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Targeted therapies
Advanced oesophagogastric cancers

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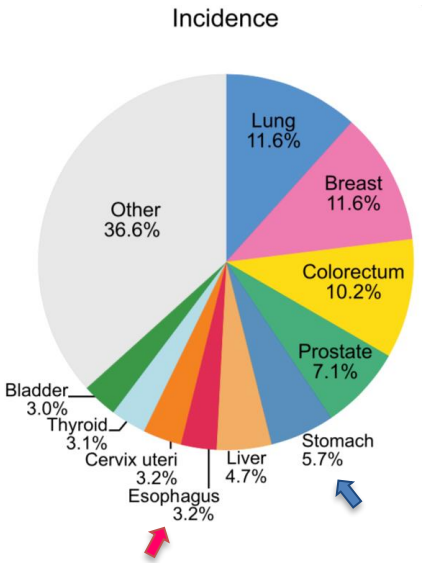
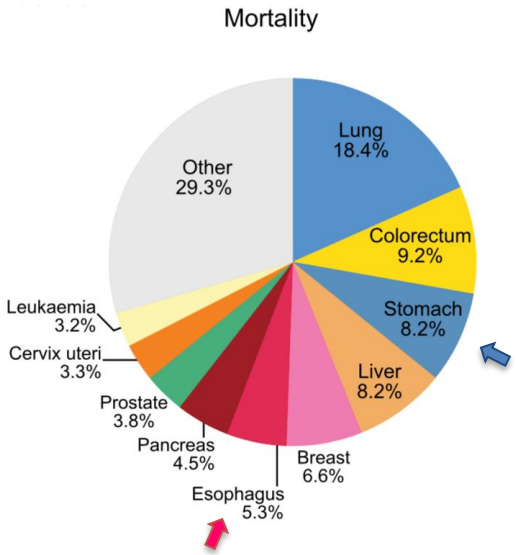
Disclosure

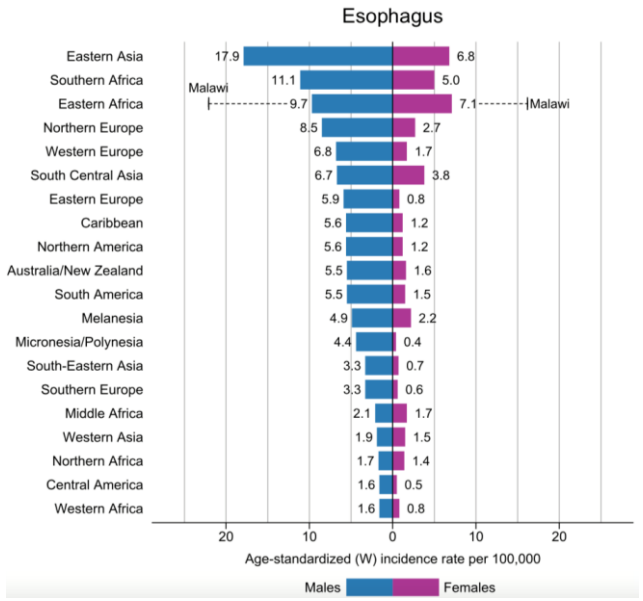
- Travel expenses: Bayer

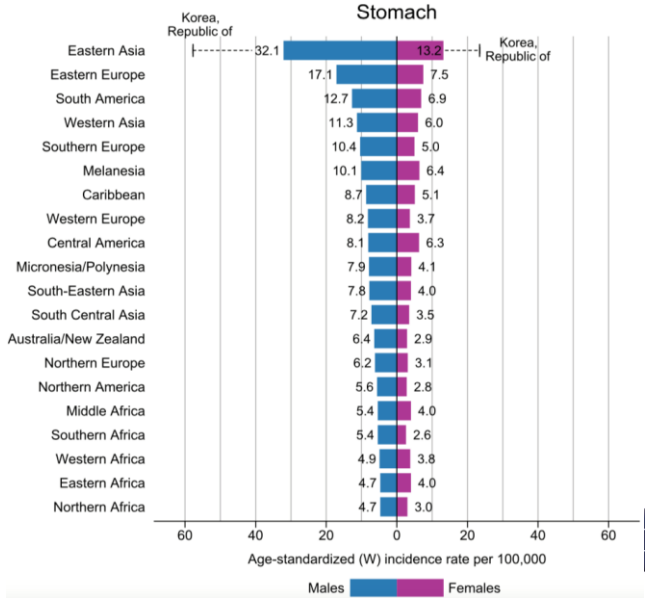
Incidence and mortality of OGCs worldwide

- Oesophageal cancer
  - 7th most common cancer
  - 6th cause of cancer-related death
- Gastric cancer
  - 5th most common cancer
  - 3rd cause of cancer-related death









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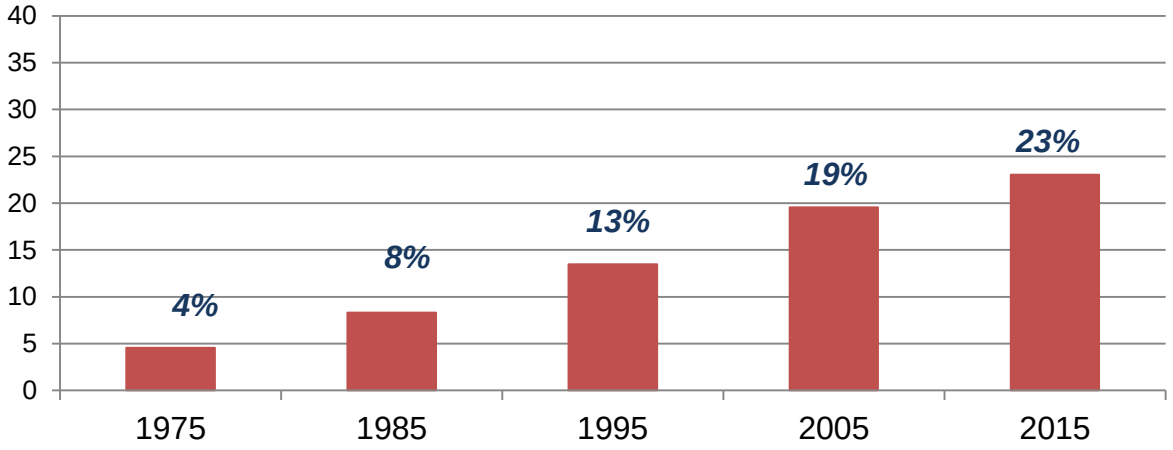
GLOBOCAN 2018

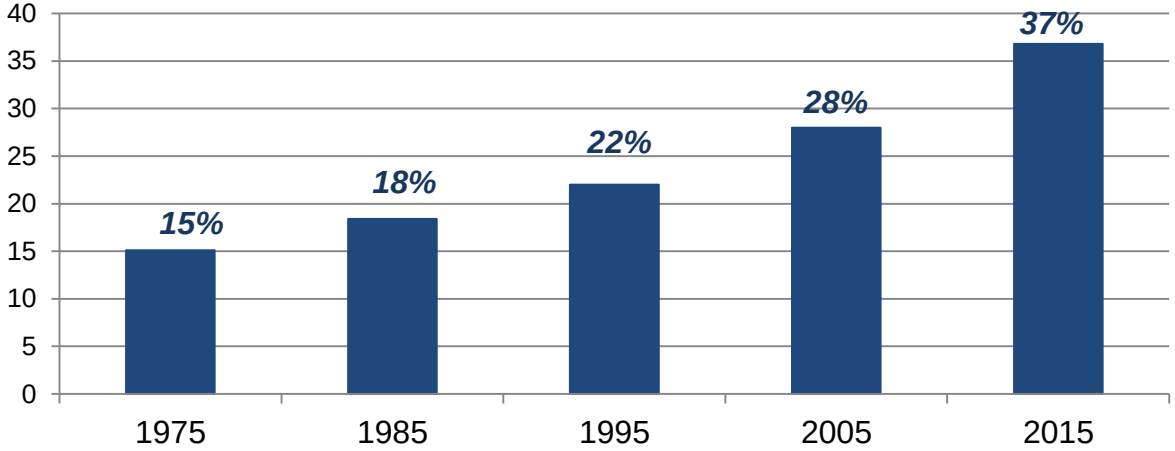
Trends in 5-year relative survival for OGCs in the US

Oesophageal cancer



+19%

Gastric cancer



+22%

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seer.cancer.gov

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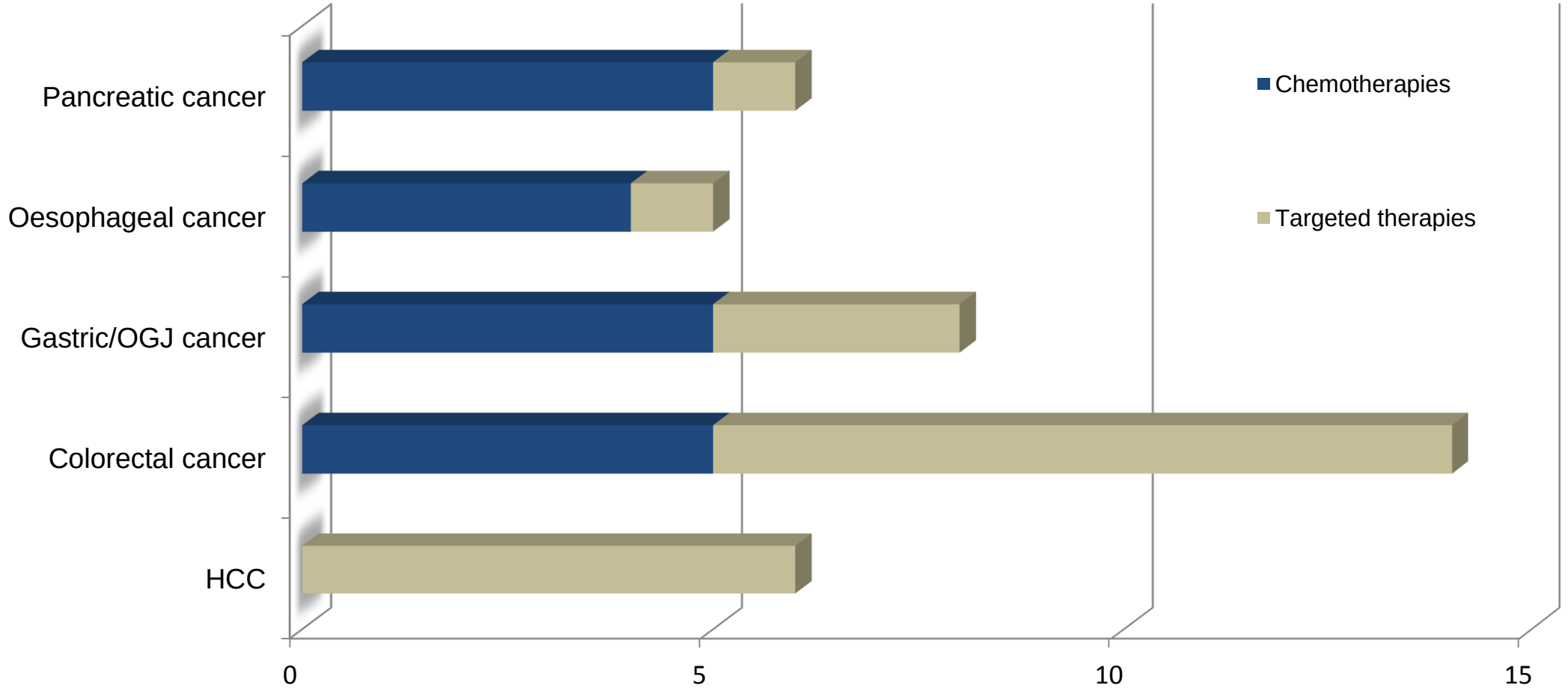
Type of drugs approved by FDA for main GI cancers



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National Cancer Institute

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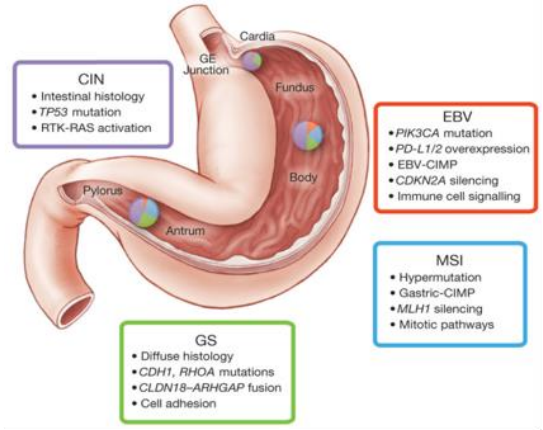
Evolution of understanding the biology of OGCs

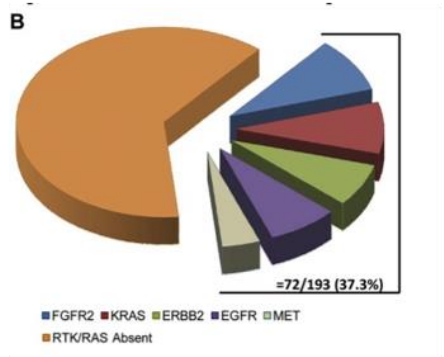
2011

Identification of RTK amplification



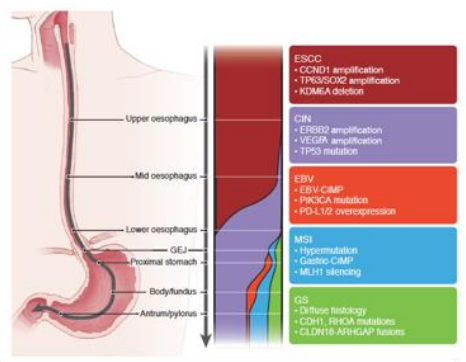
2014

Gastric cancer TCGA



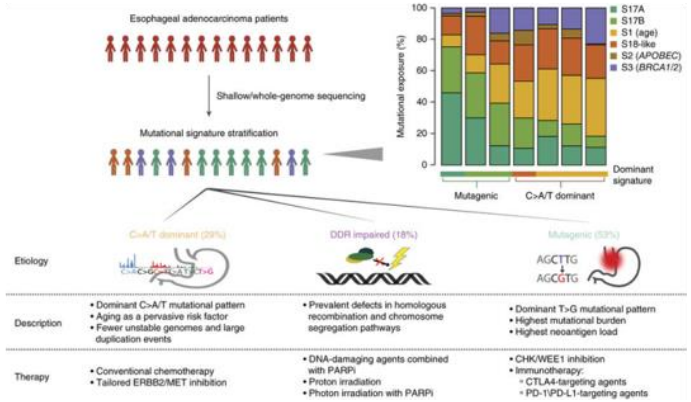
2016

Subclassification of oesophageal adenocarcinoma



2017

Oesophageal cancer TCGA



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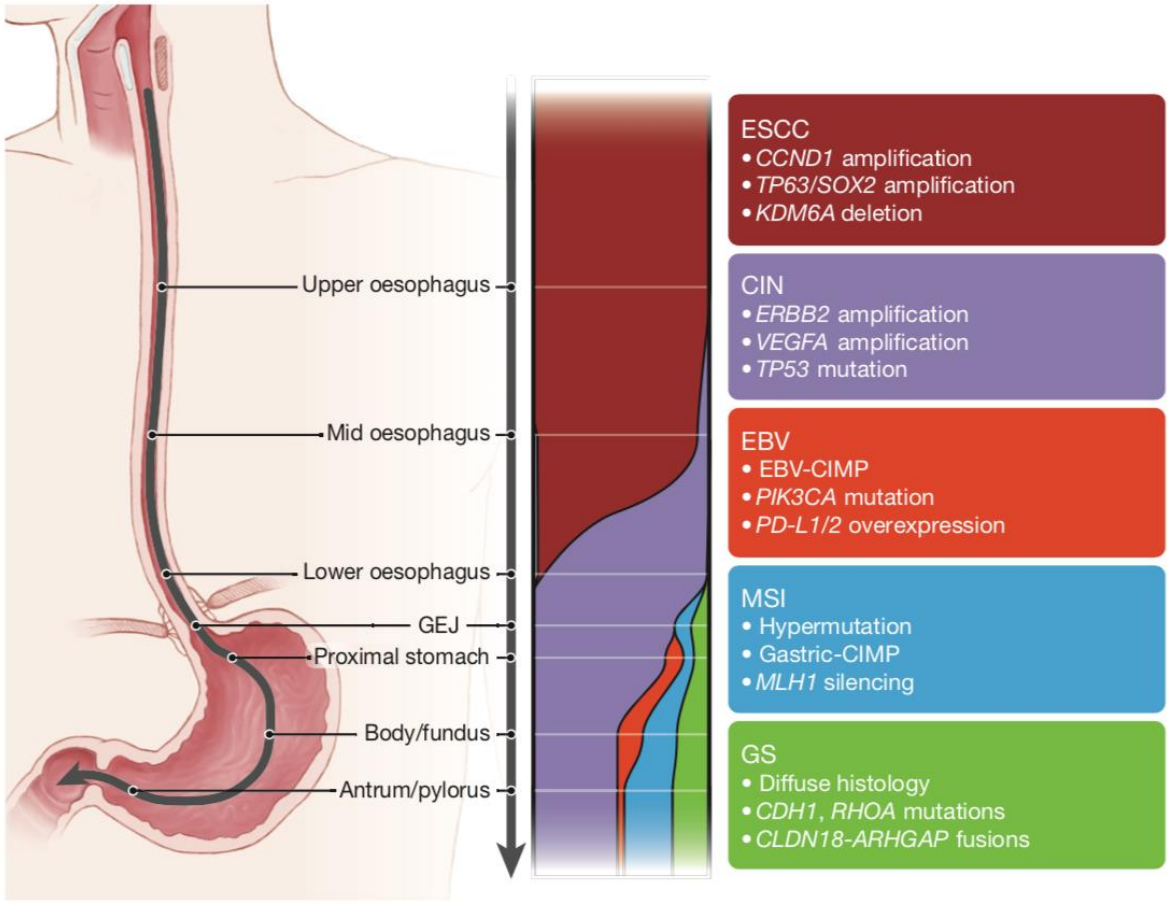
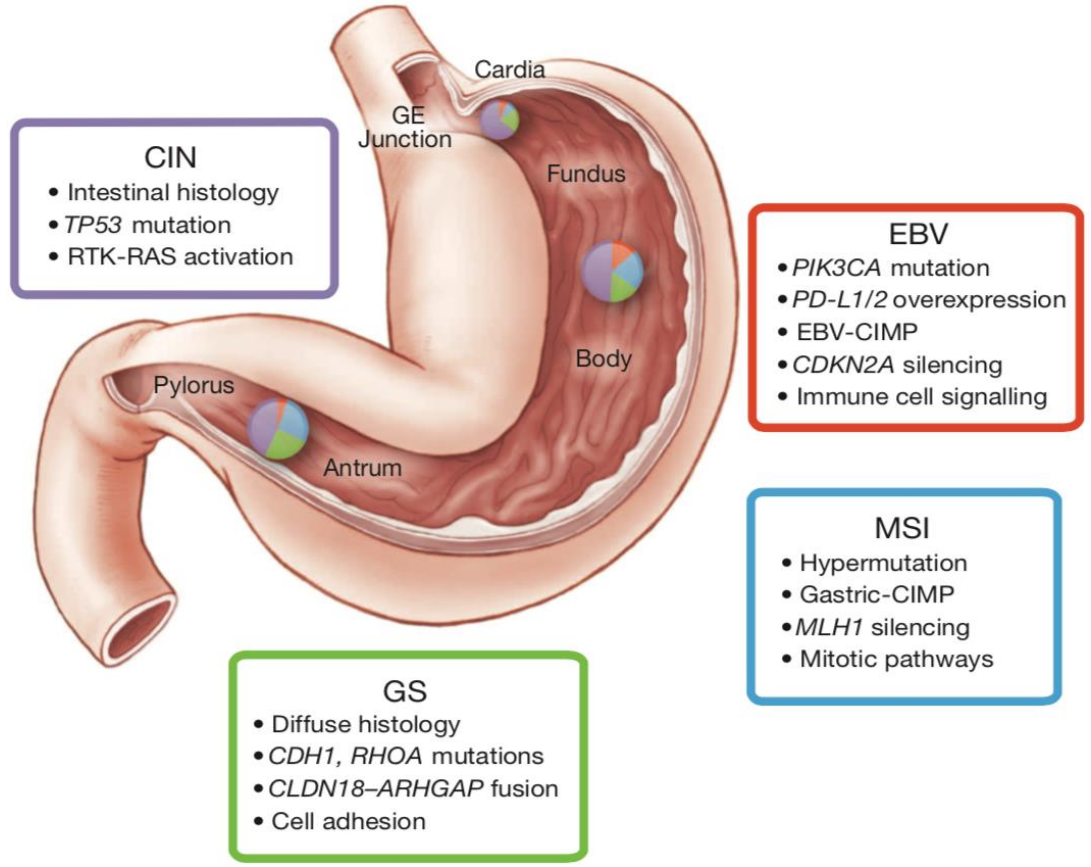
Integrated genomic characterisation of OGCs





