20th Dec, 2015
ESMO ASIA in Singapore

Proffered Paper Session
Gastrointestinal tumours 2

What's a Next Step for Advanced Gastric Cancer?

Kei Muro, MD.

Department of Clinical Oncology

Aichi Cancer Center Hospital

Disclosure

- Kei Muro

  - Consulting or Advisory Role:
    Ono, Merck-Serono

  - Honoraria:
    Taiho, Takeda, Chugai, Merck-Serono, Yakult, Bristol- Myers

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Gastrointestinal tumours 2

1440

Comparison of efficacy and safety of combination therapy of paclitaxel and capecitabine followed by capecitabine monotherapy as maintenance therapy versus cisplatin and capecitabine combination therapy for advanced gastric cancer: A multicentre, open-label, active-controlled phase III study

Xiaotian Zhang, et al. China

1450

Phase II study of AZD4547 in *FGFR* amplified tumours: gastroesophageal cancer (GC) cohort clinical and translational results

Elizabeth Smyth, et al. UK

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Study design

Eligible for all comers despite HER2 status

N=320
- confirmed gastric or GEJ adenocarcinoma, previously untreated
- aged ≥18 years
- KPS ≥70
- life expectancy of ≥3 months

R

PACX n=160 → Paclitaxel 80mg/m² over 3 h on days 1 and 8, Capecitabine 1000 mg/m² twice daily on days 1-14, q3w×4 cycles → Capecitabine monotherapy

XP n=160 → Cisplatin 80 mg/m² for 2 hours on day 1 , Capecitabine 1000 mg/m² twice daily on days 1-14, q3w×4 cycles → Cisplatin and Capecitabine combination therapy

Stratification:
- KPS (≥80/<80)
- resection of primary tumour (performed/not performed)
- weight loss within last 3 months (≥5%/<5%)
- primary tumour site at the gastroesophageal junction (GEJ; yes/no)

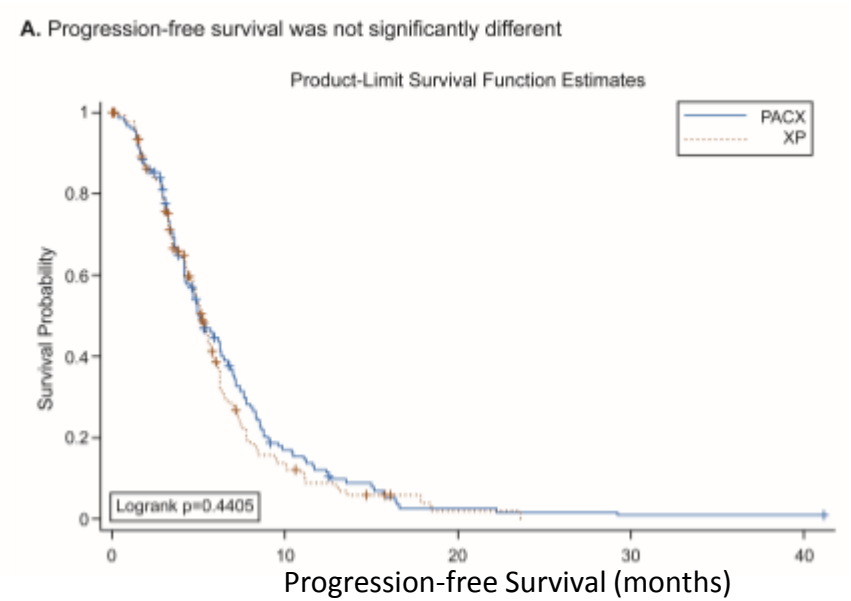
- Primary endpoint: progression-free survival (PFS)
- Secondary endpoints: DCR (CR/PR/SD); ORR (CR/PR); OS; AEs, serious AEs (SAEs) and QoL

PACX, combination therapy of paclitaxel and capecitabine followed by capecitabine monotherapy as maintenance therapy
XP, cisplatin and capecitabine combination therapy

Zhang X, et al. ESMO ASIA 2015

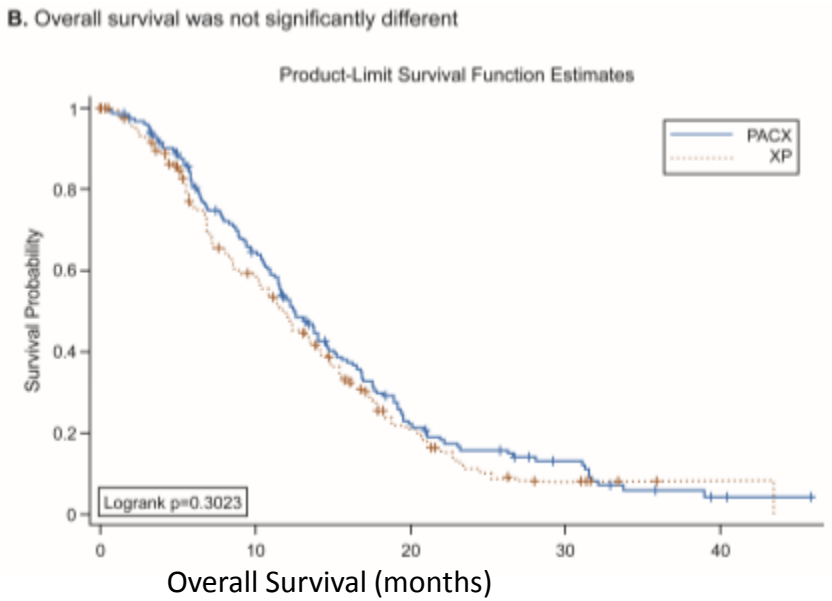
Efficacy: PFS & OS, ORR

PFS



	No.	Event	Censored	Median	Survival(95% CI)
PACX	160	83%(133)	17%(27)	4.994	(4.304 6.275)
XP	160	73%(117)	27%(43)	5.257	(4665 5.815)

