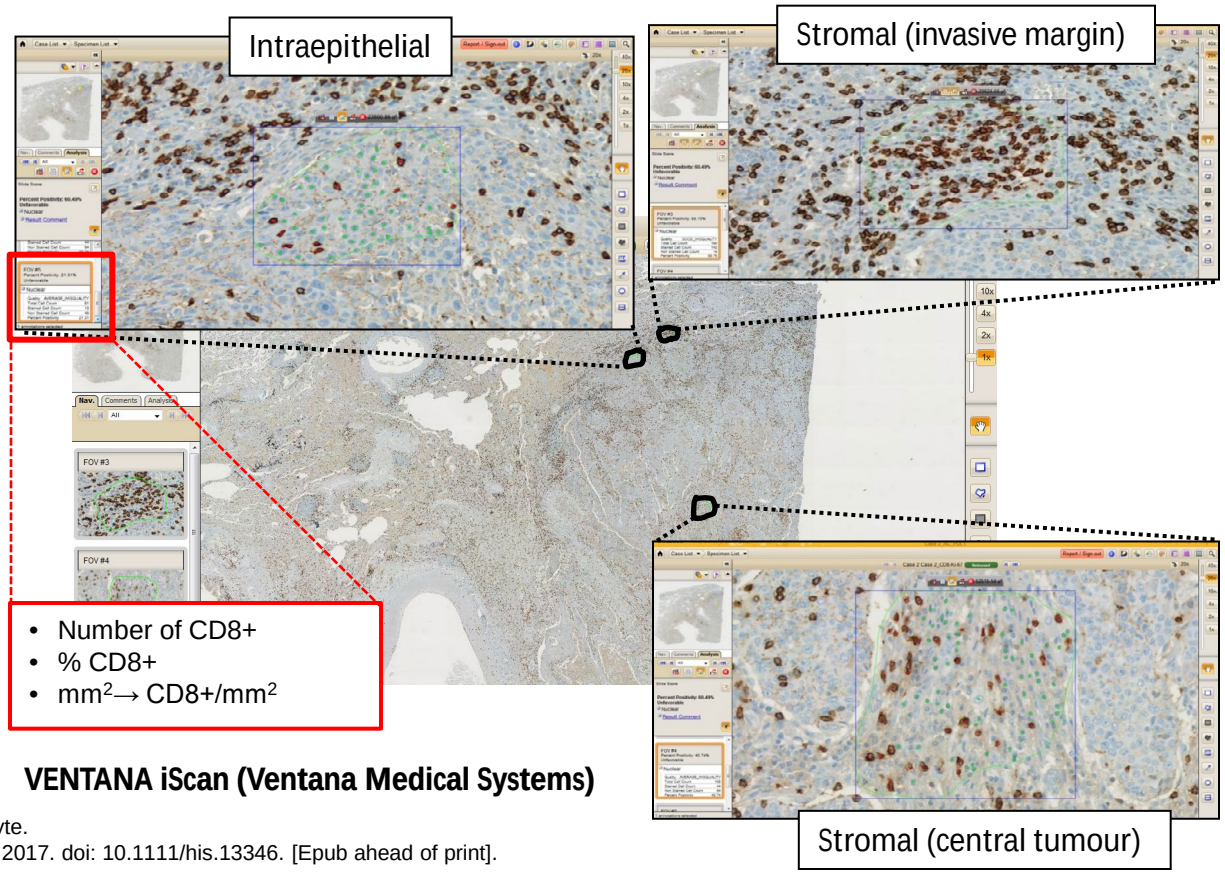
Tumour Microenvironment



PD-L1, programmed death ligand 1.

Ock CY et al. *Clin Cancer Res.* 2016;22(9):2261-2270.

Tumour Microenvironment: Automated Assessment of TILs CD8+

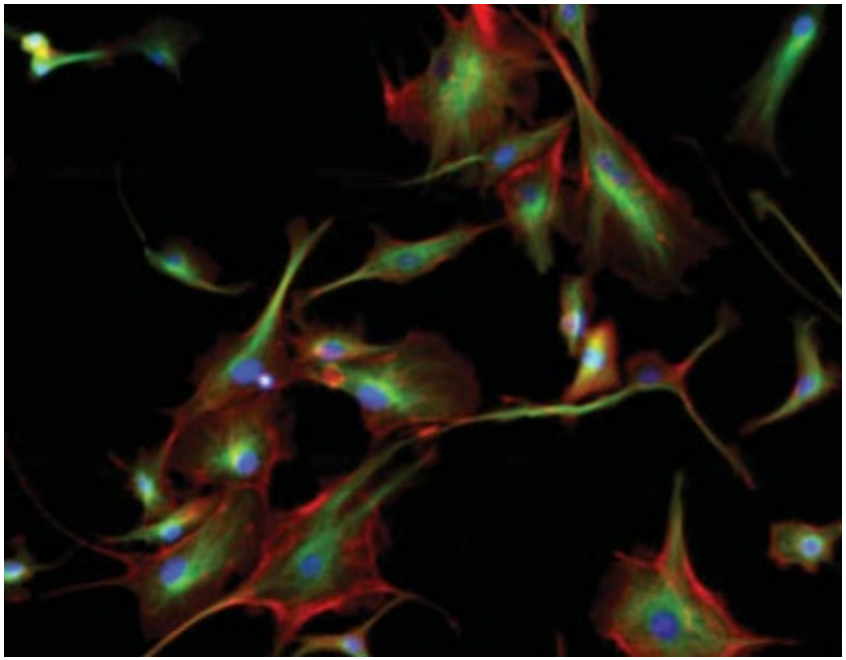


TIL, tumour-infiltrating lymphocyte.

Conde E. et al. *Histopathology*. 2017. doi: 10.1111/his.13346. [Epub ahead of print].

Fluorescence Whole-Slide Imaging

- Fluorescence whole-slide imaging is a quantitative approach that allows for side-by-side viewing of different IHC markers on the same sample[1,2]

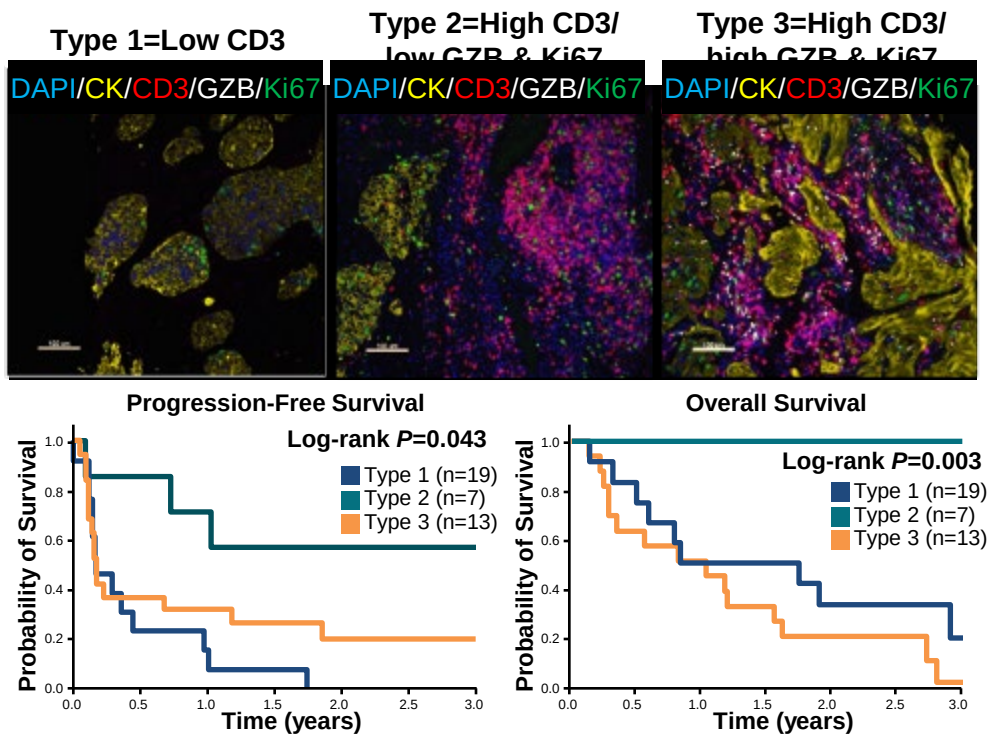


MIRAX viewer[3]

1. Hamilton PW et al. *Methods.* 2014;70(1):59-73. 2. Stack EC et al. *Methods.* 2014;70(1):46-58. 3. Varga VS et al. *Cytometry A*. 2009;75(12):1020-1030.

