What lessons can we learn from targeting cMET and IGFR in gastrointestinal cancers?

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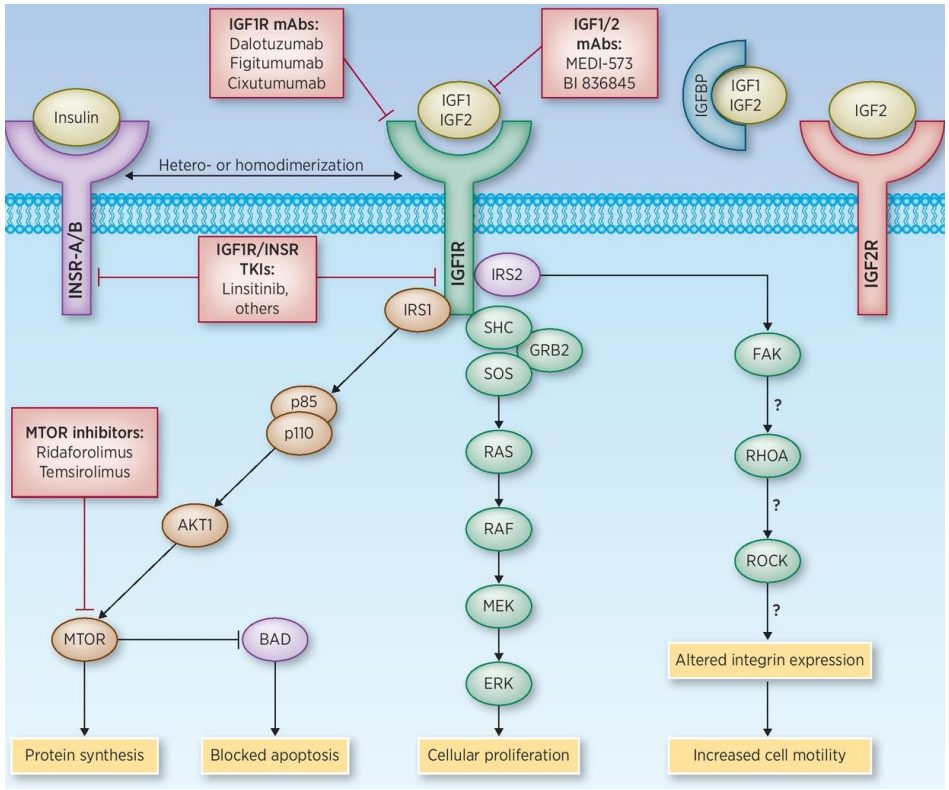
NHS
National Institute for Health Research

Disclosure

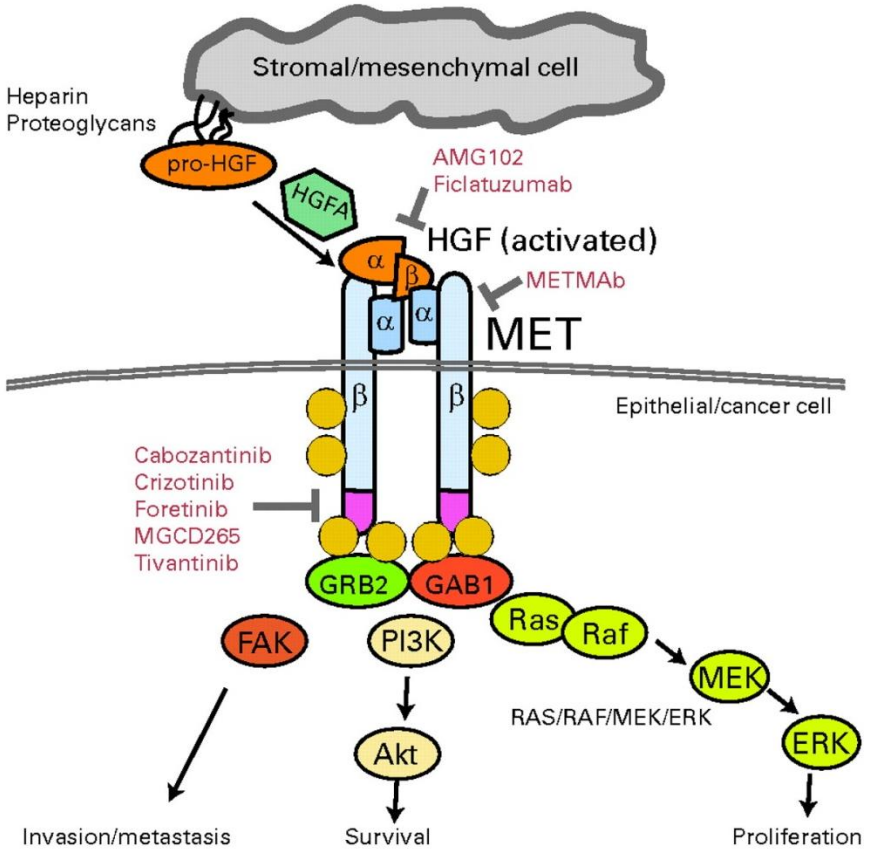
- Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, Merck Serono, Gilead Science
- Research funding: Sanofi Oncology, Roche, Merck-Serono, Novartis
- Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly, Bayer

IGF-1R and MET signalling pathways

IGF-1R



MET



Iams and Lovly Clin Cancer Res 2015;
Appleman et al J Clin Oncol 2011

Similarities and differences of IGFR and MET targeted therapy

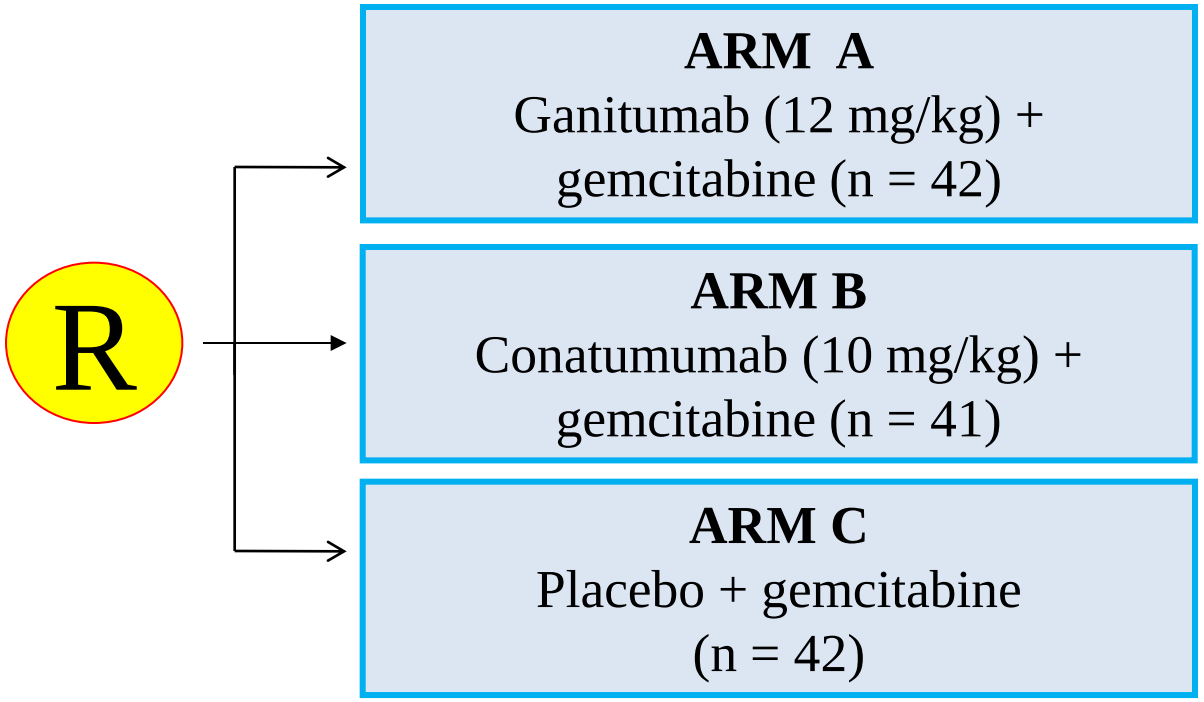
Similarities

- Upstream of MAPK and PI3K-AKT-mTOR pathways
- Abundant preclinical data to support targeting these pathways
- Resistance mechanisms of existing therapy for GI cancers
- Multiple phase II and III trials conducted in many solid tumour types
- Testing in combination with cytotoxic chemotherapy or other seemingly rational targeted therapy (with almost universal failures)

Differences

- IGFR phase III trials
  - no patient or biomarker pre-selection
  - Biomarker retrospectively explored
- cMET phase III trials
  - Biomarker pre-specified
  - Validity of biomarker cutoff retrospectively explored

Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer



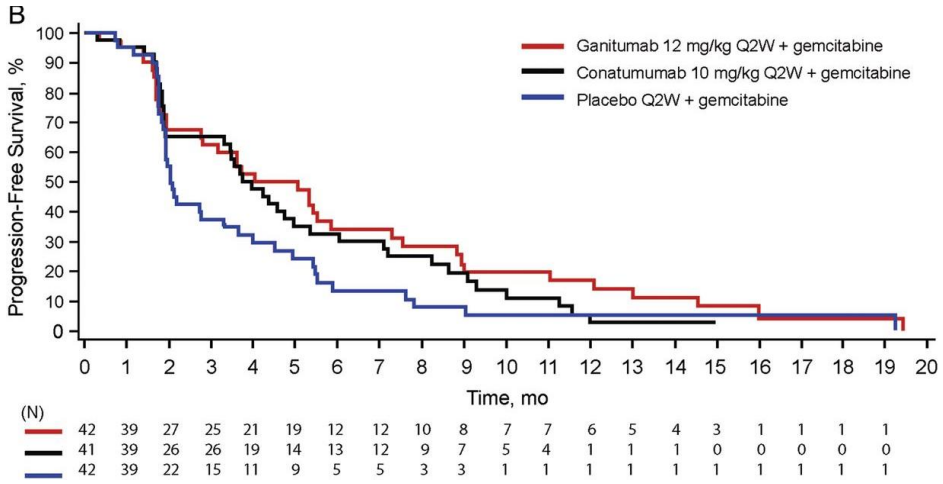
Stratification factor:
ECOG PS 0 vs 1

Gemcitabine: 1000 mg/m^2 IV, Day 1, 8 and 15
Q4 weeks

Kindler et al Ann Oncol 2012

Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer

Progression free survival



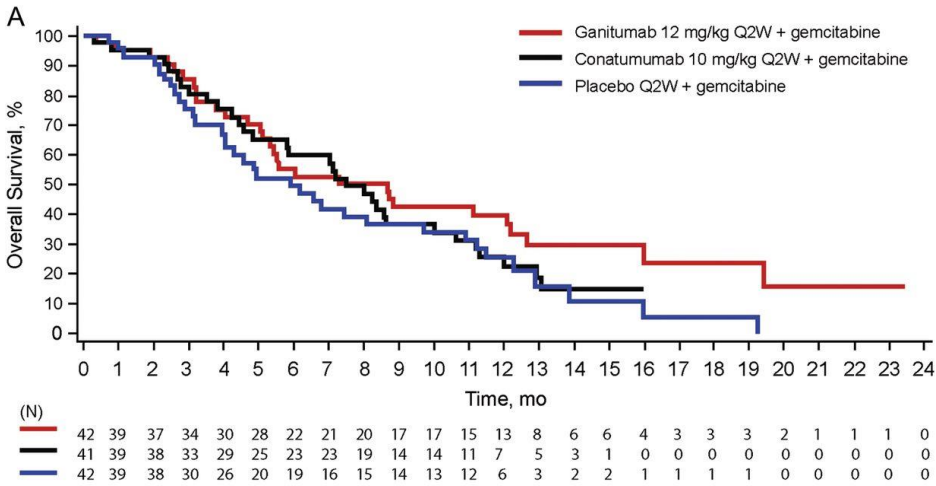
Gem + ganitumumab Gem + placebo

mPFS 5.1 months 2.1 months

Hazard Ratio 0.65 (95% CI: 0.41, 1.04)

p=0.072

Overall survival



Gem + ganitumumab Gem + placebo

mOS 8.7 months 5.9 months

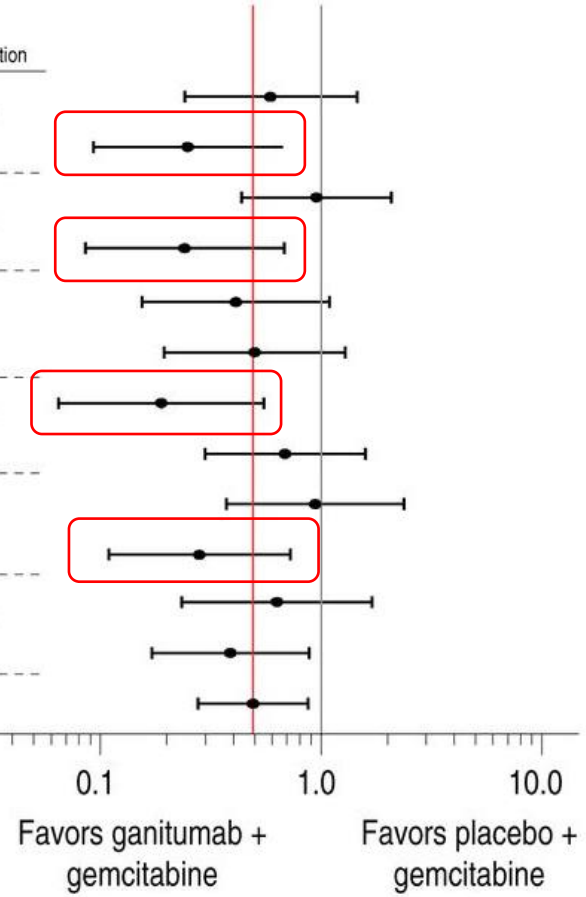
Hazard Ratio 0.67 (95% CI: 0.41, 1.12)