OS



	No	Event	Censored	Median	Survival(95% CI)
PACX	160	81%(130)	19%(30)	12.52	(11.47 14.52)
XP	160	76%(122)	24%(38)	11.83	(9.99 13.67)

ORR

PACX: 45.4% (95%CI, 37.3-53.7) vs. XP: 31.7% (95% CI, 24.3-40.0)

p=0.012

Zhang X, et al. ESMO ASIA 2015

Adverse events at Grade 3 or 4 according to NCI-CTC and serious adverse events

Adverse event, n (%)	PACX (N=156)	XP (N=147)	p value
≥3 AE	53 (34·0)	59 (40·1)	0·26
Hematologic toxicity	43 (27·6)	37 (25·2)	0·64
Neutropenia	33 (21·2)	23 (15·6)	0·22
Leukopenia	20 (12·8)	14 (9·5)	0·36
Anaemia	**3 (1·9)**	10 (6·8)	**0·036**
Thrombocytopenia	**1 (0·6)**	7 (4·8)	**0·025**
Adverse gastrointestinal reaction	**8 (5·1)**	18 (12·2)	**0·027**
Vomiting	**4 (2·6)**	14 (9·5)	**0·010**
Nausea	**3 (1·9)**	12 (8·2)	**0·012**
Abnormal laboratory test	1 (0·6)	5 (3·4)	0·085
Serum bilirubin elevation	0 (0·0)	3 (2·0)	0·073
Adverse reaction in skin and subcutaneous tissue	3 (1·9)	3 (2·0)	0·94
Palmoplantar pustules and pain syndrome	2 (1·3)	2 (1·4)	0·95

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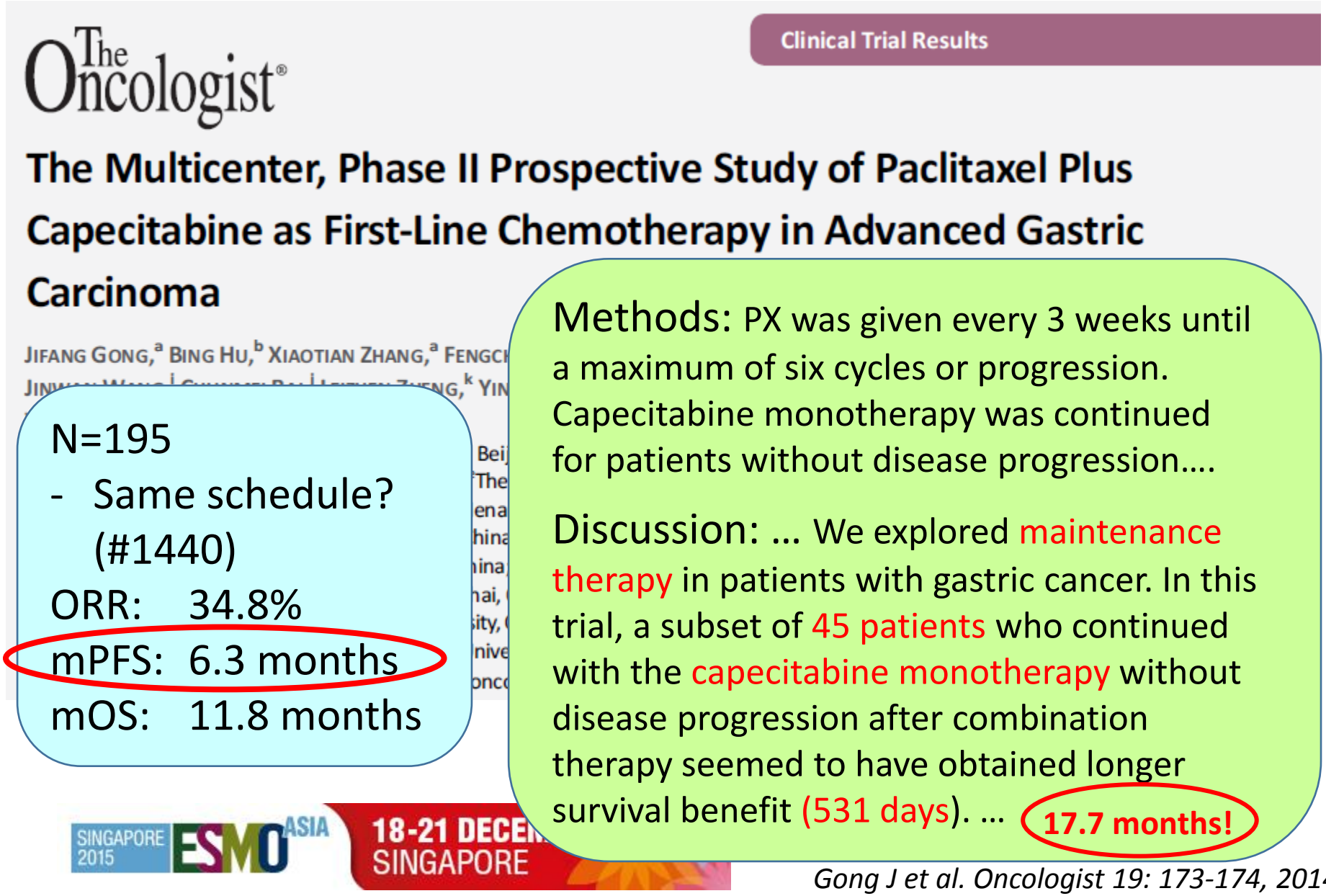
Discussion Points on This Trial (#1440)

- Alternative chemotherapy development without cisplatin
  - oxaliplatin can replace cisplatin
    (REAL-2 <EOF/EOX vs. ECF/ECX>, G-SOX <SOX vs. SP>, FLO <FLO vs. FLP>)
  - irinotecan may replace cisplatin
    (V306 <IF vs. PF>, FOLFIRI <FOLFIRI vs. ECX>)
  - other agents (e.g. taxane)?