Multiplexed System Development: Fluorescent IHC

- Immunofluorescence technology is used to visualise multiple markers in a single section, while completely conserving the tissue context being viewed[1]
- IF has been successfully demonstrated in FFPE tissue in differing multiplex levels[1]
- Considerations[3]:
  - Antibody blocking
  - Cross-reactivity
  - Masking

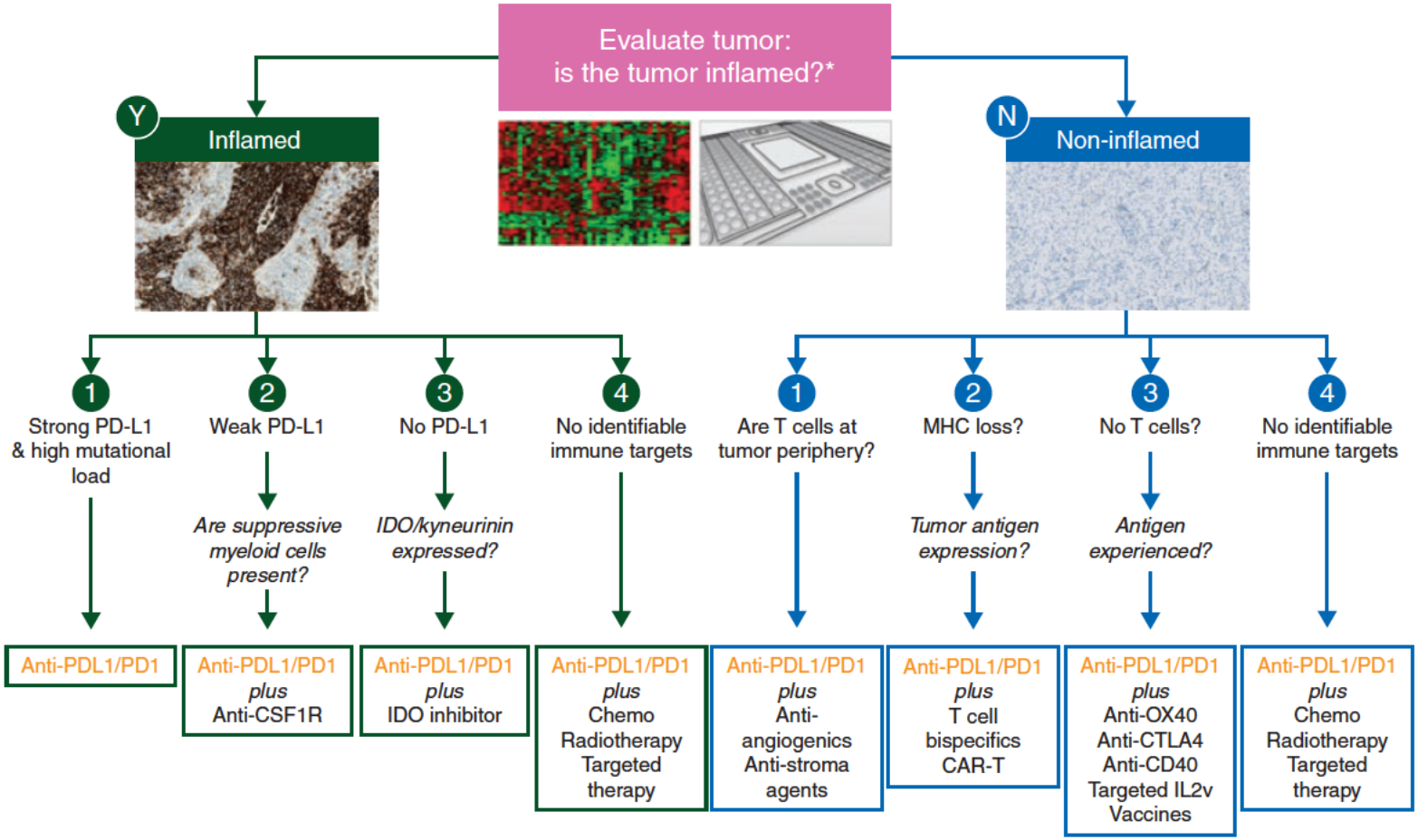


Simultaneous F-IHC staining of DAPI, cytokeratin, CD3, GZB, and Ki67 in lung cancer samples[2]

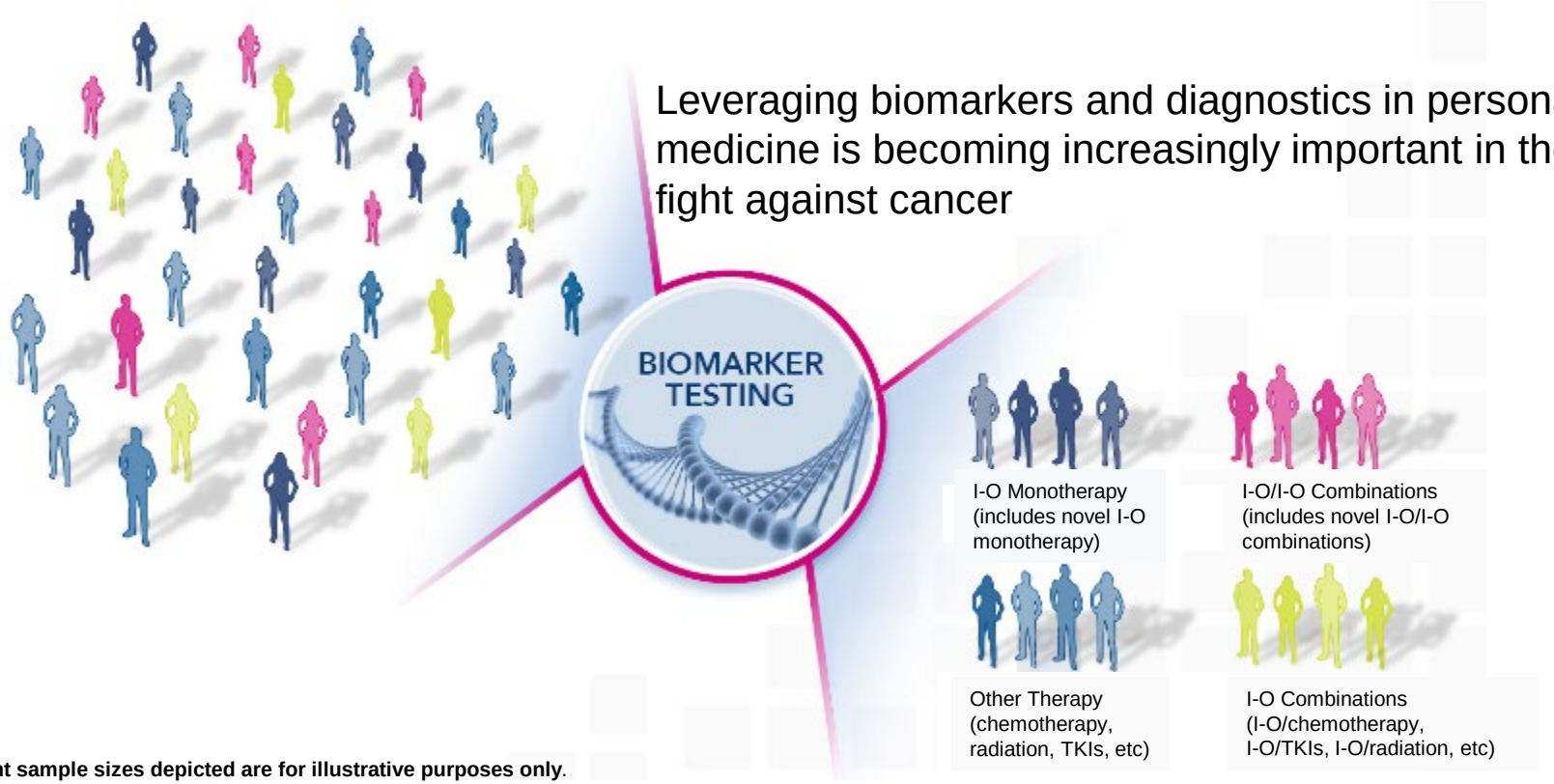
FFPE, formalin-fixed paraffin-embedded; IF, immunofluorescence; IHC, immunohistochemistry.

1. Stack EC et al. *Methods.* 2014;70(1):46-58. 2. Schalper KA et al. Presented at WCLC 2016. 3. Galetta H et al. *J Immunother Cancer.* 2015;3(suppl 2):P411.