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The Cancer Genome Atlas Research Network, Nature 2014; The Cancer Genome Atlas Research Network, Nature 2017

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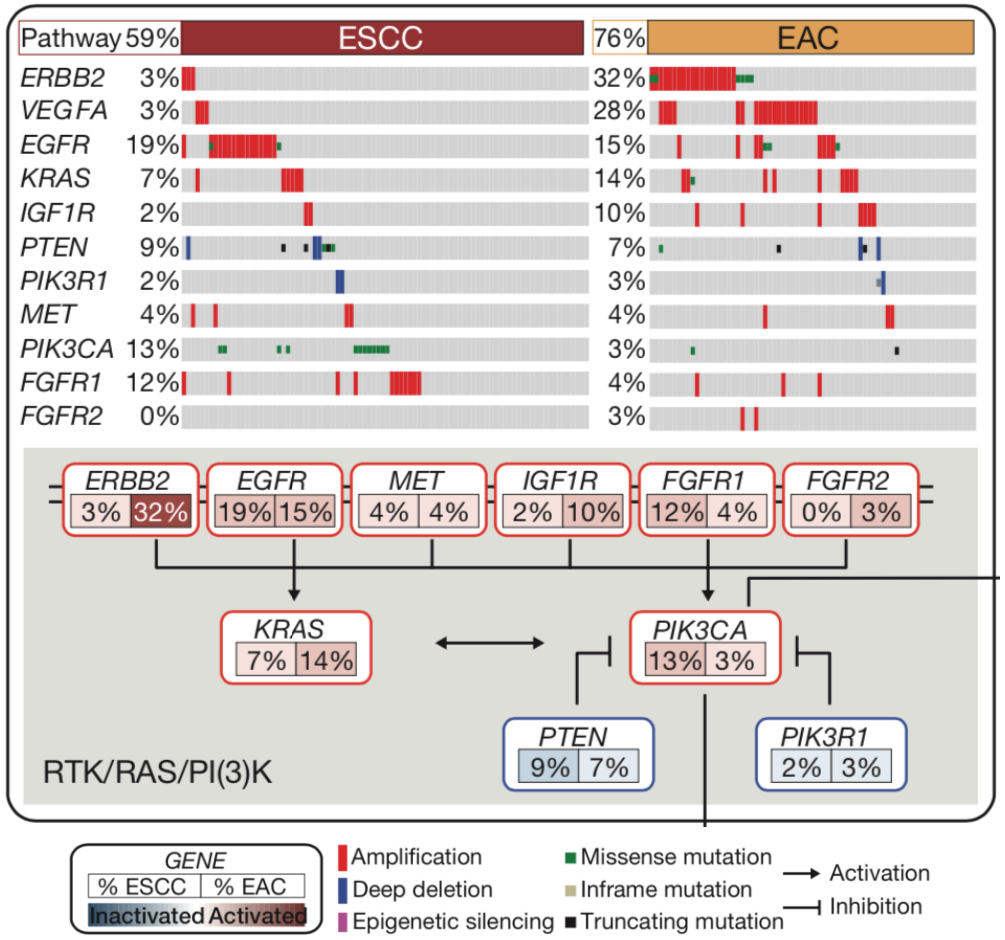
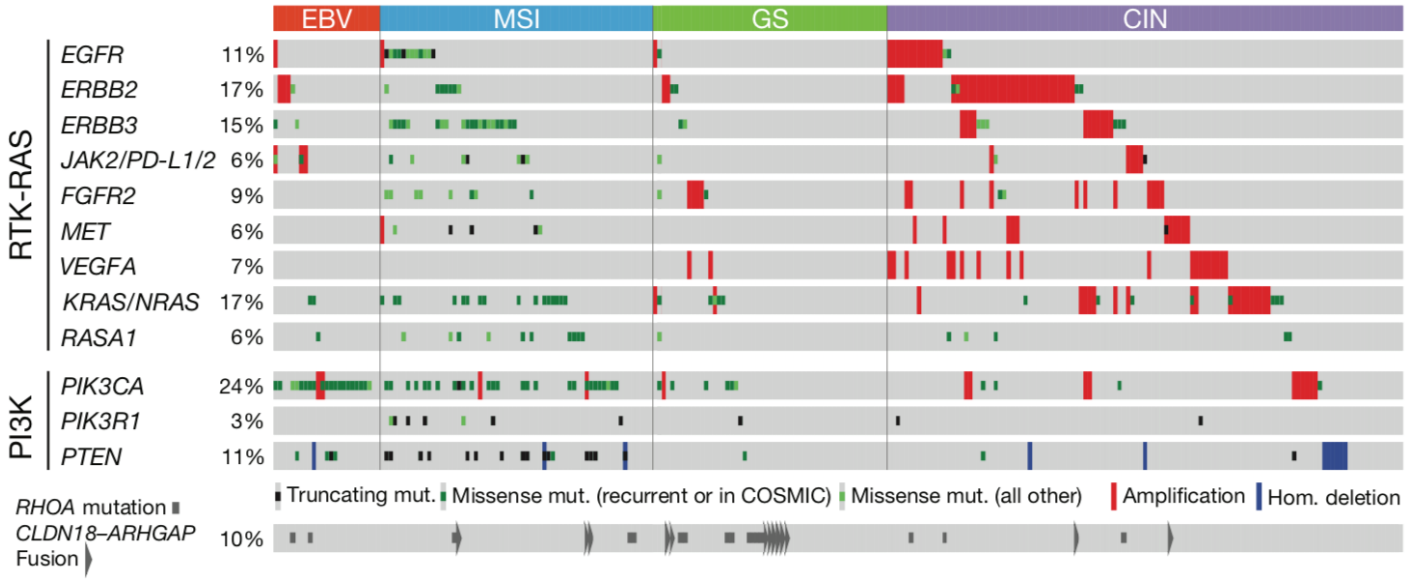
Rationale for using/investigating targeted therapies in OGCs





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The Cancer Genome Atlas Research Network, Nature 2014; The Cancer Genome Atlas Research Network, Nature 2017

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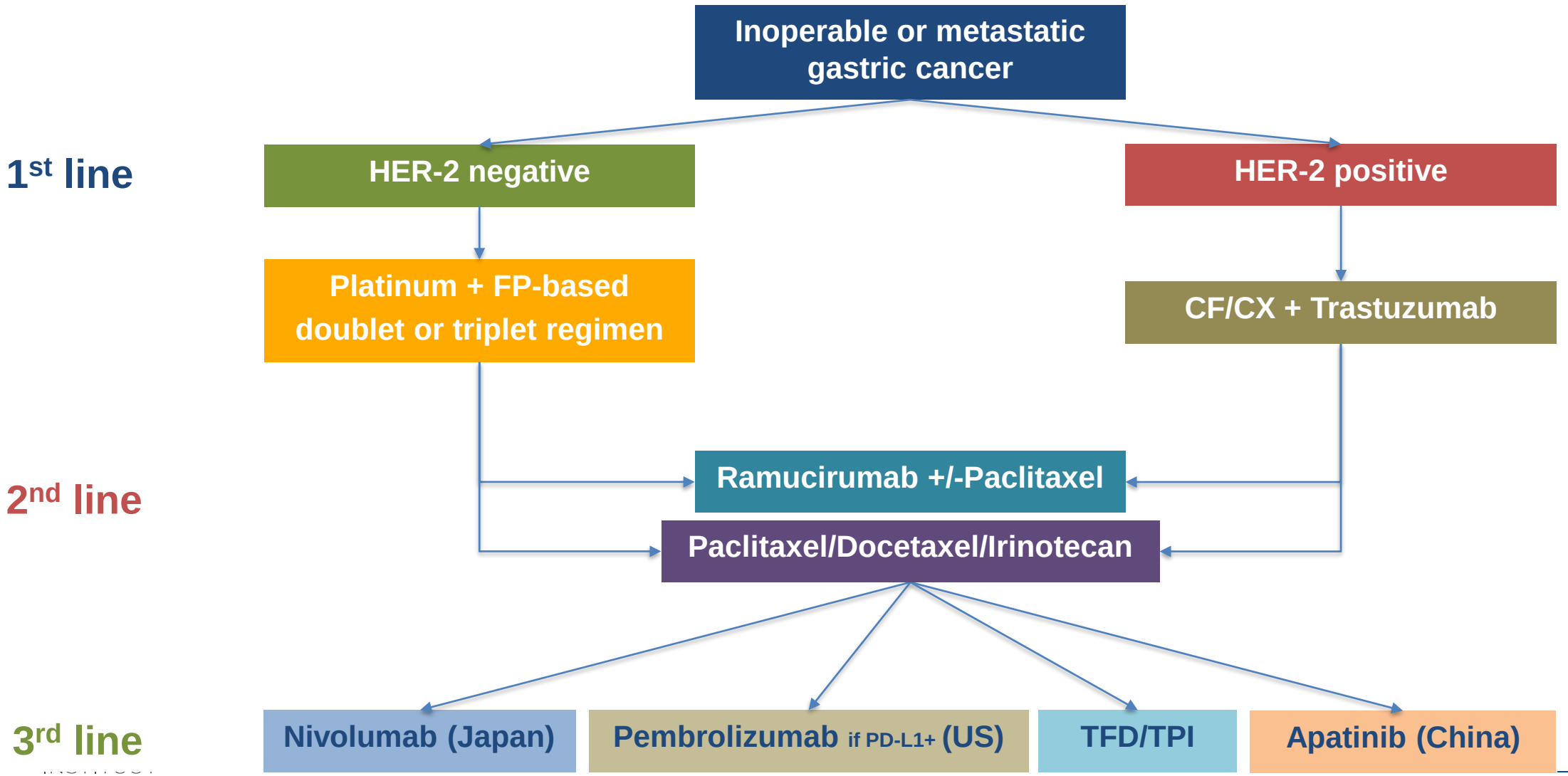
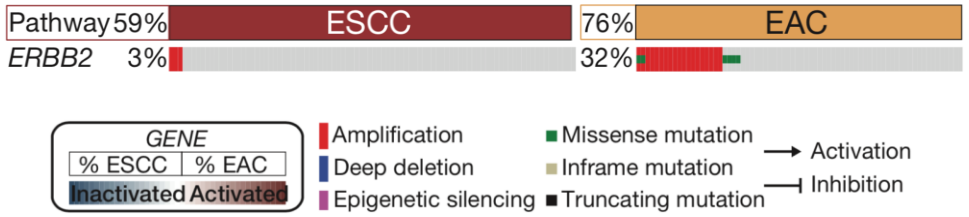
Treatment algorithm for advanced gastric cancer

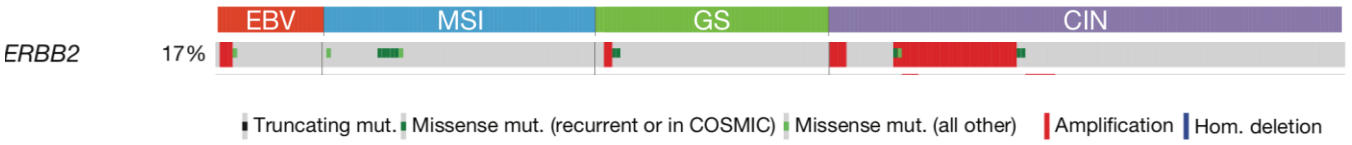


HER-2

Oesophageal TCGA



Gastric TCGA



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The Cancer Genome Atlas Research Network, Nature 2014; The Cancer Genome Atlas Research Network, Nature 2017

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Successful inhibition of HER-2 in OGCs

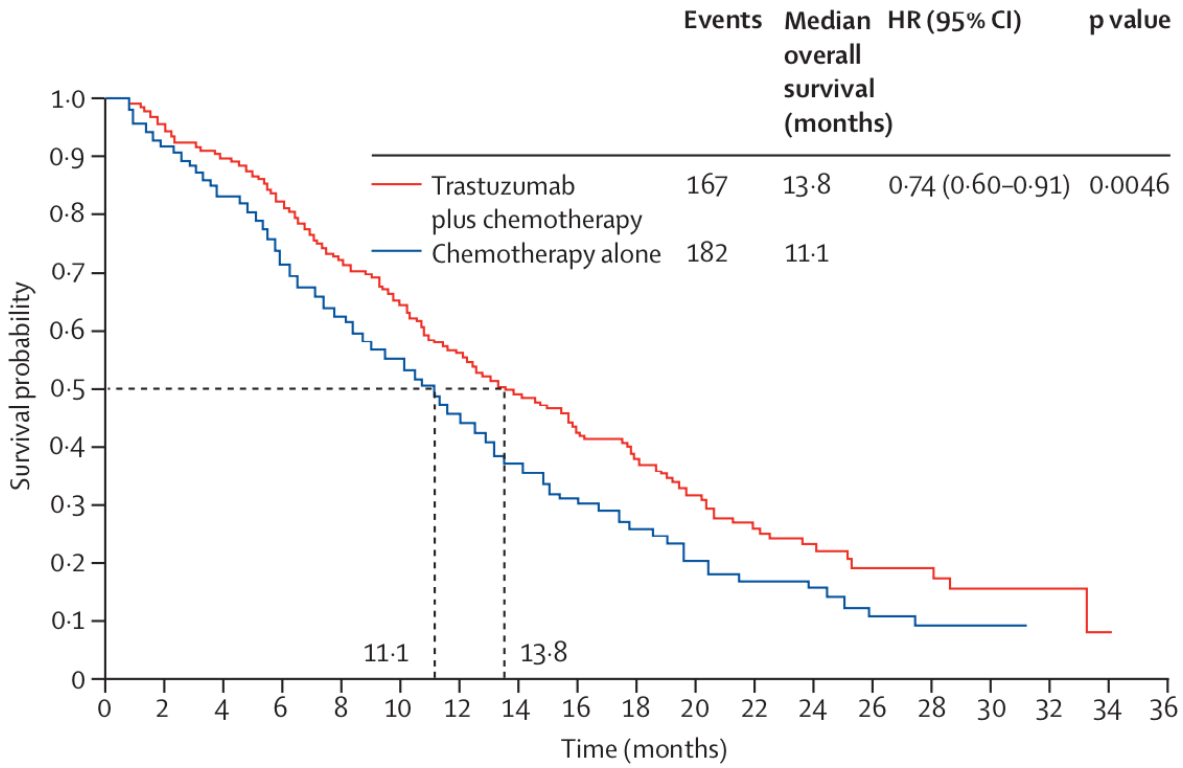
TOGA trial

Primary endpoint OS

Treatment naïve advanced HER2+* gastric cancer

- Cisplatin-5FU/X (n=296)
- Cisplatin-5FU/X + Trastuzumab (n=298)

*IHC 3+ or FISH positive



Addition of trastuzumab to CF/X ↑ RR, PFS and OS

mOS 13.8 m vs. 11.1 m
HR 0.74 (95% CI: 0.60 – 0.91)
p=0.0046

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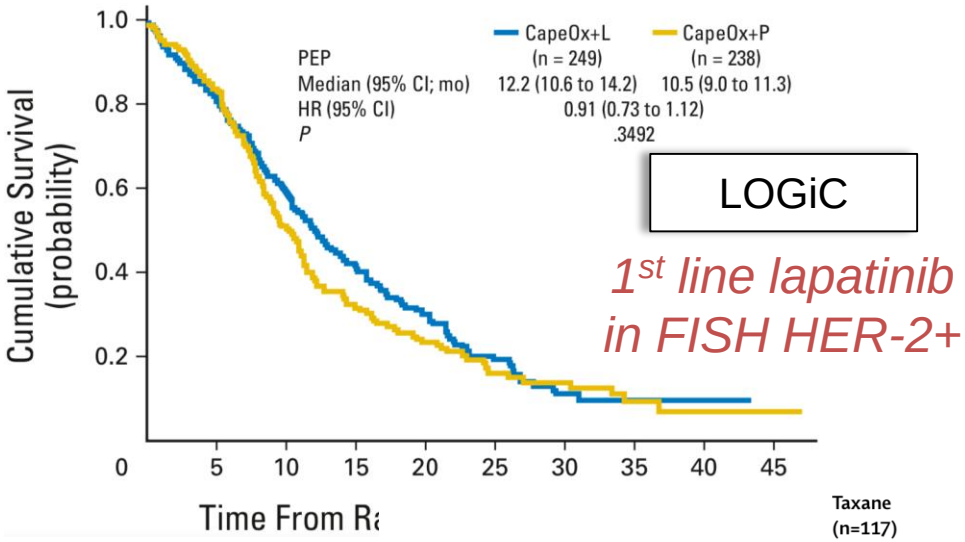
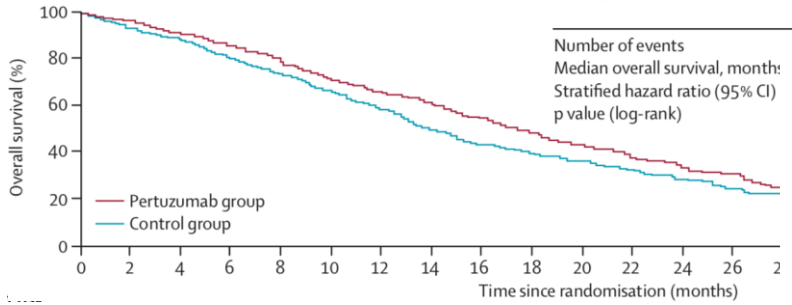
Unsuccessful trials of HER-2 inhibitors in OGCs