p=0.12

Kindler et al Ann Oncol 2012

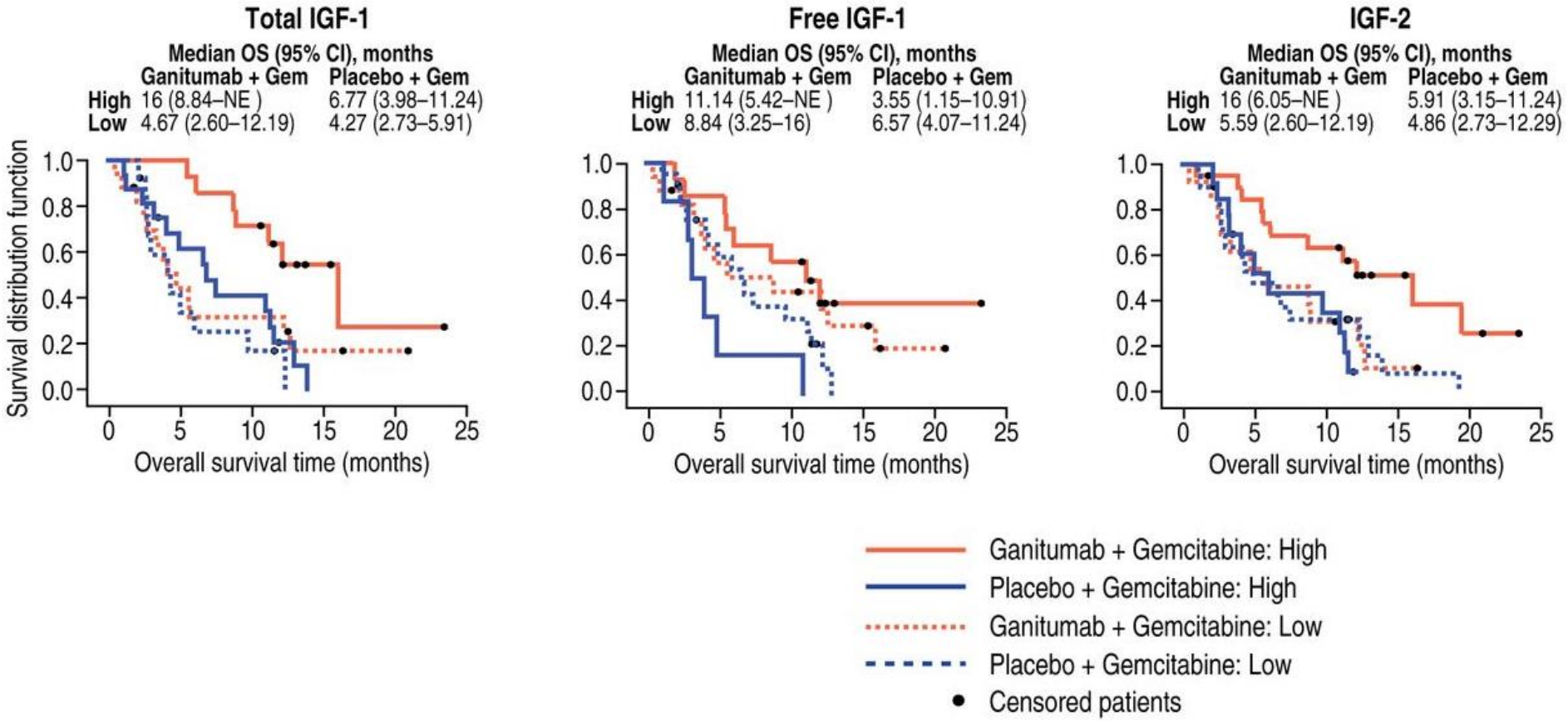
Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer

Baseline biomarker	Biomarker subgroup	Number of Patients (Number of events): Ganitumab + Gemcitabine	Placebo + Gemcitabine	HR (95% CI)	*P*	$P_{interaction}$
Total IGF-1	Low (≤105)	17 (13)	13 (11)	0.59 (0.24–1.43)	0.24	0.27
	High (>105)	14 (7)	16 (14)	0.25 (0.09–0.67)	0.006	
IGF-2	Low (≤1800)	13 (11)	20 (17)	0.95 (0.44–2.08)	0.91	0.05
	High (>1800)	20 (11)	13 (11)	0.24 (0.09–0.68)	0.007	
IGFBP-1	Low (≤28)	15 (7)	13 (11)	0.41 (0.16–1.09)	0.07	0.92
	High (>28)	16 (13)	13 (11)	0.50 (0.19–1.29)	0.15	
IGFBP-2	Low (≤158)	16 (8)	13 (11)	0.19 (0.07–0.55)	0.002	0.38
	High (>158)	14 (11)	15 (13)	0.69 (0.30–1.59)	0.38	
IGFBP-3	Low (≤2)	15 (12)	14 (12)	0.94 (0.37–2.38)	0.90	0.11
	High (>2)	16 (8)	15 (13)	0.28 (0.11–0.73)	0.009	
IGFBP-4	Low (≤43)	14 (8)	19 (15)	0.63 (0.23–1.70)	0.36	0.76
	High (>43)	19 (14)	14 (13)	0.39 (0.17–0.88)	0.02	
Patients with data for ≥1 biomarker		34 (22)	33 (28)	0.49 (0.28–0.87)	0.02	



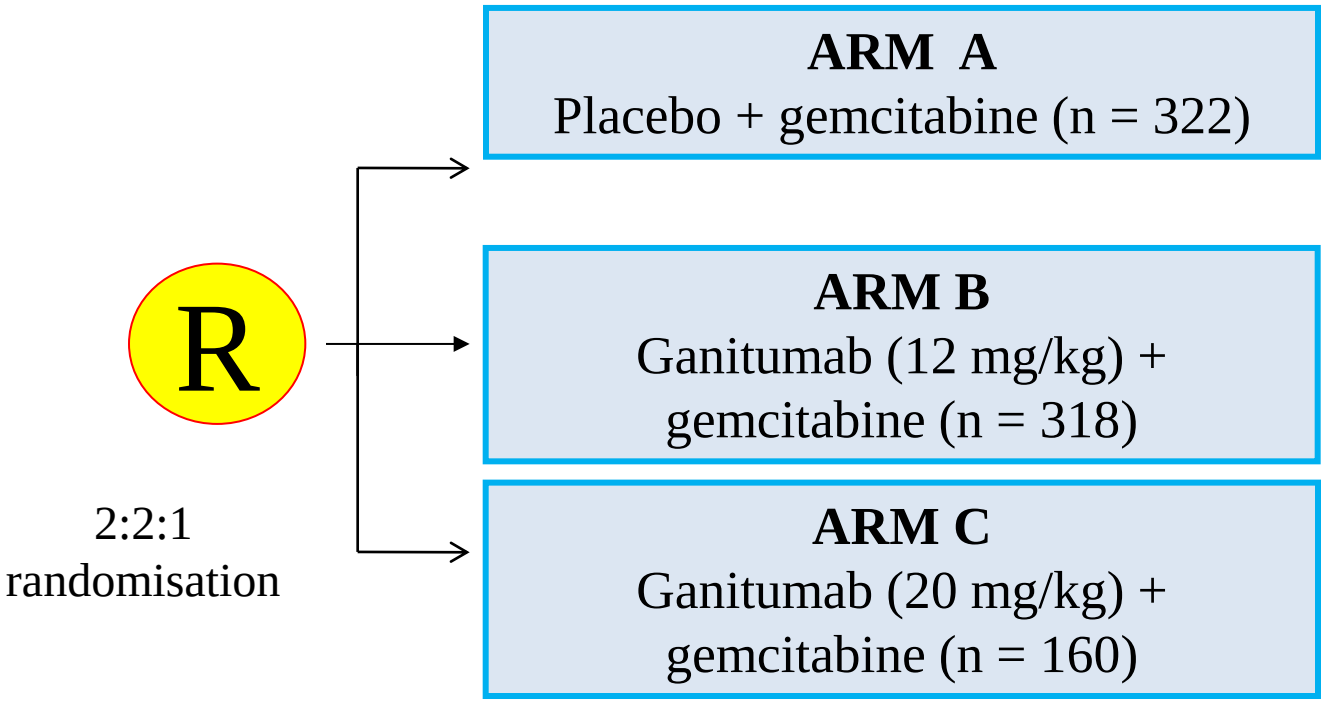
McCaffery et al Clin Cancer Res 2013

Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer



McCaffery et al Clin Cancer Res 2013

Randomised phase III study of gemcitabine ± ganitumab at 2 different doses in metastatic pancreatic cancer (GAMMA)



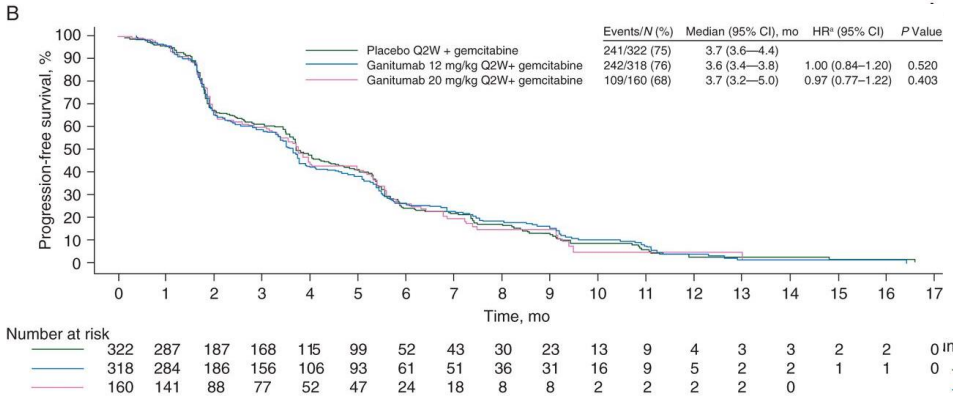
Stratification factors:
ECOG PS 0 vs 1
Liver mets yes vs. no
Geographical regions

Gemcitabine: 1000 mg/m^2 IV, Day 1, 8 and 15
Q4 weeks

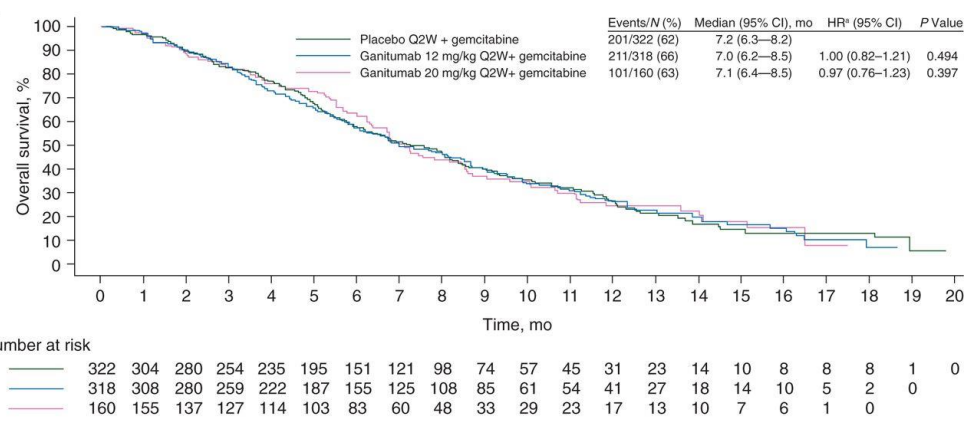
Fuchs et al Ann Oncol 2015

Randomised phase III study of gemcitabine ± ganitumab at 2 different doses in metastatic pancreatic cancer (GAMMA)

Progression free survival



Overall survival



	Median PFS	HR (95%CI)	p
Placebo	3.7 months		
Ganitumb (12mg/kg)	3.6 months	1.00 (0.84,1.20)	0.520
Ganitumab (20mg/kg)	3.7 months	0.97 (0.77-1.22)	0.403

	Median OS	HR (95%CI)	p
Placebo	7.2 months		
Ganitumb (12mg/kg)	7.0 months	1.00 (0.82,1.21)	0.494
Ganitumab (20mg/kg)	7.1 months	0.97 (0.76-1.23)	0.397

Fuchs et al Ann Oncol 2015

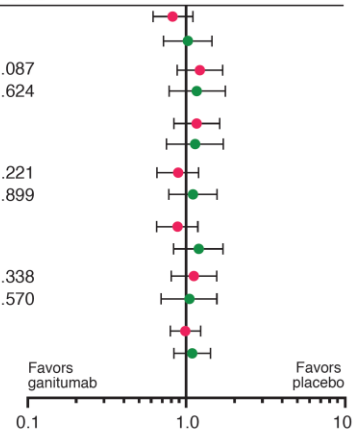
Randomised phase III study of gemcitabine ± ganitumab in metastatic pancreatic cancer (GAMMA)