Personalized cancer immunotherapy paradigm



The Importance of Personalised Medicine



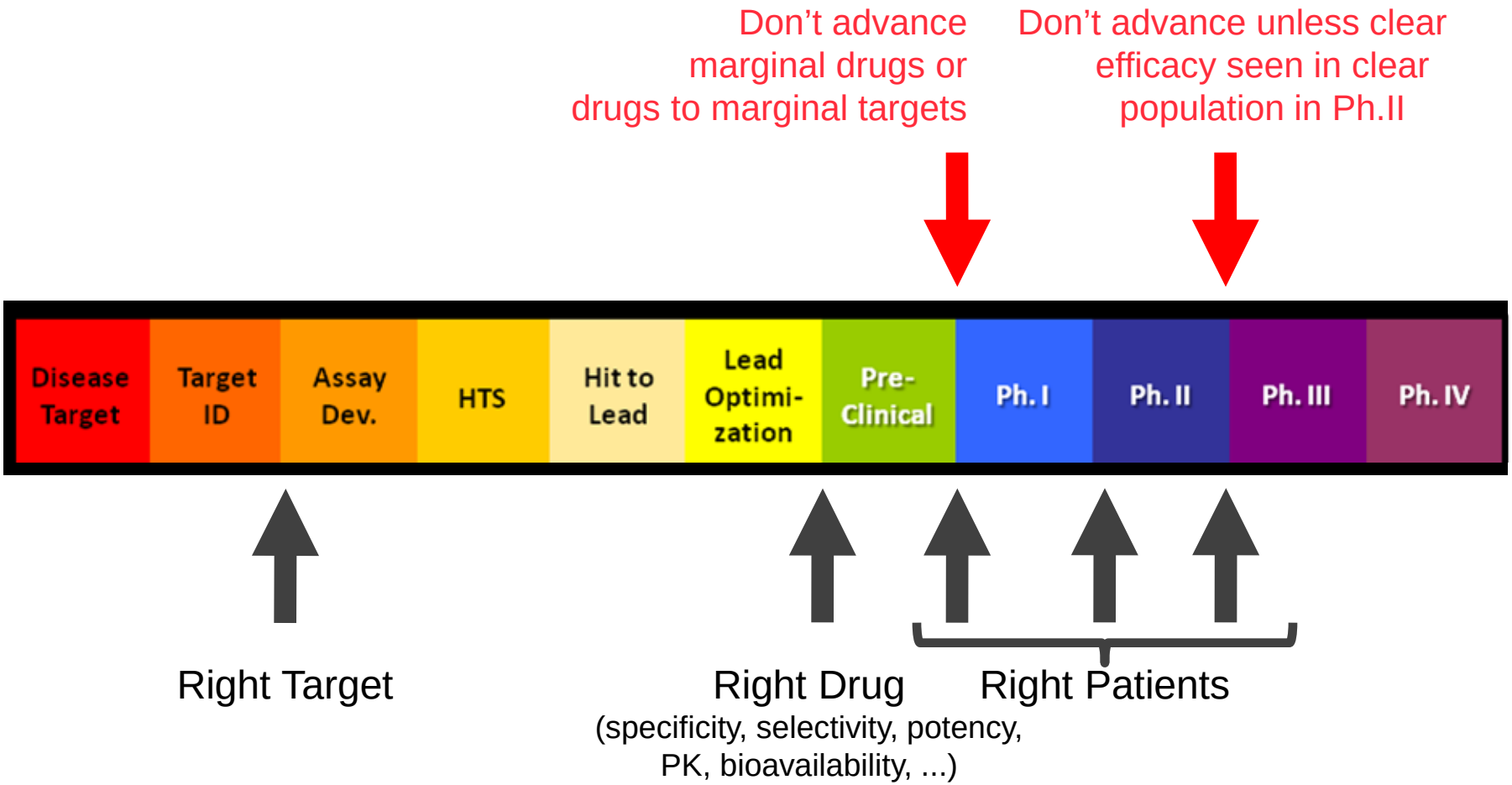
Leveraging biomarkers and diagnostics in personalised medicine is becoming increasingly important in the fight against cancer

***Patient sample sizes depicted are for illustrative purposes only**.
I-O, Immuno-Oncology; TKI, tyrosine kinase inhibitor.

Temas

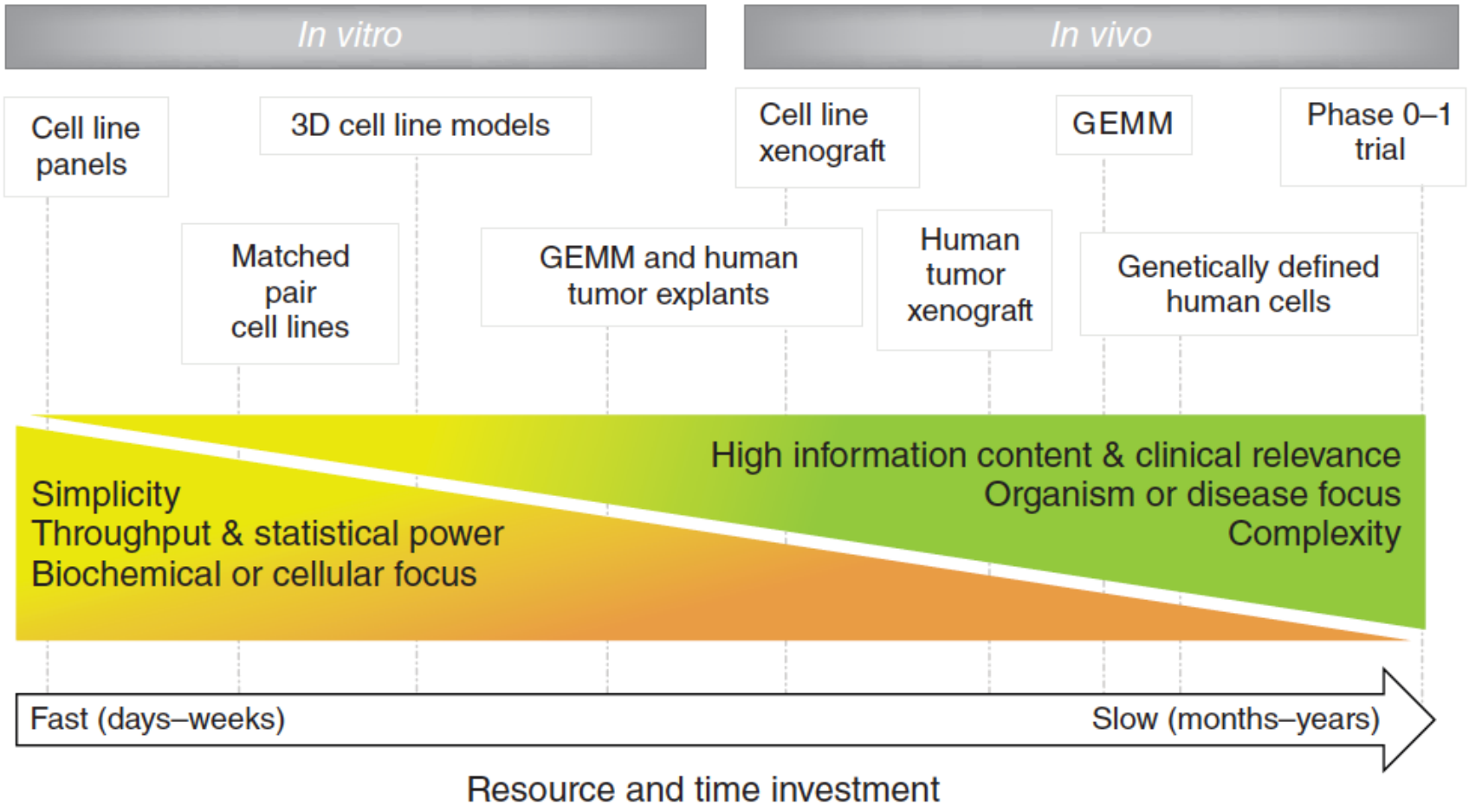
- Agentes dirigidos a Dianas moleculares específicas
- Inmunoterapia
- **Desarrollo de nuevos fármacos y EECC**
- Implementación

Three ingredients for effective drug discovery - how to maximize?



Marc Tessier-Lavigne, Yale Lecture 2011

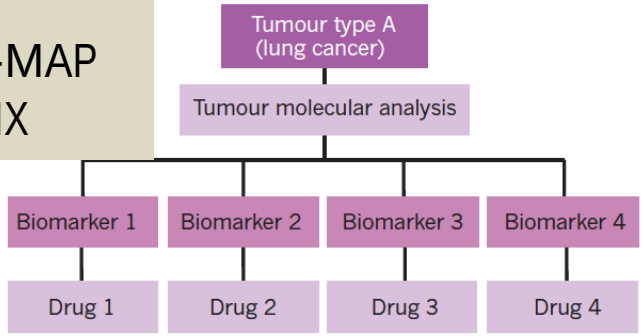
Trade-off among commonly used experimental systems for functional validation