LOGiC

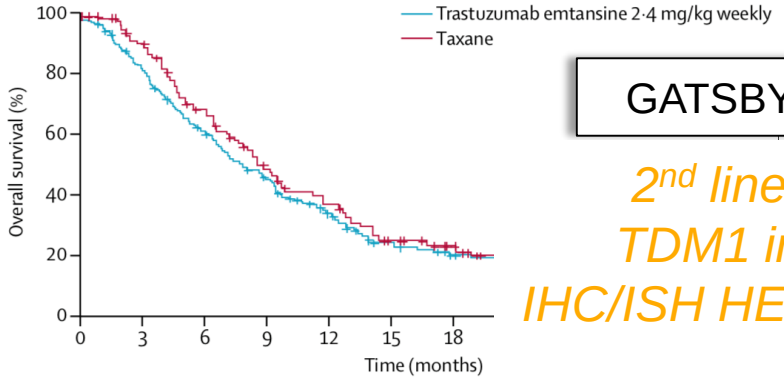
1st line lapatinib in FISH HER-2+



JACOBS

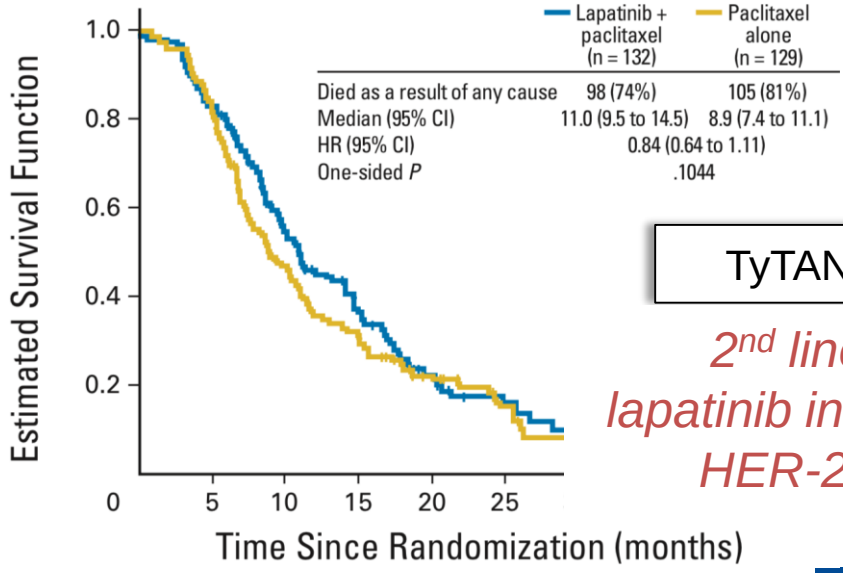
1st line pertuzumab + trastuzumab in IHC/ISH HER-2+

	Taxane (n=117)	Trastuzumab emtansine 2·4 mg/kg weekly (n=228)
Median overall survival, months (95% CI)	8·6 (7·1–11·2)	7·9 (6·7–9·5)
Number of events	71 (60·7%)	164 (71·9%)
Unstratified hazard ratio (95% CI) weekly trastuzumab emtansine *vs* taxane	1·15 (0·87–1·51), p=0·86*	



GATSBY

2nd line TDM1 in IHC/ISH HER-2+



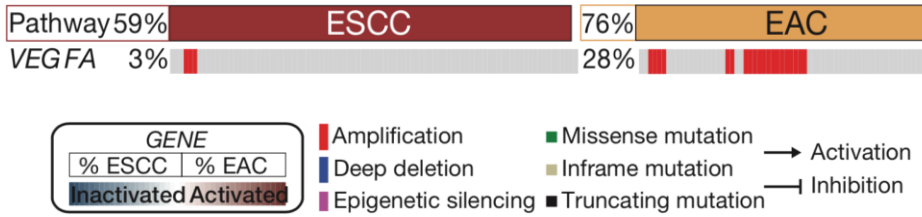
TyTAN

2nd line lapatinib in FISH HER-2+

Satoh, J Clin Oncol 2014; Hecht, J Clin Oncol 2016; Thuss-Patience, Lancet Oncol 2017; Tabernero, Lancet Oncol 2018

VEGF

Oesophageal TCGA



Gastric TCGA

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The Cancer Genome Atlas Research Network, Nature 2014; The Cancer Genome Atlas Research Network, Nature 2017

Successful trials of anti-angiogenic therapy in OGCs

Trial	Patients	Comparison	Endpoint	Outcomes	HR / p value
REGARD*	2nd line advanced GC/GEJ	**Ramucirumab** BSC	OS	5.2 m 3.8 m	HR 0.776 p=0.047
RAINBOW°	2nd line advanced GC/GEJ	**Paclitaxel + Ramucirumab** Paclitaxel	OS	9.6 m 7.4 m	HR 0.807 p=0.017
APATINIB^ (China)	≥3rd line advanced GC/GEJ	**Apatinib** BSC	OS	6.5 m 4.7 m	HR 0.709 p=0.0149

***** *Also statistically significant improvement in PFS*
° *Also statistically significant improvement in RR and PFS*
^ *Also statistically significant improvement in DCR and PFS*

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Fuchs, Lancet 2014; Wilke, Lancet Oncol 2014; Li, J Clin Oncol 2016

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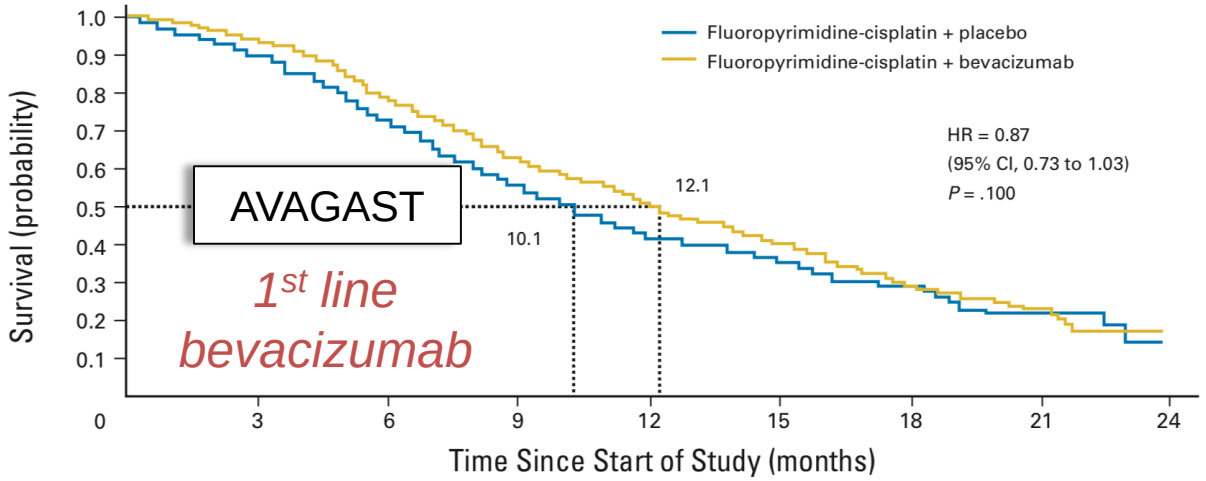
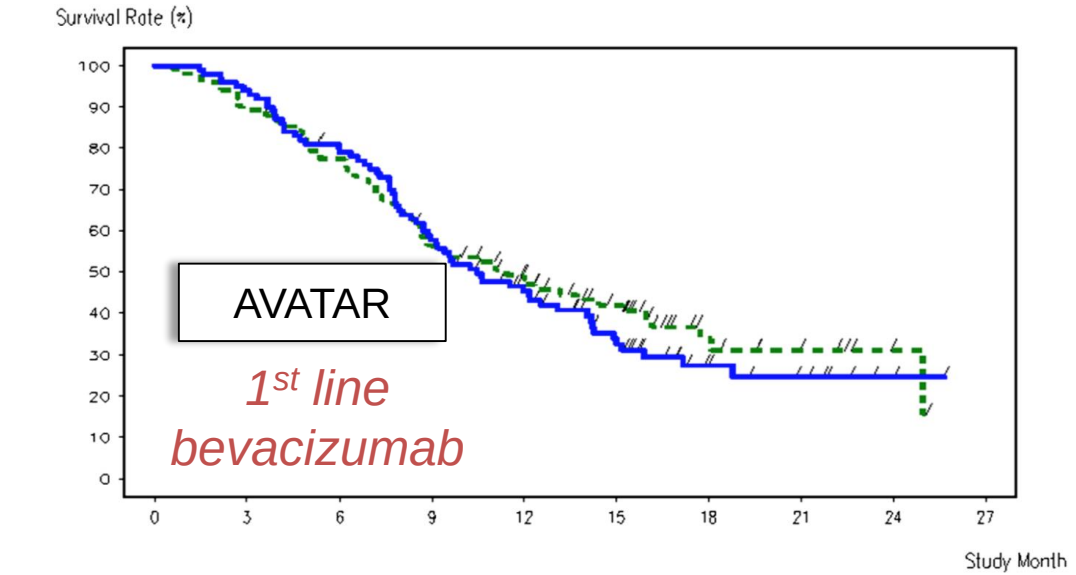
Unsuccessful trials of anti-angiogenic therapy in OGCs



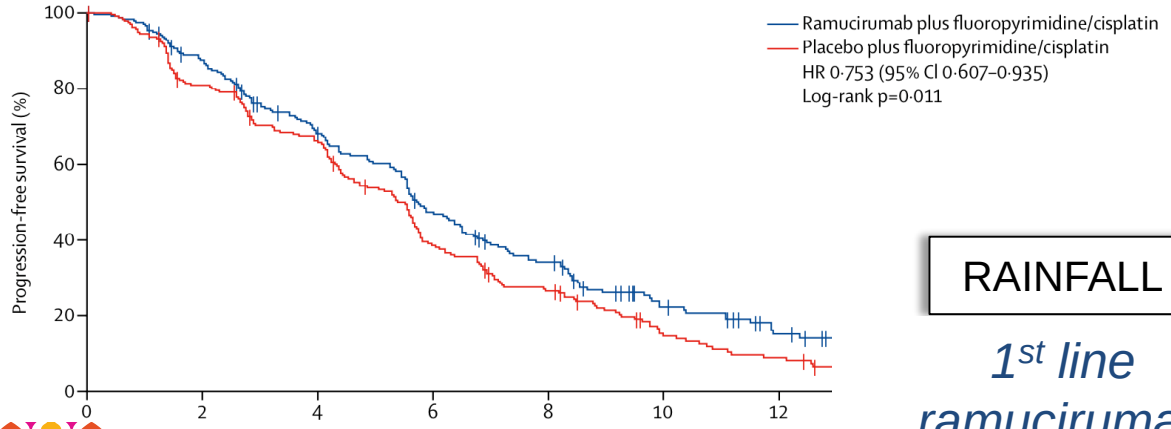
AVAGAST

1st line bevacizumab



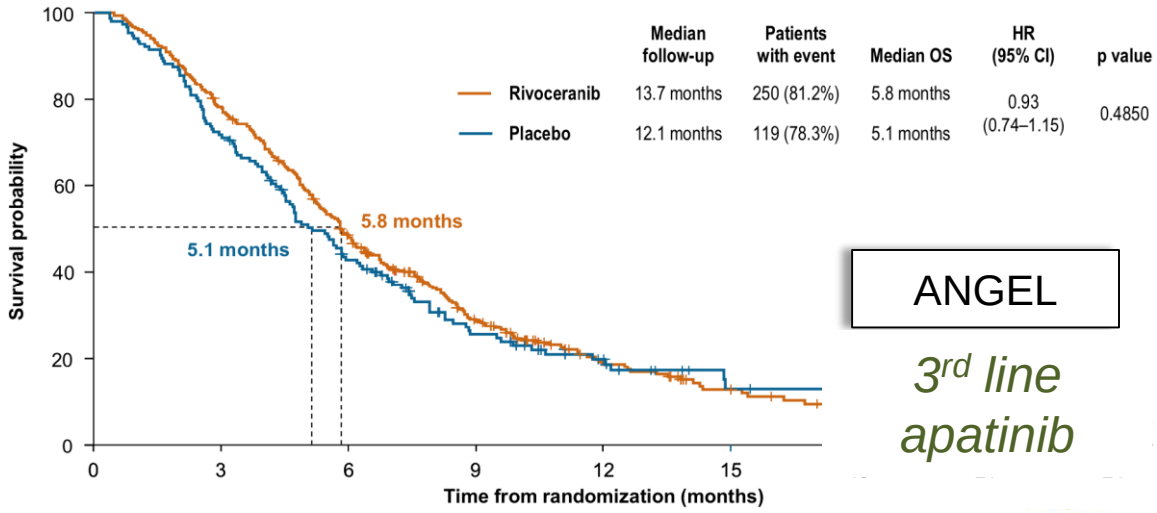
AVATAR

1st line bevacizumab



RAINFALL

1st line ramucirumab



ANGEL

3rd line apatinib

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Ohtsu, J Clin Oncol 2011; Shen, Gastric Cancer 2015; Fuchs, Lancet Oncol 2019; Kang, ESMO 2019

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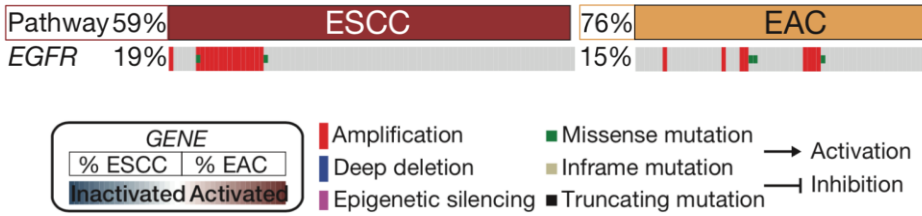
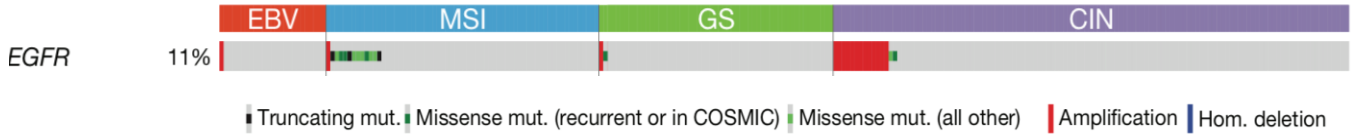
EGFR

Oesophageal TCGA



Gastric TCGA



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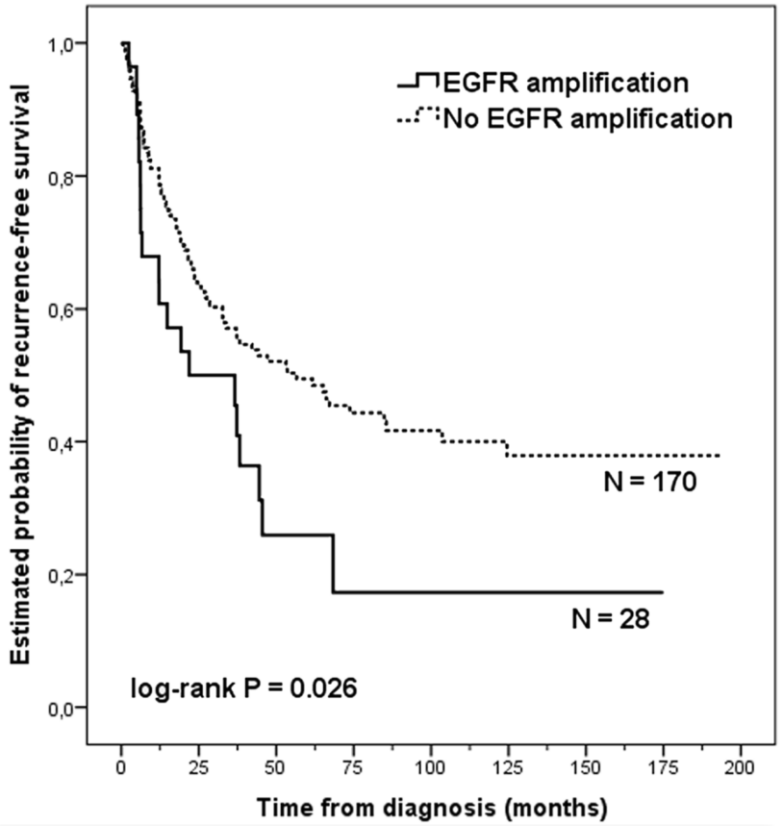
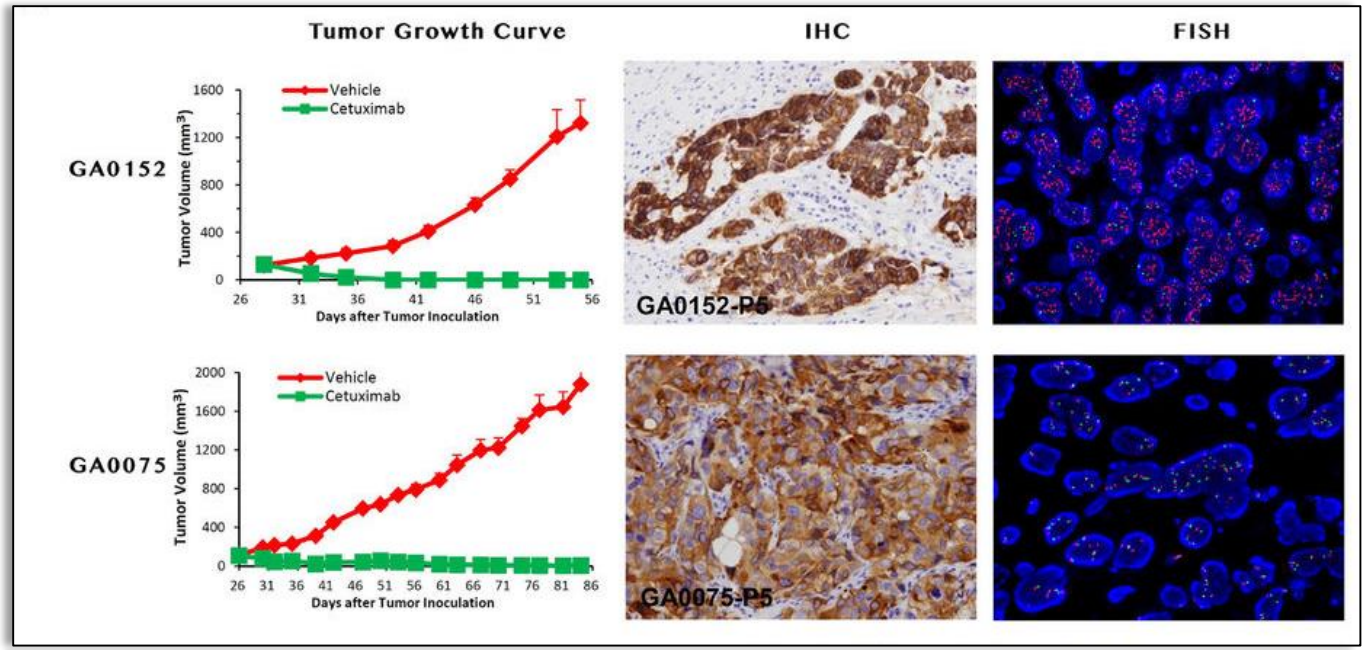
The Cancer Genome Atlas Research Network, Nature 2014; The Cancer Genome Atlas Research Network, Nature 2017

Prognostic and predictive role of EGFR in OGCs



EGFR amplification is negatively prognostic



EGFR amplified GC PDX models are addicted to EGFR signalling

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Zhang, Sci Rep 2013; Brikman, BMC Cancer 2016