Overall survival

Progression free survival

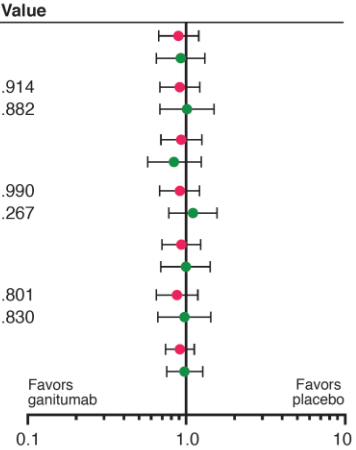
A

Baseline Biomarker	Biomarker Subgroup	Ganitumab Dose	Patients Receiving Ganitumab, *n* (Events, *n*)	Patients Receiving Placebo, *n* (Events, *n*)	HR	95% CI	*P* Value	Interaction *P* Value
IGF-1	Low (≤74 ng/mL)	12 mg/kg	111 (81)	121 (93)	0.82	0.61–1.10	.189	
		20 mg/kg	61 (46)		1.02	0.71–1.45	.931	
	High (>74 ng/mL)	12 mg/kg	115 (77)	122 (67)	1.22	0.87–1.69	.246	.087
		20 mg/kg	52 (35)		1.17	0.78–1.77	.448	.624
IGFBP-2	Low (≤1706 ng/mL)	12 mg/kg	124 (80)	114 (64)	1.17	0.84–1.63	.358	
		20 mg/kg	53 (36)		1.14	0.75–1.72	.537	
	High (>1706 ng/mL)	12 mg/kg	102 (78)	129 (96)	0.88	0.66–1.19	.423	.221
		20 mg/kg	60 (45)		1.09	0.77–1.56	.622	.899
IGFBP-3	Low (≤1.95 mg/L)	12 mg/kg	111 (80)	124 (92)	0.88	0.65–1.19	.397	
		20 mg/kg	56 (45)		1.19	0.83–1.71	.332	
	High (>1.95 mg/L)	12 mg/kg	115 (78)	119 (68)	1.12	0.81–1.55	.505	.338
		20 mg/kg	57 (36)		1.04	0.69–1.57	.839	.570
ESCIPA Analysis Set		12 mg/kg	226 (158)	243 (160)	0.98	0.79–1.23	.884	
		20 mg/kg	113 (81)		1.09	0.83–1.43	.528	



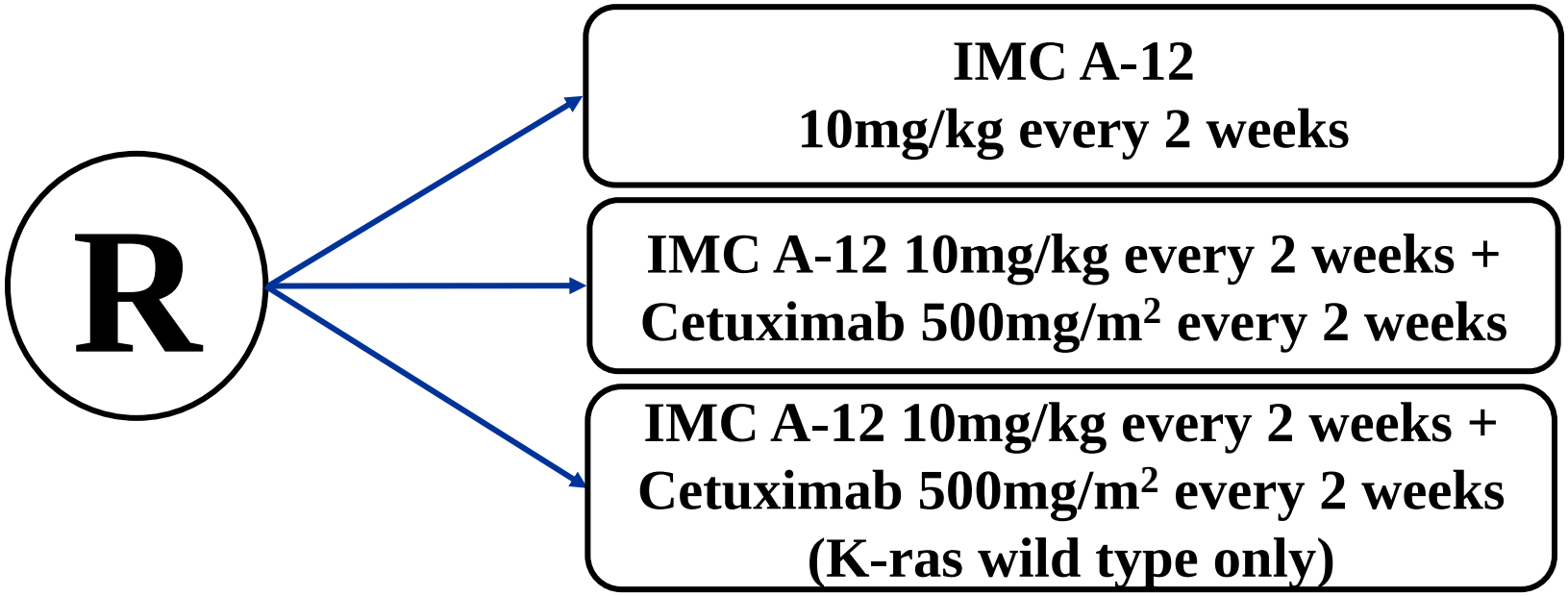
B

Baseline Biomarker	Biomarker Subgroup	Ganitumab Dose	Patients Receiving Ganitumab, *n* (Events, *n*)	Patients Receiving Placebo, *n* (Events, *n*)	HR	95% CI	*P* Value	Interaction *P* Value
IGF-1	Low (≤74 ng/mL)	12 mg/kg	111 (88)	121 (97)	0.91	0.68–1.21	.503	
		20 mg/kg	61 (45)		0.94	0.66–1.34	.719	
	High (>74 ng/mL)	12 mg/kg	115 (87)	122 (93)	0.92	0.69–1.24	.596	.914
		20 mg/kg	52 (35)		1.03	0.69–1.52	.899	.882
IGFBP-2	Low (≤1706 ng/mL)	12 mg/kg	124 (91)	114 (87)	0.94	0.70–1.27	.707	
		20 mg/kg	53 (35)		0.85	0.58–1.27	.432	
	High (>1706 ng/mL)	12 mg/kg	102 (84)	129 (103)	0.92	0.69–1.23	.578	.990
		20 mg/kg	60 (45)		1.12	0.79–1.59	.526	.267
IGFBP-3	Low (≤1.95 mg/L)	12 mg/kg	111 (88)	124 (102)	0.94	0.71–1.26	.696	
		20 mg/kg	56 (43)		1.01	0.70–1.44	.974	
	High (>1.95 mg/L)	12 mg/kg	115 (87)	119 (88)	0.89	0.66–1.20	.432	.801
		20 mg/kg	57 (37)		0.99	0.67–1.45	.945	.830
ESCIPA Analysis Set		12 mg/kg	226 (175)	243 (190)	0.93	0.75–1.14	.463	
		20 mg/kg	113 (80)		0.99	0.76–1.29	.941	



Fuchs et al Ann Oncol 2015

Randomised phase II study of cixutumumab (IMC A-12) in patients with colorectal cancer failed on 1 prior EGFR antibody



IMC A-12: cixutumumab

Reidy et al J Clin Oncol 2010

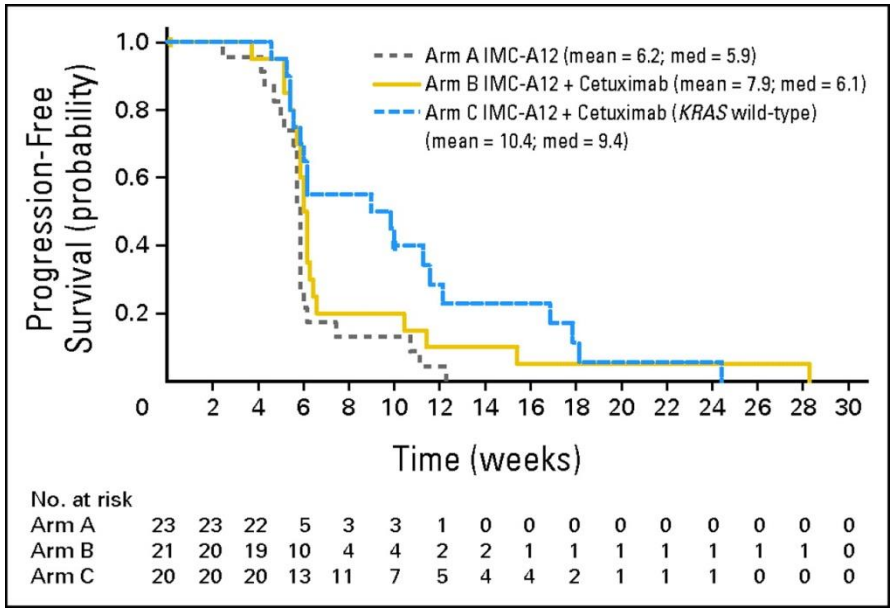
Objective response rate

Arms	A-12 alone	A-12 + cetux	A-12 + cetux (K-ras wild type)
N	23	21	20
Response	0	1	0
Response rate	0%	5%	0%
95% CI	0-15%	0-24%	0-17%

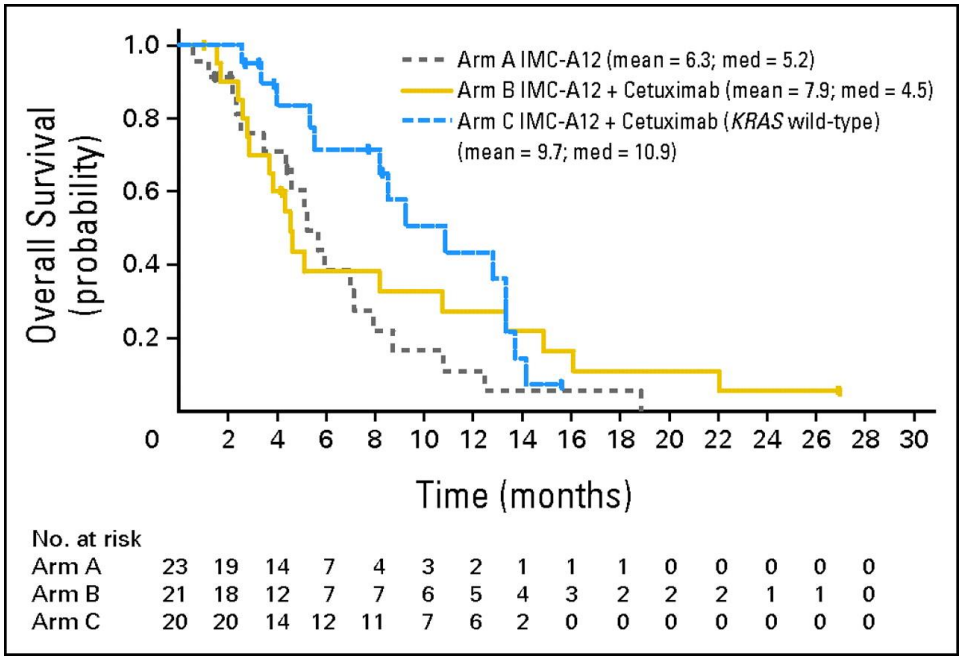
Reidy et al J Clin Oncol 2010

Survival outcome

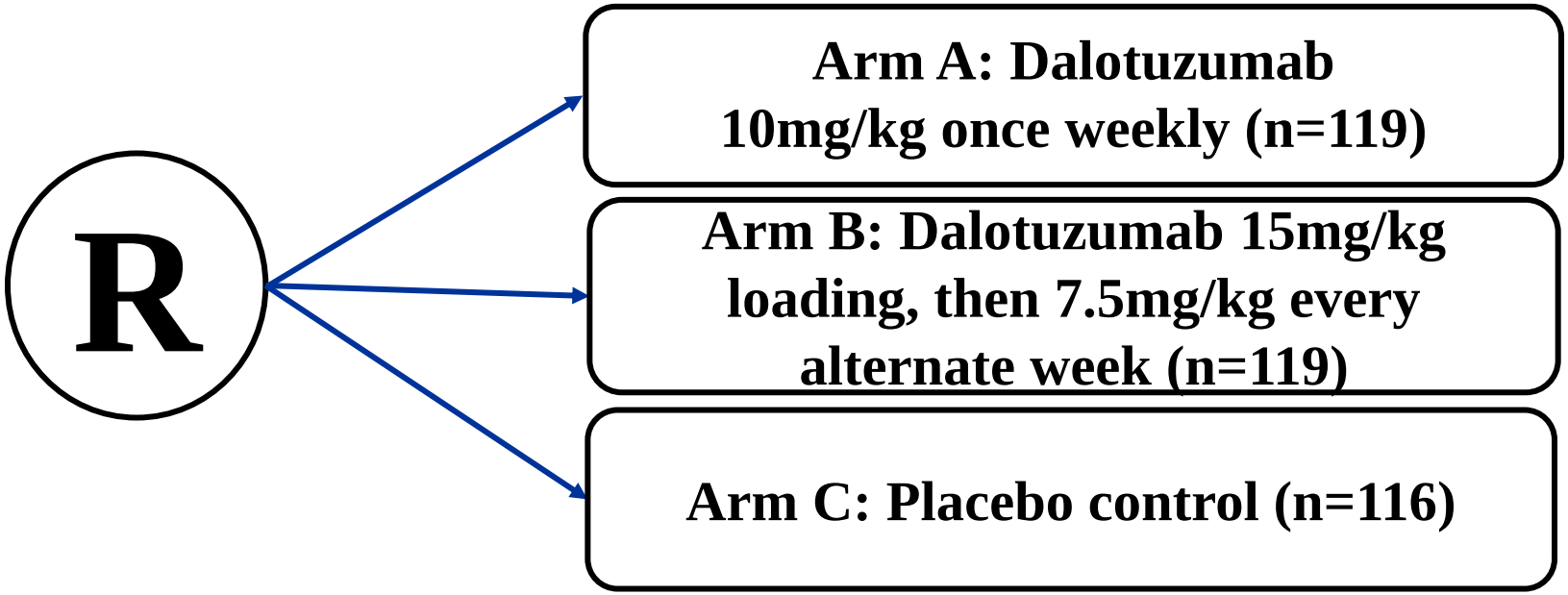
Progression free survival



Overall survival



Double blind randomised phase II/III study of irinotecan/cetuximab ± dalotuzumab in patients with chemorefractory colorectal cancer