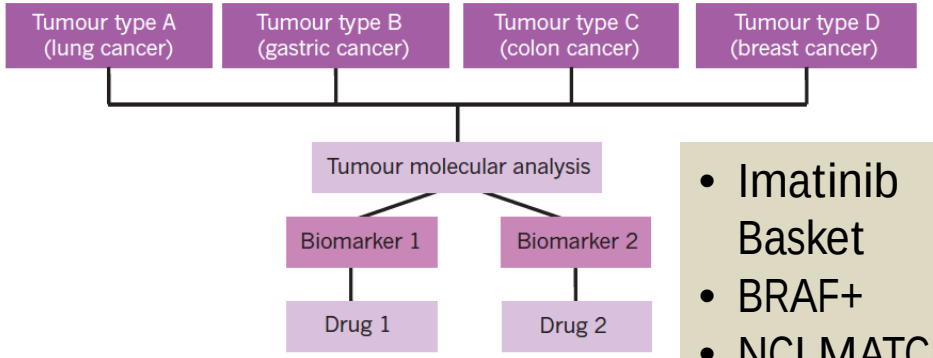


Chin L. et al. Nat. Med. 2011; 17:297

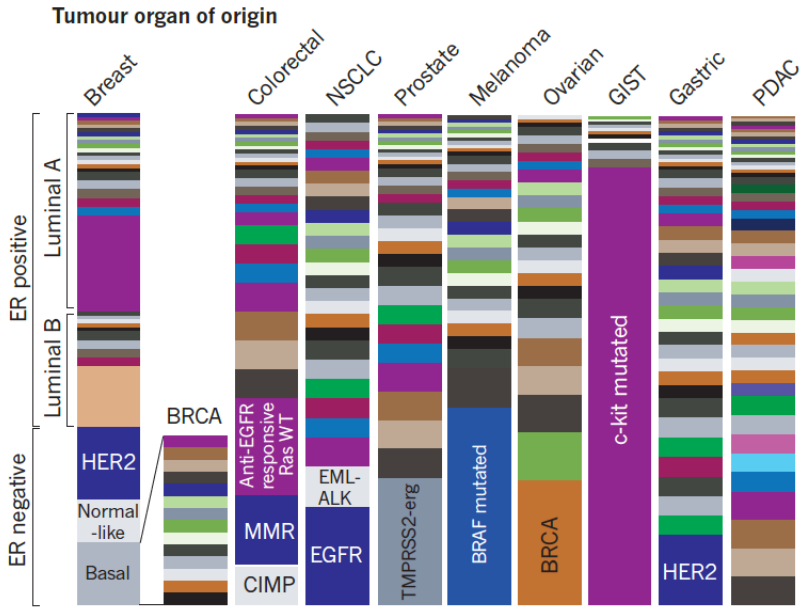
Umbrella & basket studies

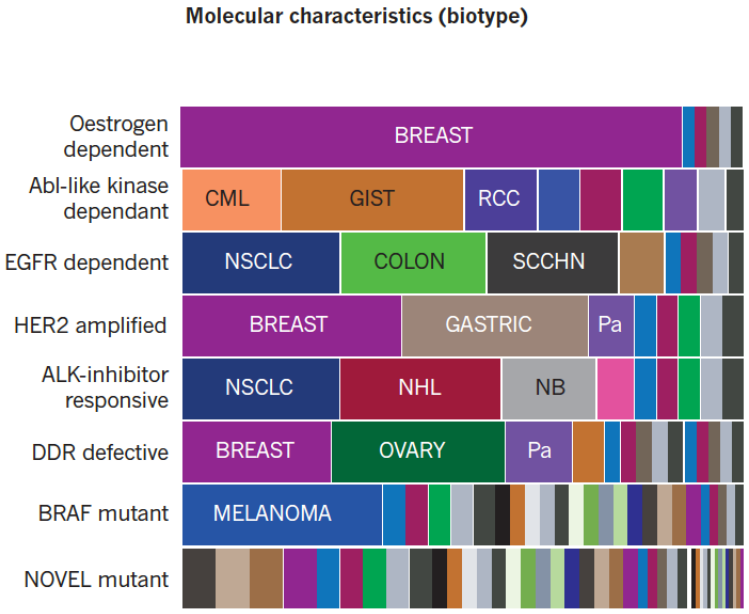
- BATTLE
- I-SPY2
- LUNG-MAP
- MATRIX





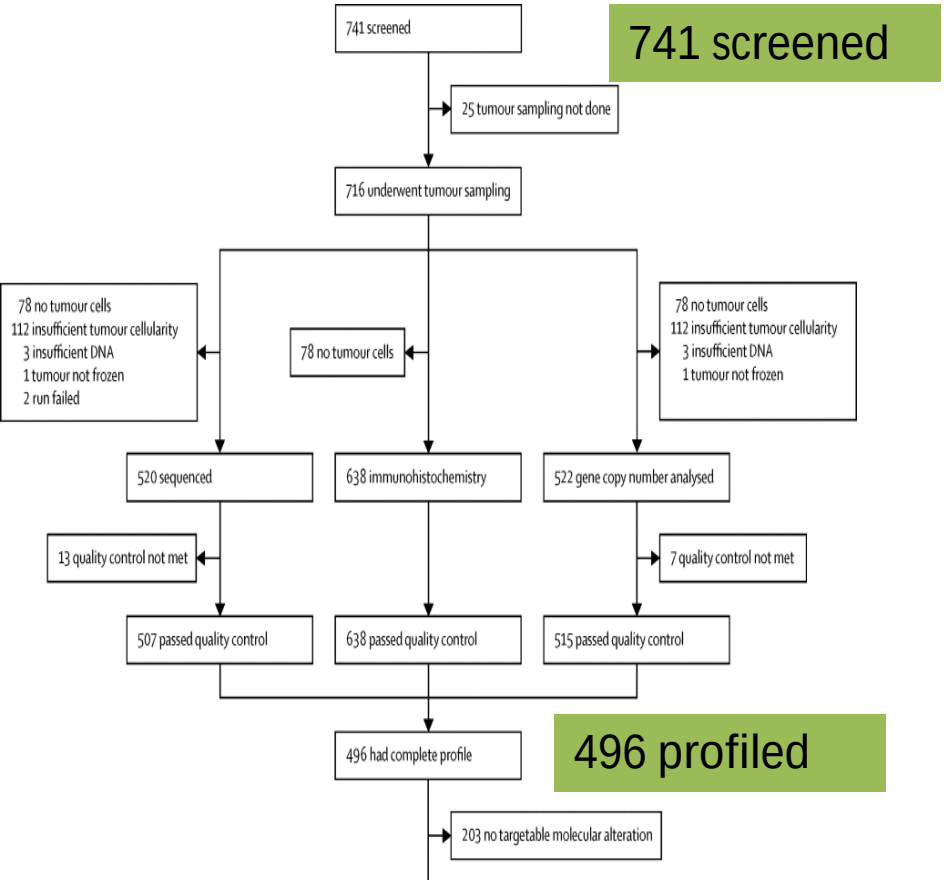
- Imatinib Basket
- BRAF+
- NCI MATCH

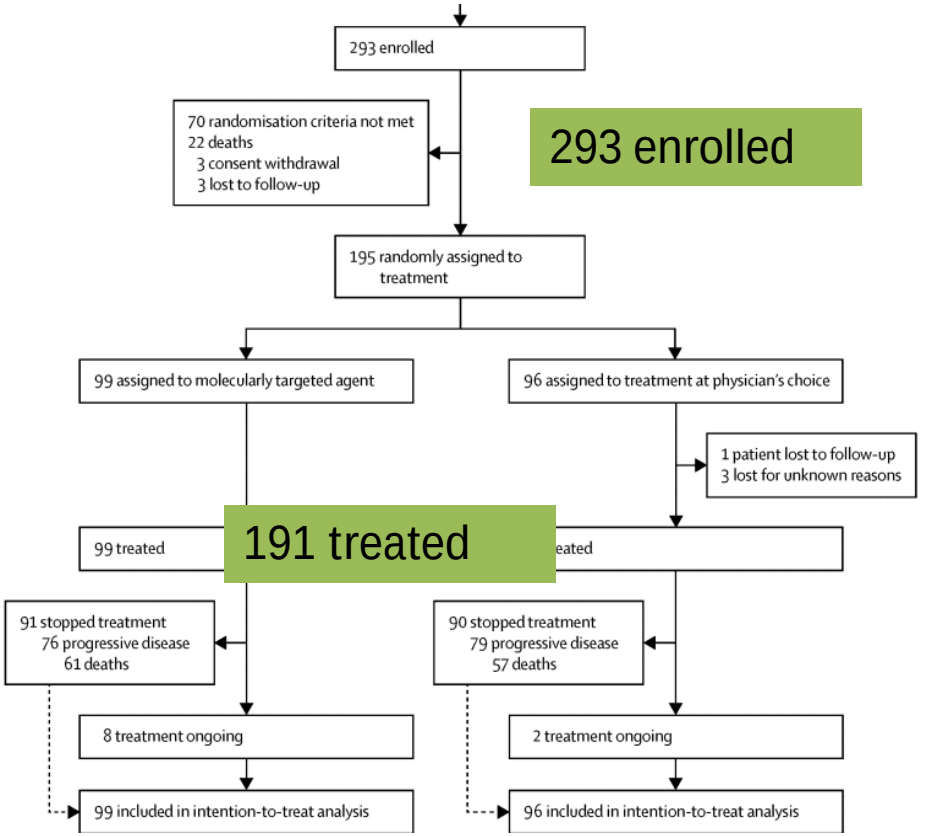




Biankin AV et al. Nature 2015; 526:361

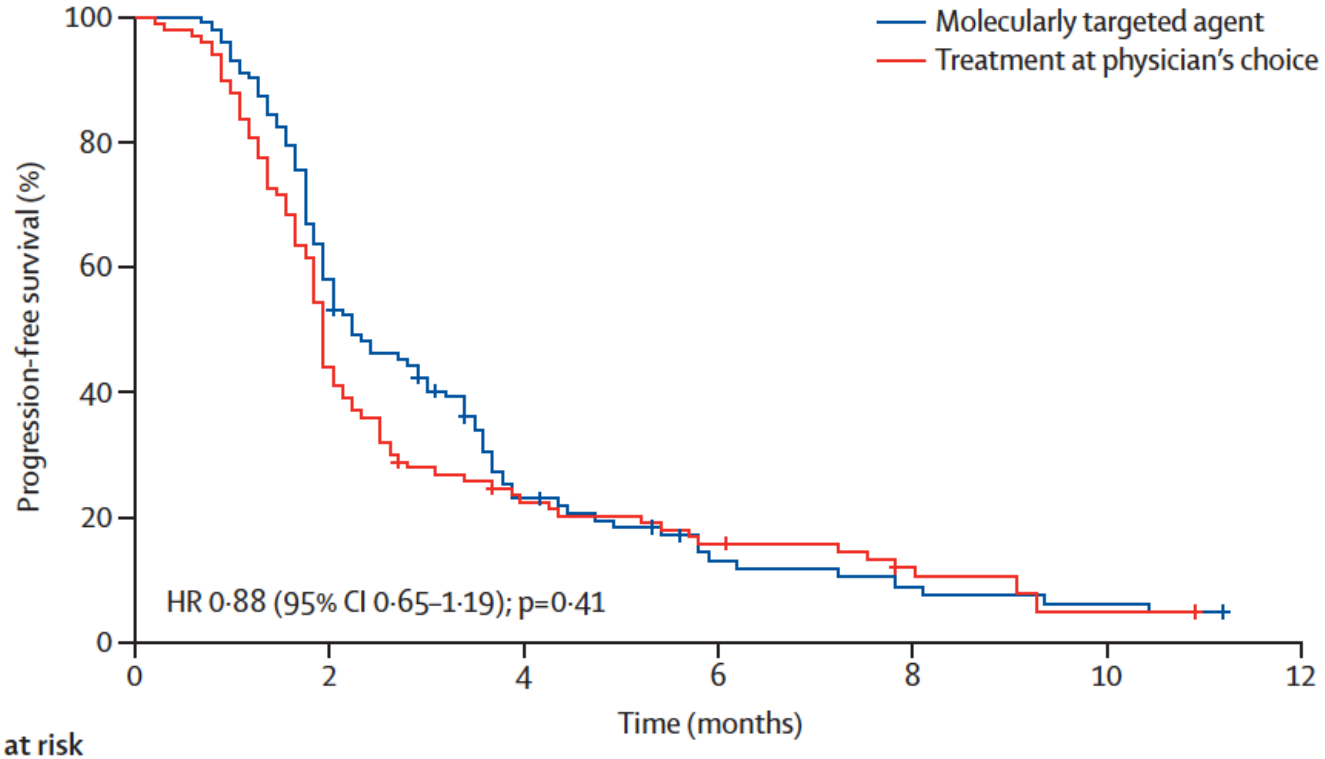
The SHIVA Study





Le Tourneau C. et al. Lancet Oncol 2015;16:1324

The SHIVA Study



Number at risk							
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

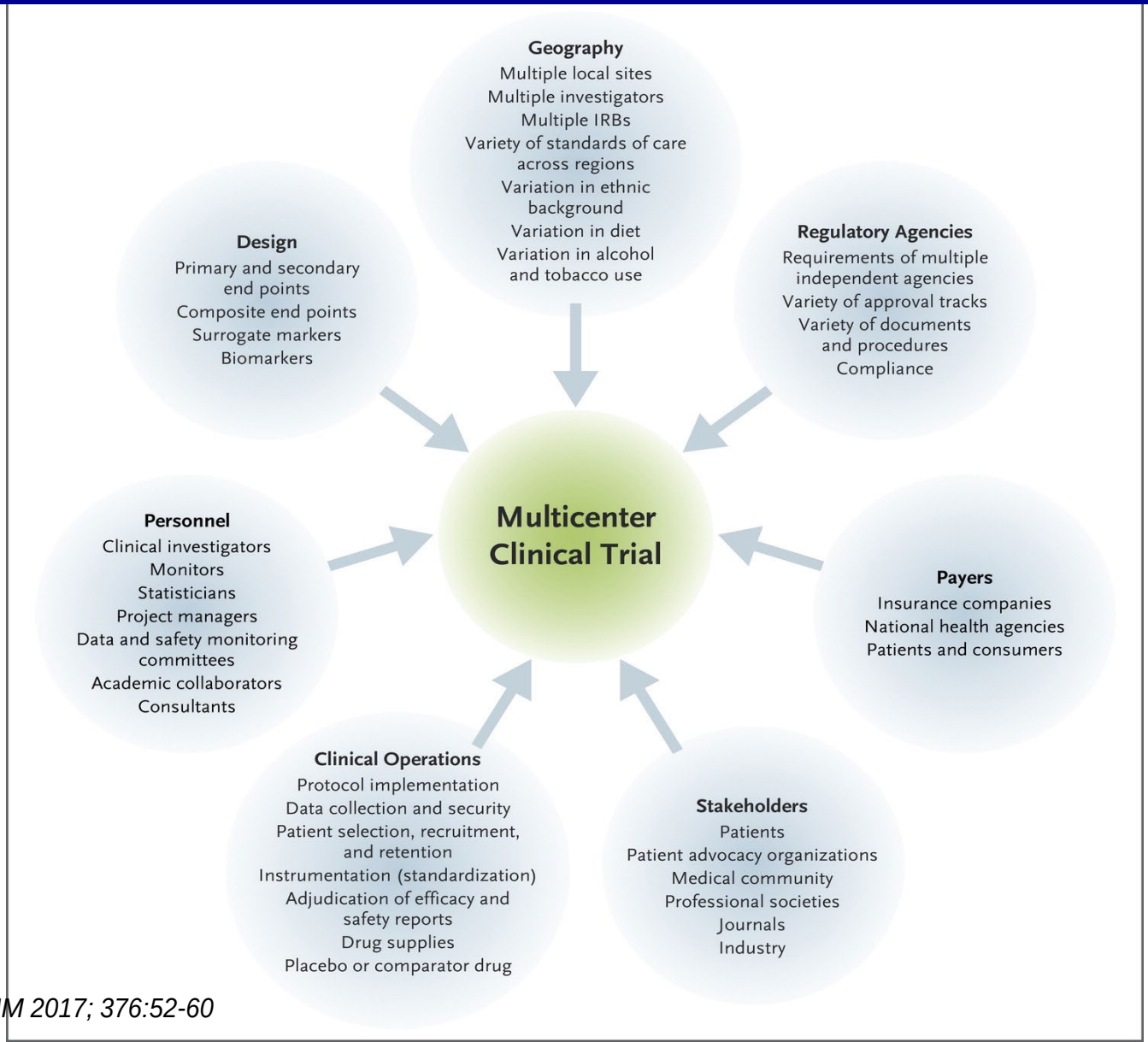
In the safety population, 43 (43%) of 100 patients treated with a molecularly targeted agent and 32 (35%) of 91 patients treated with cytotoxic chemotherapy had grade 3–4 adverse events (p=0·30).

Le Tourneau C. et al. Lancet Oncol 2015;16:1324