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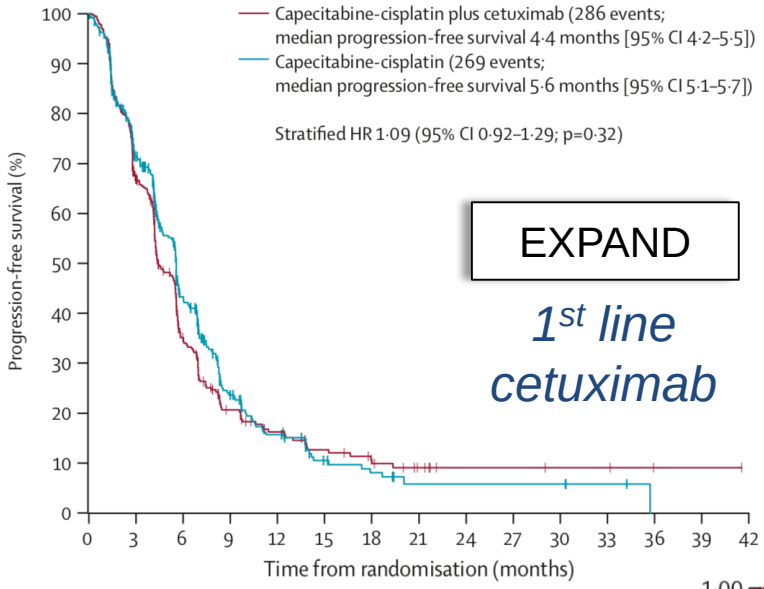
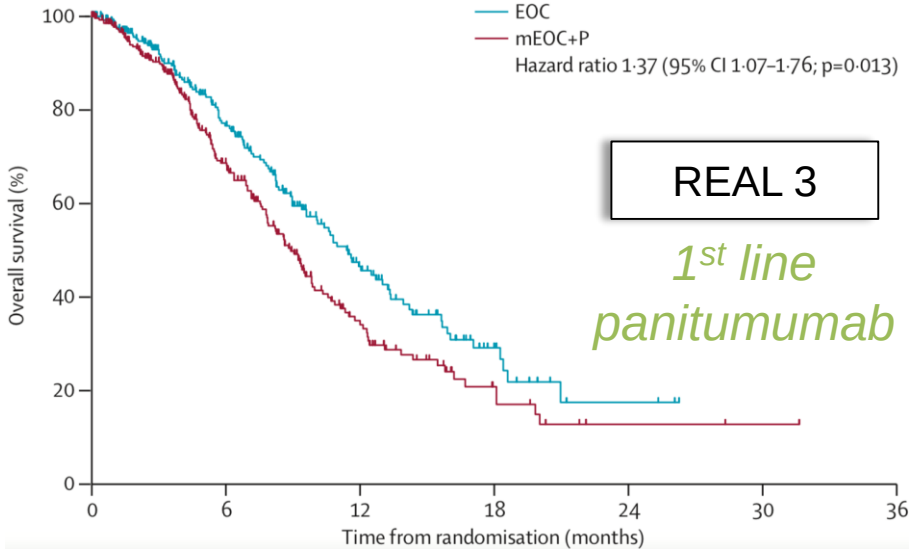
Unsuccessful trials of anti-EGFR agents in OGCs



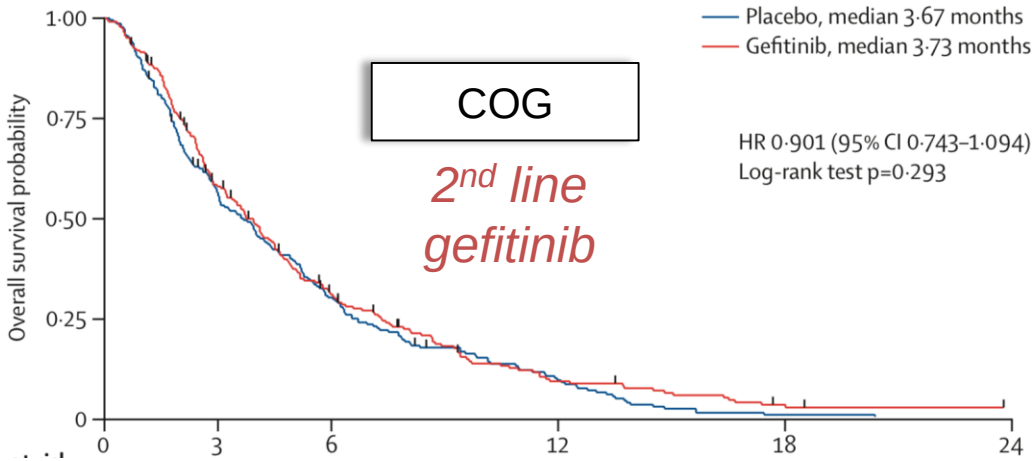
EXPAND

1st line cetuximab



REAL 3

1st line panitumumab



COG

2nd line gefitinib

Waddell, Lancet Oncol 2013; Lordick, Lancet Oncol 2013; Dutton, Lancet Oncol 2014;

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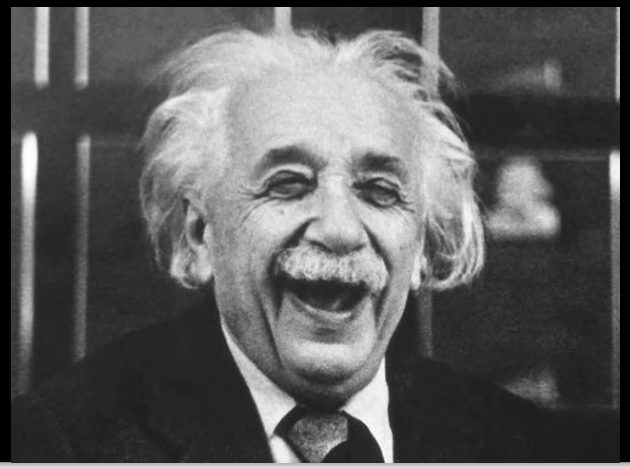
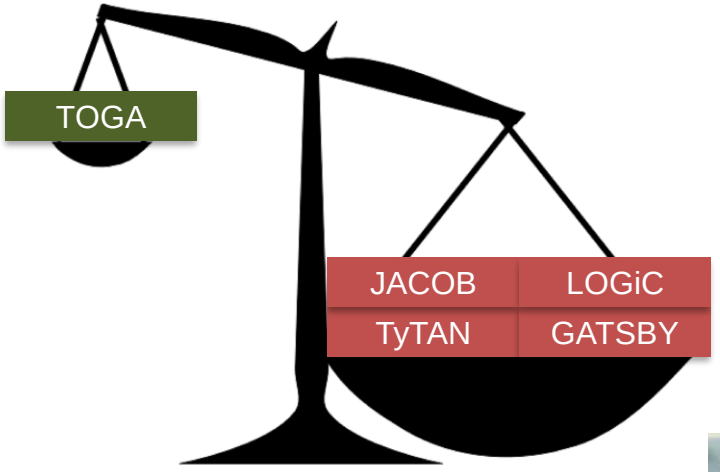
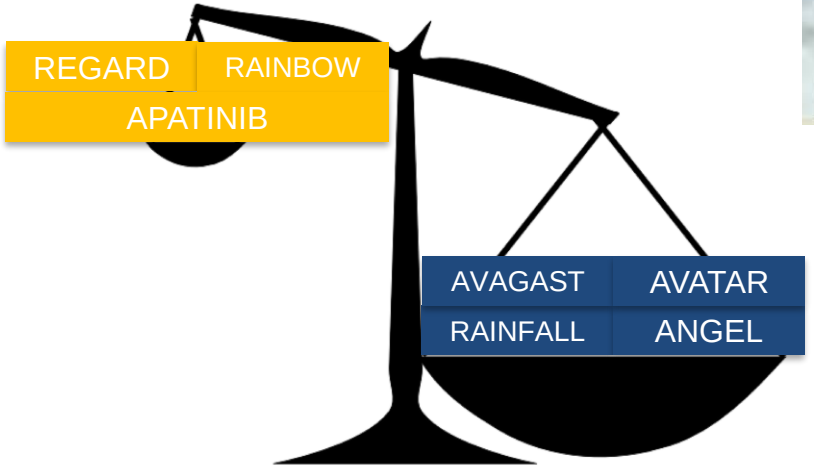
HER-2, EGFR and VEFG: still useful therapeutic target?

"Insanity is doing the same thing over and over again and expecting different results"







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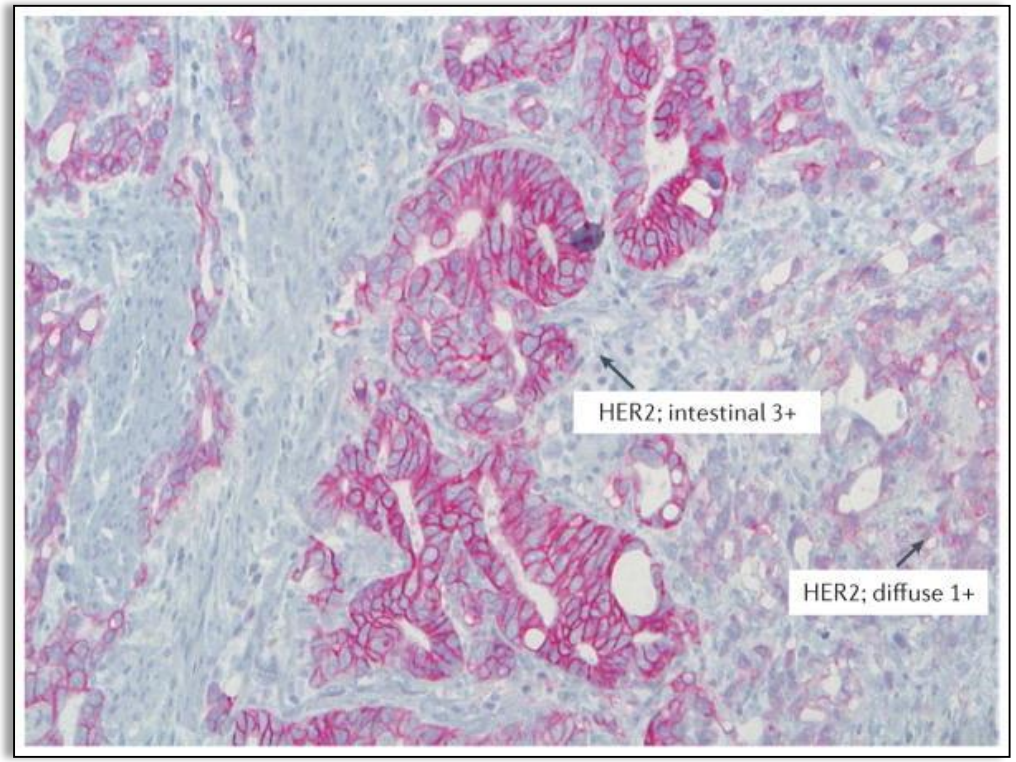
Mind the intratumour HER-2 heterogeneity in OGCs

And the impact that this may have in terms of treatment outcomes



HER2 % of positive cells in IHC 3+ patients from TOGA trial				
% cells	<10%	10-30%	31-79%	≥80%
% patients	3%	27%	31%	39%

Survival outcome according to HER-2 heterogeneity in TOGA trial				
	Chemo	**Chemo + T**		
% stained cells	**mOS**	**mOS**	**HR**	**95 % CI**
IHC 2+				
0 % to ≤30 %	11.7	11.4	0.83	0.50–1.41
>30 % to 100 %	9.2	12.5	0.66	0.36–1.18
IHC 3+				
0 % to ≤30 %	13.6	18.0	0.71	0.40–1.25
>30 % to 100 %	12.3	17.9	0.55	0.37–0.81

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Van Cutsem, Gastric Cancer 2015

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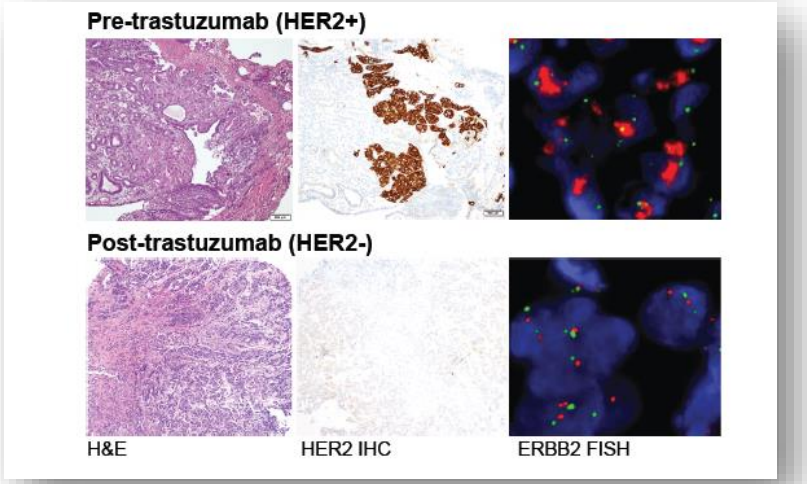
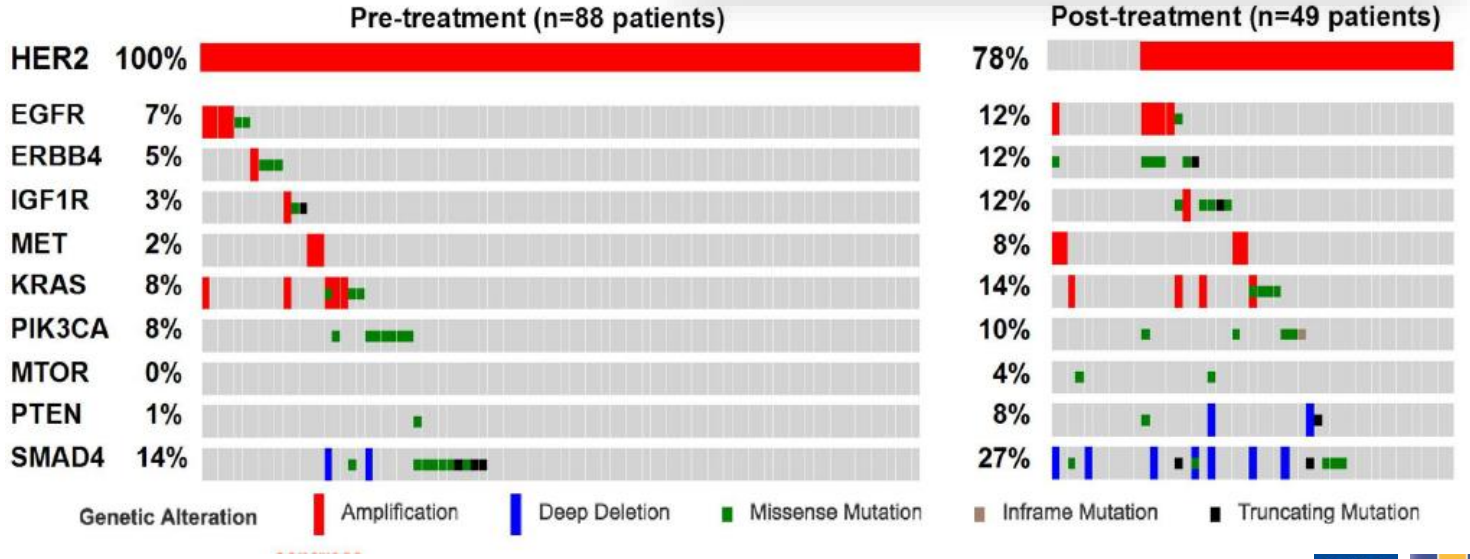
HER-2 is not a static biomarker

Something to consider when investigating anti-HER-2 strategies beyond progression

- HER-2 status changes post trastuzumab therapy (up to 32% of HER-2 positive tumours become HER-2 negative following anti-HER-2 treatment, more common in IHC2+ *vs* IHC3+)



- Non-HER-2 biomarkers become important when HER-2 changes



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Pietrantonio, Int J Cancer 2016; Janjigian, Cancer Discov 2017; Seo, Gastric Cancer 2019

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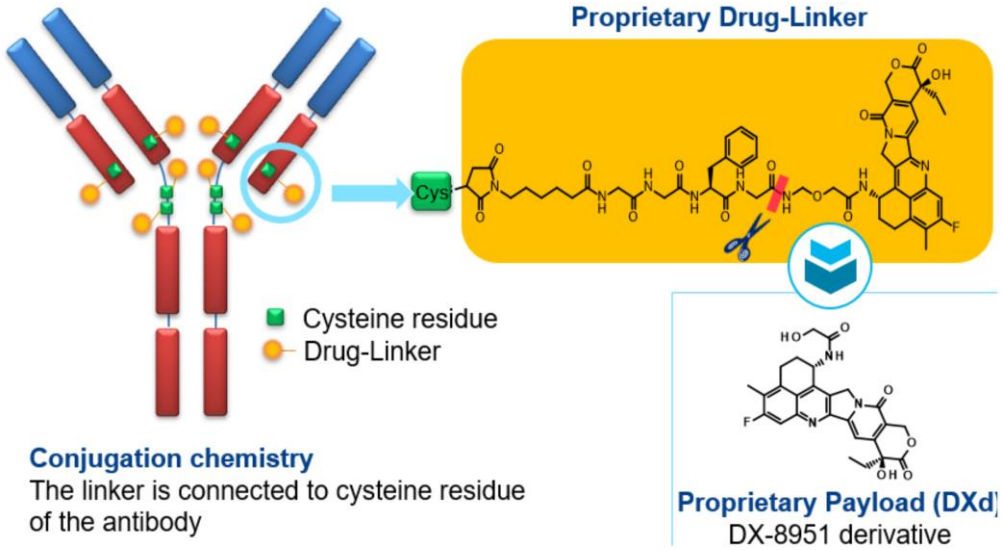
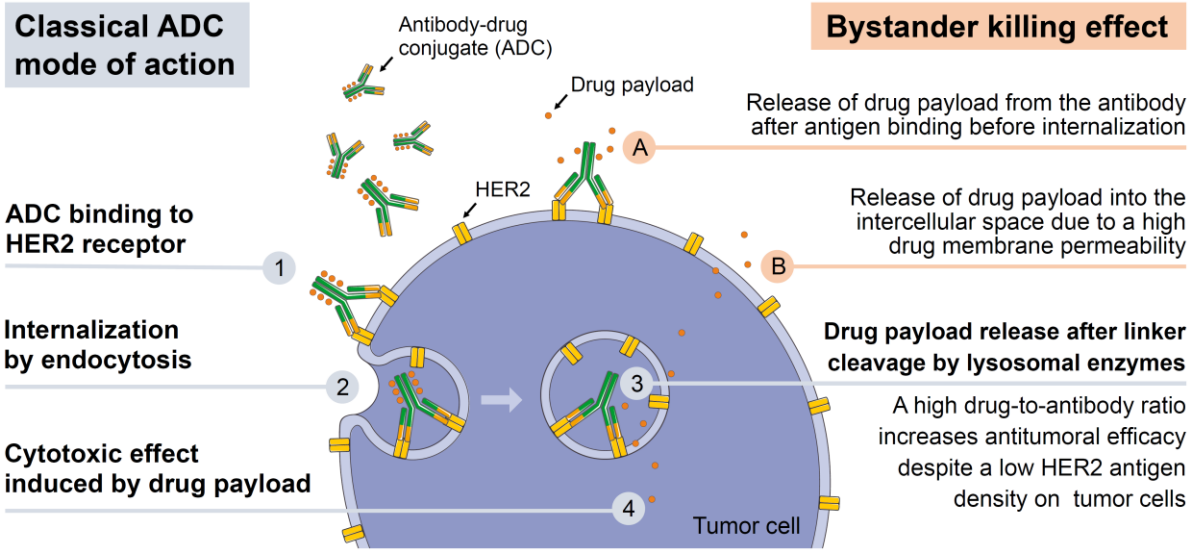
Bypassing HER-2 heterogeneity: trastuzumab deruxtecan