- Possibility of maintenance therapy for gastric cancer
  - capecitabine monotherapy as maintenance is reasonable

Previous Study



Gong J et al. Oncologist 19: 173-174, 2014

I guess statistical assumption was carried out based on good outcome in previous phase II

Statistical analysis

- Assuming an expected PFS of **6·5 and 4·5 months in PACX and XP groups**, respectively
  - two-sided α of 0·05, 80% power, and 10% dropout rate
  - a minimum sample size of 160 patients was required in each group.

Too low estimation of PFS on XP?

In case of comparison study using cytotoxic agents, basically, confirmation of superiority in OS is quite difficult!

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Recent PIIIs in 1st Line for Advanced Gastric Cancer

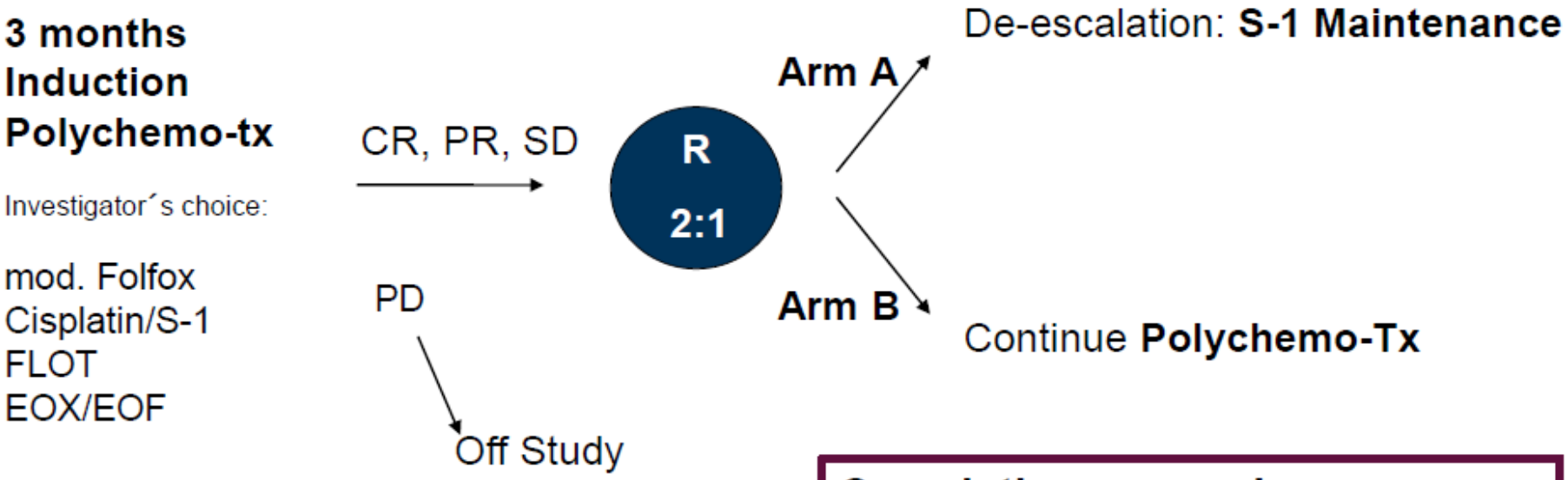
Cytotoxic Agents

Study	*Regimen*	*n*	*Primary endpoint*	*superiority/ non-inferiority*	*OS (MST)*	*PFS (mTTP)*	*TTF*	*RR.*	*Interpretation*
JCOG 9912	5FU vs. S1 vs. IP	704	OS	superiority/ non-inferiority	10.8M vs. 11.3M vs. 12.4M	2.9M vs. 4.2M vs. 4.8M	2.3M vs. 4.0M vs. 3.7M	9% vs. 28% vs. 38%	Non-inferiority of S1compared with 5FU in OS was only met
SPIRITS	S1 vs. SP	305	OS	superiority	11M vs. 13M	4M vs. 6M	3.9M vs. 4.8M	31% vs. 54%	Superiority in OS was met
TOP 002	S1 vs. IRIS (S-1+IRI)	315	OS	superiority	10.5M vs. 12.8M	3.4M vs. 5.0M	3.6M vs. 4.5M	26.9% vs. 41.5%	Superiority in OS was not met
START	S1 vs. S1+DTX	639	OS	superiority	11.1M vs. 13.0M	4.2 vs. 5.4M		18.4% vs. 30.3%	Superiority in OS was not met
V325	CF vs. DCF	445	TTP	superiority	8.6M vs. 9.2M	3.7M vs. 5.6M		25% vs. 37%	Superiorities in PFS & OS were met
V306	CF vs. IF	333	TTP	superiority→ non-inferiority	8.7M vs. 9.0M	4.2M vs. 5.0M	3.4M vs. 4.0M	25.8% vs. 31.8%	Superiority & non-inferiority was not met IF is recommended as alternative therapy
FLP/FLO	FLP vs. FLO	220	PFS	superiority	8.8M vs. 10.7M	3.9M vs. 5.8M	3.1M vs. 5.1M	16.7% vs. 41.3%	Superiority in PFS was not met FLO is recommended as alternative therapy
ML17032	FP vs. XP	316	PFS	non-inferiority	9.3M vs. 10.5M	5.0M vs. 5.6M		32% vs. 46%	Non-inferiority in PFS was met
FLAGS	CF vs. CS	1053	OS	superiority	7.9M vs. 8.6M	5.5M vs. 4.8M	3.8M vs. 3.8M	31.9% vs. 29.1%	Superiority in OS was not met CS is similar in efficacy and less toxic compared to CF

AIO-YMO-0111/STO MATEO

AIO-Studien-gGmbH

MATEO: Maintenace Tesyuno in esophagogastric carcinoma



Correlative research
Polymorphisms, Target expression
Gene expression….