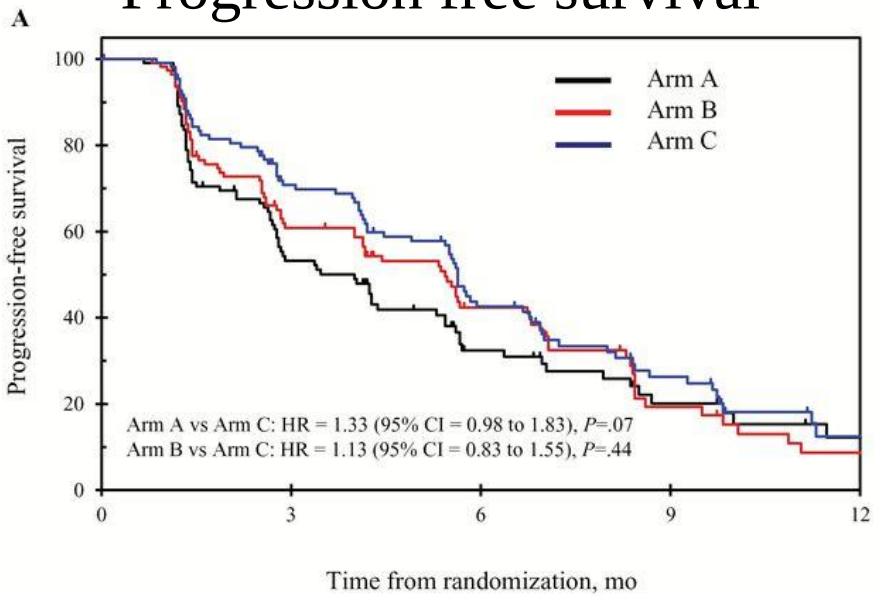


- All patients received:
  - Irinotecan - as per prior dose/schedule
  - Cetuximab - 400mg/m^2 loading, then 250mg/m^2 weekly

Sclafani et al J Natl Cancer Inst 2015

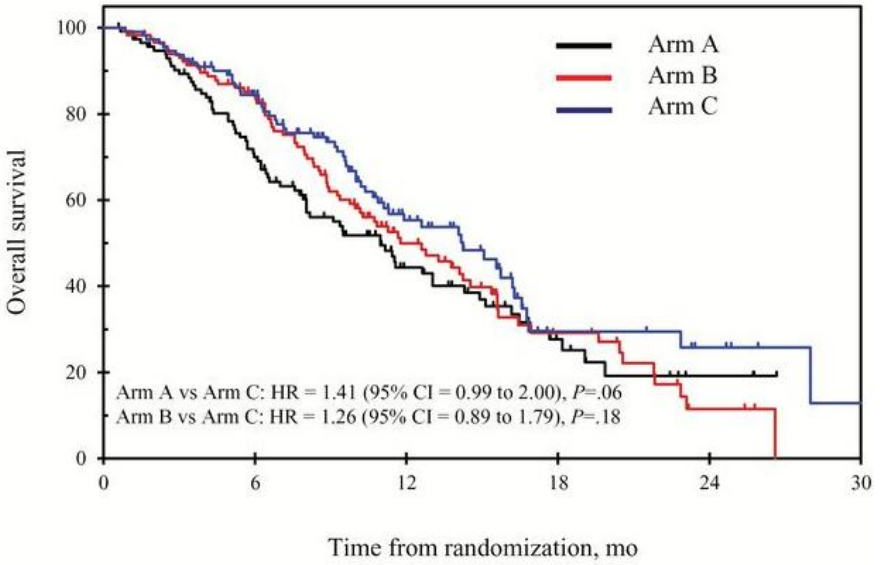
Double blind randomised phase II/III study of irinotecan/cetuximab ± dalotuzumab in patients with chemorefractory colorectal cancer

Progression free survival



	Median PFS	HR (95%CI)	p
Dalotuzuamb Weekly	3.9 months	1.33 (0.98, 1.83)	0.07
Dalotuzumab 2-weekly	5.4 months	1.13 (0.83, 1.55)	0.44
Placebo	5.6 months	-	

Overall survival



	Median OS	HR (95%CI)	p
Dalotuzuamb Weekly	10.8 months	1.41 (0.99, 2.00)	0.06
Dalotuzumab 2-weekly	11.6 months	1.26 (0.89, 1.79)	0.18
Placebo	14.0 months	-	

Sclafani et al J Natl Cancer Inst 2015

Pre-specified biomarker analysis

IGF-1R
Immunohistochemistry*

Epiregulin (*EREG*)
q-rtPCR

Combined
dalotuzumab arms
Vs
Placebo control

- Cut points for each biomarker were predefined
- PFS endpoint

*rabbit monoclonal antibody
CONFIRM® anti-IGF-1R (G11)
(Ventana, Arizona, US)

Sclafani et al J Natl Cancer Inst 2015

Pre-specified biomarker analysis

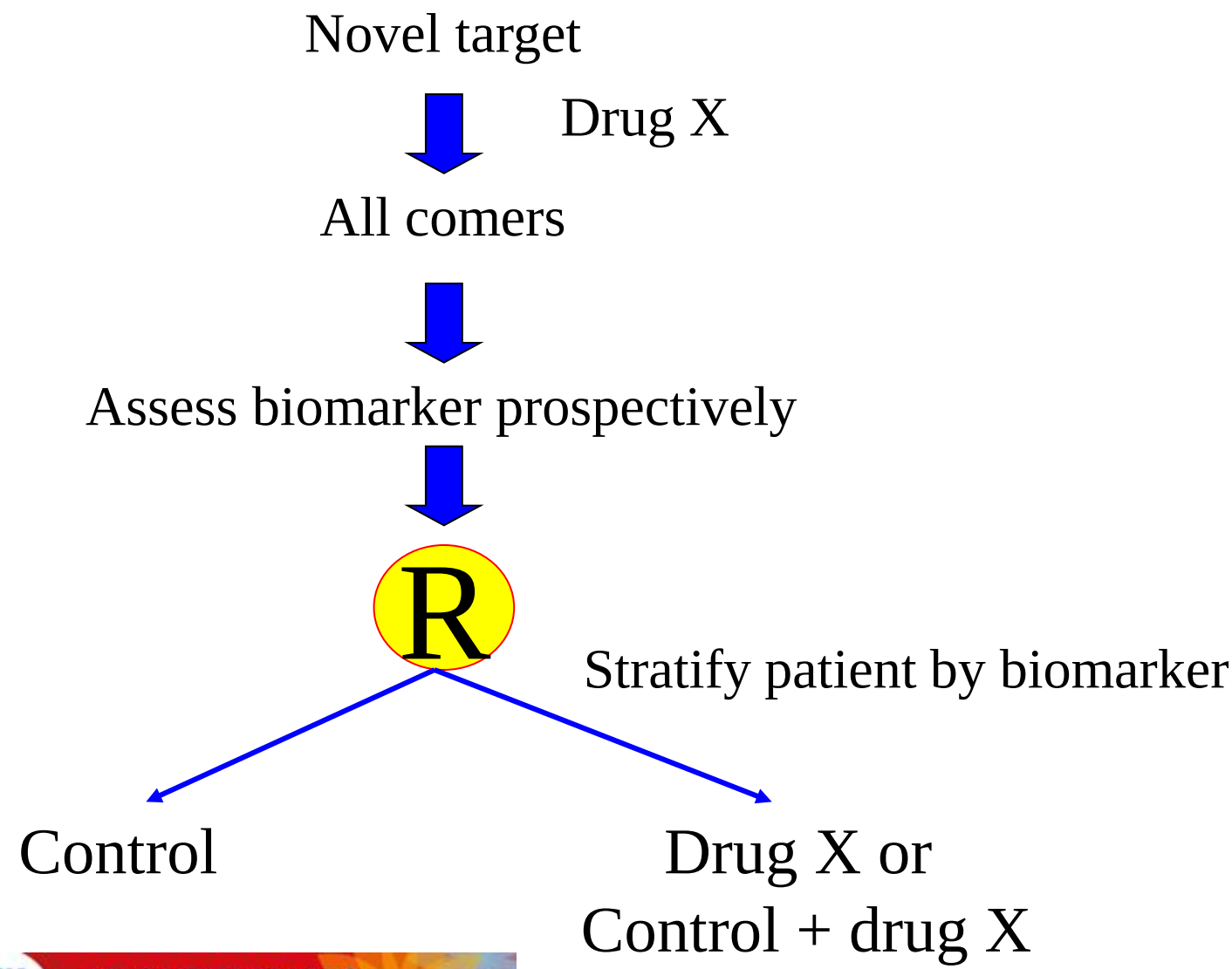
	Dalotuzumab (n)	**Control** (n)	**PFS HR (95% CI)**
Overall n=345	233	112	1.27 (0.96-1.69)
IGF-1R‡ n=187			
High	54	34	1.78 (1.01-3.13)
Low	67	32	1.02 (0.60-1.73)
EREG n=288			
High	97	47	1.26 (0.80-1.96)
Low	96	48	1.41 (0.92-2.16)

Sclafani et al J Natl Cancer Inst 2015

Important considerations in phase III trials

- ?biomarker assay correct
- ?Assay cut-point correct
  - % of cell staining and intensity of cell staining
  - median level of circulating biomarkers (different median levels between phase II and III trials)
- Circulating vs. tissue based biomarkers

Evaluating targets and predictive biomarkers

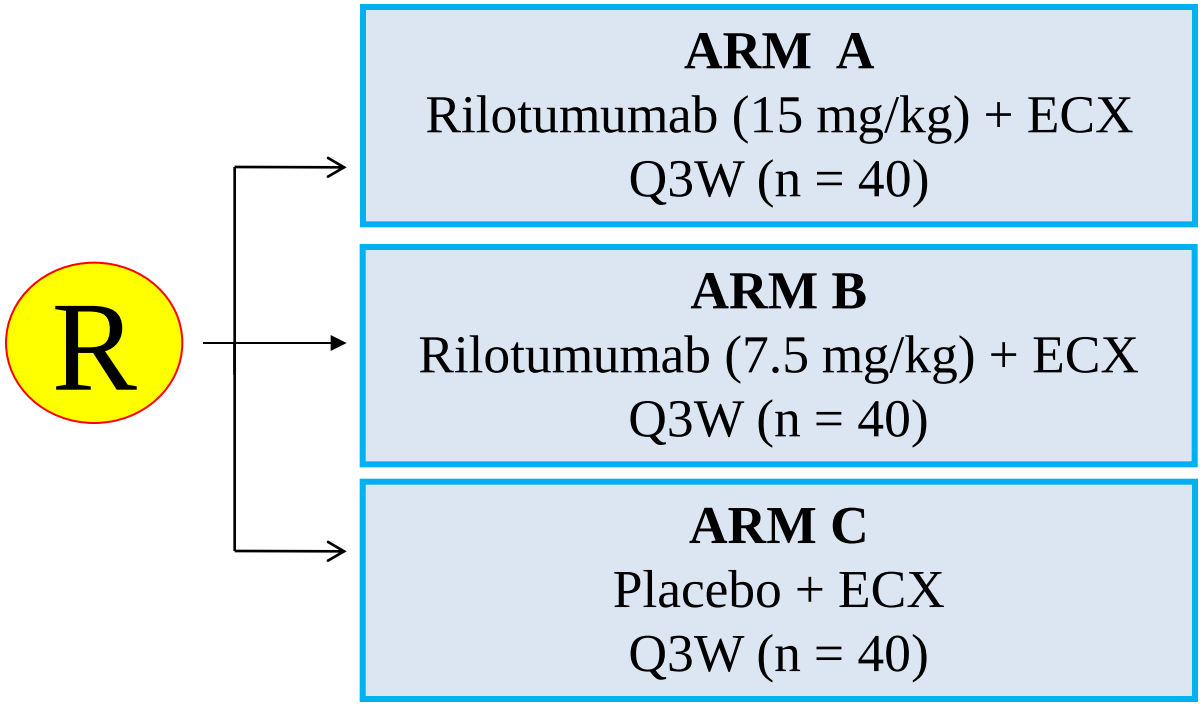


Biomarker validation -IHC

DRUG	CANCER	IHC Antibody	Biomarker +ve (i.e. MET positive/high)
Rilotumumab[1]	OG cancer	MET4 mAb (Dako, CA)	≥25% membrane staining of tumour cells at any intensity
Onartuzumab[2]	Non small cell lung cancer	CONFIRM SP44 anti-MET monoclonal antibody (Ventana AZ)	≥50% tumour cells with strong intensity OR ≥50% tumours cells with moderate or higher staining but <50% with strong intensity
Tivantinib[3]	Hepatocellular carcinoma	CONFIRM SP44 anti-MET monoclonal antibody (Ventana AZ)	≥50% tumour cells with at least moderate intensity