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Rinnerthaler, Int J Mol Sci 2019; Baselga, ASCO 2019;

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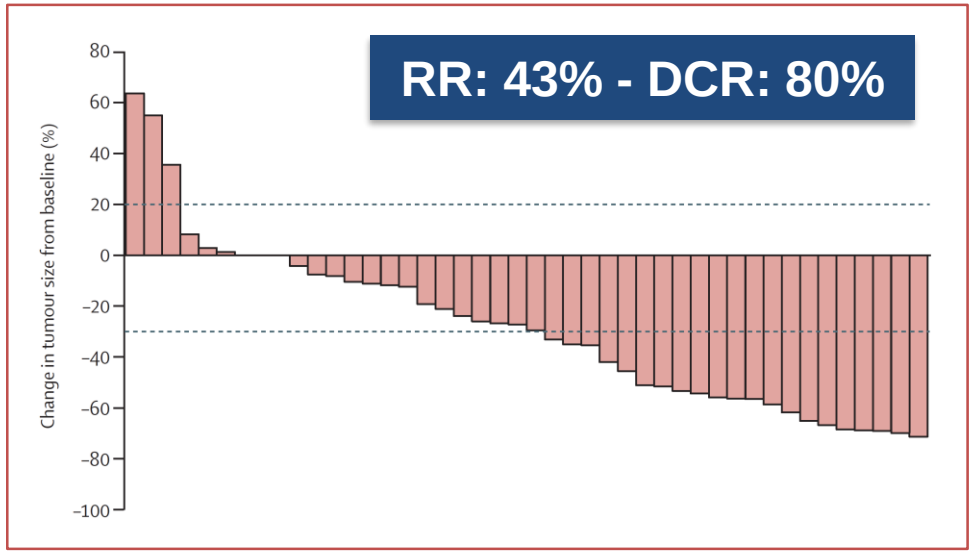
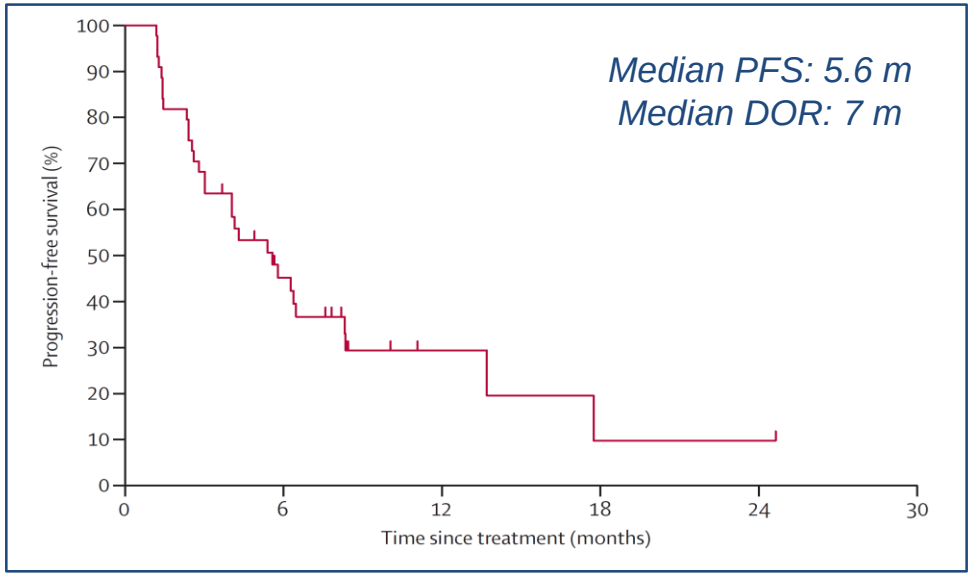
Bypassing HER-2 heterogeneity: trastuzumab deruxtecan

- Dose expansion phase I trial (n=44)
- OGJ/Gastric cancer, HER-2 3+ or 2+/ISH+
- Median number of prior therapy 3 (2-5)
- 100% prior trastuzumab
- 55% prior irinotecan

Randomised phase II trial ongoing (DESTINY-GASTRIC01)
≥3rd line trastuzumab deruxtecan *vs* investigator's choice





Shitara, Lancet Oncol 2019

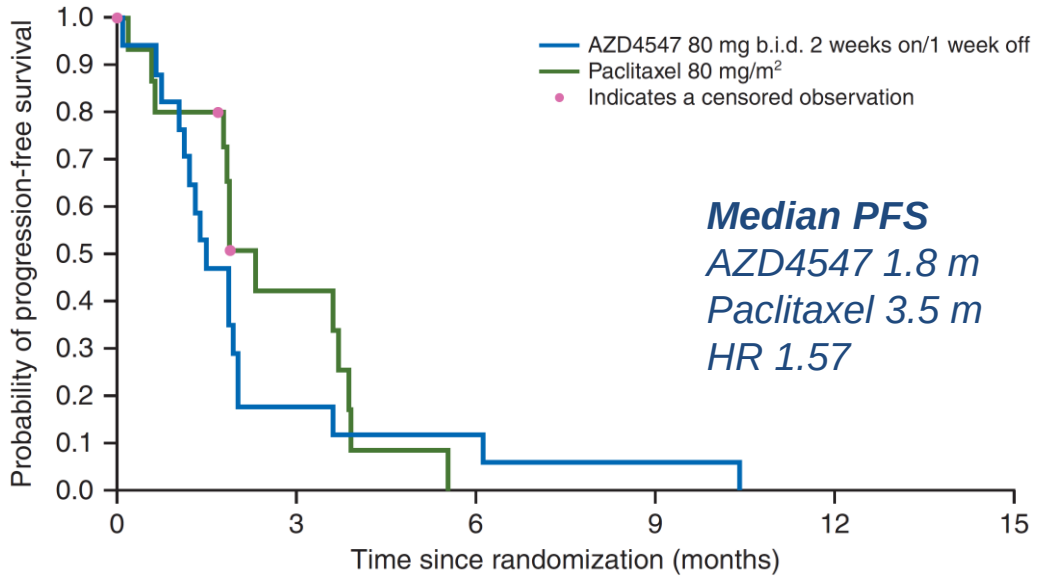
Intratumour heterogeneity in OGCs – the case of FGFR2

SHINE Trial

≥2nd line advanced GC with FGFR2 polysomy or amplification

- AZD4547 (n=41)
- Paclitaxel (n=30)

Primary endpoint PFS



Median PFS
AZD4547 1.8 m
Paclitaxel 3.5 m
HR 1.57

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Van Cutsem, Ann Oncol 2017

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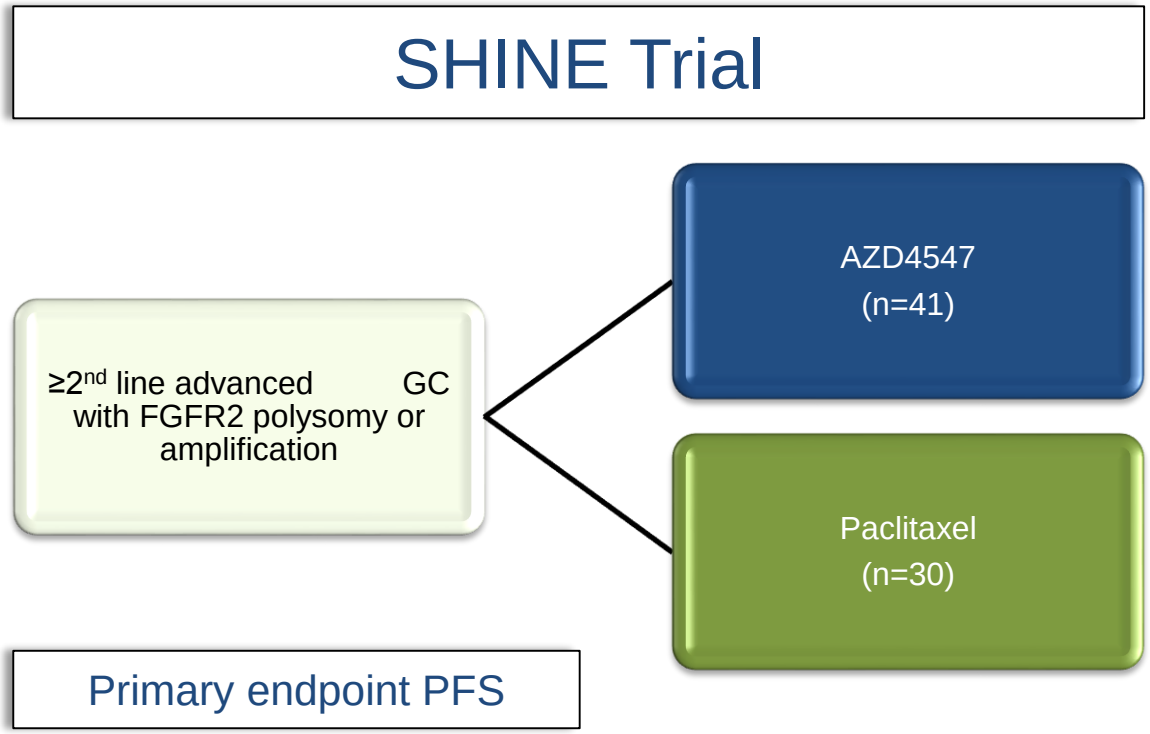
Intratumour heterogeneity in OGCs – the case of FGFR2



Best response	AZD4547		Paclitaxel	
	FISH L-amp	FISH H-amp	FISH L-amp	FISH H-amp
CR (%)	0	0	0	0
PR (%)	0	0	1 (10%)	2 (40%)
SD (%)	1 (11%)	2 (25%)	3 (30%)	2 (40%)
PD (%)	8 (89%)	6 (75%)	6 (60%)	1 (20%)

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Van Cutsem, Ann Oncol 2017

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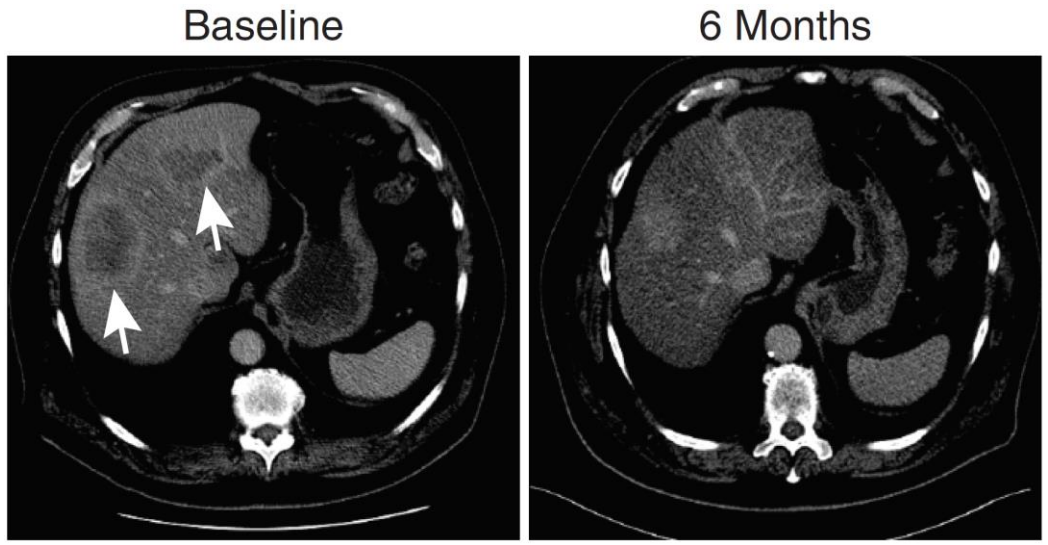
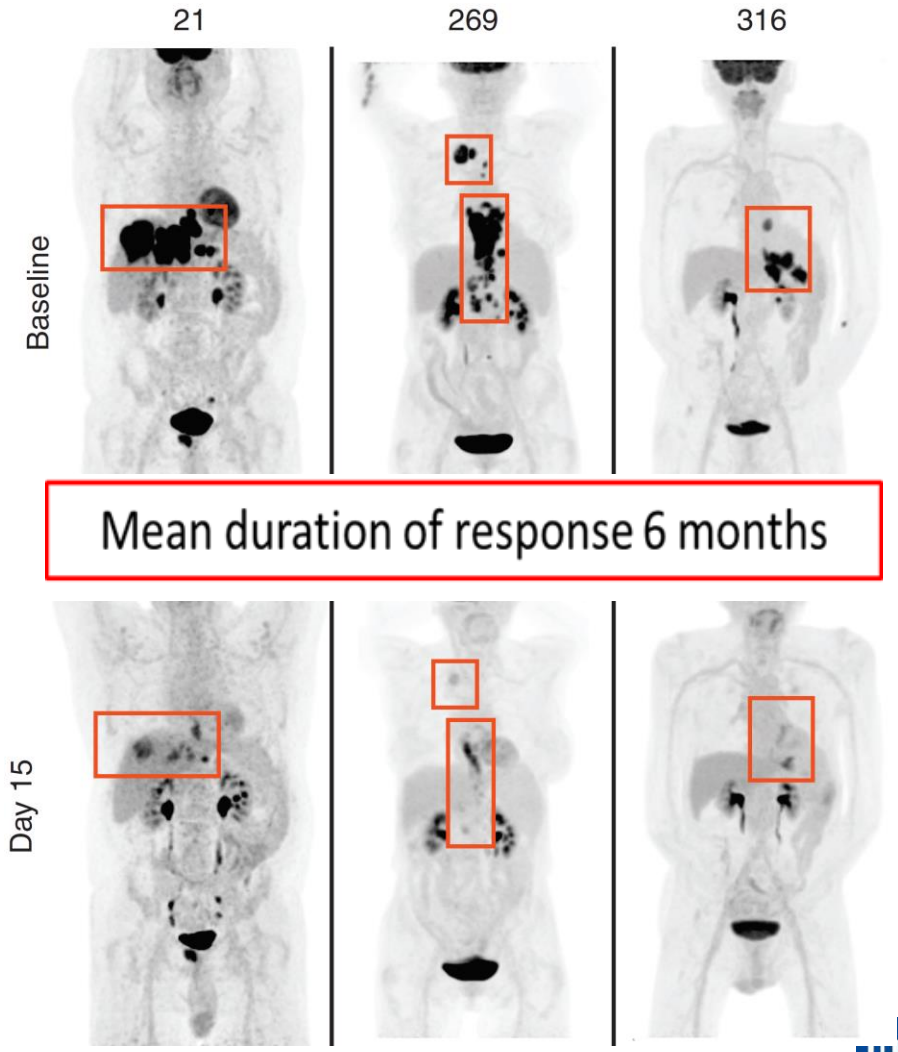
Intratumour heterogeneity in OGCs – the case of FGFR2

- RMH FGFR trial (n=9)
- Refractory, FGFR2 amplified OGC patients treated with AZD4547
- Objective response in 3/9 patients





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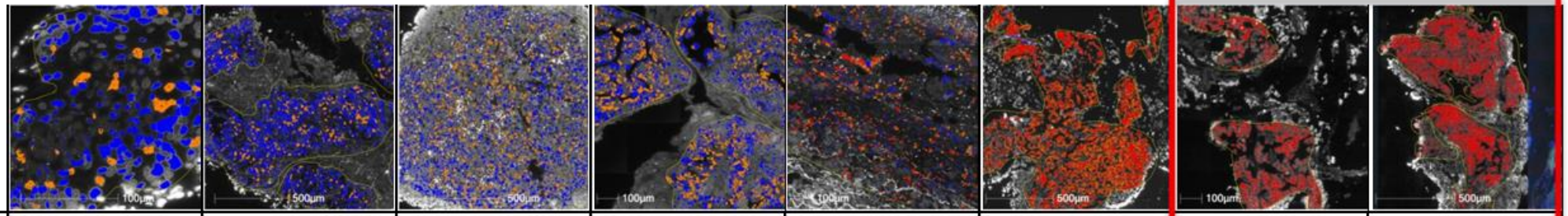
Pearson, Cancer Discov 2016

ULB iris

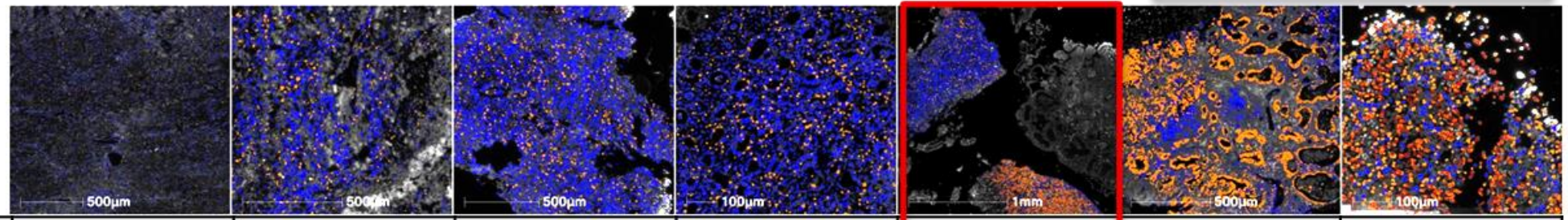
Intratumour heterogeneity in OGCs – the case of FGFR2