Some ongoing phase III studies of anti-PDL1/PD1 therapy in combination with chemotherapy and immune doublets

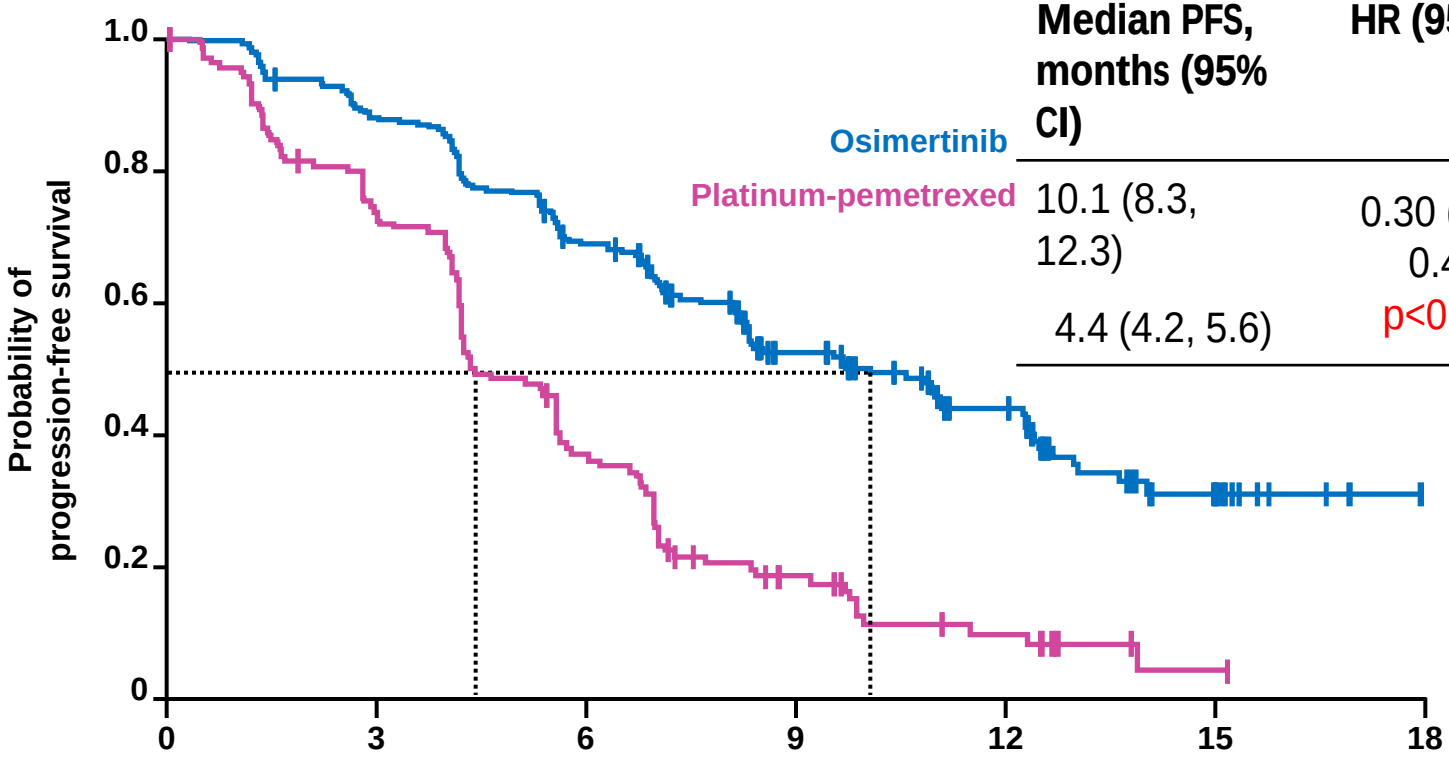
Study name	Study description	Chemo	Anti-CTLA4
Atezolizumab			
IMpower130	Atezolizumab + platinum doublet chemotherapy (non-squamous)	ü	
IMpower131	Atezolizumab + platinum doublet chemotherapy (squamous)	ü	
IMpower132	Atezolizumab + platinum doublet chemotherapy (non-squamous)	ü	
IMpower150	Atezolizumab + platinum doublet chemotherapy ± bevacizumab (non-squamous)	ü	
Pembrolizumab			
KEYNOTE-407	Pembrolizumab + platinum doublet chemotherapy (squamous)	ü	
KEYNOTE-189	Pembrolizumab + platinum doublet chemotherapy (non-squamous)	ü	
Nivolumab			
CheckMate 227	Nivolumab monotherapy or + ipilimumab or + platinum doublet chemotherapy (squamous and non-squamous)	ü	ü
Durvalumab			
MYSTIC	Durvalumab monotherapy or + tremelimumab (squamous and non-squamous)		ü
NEPTUNE	Durvalumab + tremelimumab (squamous and non-squamous)		ü