[1]Iveson et al Lancet Oncol 2014; [2]Spigel et al J Clin Oncol 2013; [3]Santoro et al Lancet Oncol 2013

Randomised phase II study of ECX ± rilotumumab (AMG102) in advanced OG cancer



Stratification factors:
ECOG PS 0 vs 1
LA vs Metastatic

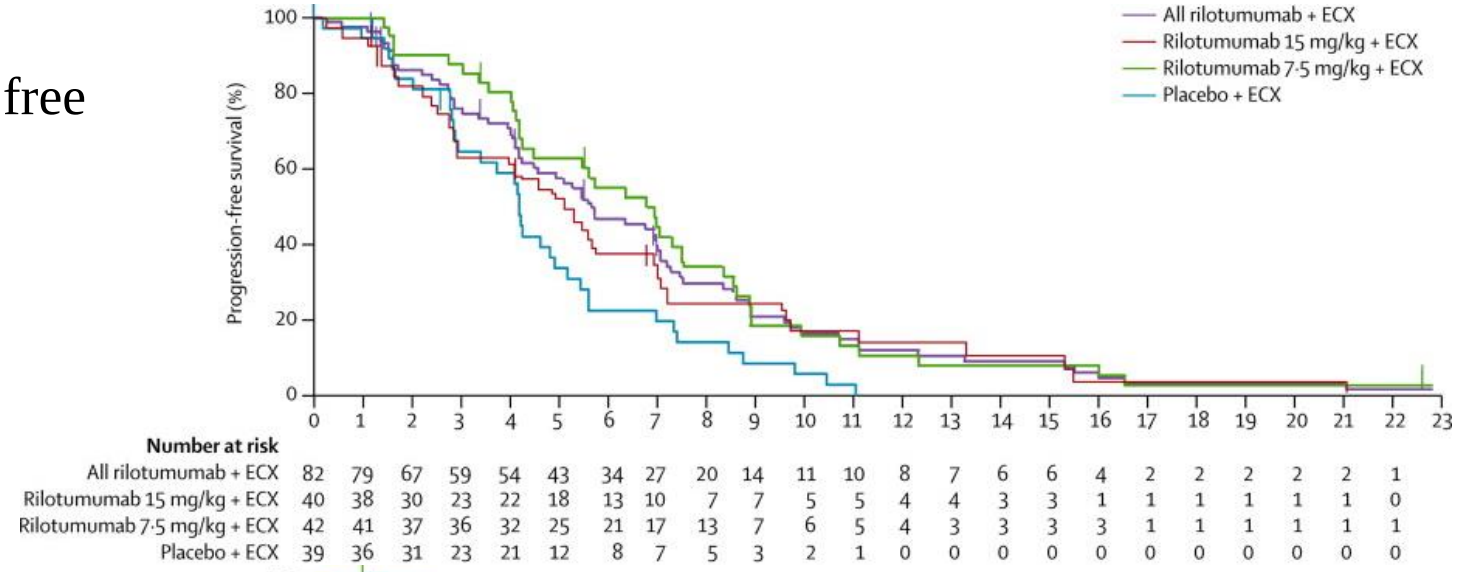
E: Epirubicin: 50 mg/m^2 IV, Day 1
C: Cisplatin: 60 mg/m^2 IV, Day 1
X: Capecitabine: 625 mg/m^2 BID orally, Days 1-21

- Rilotumumab: IV over 60 ± 10 minutes prior to chemotherapy

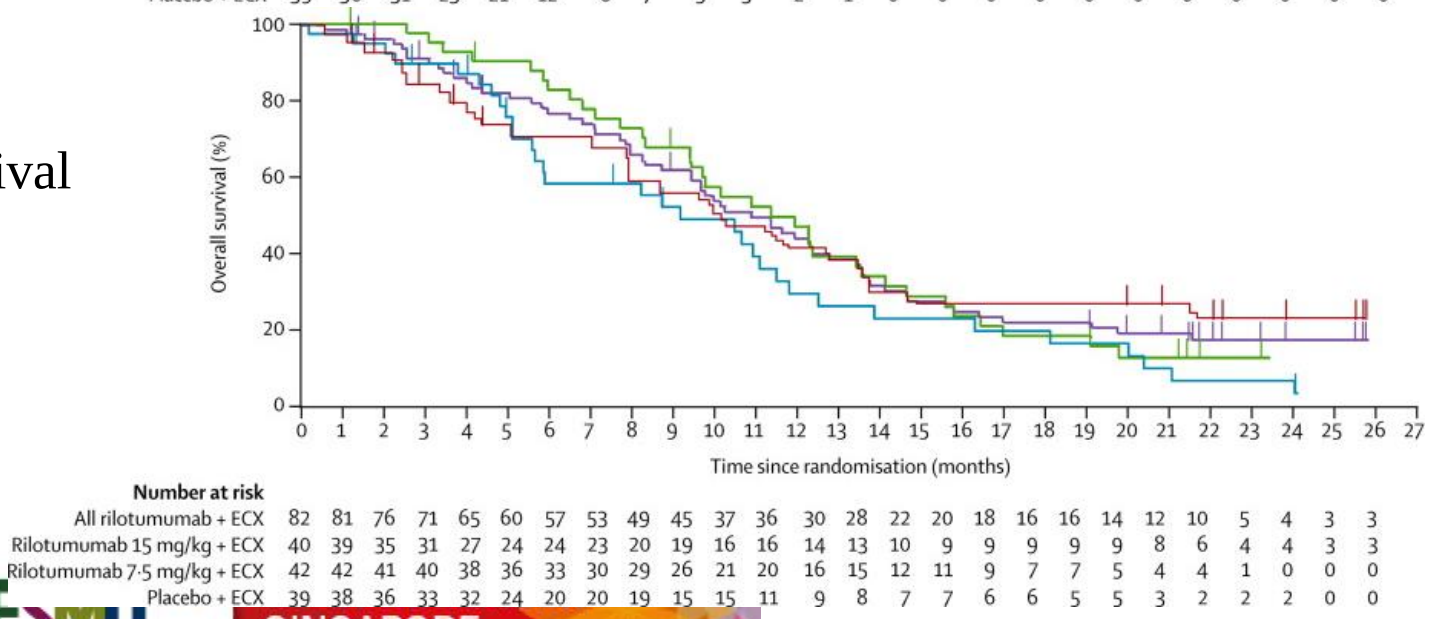
Iverson et al Lancet Oncol 2014

Survival outcome on all patients

Progression free survival



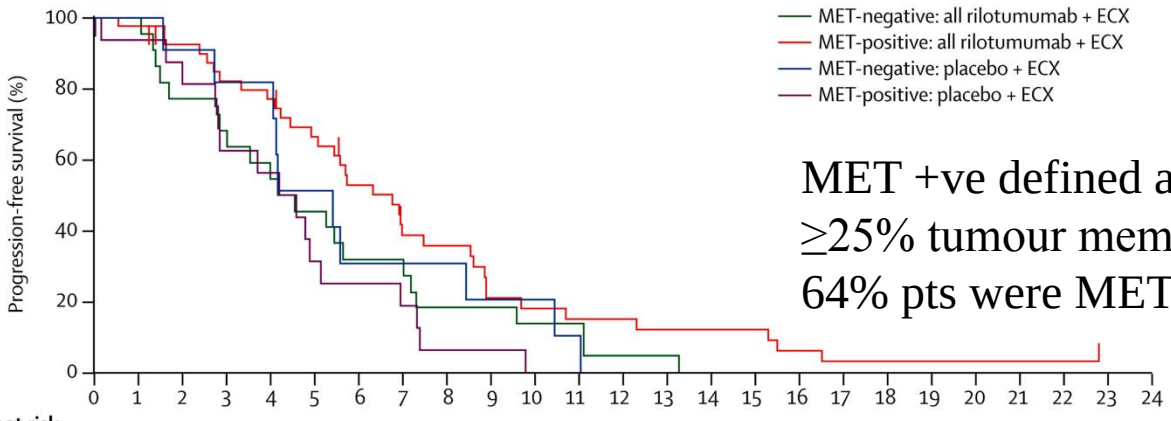
Overall survival



Iverson et al Lancet Oncol 2014

Survival outcome according to MET status

Progression free survival

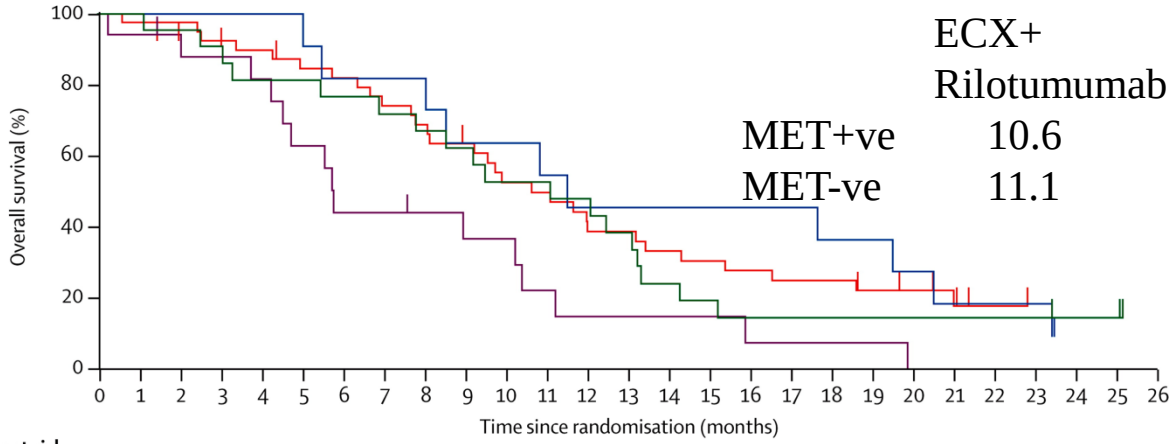


Number at risk

MET-negative: all rilotumumab + ECX	22	22	17	15	13	10	7	7	4	4	3	3	1	1	0	0	0	0	0	0	0	0	0	0	0
MET-positive: all rilotumumab + ECX	41	40	36	32	30	25	19	13	12	7	6	5	5	4	4	4	2	1	1	1	1	1	1	0	0
MET-negative: placebo + ECX	11	11	10	8	8	5	3	3	3	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
MET-positive: placebo + ECX	17	15	14	10	9	5	4	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

MET +ve defined as:
≥25% tumour membrane staining
64% pts were MET +ve

Overall survival



Number at risk

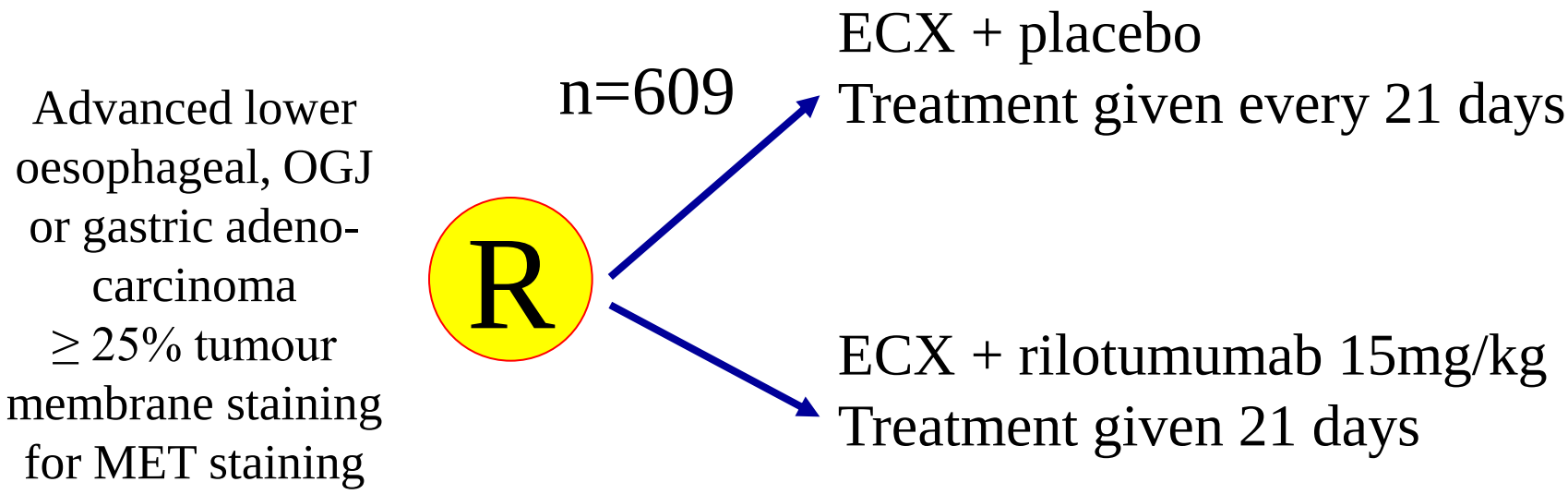
MET-negative: all rilotumumab + ECX	22	22	21	19	17	17	16	15	14	13	11	11	10	8	5	4	3	3	3	3	3	3	3	2	2	0
MET-positive: all rilotumumab + ECX	41	40	38	36	35	32	31	28	26	23	19	18	14	14	12	11	10	9	9	7	6	4	1	0	0	0
MET-negative: placebo + ECX	11	11	11	11	11	10	9	9	9	7	7	6	5	5	5	5	5	5	4	4	3	2	2	2	0	0
MET-positive: placebo + ECX	17	16	15	14	13	10	7	7	6	5	5	3	2	2	2	2	1	1	1	1	0	0	0	0	0	0