RMH FGFR Trial
12/135 (9%) amplified



% amplified cells	14%	27%	28%	37%	44%	94%	99%	99%

AZ SHINE Trial



% amplified cells	10%	16%	16%	24%	52%	59%	70%

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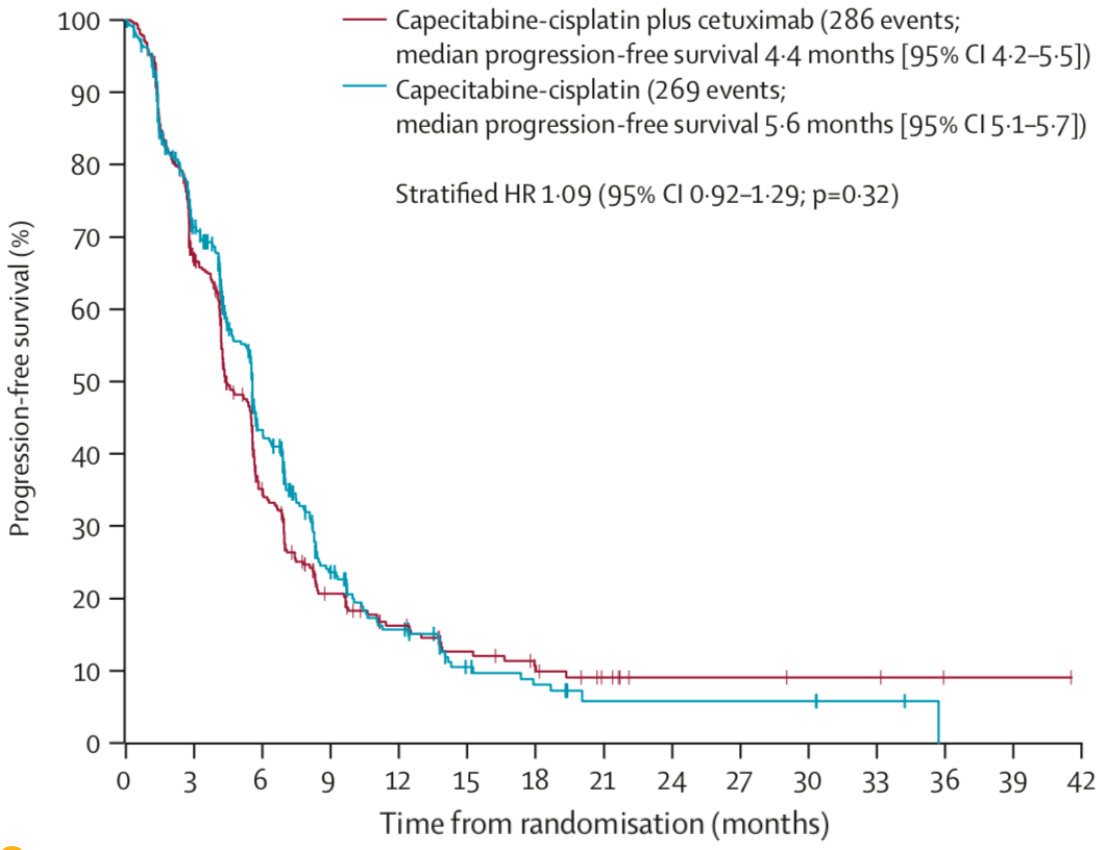
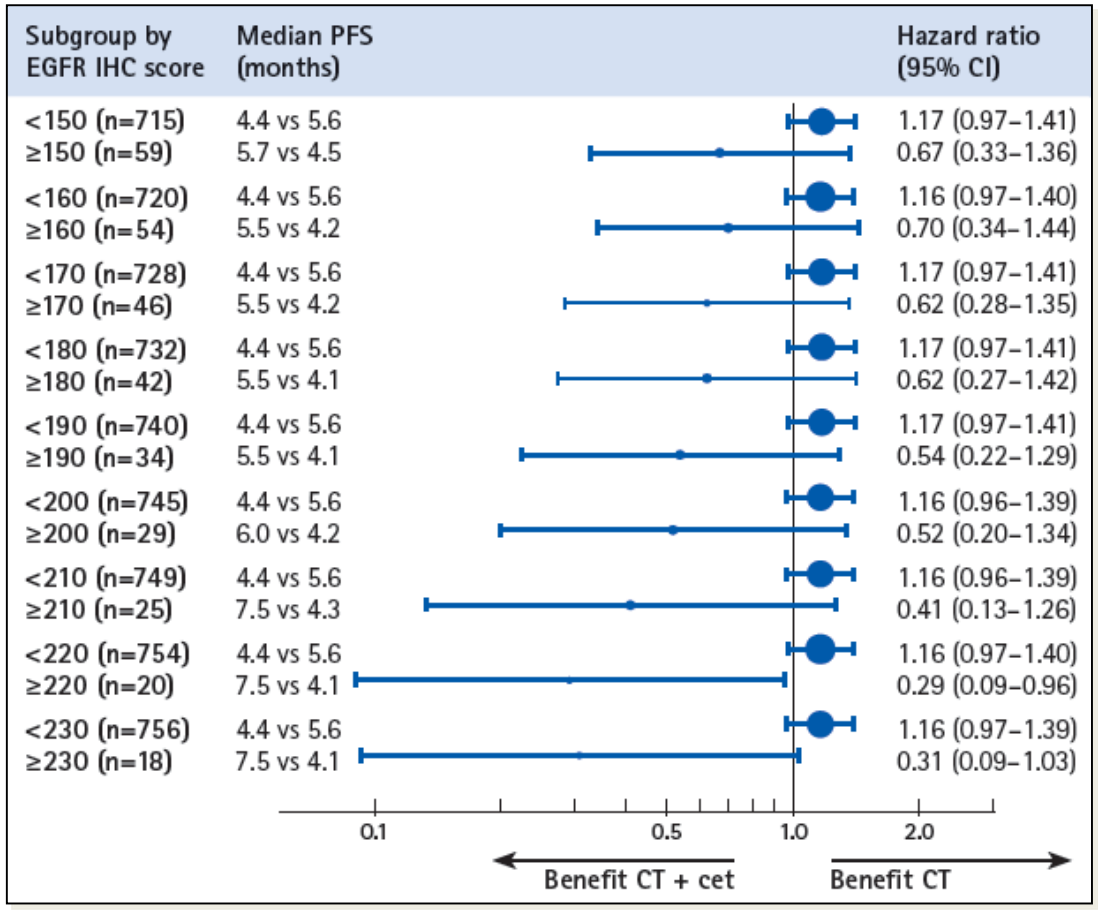
Images courtesy of Neil R Smith

ULB iris

Anti-EGFRs in OGCs: missing out on a good opportunity

Subgroup analysis of the EXPAND trial





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Lordick, Lancet Oncol 2013

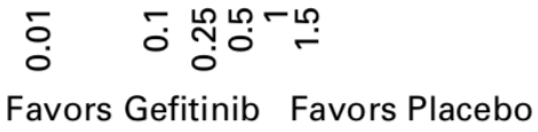
ULB iris

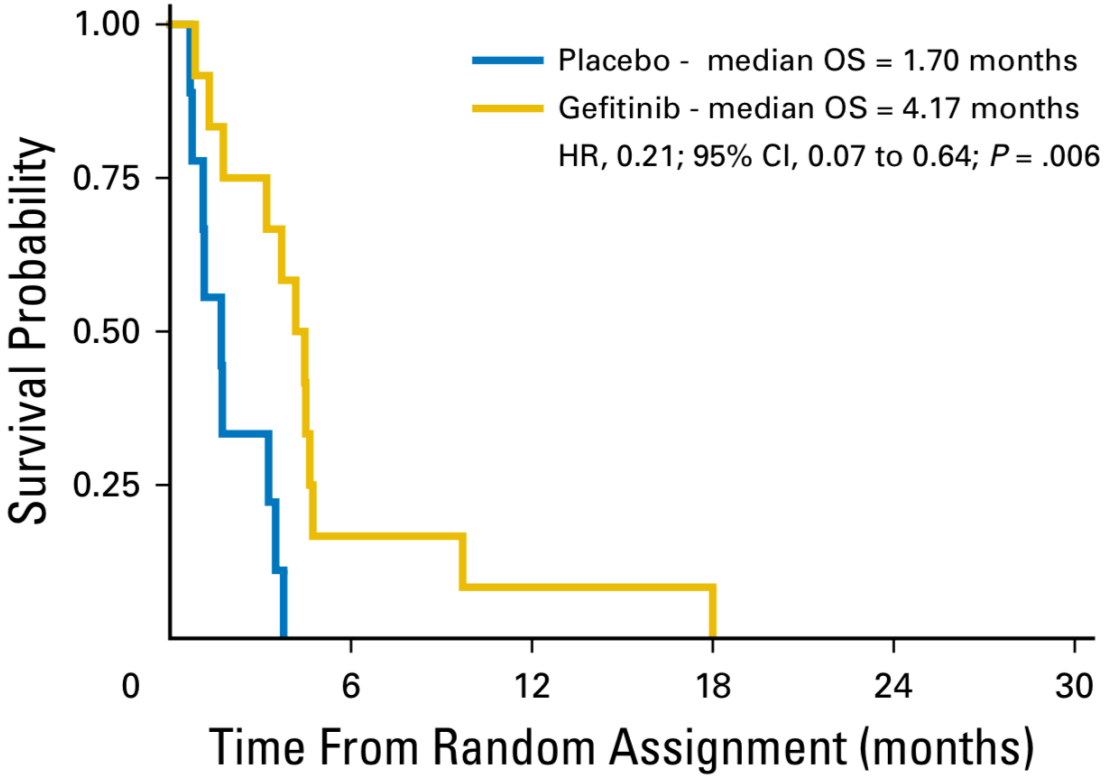
Anti-EGFRs in OGCs: missing out on a good opportunity

Subgroup analysis of the COG trial

Overall Survival

Subgroup	Events/No.	HR (95% CI)
All patients		
Unadjusted	317/340	0.88 (0.70 to 1.10)
EGFR FISH status		
FISH negative	212/233	0.90 (0.69 to 1.18)
FISH positive	57/59	0.59 (0.35 to 1.00)
Classification		
FISH negative	212/233	0.90 (0.69 to 1.18)
Polysomy	36/38	0.66 (0.34 to 1.30)
Amplified	21/21	0.21 (0.07 to 0.64)





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Petty, J Clin Oncol 2017

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Beyond HER-2, VEGF and EGFR

Other randomised phase III trials of targeted therapies in OGCs

Trial	Patients	Setting	Comparison	1° endpoint	Outcome	HR – p value
RILOMET-1	609 (100% MET pos)	1st line	ECX + Rilotumumab ECX	PFS	8.8 10.7	HR 1.34 p=0.003
METGastric	562 (100% MET pos)	1st line	FOLFOX + Onartuzumab FOLFOX	OS	11.0 11.3	HR 0.82 p=0.24
GAMMA-1	432	1st line	FOLFOX + Andecaliximab FOLFOX	OS	12.5 11.8	HR 0.93 p=0.56
GOLD	643 (15% ATM neg)	2nd line	Paclitaxel + Olaparib Paclitaxel	OS	8.8 6.9	HR 0.79 p=0.026
BRIGHTER	714	2nd line	Paclitaxel + Napabucasin Paclitaxel	OS	6.9 7.4	HR 1.01 p=0.86
GRANITE	656	≥2nd line	Everolimus Placebo	OS	5.4 4.3	HR 0.90 P=0.124

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Catenacci, Lancet Oncol 2017; Shah, JAMA Oncol 2017; Shah, ASCO 2018; Bang, Lancet Oncol 2017; Shah, GI ASCO 2019; Ohtsu, J Clin Oncol 2013

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Other randomised phase III trials of targeted therapies in OGCs

Trial	Patients	Setting	Comparison	1° endpoint	Outcome	HR – p value
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Catenacci, Lancet Oncol 2017; Shah, JAMA Oncol 2017; Shah, ASCO 2018; Bang, Lancet Oncol 2017; Shah, GI ASCO 2019; Ohtsu, J Clin Oncol 2013

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Randomised phase II trials of targeted therapies in oGCs: anything promising?

Trial	Patients	Setting	Comparison	1° endpoint	Outcome	HR – p value
STARGATE	195	1st line	CX + Sorafenib CX	PFS	5.6 5.3	HR 0.92 p=0.609
FAST	161 (100% CLDN18.2)	1st line	EOX + Zolbetuximab EOX	PFS	7.5 5.3	HR 0.44 p<0.0005
NCT00982592	124	1st line	FOLFOX + Vismodegib FOLFOX	PFS	7.3 8.0	HR na p=0.64
PaFLO	87	1st line	FLO + Pazopanib FLO	6m PFS	31.4% 25.9%	HR 0.93 p=NS
ZAMEGA	64	1st line	FOLFOX + Aflibercept FOLFOX	6m PFS	60.5% 57.1%	HR 1.11 p=0.72
NCT01238055	107	2nd line	Docetaxel + Sunitinib Docetaxel	TTP	3.9 2.6	HR 0.77 p=0.206
SHINE	71 (FGFR2 amplified)	2nd line	AZD4547 Paclitaxel	PFS	1.8 3.5	HR 1.57 p=NS
INTEGRATE	152	2nd/3° line	Regorafenib Placebo	PFS	2.6 0.9	HR 0.40 p<0.001

Kang, ESMO 2014; Sahin, GI ASCO 2019; Cohen, ASCO 2013; Thuss-Patience, ASCO 2015; Cleary, Cancer 2019; Yi, Br J Cancer 2012; Van Cutsem, Ann Oncol 2017; Pavlakis, J Clin Oncol 2016

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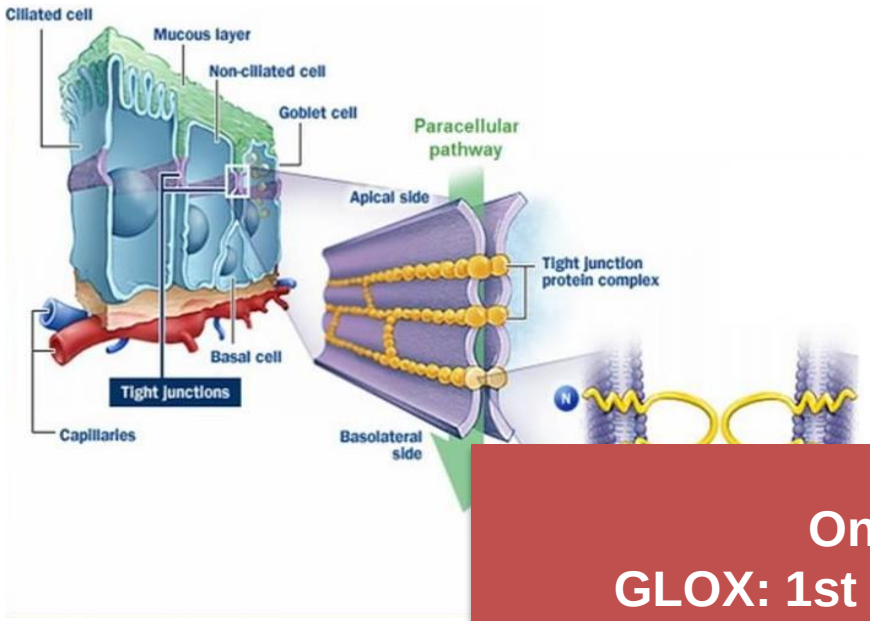
CLDN18.2: a potential new therapeutic target

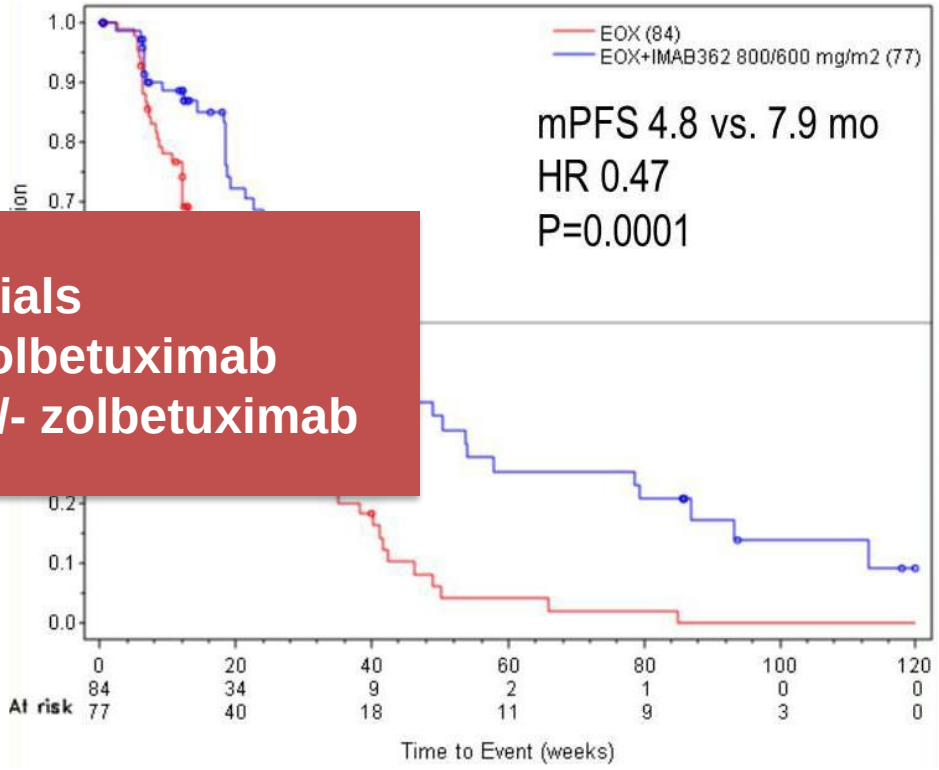


Ongoing phase III trials
GLOX: 1st line CAPOX +/- zolbetuximab
SPOTLIGHT: 1st line FOLFOX +/- zolbetuximab

Gastric tumour type (n=817)	Any positivity	≥2+ in >40% of tumour cells
All	81%	50%
Diffuse	**89%**	**60%**
Intestinal	73%	43%
Mixed	49%	30%

FAST trial

Rand phase II trial 1st line EOX +/- zolbetuximab (n=161)



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Sahin, ASCO 2016; Sahin GI ASCO 2019

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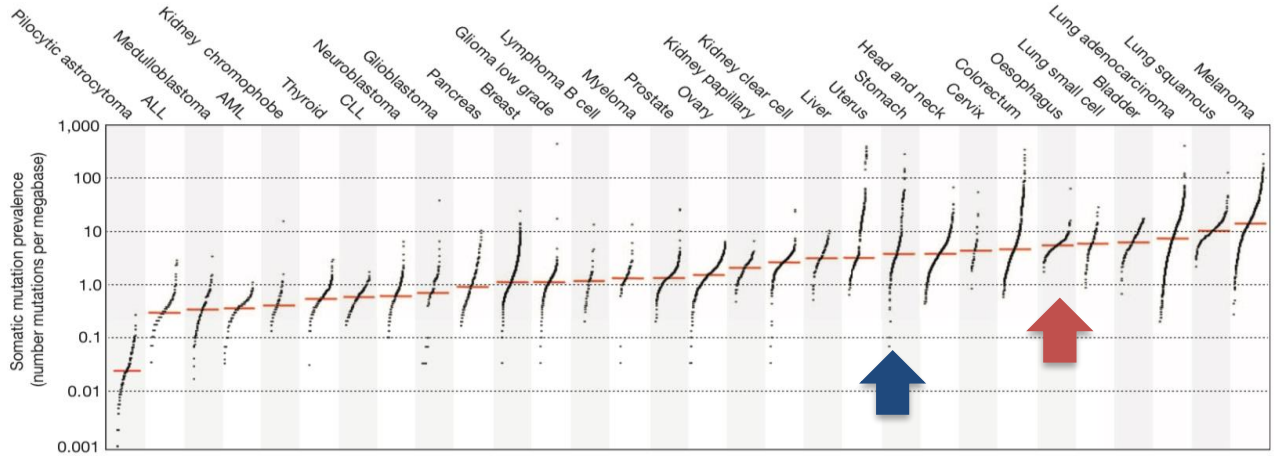
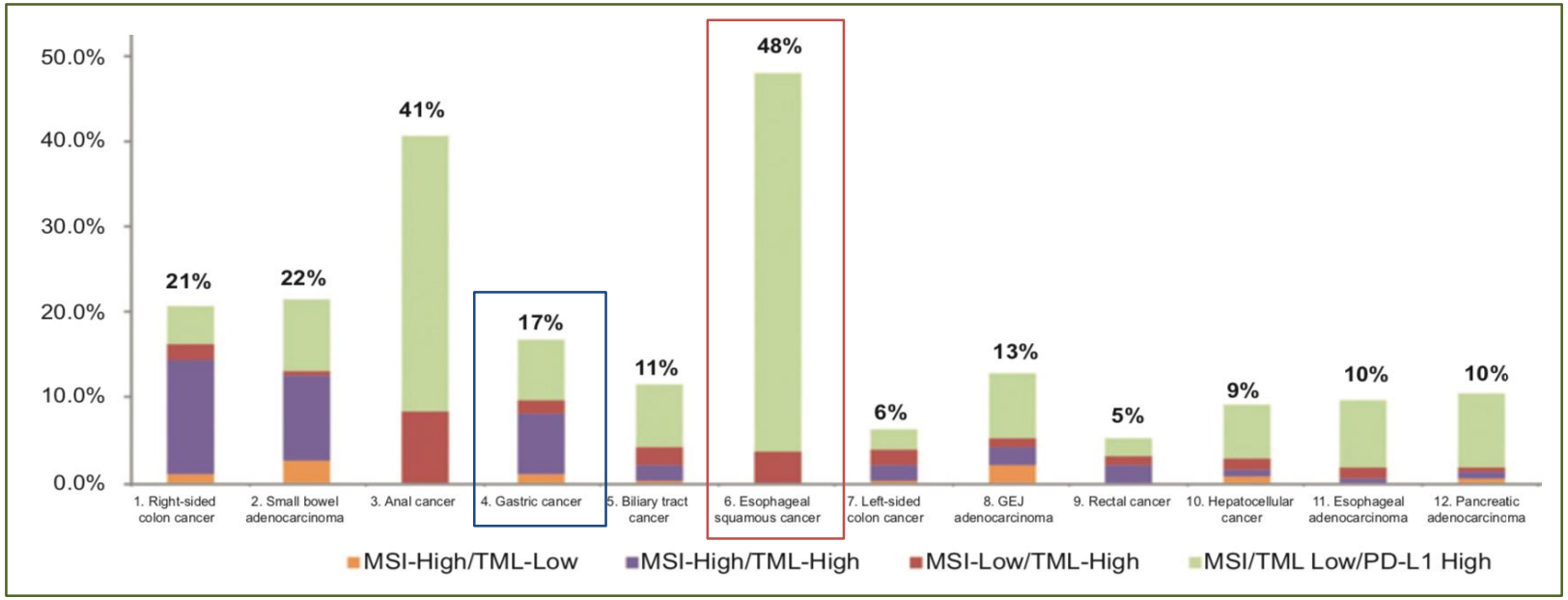
Immunotherapy