Primary Endpoint: Overall survival
297 patients will be randomized in 50 centers in Europe.

NCT02128243

Maintenance Therapy of Ipilimumab for AGC

Primary Endpoints
ir-PFS
Secondary Endpoints
mWHO-PFS, OS , ir-BORR

Study Specific Eligibility Criteria
- Advanced gastric and gastro-esophageal junction
- Measurable disease by mWHO criteria
- **First-line pretreatment with chemotherapy using fluoropyrimidine and platinum combination without disease progression (12-18wks)**
- No HER2 positive status
- No brain metastases

rPhase II trial
N=114

R
1:1

Ipilimumab
10 mg/kg IV
q3w x 4
then q12w until PD
treat up to 3 years

Best supportive care
Can include continuation of first-line fluoropyrimidine, but no other systemic anti-cancer therapy

NCT01585987

Conclusion - My Interpretation

PACX could not show the superiority in survival (PFS/OS) over XP.

However, PACX was associated with lower incidence of hematologic/GI toxicities than XP. In addition, PACX significantly showed higher ORR and QOL compared with XP.

PACX might be alternative regimen in place of platin-fluoropyrimidine doublets, but …

Negative trial, and somewhat out of date

Platin-fluoropyrimidine doublets still remain standard of care

Maintenance strategy is warranted further investigation for gastric cancer like NSCLC or CRC, especially, maintenance by immune checkpoint inhibitor is expected

Zhang X, et al. ESMO ASIA 2015

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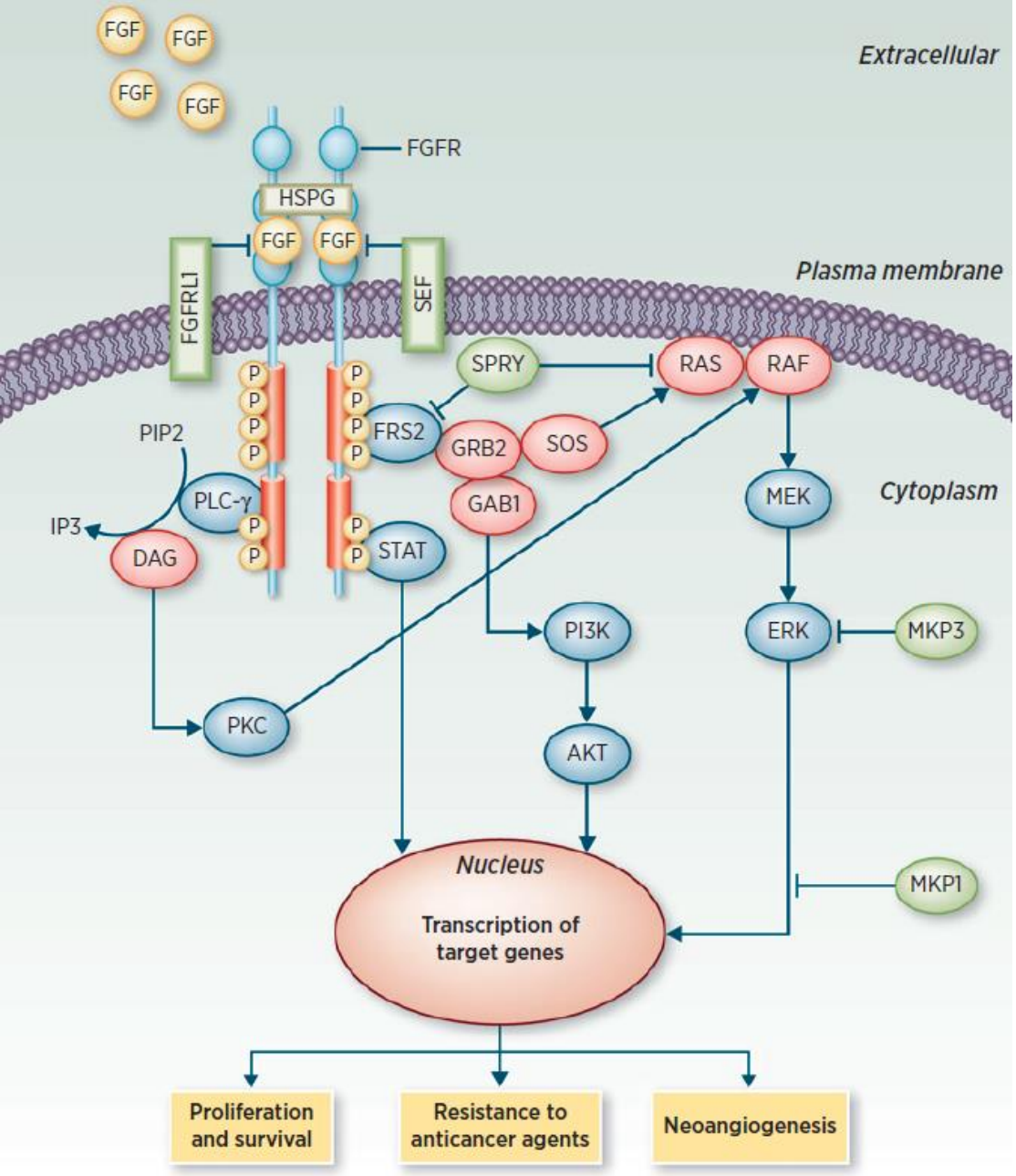
Phase II study of AZD4547 in *FGFR* amplified tumours: gastroesophageal cancer (GC) cohort clinical and translational results