Factors Contributing to Complexity in Large Clinical Outcomes Trials



Rosenblatt M. NEJM 2017; 376:52-60

AURA3 primary endpoint: PFS by investigator assessment



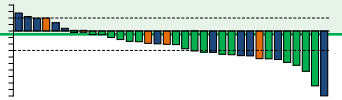
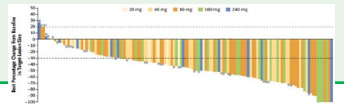
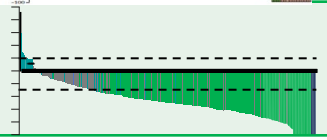
	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3, 12.3)	0.30 (0.23, 0.41)
Platinum-pemetrexed	4.4 (4.2, 5.6)	p<0.001

No. at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

Phase I/II studies of osimertinib…AURA and AURA2

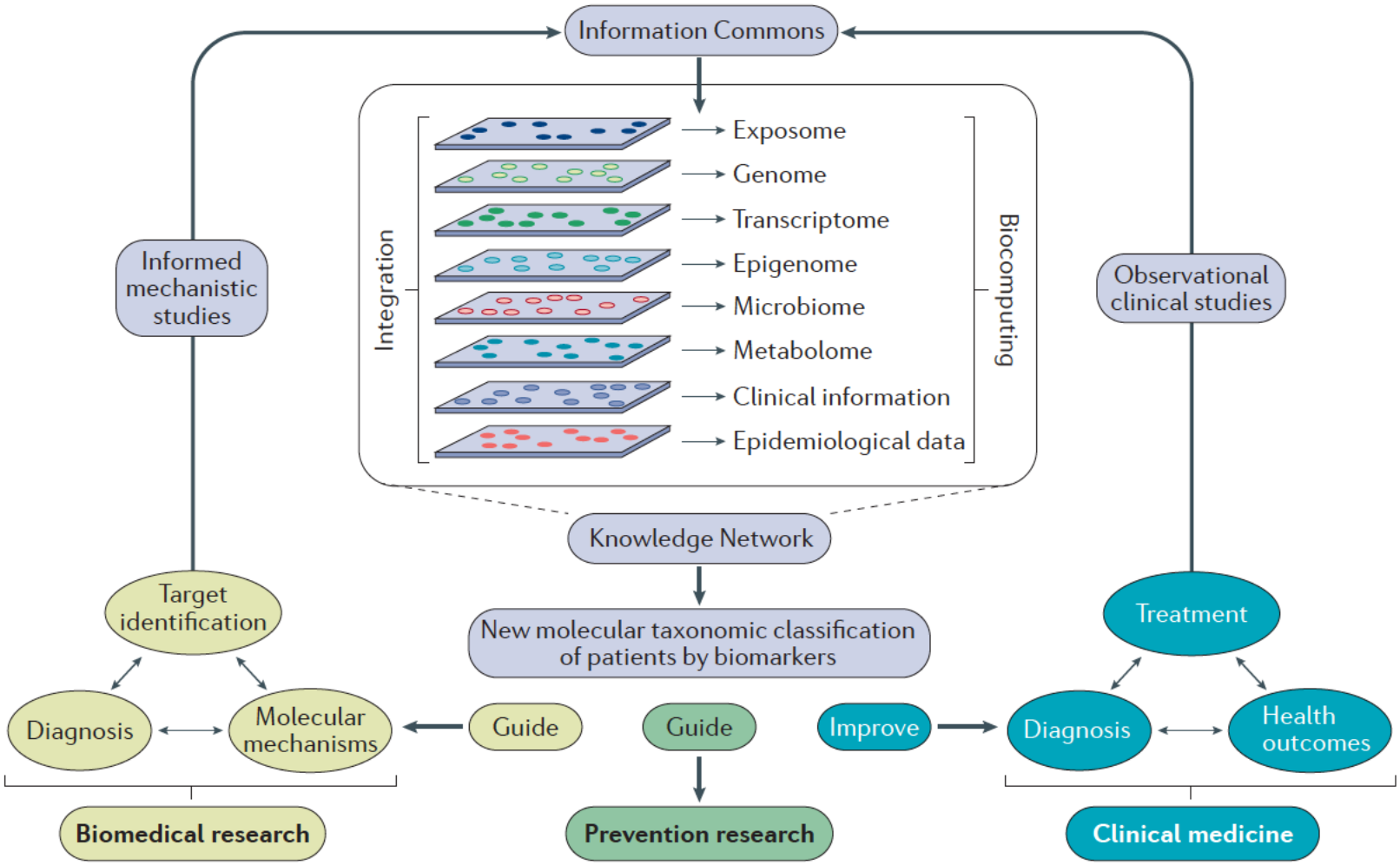
		data cut off date	Meeting/Journal	Year	Author	N	ORR for T790M	mPFS for T790M	Waterfall plot
AURA Ph 1	Various 20-240mg	9.27.2013	WCLC	2013	Ranson	34	50%	N/A	
AURA Ph 1	Various 20-240mg	4.27.2014	ASCO	2014	Janne	107	64%		
AURA Ph 1	Various 20-240mg	8.1.2014	NEJM	2015	Janne	253 (138 T790M)	61%	9.6m	
AURA Ph 1	Various 20-240mg	12.2.2014	ELCC	2015	Janne	283	59%	13.5m	
AURA extension	80mg	5.1.2015	WCLC	2015	Yang	201	61%	Not reached	
AURA 2	80mg	11.1.2015	Lancet Oncol	2016	Goss	210			
AURA		5	ELCC	2016	Yang	397	66%	11.0m	

ORR…60-70%, mPFS 10-11 months with 80mg of osimertinib for T790M+ patients

Drug Development in the Genomic Era

- Keep pace with genome discovery
- Use genomics tools in pre-clinical studies
- Consortia based molecular screening
- Smaller studies in pre-selected population
- Genotype based basket studies (agnostic of site of origin)
- Regulatory involvement- NGS as a “companion diagnostic”
- Use of genomic tools to refine patient selection using extreme responders
- Registry mechanisms- drug genome database

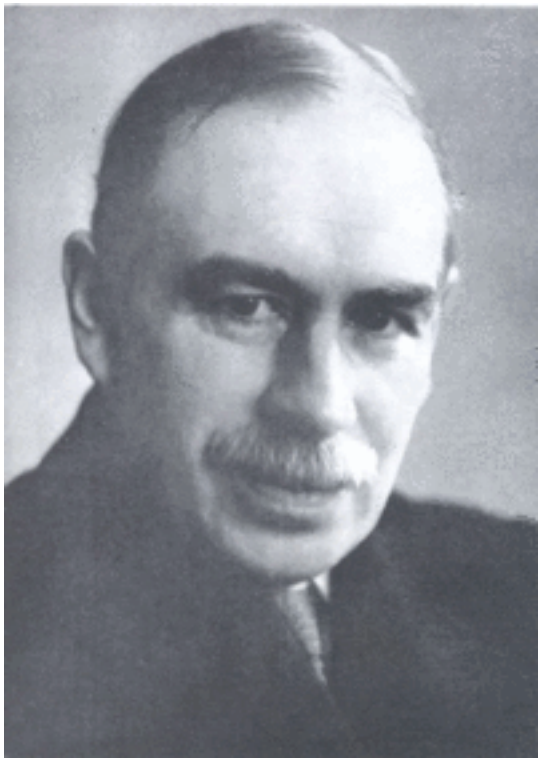
A precision medicine research strategy



Vargas AJ, Harris CC Nat. Rev. Cancer 2016; 16:525

A Precision Oncology Study

“The difficulty lies not so much in developing new ideas as in escaping from the old ones".