Median survival (months)

	ECX+ Rilotumumab	ECX + placebo
MET+ve	10.6	5.7
MET-ve	11.1	11.5

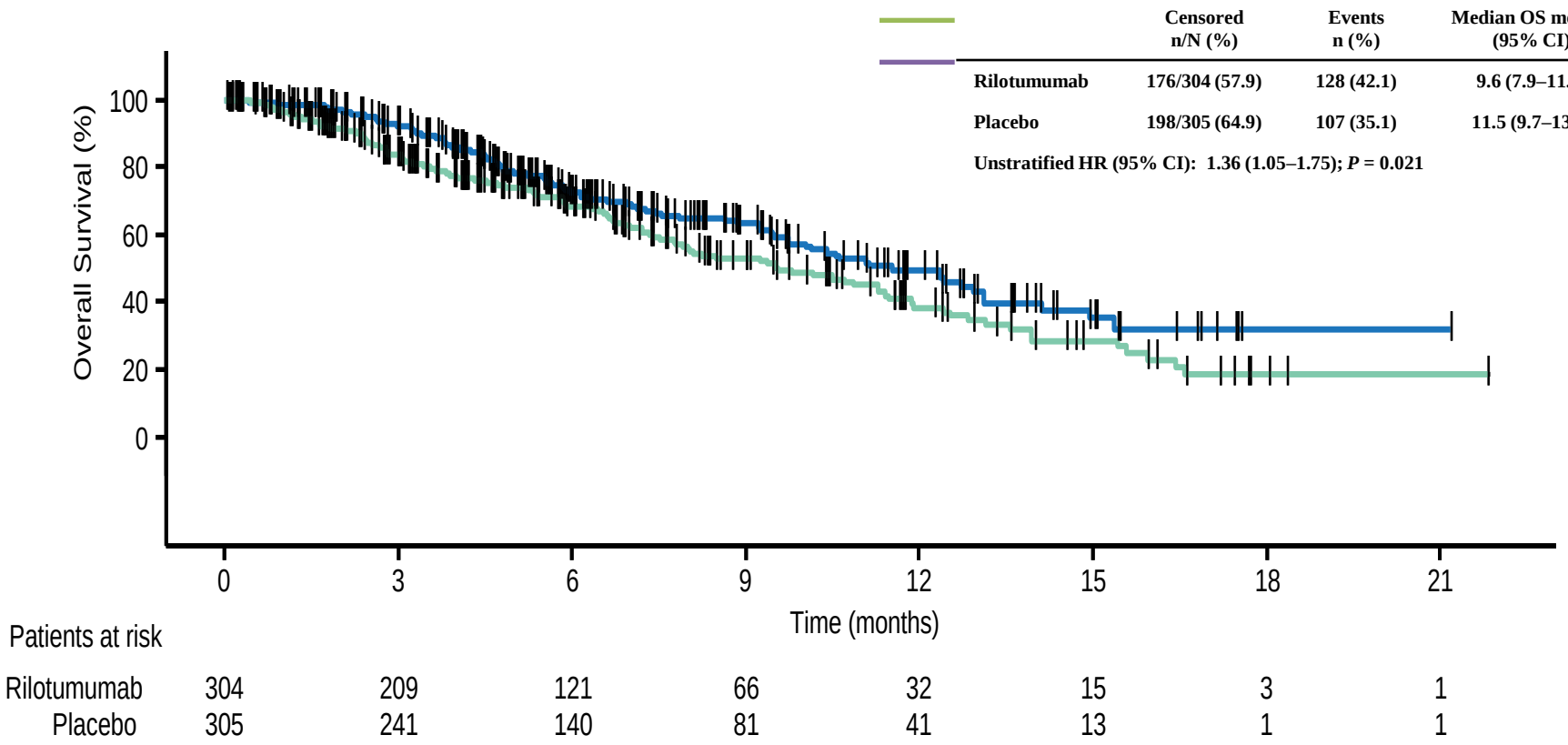
Iverson et al Lancet Oncol 2014

Randomised phase III rilotumumab in advanced OG cancer trial design (RiloMET)



Primary endpoint: Overall survival (ITT population)

Overall Survival



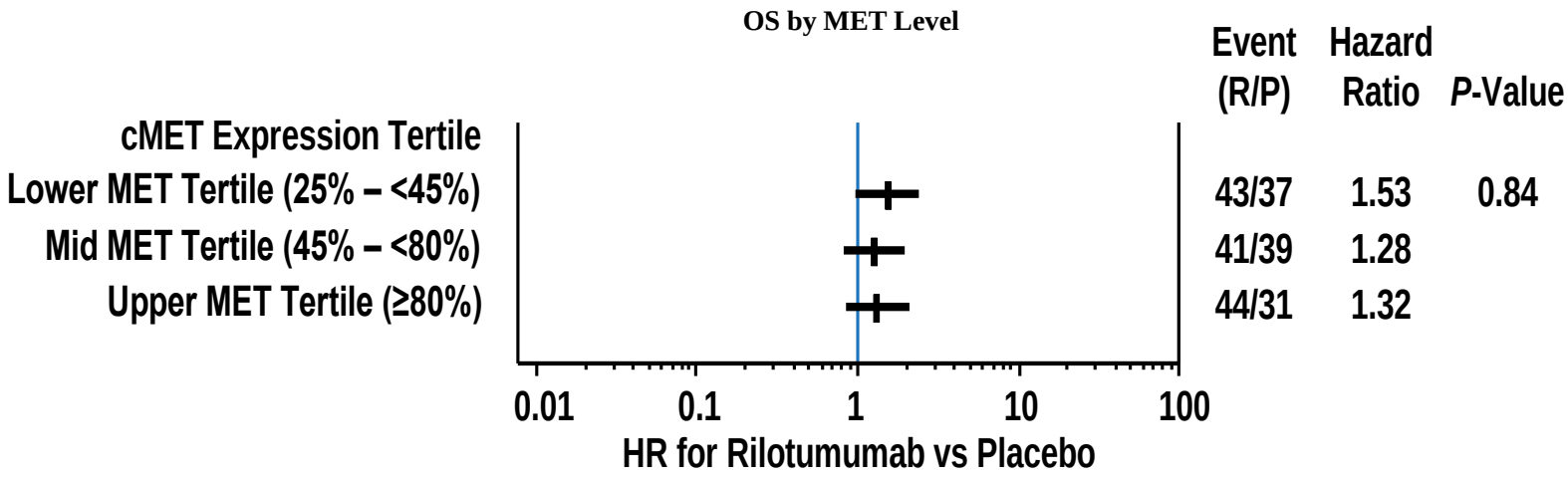
- **More deaths in the rilotumumab arm, primarily due to disease progression**

	Rilotumumab (n=304)	Placebo (n=305)
Events, n (%)	128 (42.1)	107 (35.1)
•Due to disease progression	103 (33.9)	87 (28.5)
•Not due to disease progression	25 (8.2)	20 (6.6)

Cunningham et al ASCO 2015

OS and MET Expression

Treatment Arm	MET Expression Tertile	Subjects, n	Events, n	Median OS	95% CI
Rilotumumab (n=304)	25%–<45%	95	43	10.2	7.2–12.4
	45%–<80%	98	41	8.1	6.4–11.9
	≥80%	110	44	10.7	7.2–15.9
Placebo (n=305)	25%–<45%	100	37	12.4	8.9–NE
	45%–<80%	103	39	10.4	8.6–15.4
	≥80%	102	31	11.1	9.5–NE

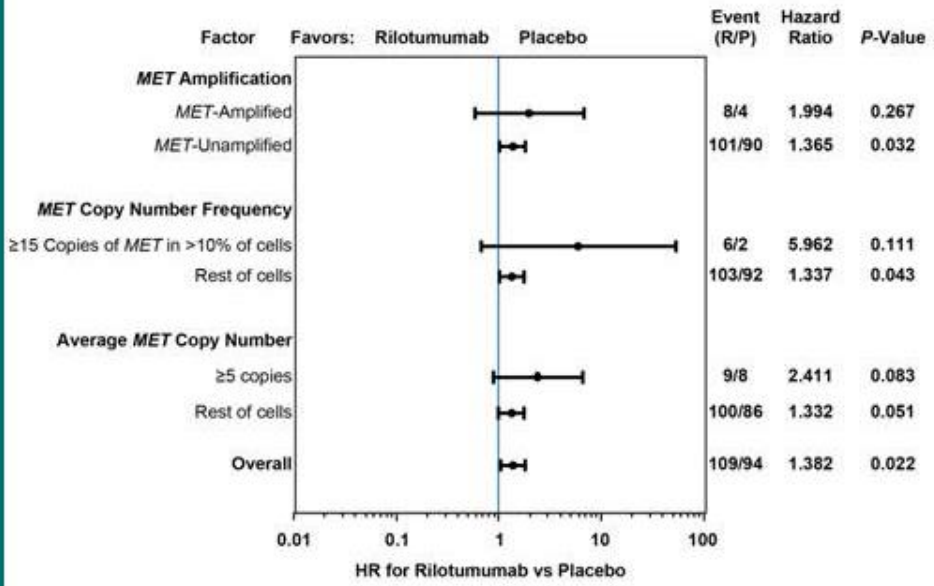


- Within the selected MET-positive population, higher MET expression did not correlate with poorer prognosis or better outcome with rilotumumab

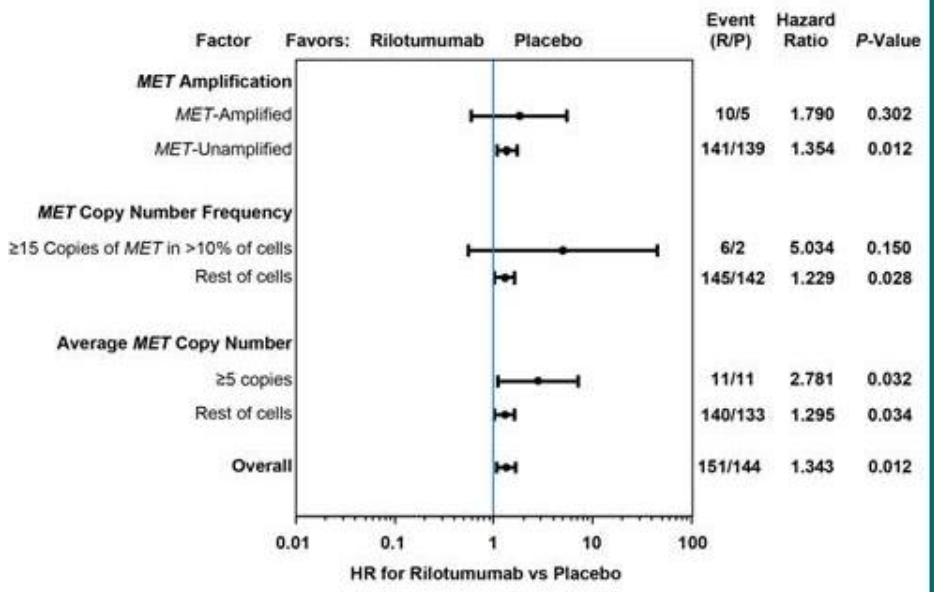
Cunningham et al ASCO 2015

Tumour MET FISH analyses

OS



PFS

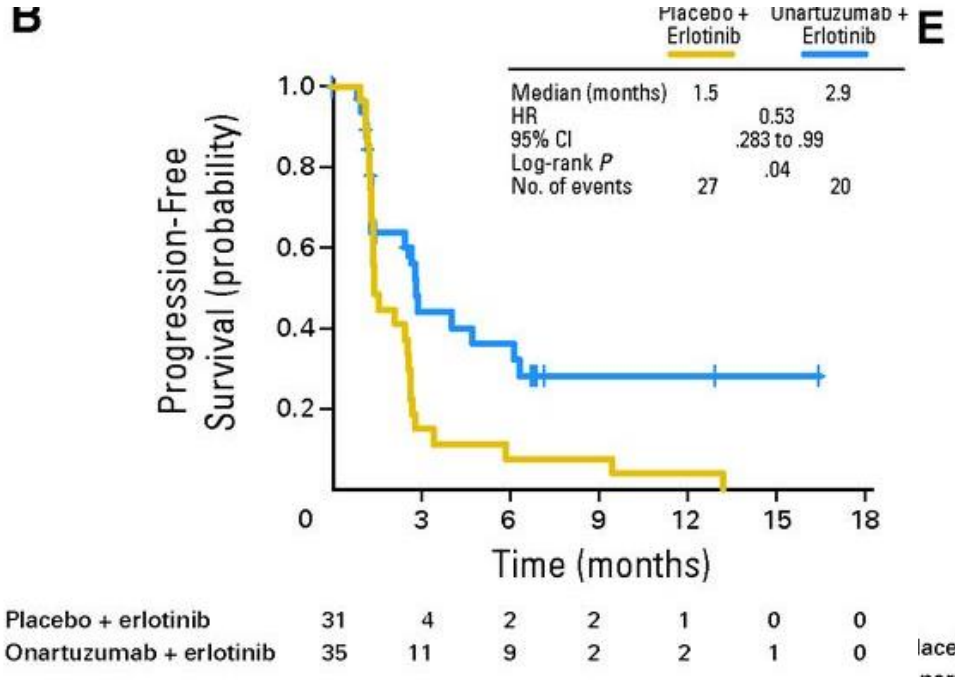


- ***MET*** **gene amplification was analyzed by FISH using the Research Use Only (RUO)** ***MET*****/CEN-7 IQFISH Probe Mix assay (Dako)**