Elizabeth Smyth, et al. UK

FGFR Signaling Network



4 key dwonstream pathways:

1) RAS-RAF-MAPK
2) PI3K-AKT
3) STAT
4) Phospolipase Cγ (PLC-γ)

4 different FGFRs:

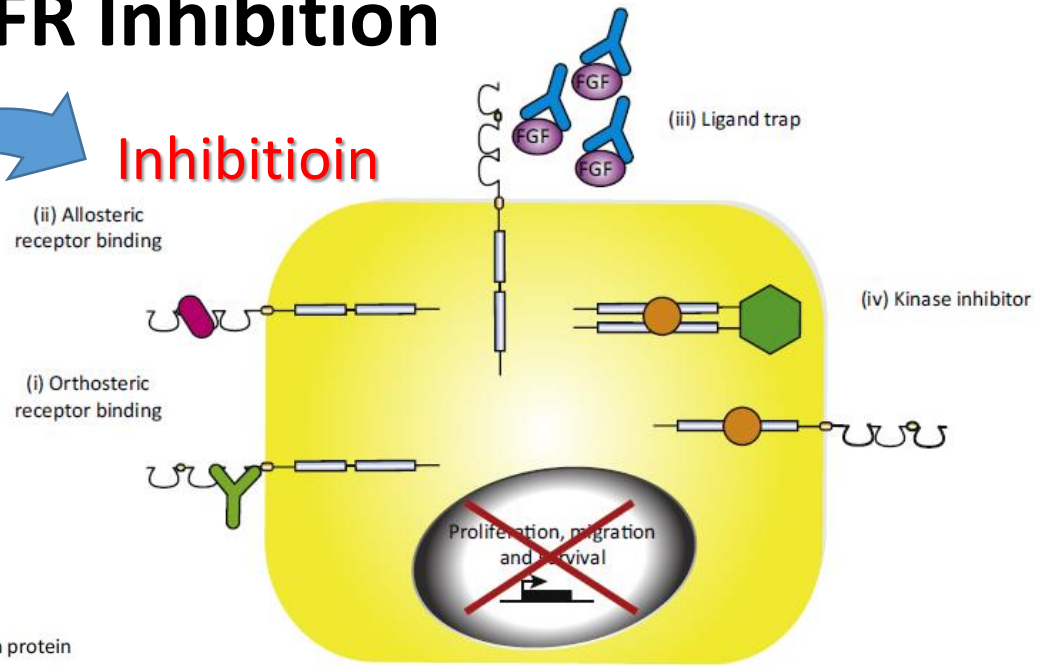
1) FGFR1
2) FGFR2
3) FGFR3
4) FGFR4

Touat M, et al. Clin Cancer Res 21: 2684-94 ,2015

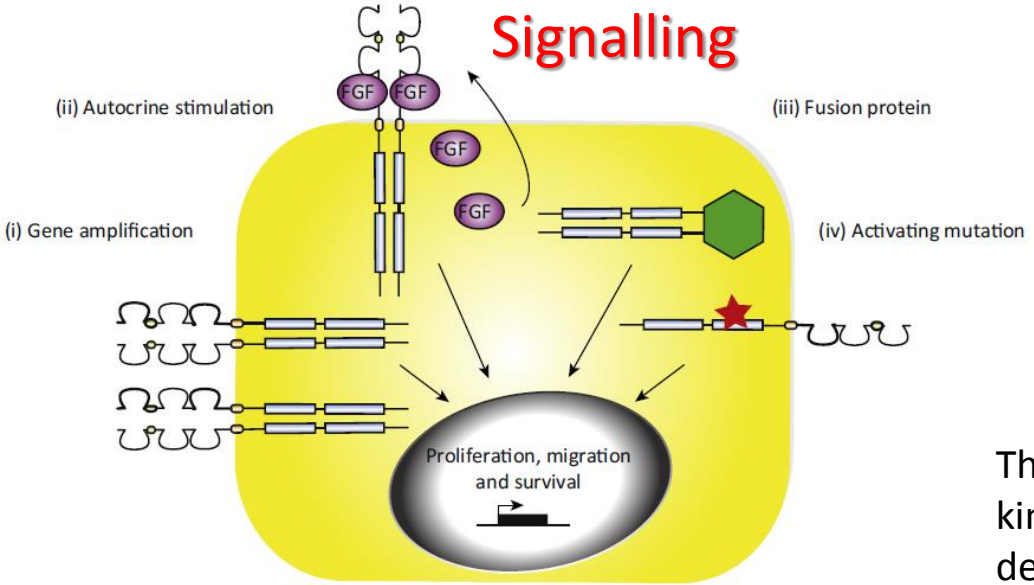
Mechanism of Aberrant FGFR Signalling in Disease And FGFR Inhibition

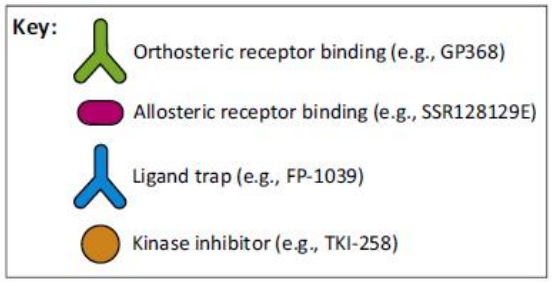
FGFR-activating mutations, gene amplifications, and translocations have been associated with neoplastic progression of breast, lung, prostate, endometrial, gastric, and urothelial carcinomas.