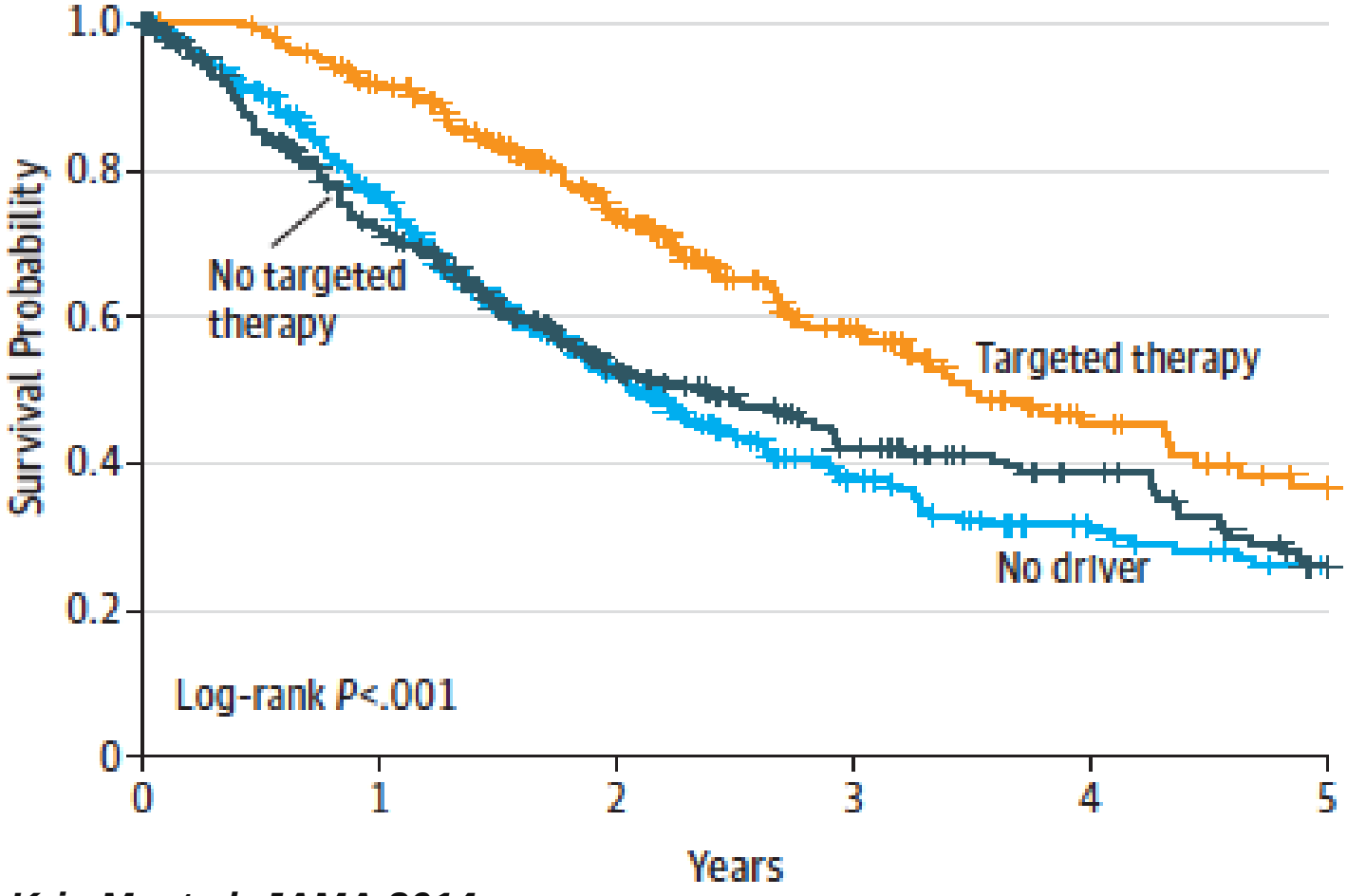


John Maynard Keynes

Temas

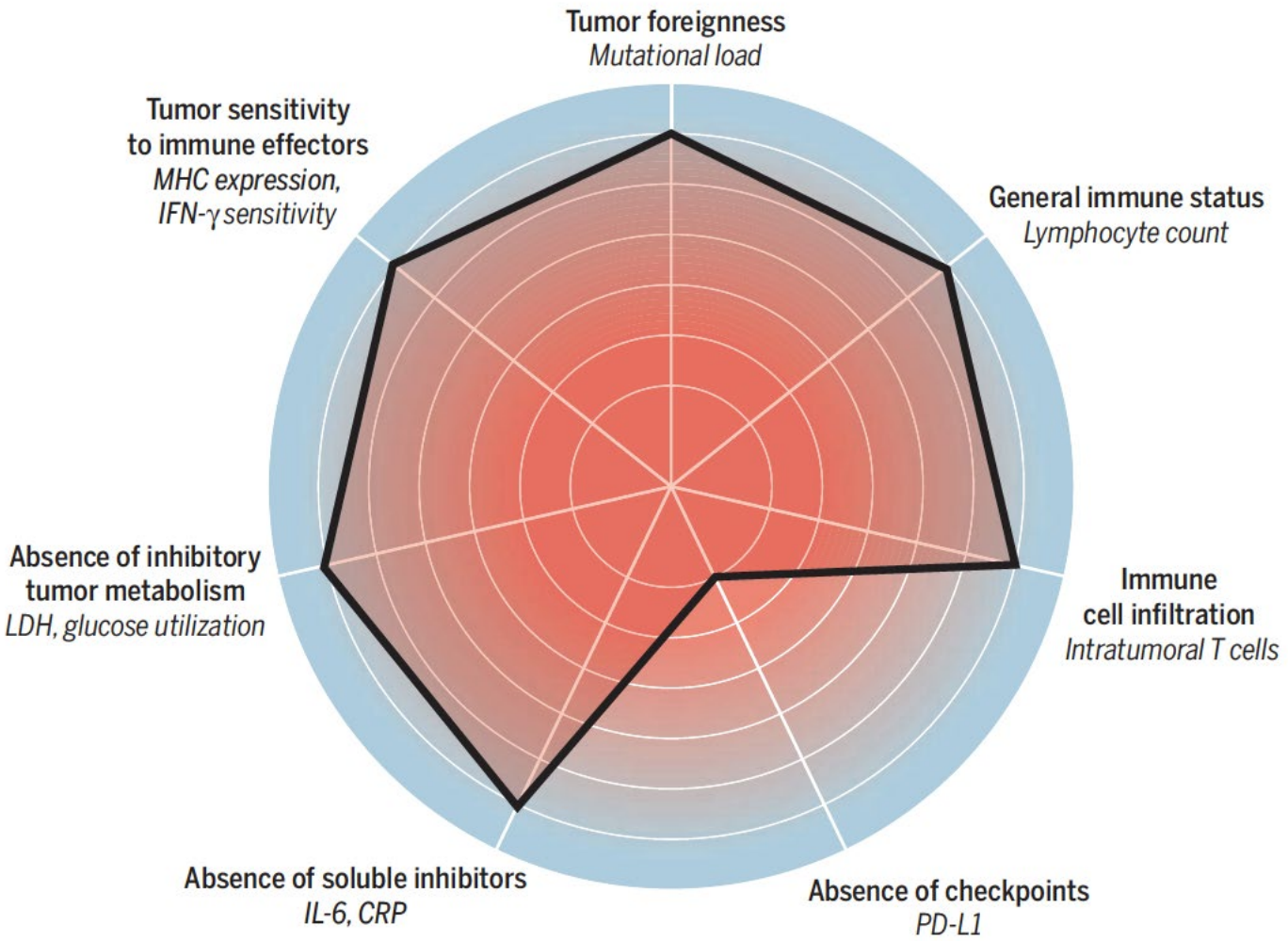
- Agentes dirigidos a Dianas moleculares específicas
- Inmunoterapia
- Desarrollo de nuevos fármacos y EECC
- **Implementación**

Multiplex Assays of Oncogenic Drivers in Lung Cancer



Kris M. et al. JAMA 2014; 311:1998

The cancer immunogram



Some Challenges

- Clinical implementation of precision oncology
- Dealing with tumor heterogeneity and resistance
- Prioritizing targets
- Low frequency aberrations - innovative trials
- Predictive biomarkers for immune-based therapies
- Drug combinations: emerging and limiting toxicities

Clinical Implementation

- Expert teams
- Tumor matherial
- Technology
- Bioinformatics
- Adequate time-frame
- Quality assurance programs
- Link to a innovative clinical trials program

Ensuring equity of access to innovation: France organisation of molecular platforms for personalised medicine

Provides nation-wide molecular diagnostic tests

The programme is operated by the INCa/Ministry of Health since 2006

- **Objectives**
  - Perform molecular testing for all patients;
  - Whatever the healthcare institution status (public hospitals, private hospitals…);
  - Perform high quality tests;
  - leukemia, solid tumours

- **28 regional platforms**
  - Partnerships between several laboratories located in University hospitals and cancer centres
  - Regional organization
  - Cooperation between pathologists and biologists