Rationale for using/investigating immunotherapy in OGCs





Alexandrov, Nature 2013; Salem, Mol Cancer Res 2018

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Summary of phase III trials of immunotherapy in OGCs

Trial	Setting	Patients	Comparison	Endpoint	Outcome
KEYNOTE-062	1st line	OGJ & gastric (CPS≥1)	Pembro Pembro + CF/X CF/X	PFS/OS	Pembro non inferior to CF/X Pembro non superior to CF/X (CPS≥10) Pembro + CF/X non superior to CF/X
KEYNOTE-061	2nd line	OGJ & gastric (CPS≥1)	Pembro Paclitaxel	PFS/OS	Pembro non superior to Paclitaxel
ATTRACTION-3	2nd line	Oesophageal SCC (PD-L1 unselected)	Nivolumab Paclitaxel/Docetaxel	OS	Nivo superior to Paclitaxel/Docetaxel
KEYNOTE-181	2nd line	Oesophageal & OGJ (PD-L1 unselected)	Pembro Investigator's choice CT	OS	Pembro superior to CT in CPS≥10) Pembro non superior to CT in SCC Pembro non superior to CT in all pts
JAVELIN GASTRIC 300	≥3rd line	OGJ and gastric (PD-L1 unselected)	Avelumab Paclitaxel/Irinotecan	OS	Avelumab non superior to Paclitaxel/Irinotecan
ATTRACTION-2	≥3rd line	OGJ and gastric (PD-L1 unselected)	Nivolumab Placebo	OS	Nivo superior to Placebo

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Tabernero, ASCO 2019; Shitara, Lancet 2018; Kato, Lancet Oncol 2019; Shah, ASCO 2019; Bang, Ann Oncol 2018; Kang, Lancet 2017

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PD-L1 expression and benefit from immunotherapy in OGCs

Trial	Setting	Patients	Comparison	HR Any/CPS<1/ PD-L1<1%	HR CPS≥1/ PD-L1 ≥1%	HR CPS≥10/ PD-L1 ≥10%
KEYNOTE-062	1st line	OGJ & gastric (CPS≥1)	Pembro vs CT Pembro + CT vs CT	- -	0,91 0.85	0,69 0.85
KEYNOTE-061	2nd line	OGJ & gastric	Pembro vs CT	1.20	0.82	0.64
ATTRACTION-3	2nd line	Oesophageal SCC (PD-L1 unselected)	Nivolumab vs CT	0.84	0.69	0.69
KEYNOTE-181	2nd line	Oesophageal & OGJ (PD-L1 unselected)	Pembro vs CT	0.85	-	0.67
JAVELIN GASTRIC 300	≥3rd line	OGJ and gastric (PD-L1 unselected)	Avelumab vs CT	1.22	0.94	-
ATTRACTION-2	≥3rd line	OGJ and gastric (PD-L1 unselected)	Nivolumab vs BSC	0.72	0.51	-

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Tabernero, ASCO 2019; Shitara, Lancet 2018; Kato, Lancet Oncol 2019; Shah, ASCO 2019; Bang, Ann Oncol 2018; Kang, Lancet 2017

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PD-L1 expression and benefit from immunotherapy in OGCs

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Tabernero, ASCO 2019; Shitara, Lancet 2018; Kato, Lancet Oncol 2019; Shah, ASCO 2019; Bang, Ann Oncol 2018; Kang, Lancet 2017

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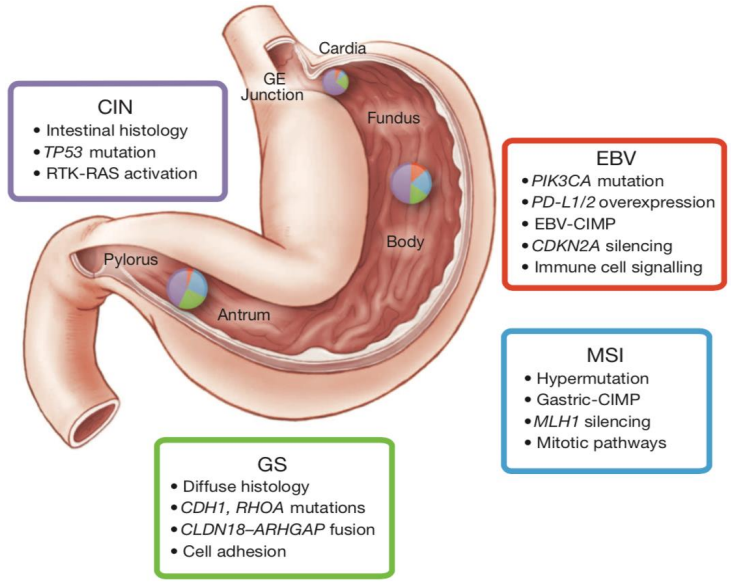
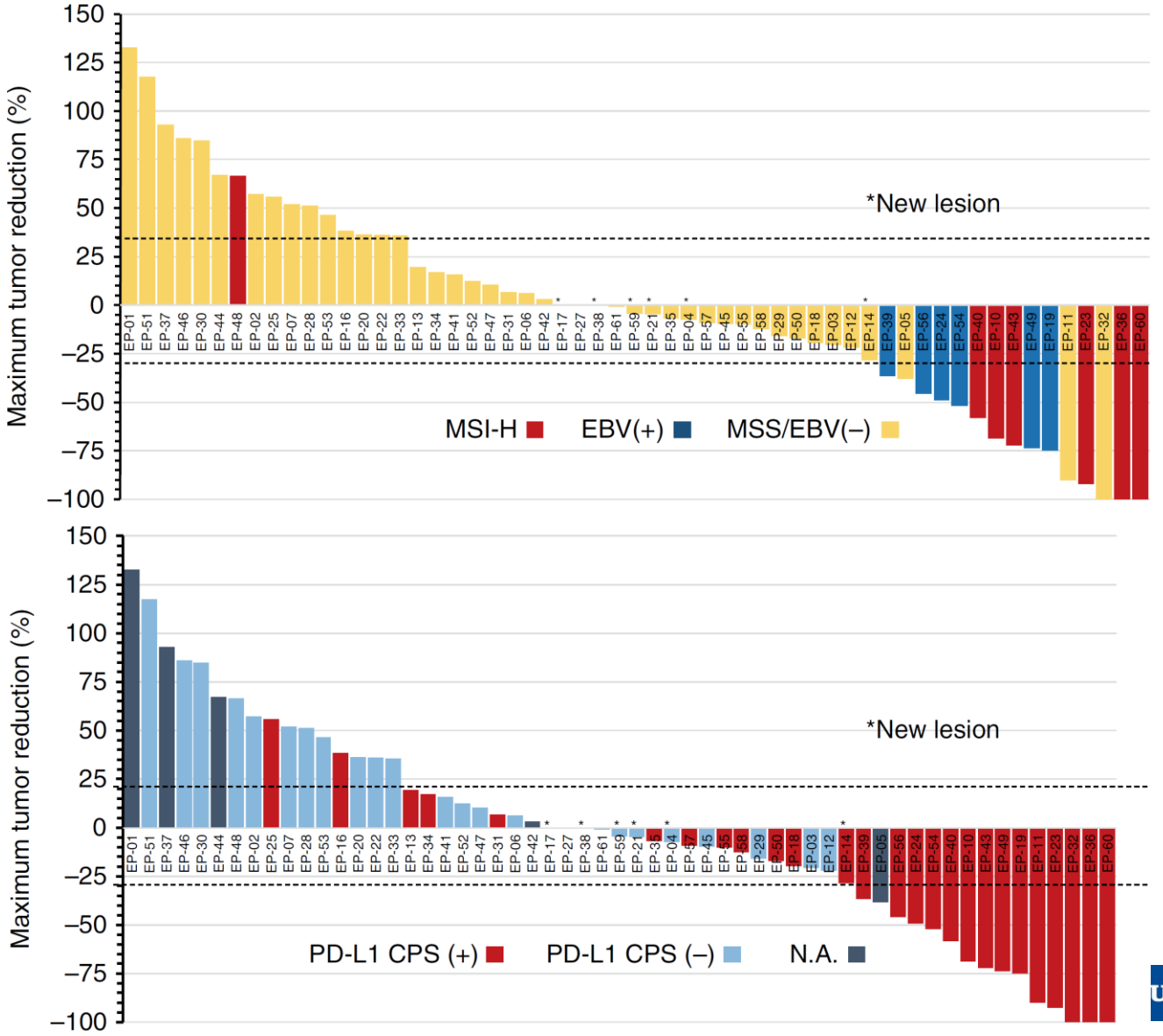
Better biomarkers for immunotherapy in OGCs





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Kim, Nat Med 2018

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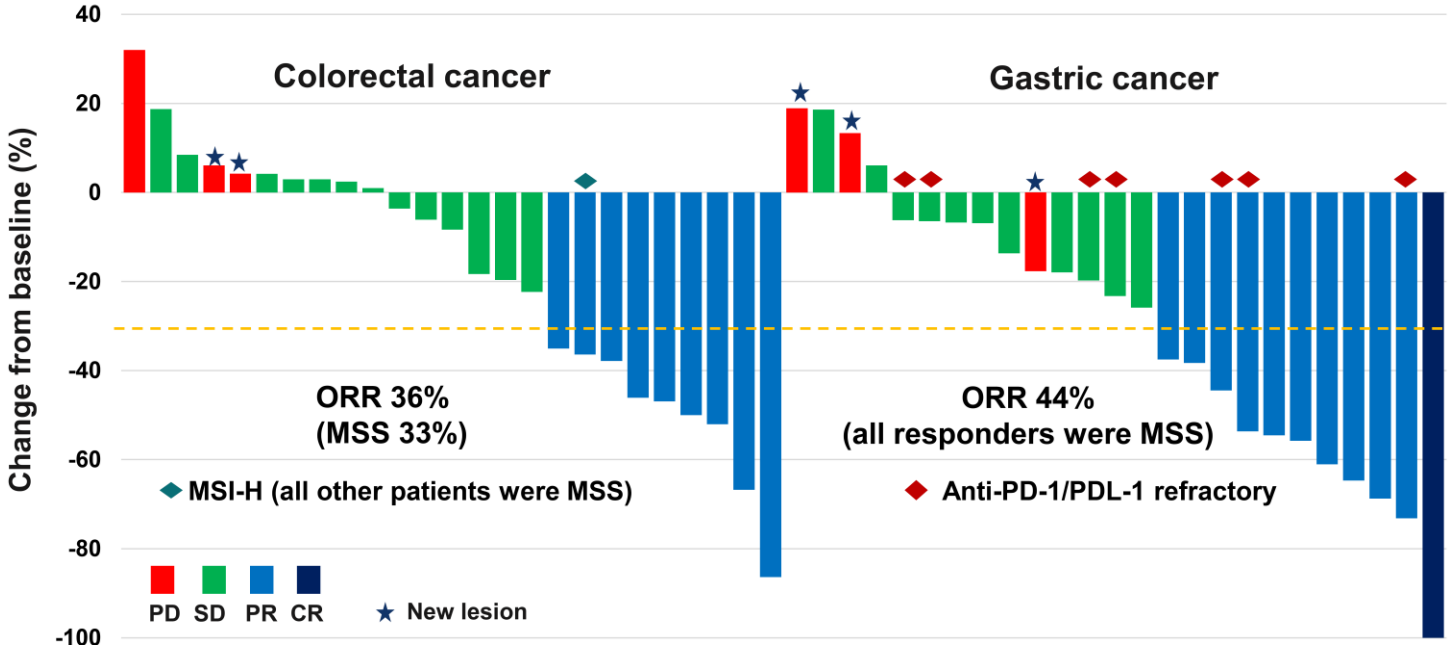
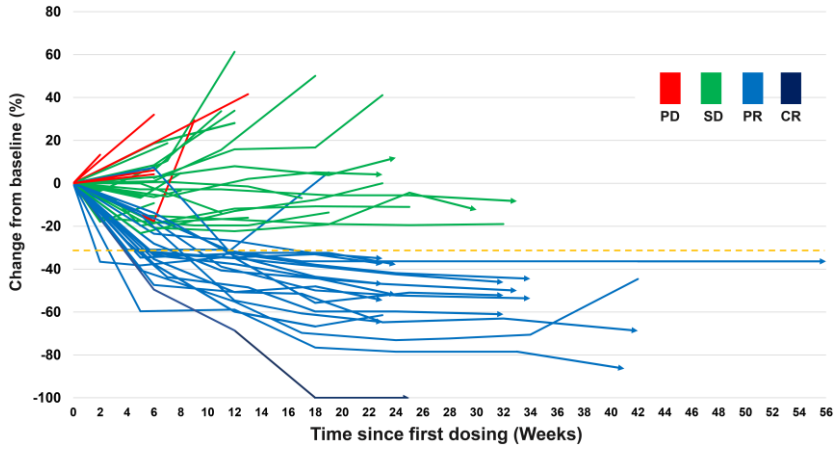
Combination treatment: anti-angiogenic + anti-PD-1 agents

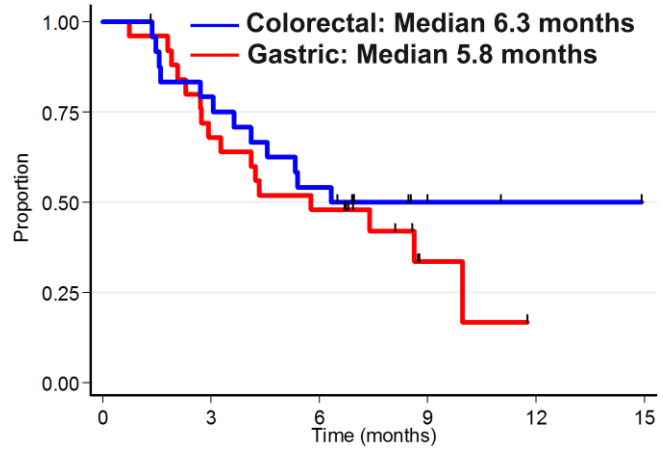
Potentially extending the benefit of immunotherapy to MSS tumours

REGONIVO/EPOC 1603 trial

- Phase I trial in Japan (n=50)
- Gastric and colorectal cancer
- 98% MSS
- Median prior therapies: 3 (2-8)
- 98% had prior anti-angiogenic therapy
- 14% had prior PD-1/PD-L1 inhibitors