Inhibitioin



Signalling



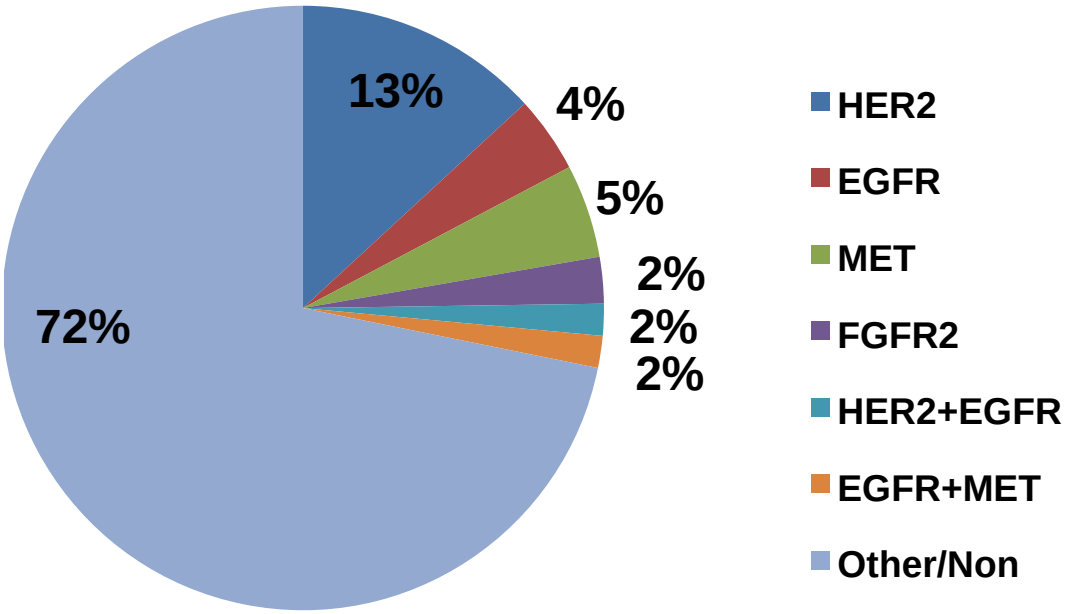


Therefore, targeting FGFRs with a small-molecule kinase inhibitor is an attractive strategy for the development of a new cancer treatment.

Tabernero J et al. J Clin Oncol 33: 3401-8 ,2015
Edward P et al. Trend Cell Biol 25: 221-233 ,2015

Epidemiology of FGFR2

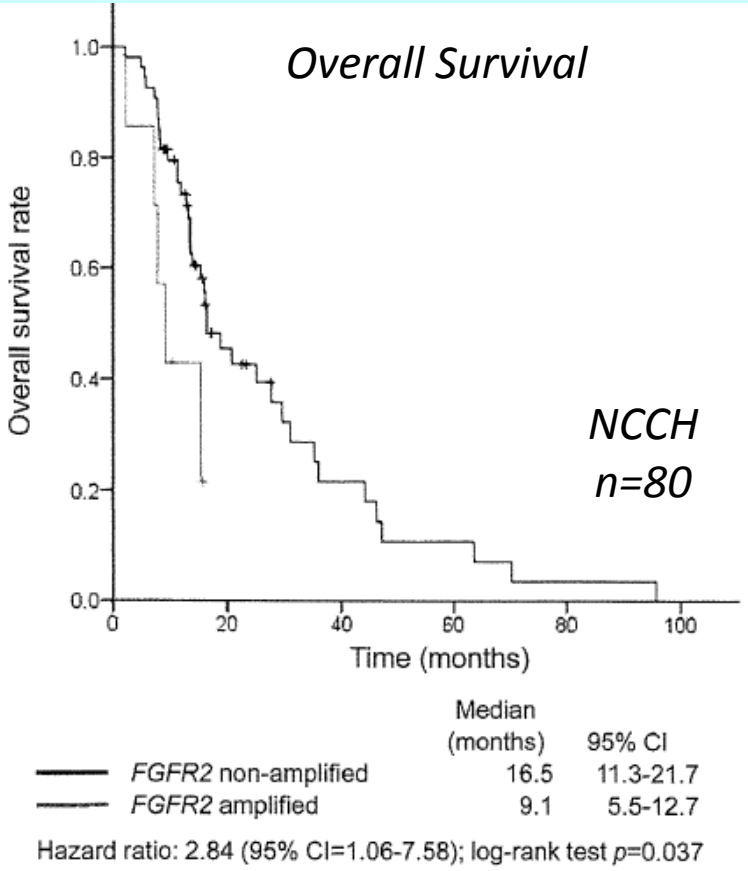
Gene Amplification Profiling in Advanced Gastric Cancer using NGS