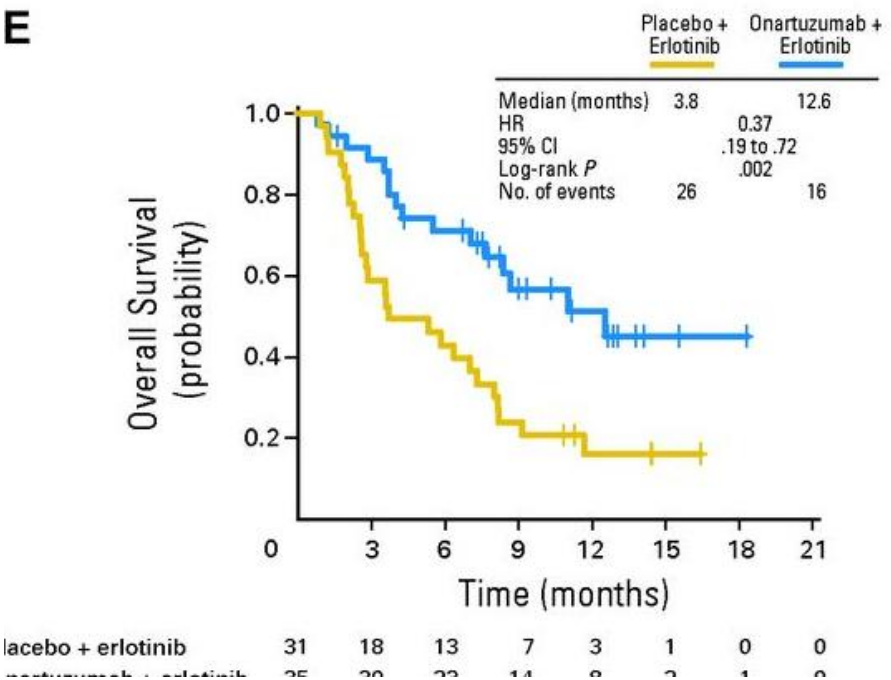
Cunningham et al ASCO 2015

Randomized phase II trial of onartuzumab in combination with erlotinib in patients with advanced non–small-cell lung cancer

Progression free survival



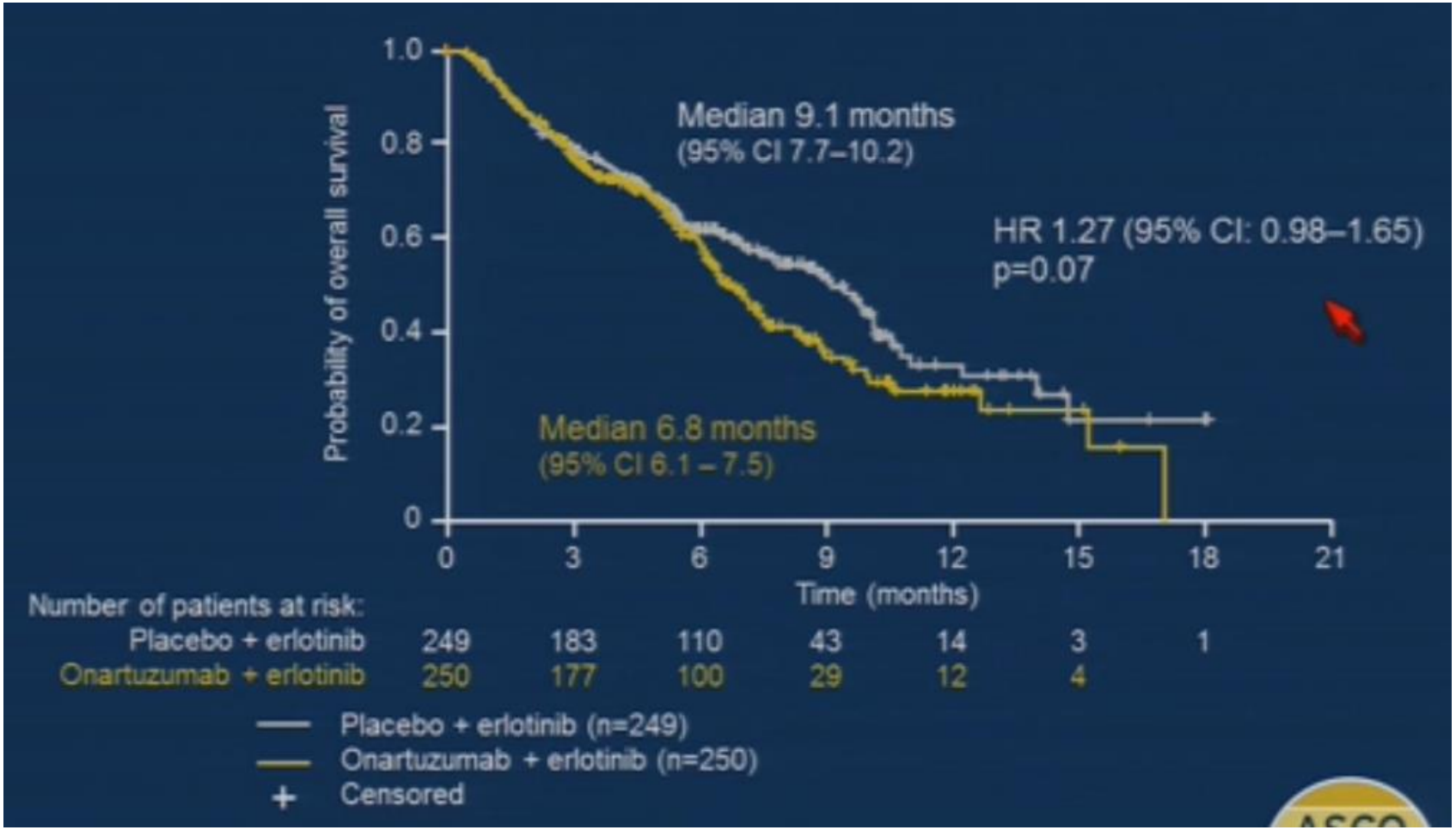
Overall survival



MET positivity was defined as a score of 2+ (≥ 50% of tumour cells with moderate or higher staining but < 50% with strong intensity); or 3+ (≥ 50% of tumour cells staining with strong intensity)

Spigel et al J Clin Oncol 2013

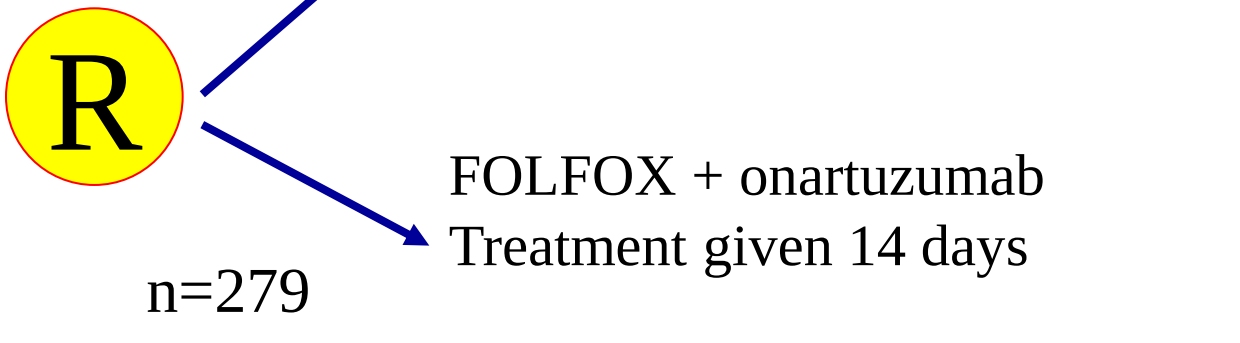
Phase III study of erlotinib ± onartuzumab



Spigel et al ASCO 2014

Randomised phase III onartuzumab (MetMAb) in advanced gastric cancer trial design (METGastric)

Advanced OGJ or gastric adeno-carcinoma ≥50% of tumour cells showing weak, moderate and/or strong staining intensity



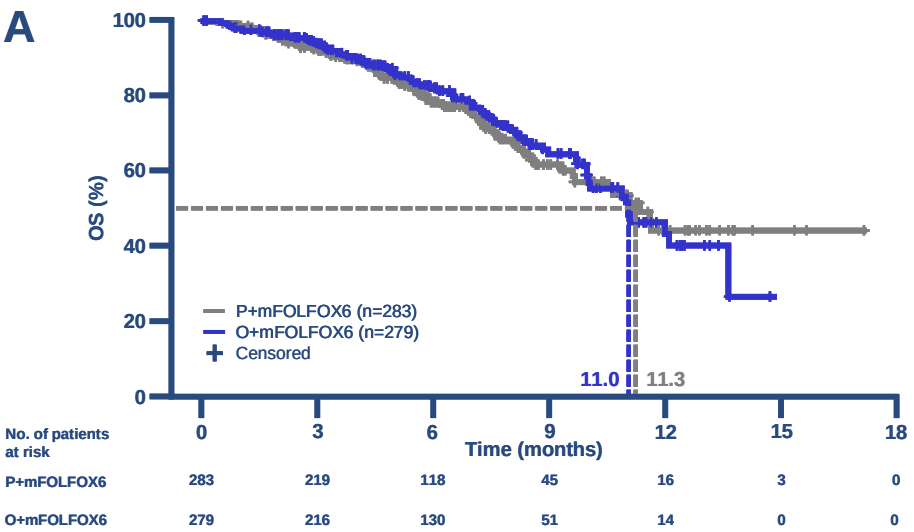
Co-primary endpoint: Overall survival (ITT population)

Overall survival (Met-IHC 2+ or 3+ subgroup)