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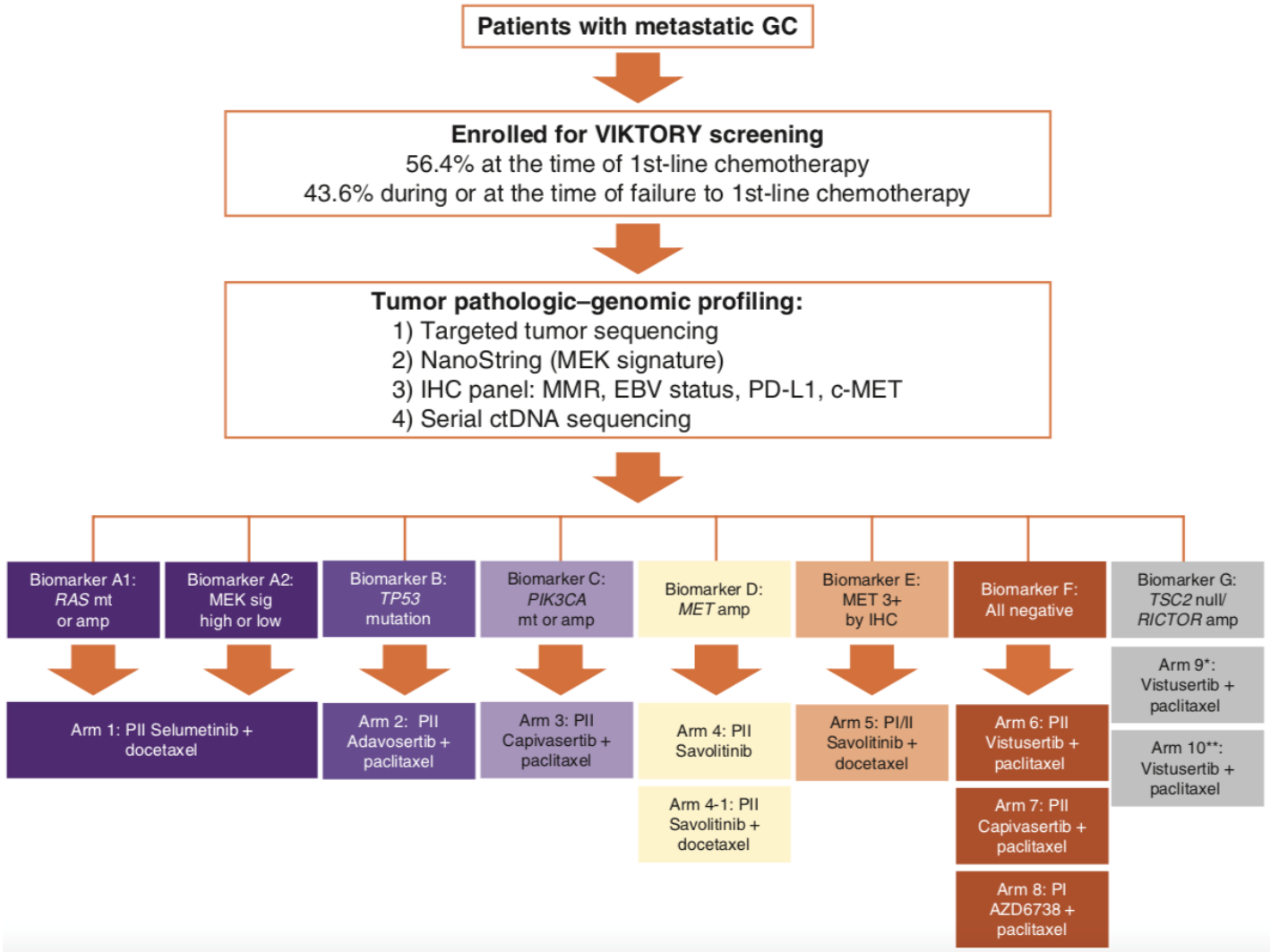
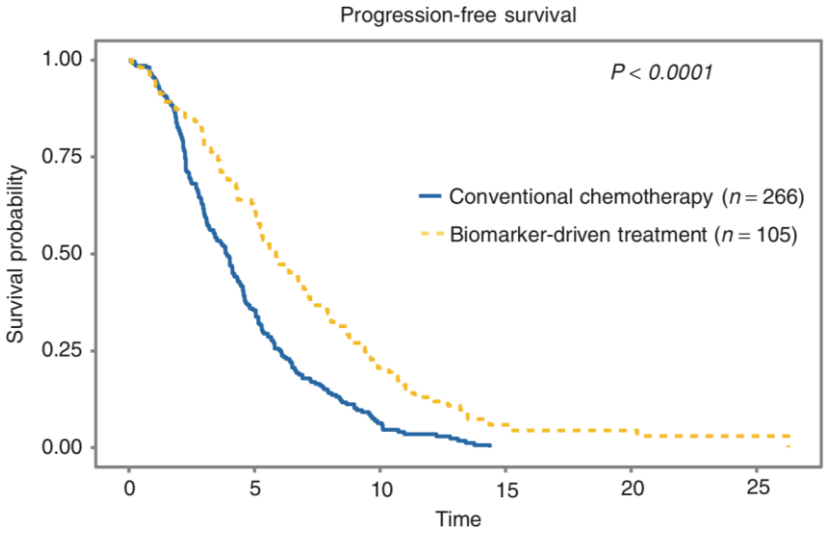
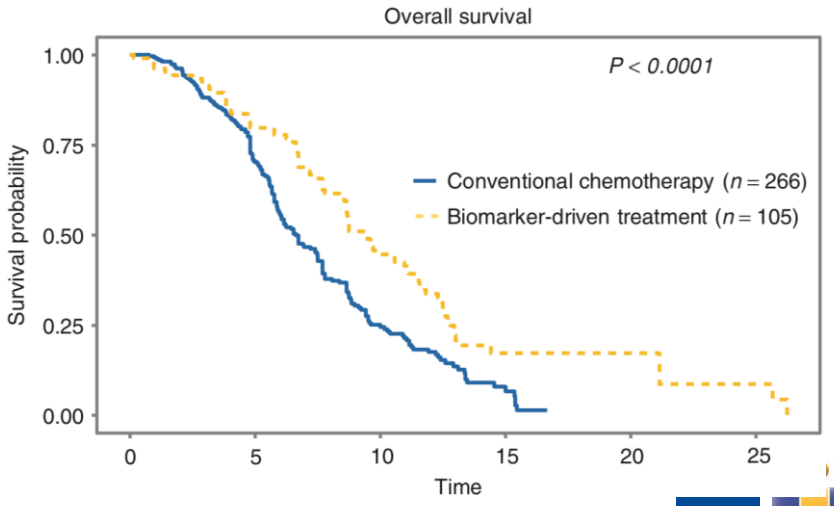
Fukuoka, ASCO 2019

The ideal scenario

Biomarker screening and molecularly matched therapies







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Lee, Cancer Discov 2019

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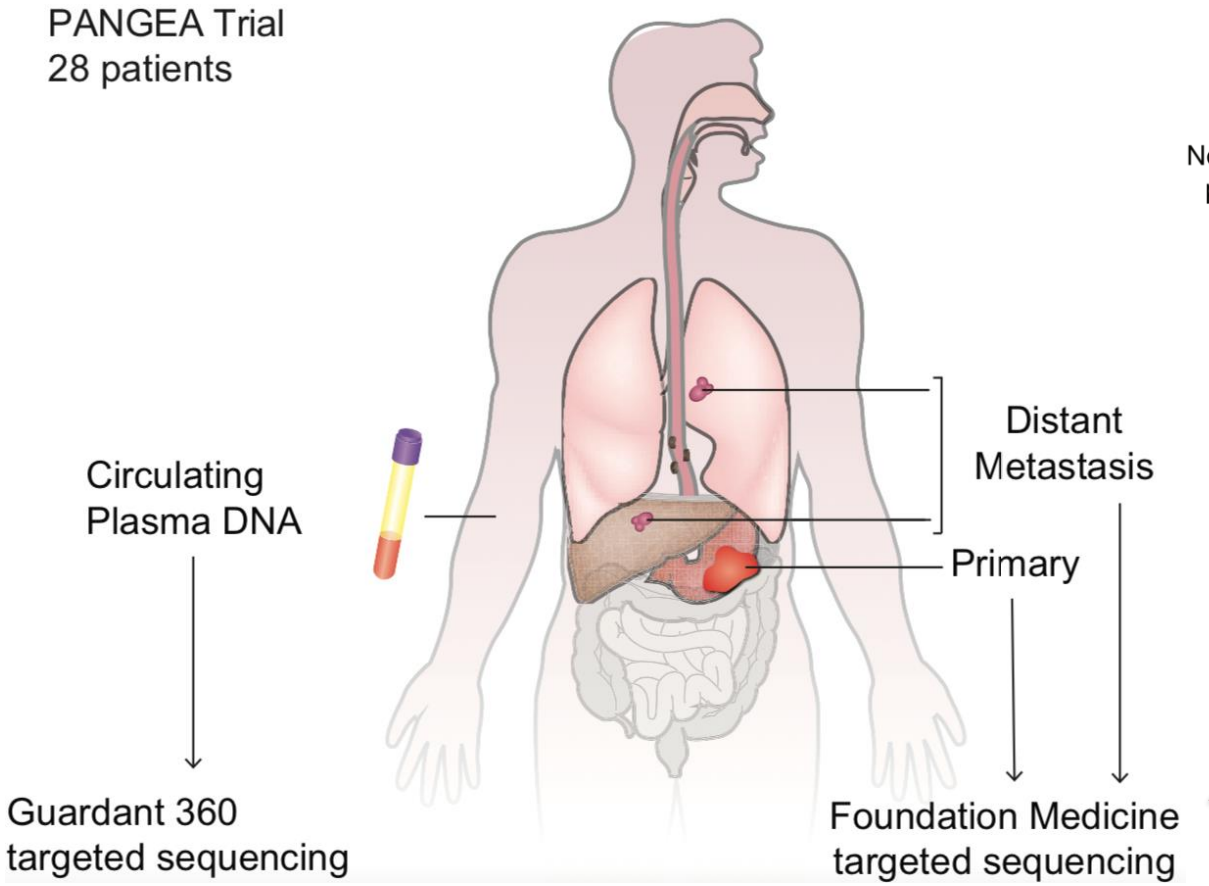
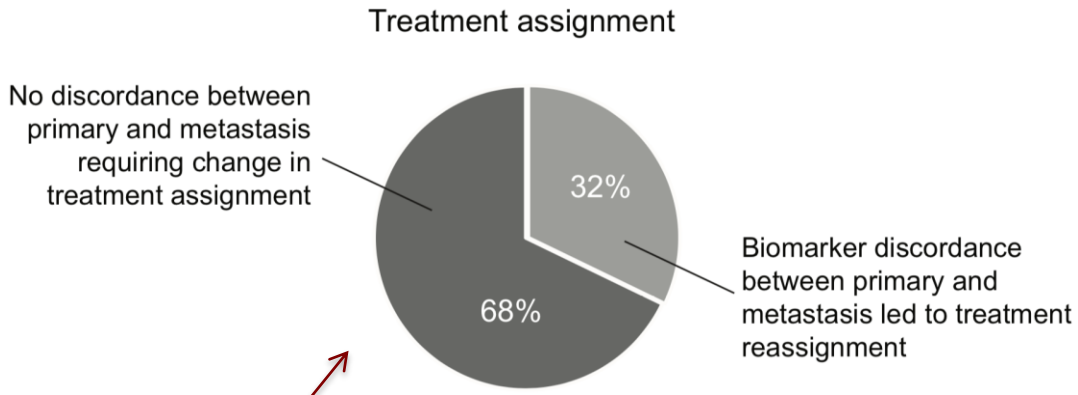
Inter-tumoral lesions genomic heterogeneity

A cautionary note and useful insight for future drug development and trial designs





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Pectasides, Cancer Discov 2017

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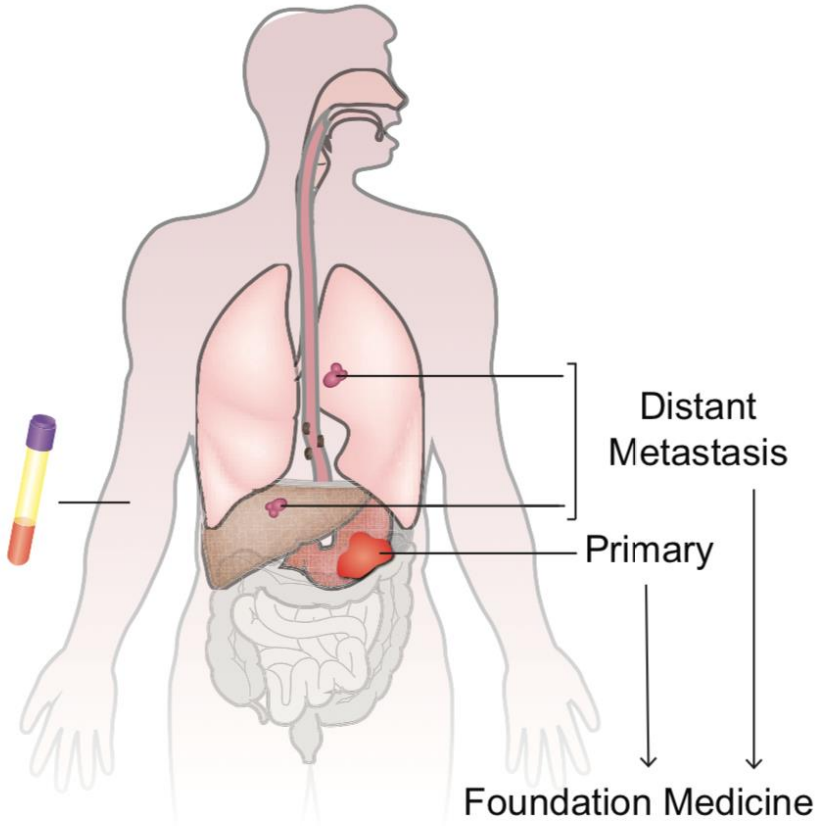
Inter-tumoral lesions genomic heterogeneity

Genomic profiling of ctDNA may help to address inter-tumoral lesion heterogeneity

PANGEA Trial
28 patients



			primary	metastasis	cfDNA
PANGEA 1	TP53	NGS	R175H	R175H	R175H
	EGFR	MS	POS		
	MET	NGS	NEG	AMP	AMP
PANGEA 2	TP53	NGS	R175H	R175H	R175H
	KRAS	NGS	AMP	AMP	AMP
	ERBB2	NGS	NEG	AMP	AMP
	ERBB2	IHC/FISH	NEG	POS	
PANGEA 3	TP53	NGS	NGR175H	R175H	R175H
	ERBB2	NGS	AMP	NEG	NEG
	ERBB2	IHC/FISH	POS	NEG	NEG
	EGFR	NGS	AMP	AMP	AMP
	EGFR	IHC/FISH	POS	POS	
PANGEA 4	TP53	NGS	R273C	R273C	R273C
	EGFR	NGS		AMP	AMP
PANGEA 5	TP53	NGS	R282G	R282G	R282G
	ERBB2	NGS	NEG	AMP	AMP
	ERBB2	IHC/FISH	NEG	AMP	AMP
PANGEA 6	TP53	NGS	C176F		C176F
	FGFR2	NGS	NEG		AMP
PANGEA 7	TP53	NGS	N239D	N239D	N239D
	ERBB2	NGS	AMP	NEG	NEG
	ERBB2	IHC/FISH	POS	NEG	
	FGFR2	NGS	NEG	AMP	AMP
PANGEA 8	EGFR	NGS	POS	NEG	NEG
	EGFR	MS		POS	
PANGEA 9	ARID1A	NGS	R1335insQ	R1335insQ	R1335insQ
	TP53	NGS	R342*	NEG	R342*
	EGFR	NGS	AMP	NEG	NEG
	EGFR	NGS	FUSION	NEG	L858M

In 88% of cases where discrepant genomic alterations between primary tumour and metastasis were found, results were concordant between metastasis and ctDNA

missense mutation amplification/overexpression
insertion fusion indeterminate
NGS: next generation sequencing MS: mass spectometry
IHC: immunohistochemistry FISH: fluorescent in situ hybridization

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Pectasides, Cancer Discov 2017

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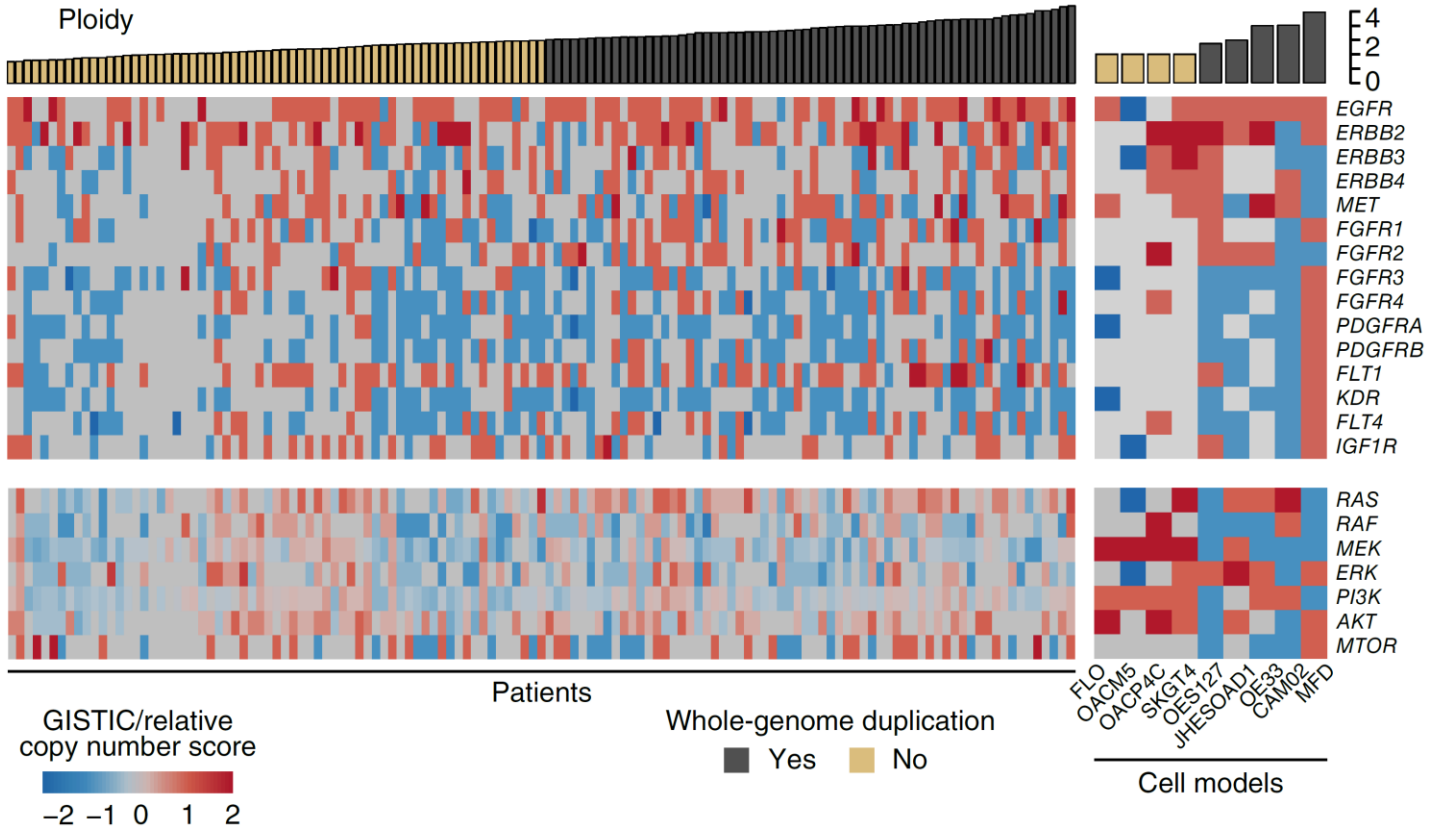
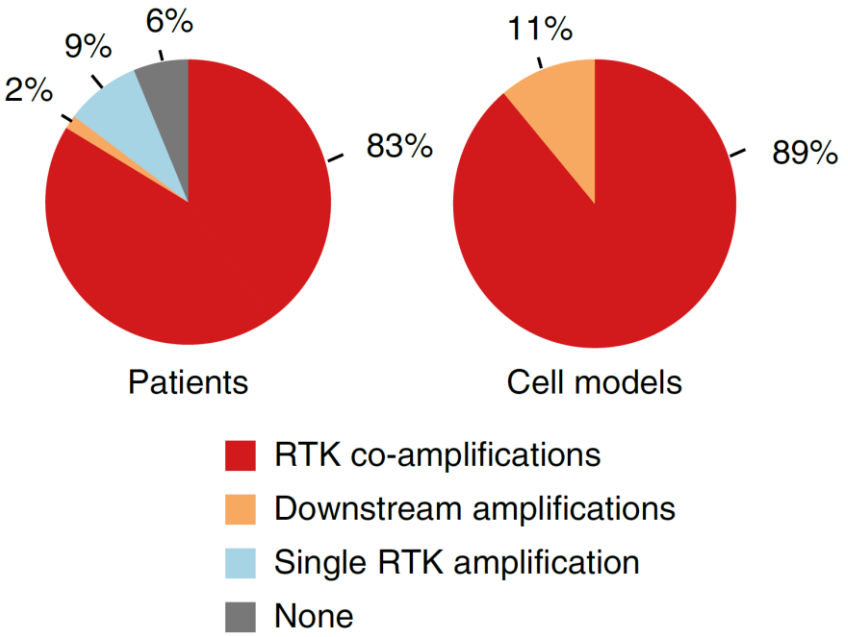
The genomic complexity of OGCs

Another cautionary note and useful insight for future drug development and trial designs





Co-amplification of RTKs and/or downstream mitogenic activation is almost ubiquitous!

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Conclusions

- Targeted therapies are an important component of the therapeutic algorithm of advanced OGCs and will possibly shape the treatment paradigm of early stage tumours
- Lack of optimal, biomarker-driven patient selection, intratumour heterogeneity and genomic complexity of OGCs are likely responsible for the failure of unsuccessful trials and should be kept in mind when designing future studies
- ctDNA-based genomic profiling and combination target treatment may represent successful strategies to pursue in future clinical trials

Thanks

Questions?