NCCHE
n=121

Kuboki Y, et al. JSMO, 2014
Kuboki Y, et al. Ann Oncol, 2015

Chemotherapy for FGFR2-Amplified Advanced Gastric Cancer



Shoji H, et al. Anticancer Res 35: 5055-5062, 2015

Compounds And Clinical Trials on FGF(R) Targeting

Compound	Company	Status	Indication
Multi TKI inhibitors			
AP24534 (Ponatinib)	Ariad Pharma	Approved Phase II	CML, ALL Gastrointestinal stromal tumours, lung/thyroid cancer, AML
BIBF1120 (Nintedanib)	Boehringer Ingelheim	Submitted Phase III	NSCLC Ovarian cancer, IPF
E7080 (Lenvatinib)	Eisai	Submitted Phase II/III	Thyroid cancer Hepatocellular carcinoma, endometrial cancer, melanoma, glioma, NSCLC
TSU-68 (Orantinib)	Taiho Pharma	Phase III	Hepatocellular carcinoma
ENMD-2076	CASI Pharma	Phase I/II	Breast/ovarian cancer
E3810 (Lucitanib)	Clovis Oncology/Servier	Phase I/II	ER^+ Breast cancer, Solid tumours
TKI258 (Dovitinib)	Novartis	Phase II	Multiple cancers including advanced endometrial and breast cancers
ARQ 087	ArQule	Phase I	Solid tumours
FGFR selective TKI inhibitors			
AZD4547	Astra Zeneca	Phase II	Solid tumours
BGJ398	Novartis	Phase II	Solid tumours, melanoma
LY2874455	Lilly	Phase I	Advanced cancer
Debio 1347	Debiopharm	Phase I	Solid tumours
TAS-120	Taiho Pharma	Phase I/II	Solid tumours, multiple myeloma
JNJ42756493	Astex pharma/Janssen	Phase I	Neoplasms, lymphoma
FGFR Antibodies			
MGFR1877S	Genetech/Roche	Phase I	Solid tumours, multiple myeloma
KRN23	Kyowa Hakko Kirin	Phase II	X-linked hypophosphatemia
FGF Traps			
FP-1039 (GSK3052230)	Five prime therapeutics/GSK	Phase I	Solid tumours

Edward P et al. Trend Cell Biol 25: 221-233 ,2015

Dr. Elizabeth Smyth's Conclusions

- AZD4547 demonstrated promising activity in *FGFR2* amplified oesophagogastric cancer with significant and durable responses in 33% (3/9) patients treated on study

- Response was associated with:

  High level homogenous *FGFR2* amplification in tissue

  Presence of *FGFR2* ctDNA in plasma

  Truncated C3 isoform expression on NanoString

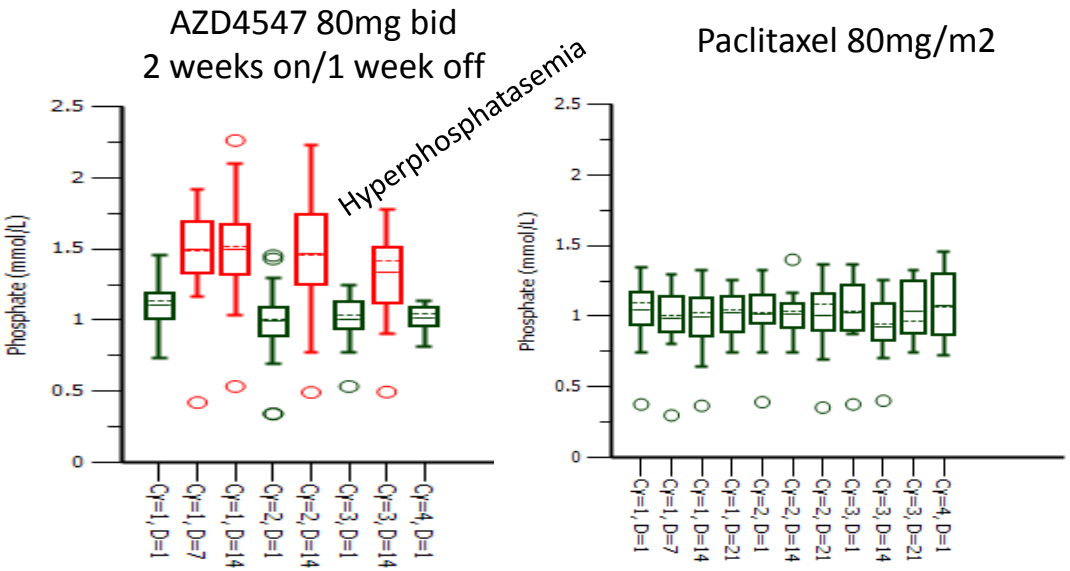
  And also, *FGFR2* IIIb and IIIC isoforms expression on NanoString

- *FGFR2* copy number gain detected in plasma ctDNA using ddPCR is currently being used to select patients for study entry

Smyth E, et al. ESMO ASIA 2015

A randomized, open-label phase II study of AZD4547 (AZD) versus Paclitaxel in previously treated patients with advanced gastric cancer (AGC) with Fibroblast Growth Factor Receptor 2 (FGFR2) polysomy or gene amplification: SHINE study

AZD4547 Treatment Increases Plasma Phosphate



AZD4547 Response

FGFR FISH score 4/5 (polisomy)

Response=1/20

FGFR FISH score 6 (amplificaton)

Response=0/18

ORR=2.6% (1/38)

Conclusion in Efficacy

The analysis of PFS (primary endpoint) did not show any statistically significant difference in favour of the AZD4547 arm, compared with the paclitaxel arm (HR 1.57, 80% CI: 1.12, 2.21). Similar results were observed for the FISH 6 strata (HR 1.30; 80% CI: 0.81, 2.12).

Bang YJ, et al. ASCO 2015

Why Were Different Efficacy Results Observed in Two AZD4547 Phase II Studies?

	SHINE (rPII)	*Current Study (PII)*
Number of Patients	ITT: 71 (AZD4547: 40)	GC cohort: 9
Screening Methodology	Centralized FISH in archival tumor	Centralized FISH in archival or fresh tumor
Subjects Criteria	FGFR2: Polysomy & Amplified (ratio >2.0)	FGFR2: Amplified (ratio >2.0)
ORR	2.6% (1/38)	33% (3/9)

Establishment of more accurate and more simplified screening system is required.
If liquid biopsy (ctDNA) is available, It is definitely desirable.