Shah et al ASCO 2015

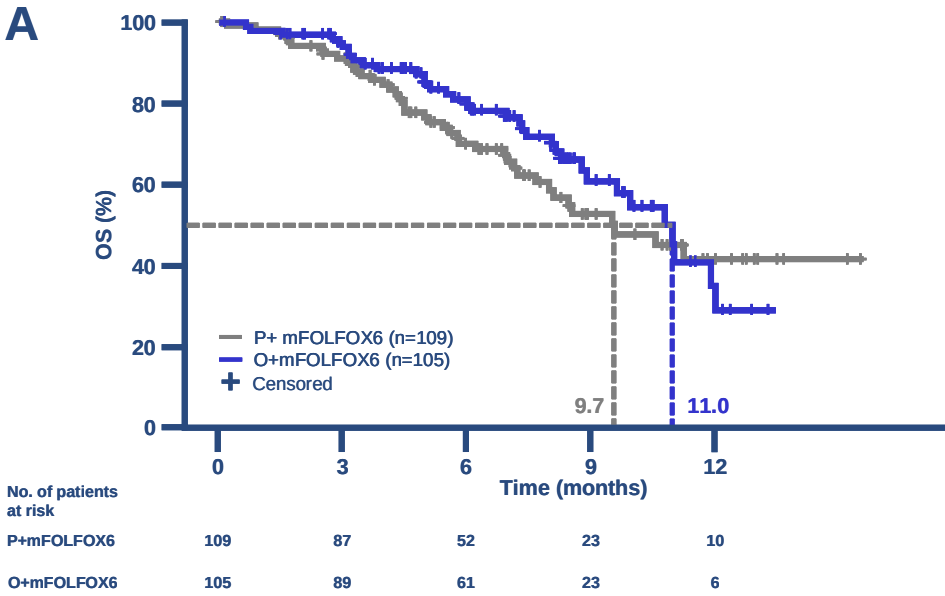
Overall survival

Intention-to-treat



HR: 0.82
95% CI: 0.59, 1.15
p=0.24

MET 2+/3+

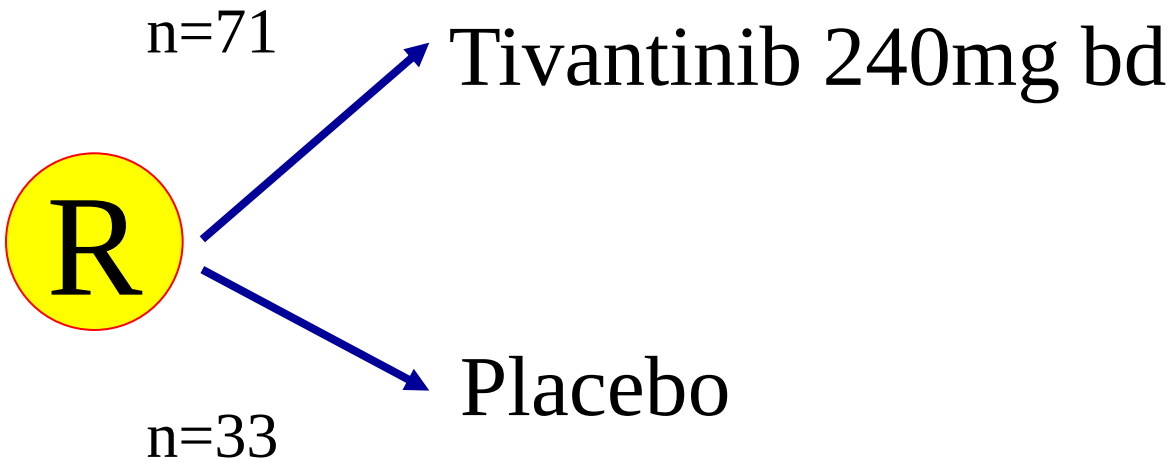


HR: 0.64
95% CI: 0.40, 1.03
p=0.062

Shah et al ASCO 2015

Randomised phase II tivantinib in advanced hepatocellular cancer trial design

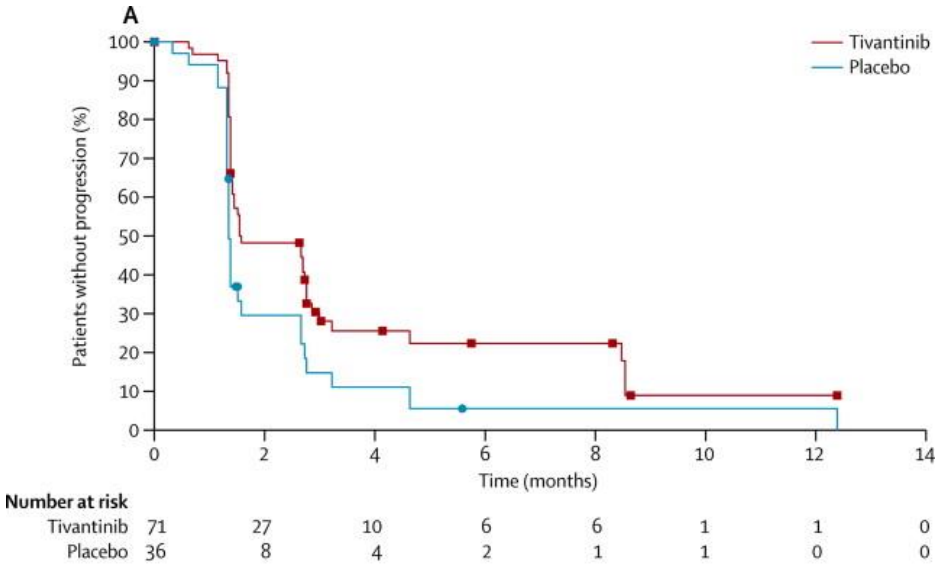
Advanced HCC patients with 1 prior systemic therapy and radiological progression or intolerance to therapy



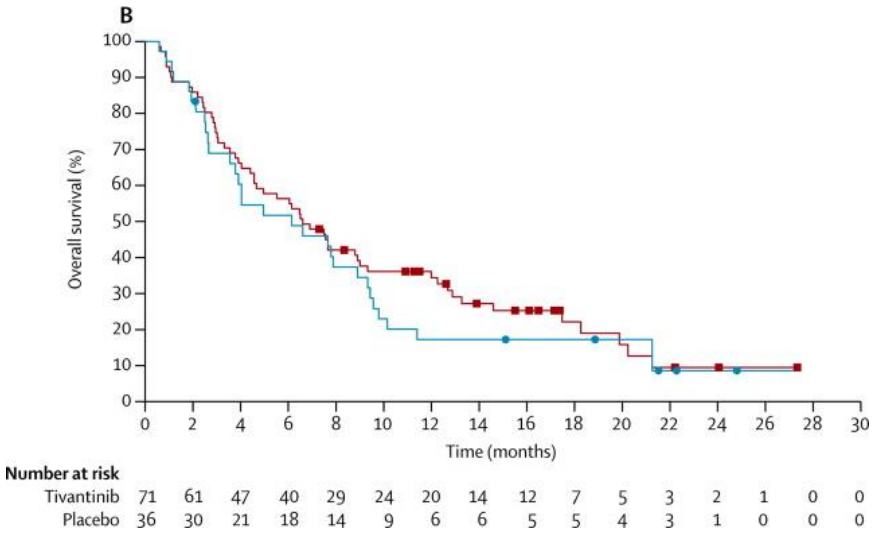
Santoro et al Lancet Oncol 2013

Randomised phase II tivantinib in advanced hepatocellular cancer (ITT population)

Time to progression



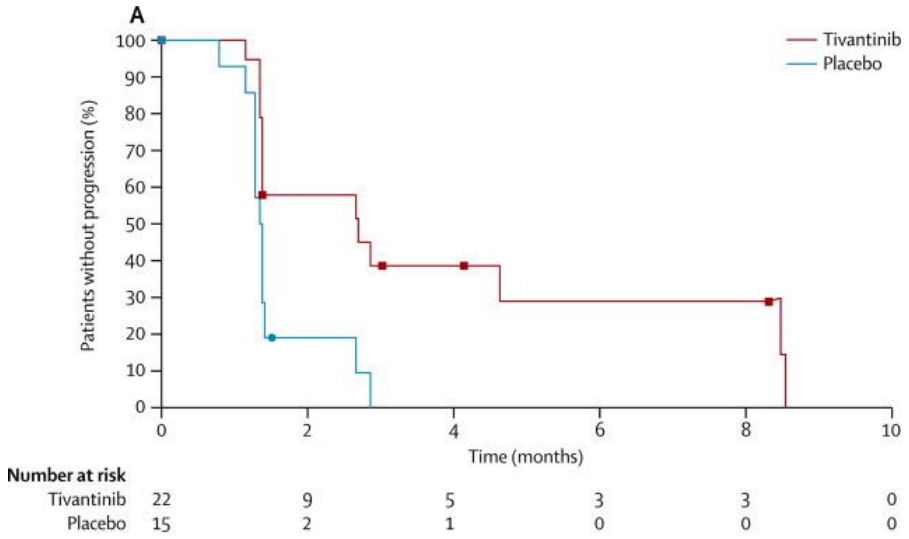
Overall survival



Santoro et al Lancet Oncol 2013

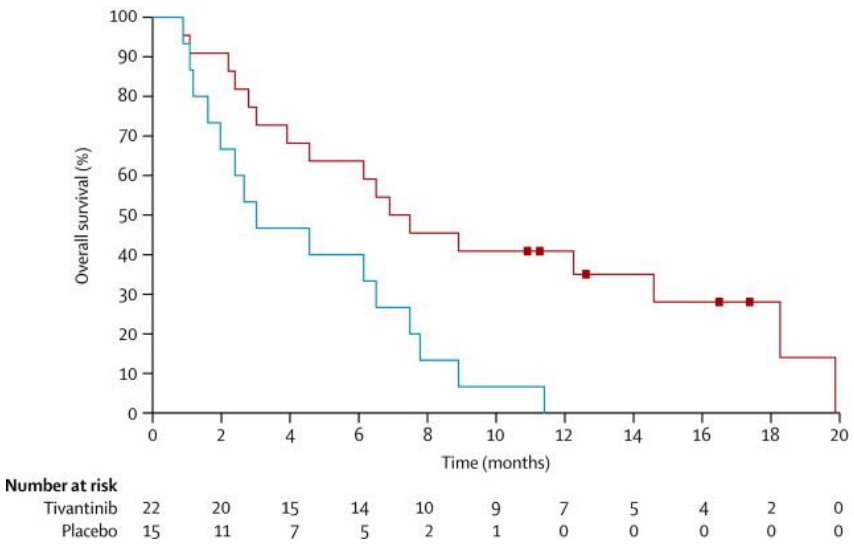
Randomised phase II tivantinib in advanced hepatocellular cancer (MET high subgroup)

Time to progression



HR: 0.43; 95% CI:0.19-0.97; p=0.03)

Overall survival

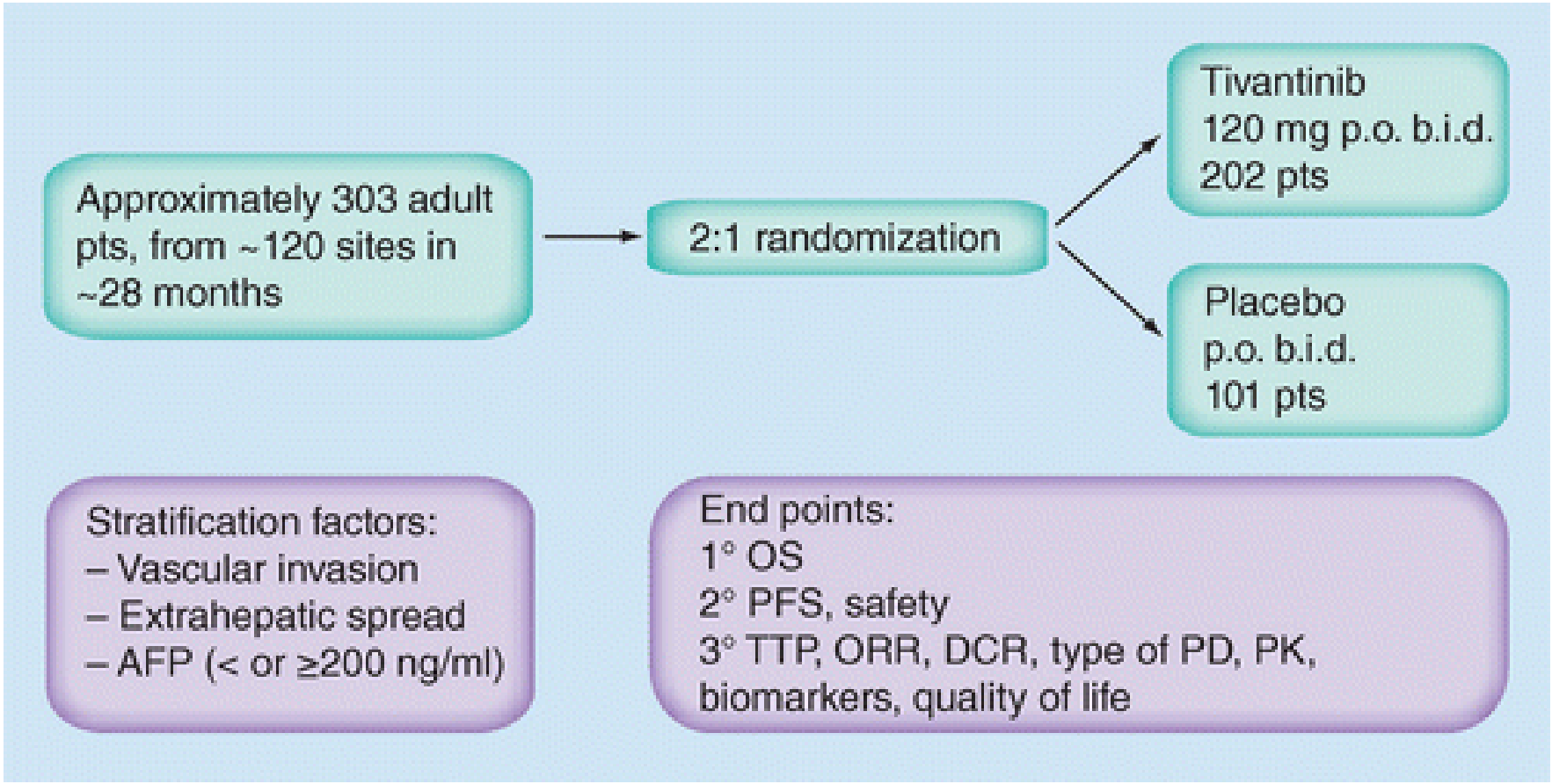


HR: 0.38; 95% CI:0.18-0.81; p=0.01)

Samples that scored at least 2+ in at least 50% of tumour cells were regarded as having high MET expression (MET-high)

Santoro et al Lancet Oncol 2013

Phase III randomized double-blind study of tivantinib monotherapy as second-line treatment in patients with advanced, pretreated, MET-high HCC (METIV-HCC)



Rimassa et al Hepatic Oncol 2014

Conclusions

- Suppressing one growth factor receptor pathway might lead to activation of other compensatory resistant pathways
- Drugs evaluated with the putative mechanism of actions might be inadequate
- Definition of tissue-based biomarker positivity could be subjective and varied (expression vs. median level)
- Parallel effort in optimising biomarker might be necessary during phase III studies

Acknowledgement

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