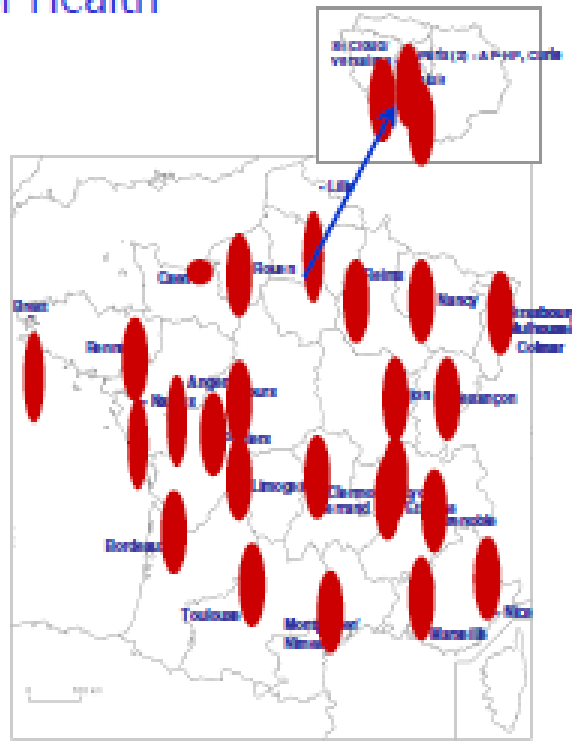
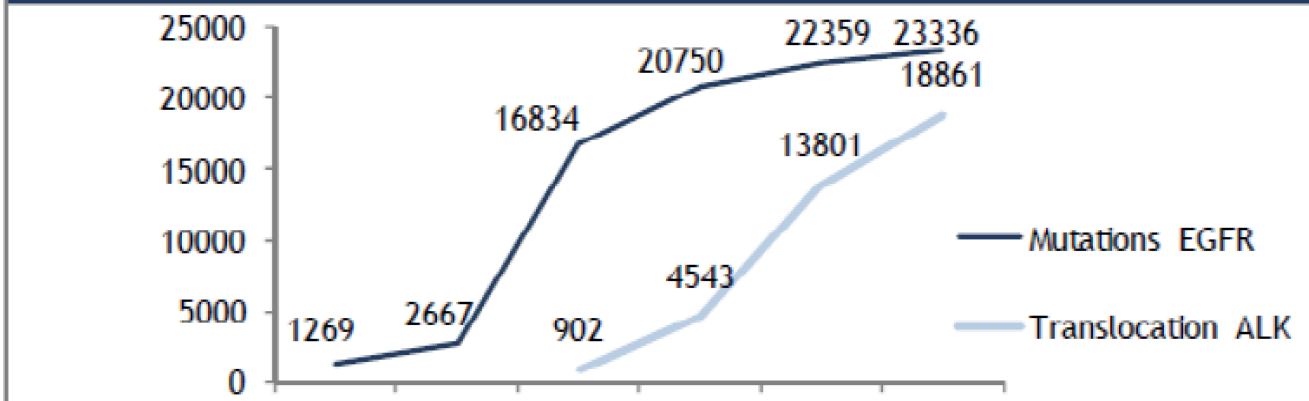


Tableau 11. Activité 2013 dans le cancer du poumon

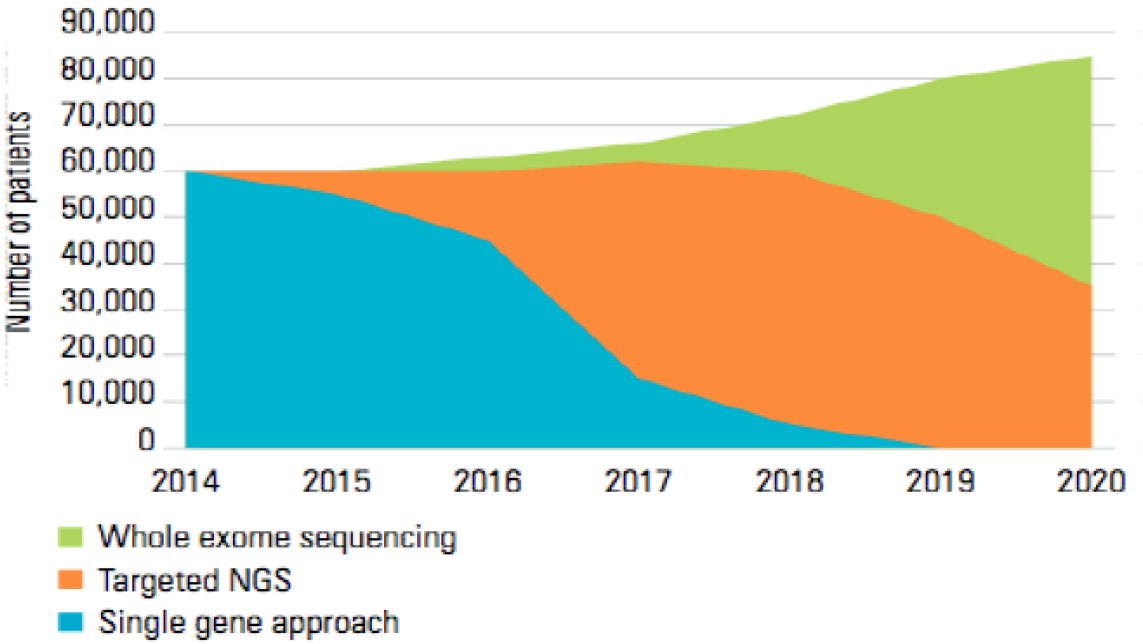
Marqueur	Nombre de patients	% d'altérations moléculaires	% de non interprétables
Mutations *EGFR*	23 336	10,0 %	8,0 %
Translocation *ALK*	18 861	3,5 %	13,4 %
Mutations *KRAS*	22 958	27,0 %	7,9 %
Mutations *BRAF*	20 100	2,0 %	8,9 %
Mutations *HER2*	17 843	0,7 %	10,1 %
Mutations *PI3KCA*	17 375	2,4 %	10,4 %

Figure 17. Évolution de l'activité

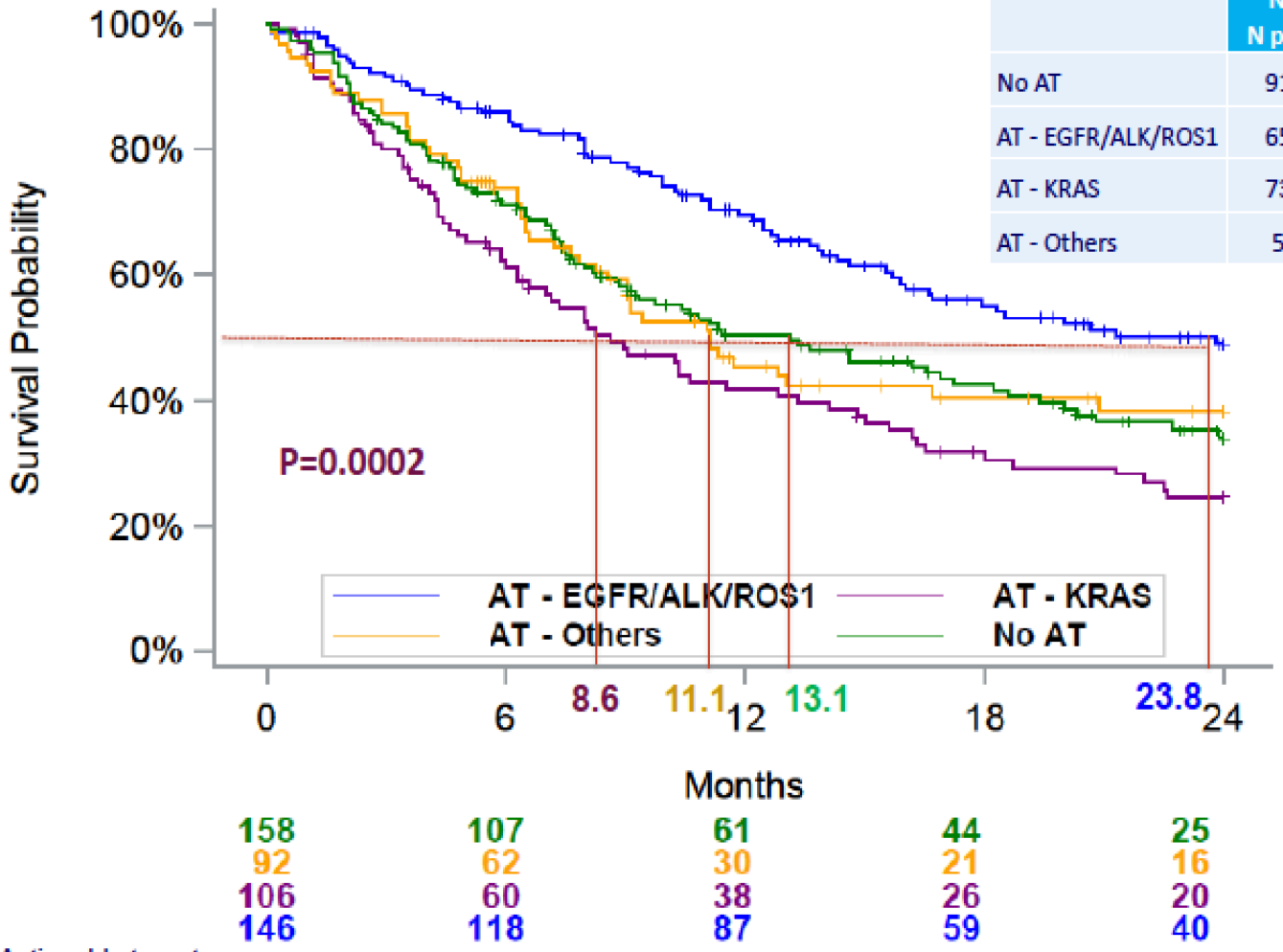


Progressive shift from targeted NGS to WES and RNA seq

Fig. 40. Projected trends in extensive tumour genome sequencing by the end of the Cancer Control Plan



Patients with an actionable target and No actionable target



	N evt/ N patients	HR [95% IC]	p-value (Wald)
No AT	91/158	1	0.0002*
AT - EGFR/ALK/ROS1	65/146	0.62 [0.45-0.85]	
AT - KRAS	73/106	1.32 [0.97-1.80]	
AT - Others	50/92	0.99 [0.70-1.40]	

* No adjusted

AT: Actionable target

David.Planchard et al, IASLC 2015

> 175
NGM Members
In Germany

Molecular testing in Europe: C Mascaux/S Lantuejoul

SEAP-IAP Sociedad Española de Anatomía Patológica
División española de la International Academy of Pathology

SEOM
Sociedad Española
de Oncología Médica

PBC Plataforma de Biomarcadores en Cáncer

Gracias

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