Bang YJ, et al. ASCO 2015
Smyth E, et al. ESMO ASIA 2015

Treatment Pathways Currently under Evaluation as Phase III Trial for Gastric Cancer

FGFR?? No PIII

MET? (Rilotumumab ×, Onartuzumab ×)

EGFR? (Panitumumab ×, Cetuximab ×)

HER2 (Trastuzumab○, T-DM1 ×, Lapatinib ×)

Angiogenesis (Bev ×, RAM○)

PARP

STAT3

Checkpoint Inhibitor

>5,000 patients are planned to be enrolled in 19 ongoing studies, with additional studies being planned

Shah MA. J Clin Oncol 33:1760–1769, 2015, substantially modified

Back Up

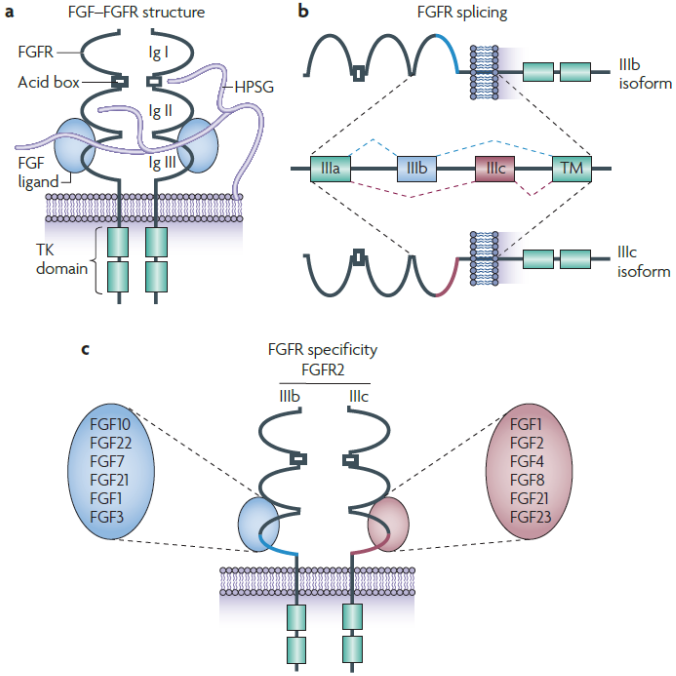


Figure 1 | **FGFR structure and control of ligand specificity. a** | The basic structure of the fibroblast growth factor (FGF) –FGF receptor (FGFR) complex comprises two receptor molecules, two FGFs and one heparan sulphate proteoglycan (HSPG) chain. The FGF signalling pathway comprises 4 highly conserved transmembrane receptors and 18 FGF ligands (BOX 1). FGFs bind with low affinity to cell surface HSPGs (purple) and with high affinity to specific FGFRs. The FGFRs, which are phylogenetically closely related to the vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), consist of three extracellular immunoglobulin (Ig) domains, a single transmembrane helix and an intracellular split tyrosine kinase (TK) domain. The second and third Ig domains form the ligand-binding pocket and have distinct domains that bind both FGFs and HSPGs. **b** | Ligand-binding specificity is generated by alternative splicing of the Ig III domain. The first half of Ig III is encoded by an invariant exon (IIIa), which is spliced to either exon IIIb or IIIc, both of which splice to the exon that encodes the transmembrane (TM) region. Epithelial tissues predominantly express the IIIb isoform and mesenchymal tissues express IIIc. FGFR4 is expressed as a single isoform that is paralogous to FGFR-IIIc. **c** | Examples of the extent to which ligand specificity can differ between FGFR-IIIb and FGFR-IIIc isoforms, illustrated with the differing ligand specificty of FGFR2 isoforms. The FGFR2-IIIb ligands are shown in blue and the FGFR2-IIIc ligands are shown in brown. For example, FGF7 and FGF10 bind specifically to FGFR2-IIIb and have essentially no binding to FGFR2-IIIc[7]. The mechanisms controlling splice isoform choice are becoming clearer and defined control elements have been identified in the introns surrounding alternatively spliced exons[177–179].

RCTs with Targeting Agents for Metastatic GC

Line	Study	Agent Tested	Molecular Target	Control Arm	Pri. End.
1st	ToGA (HER2)	trastuzumab	HER2	XP/FP	OS
	LOGiC(HER2)	lapatinib	HER2	XELOX	OS
	JACOB (HER2)	pertuzumab	HER2	XP + trastuzumab	OS
	AVAGAST	bevacizumab	VEGF	XP	OS
	EXPAND	cetuximab	EGFR	XP	PFS
	REAL-3	panitumumab	EGFR	EOX	OS
	RILOMET-1, 2	rilotumumab	cMET	ECX, XP	OS
	RAINFALL	ramucirumab	VEGFR2	XP	PFS
2nd	TyTAN (HER2)	lapatinib	HER2	weekly paclitaxel	OS
	GATSBY (HER2)	TDM-1	HER2	weekly paclitaxel	OS
	RAINBOW	ramucirumab	VEGFR2	weekly paclitaxel	OS
	GRANITE2	everolimus	HER2	weekly paclitaxel	PFS
	ENRICH	nimotuzumab	EGFR	irinotecan	OS
	REGARD	ramucirumab	VEGFR2	BSC (placebo)	OS
	GOLD	olaparib	PARP	weekly paclitaxel	OS
	BRIGHTER	BBI-608	STAT3	weekly paclitaxel	OS
	KEYNOTE 061	pembrolizumab	PD-1	weekly paclitaxel	OS
2nd / 3rd	GRANITE1	everolimus	mTOR	BSC (placebo)	OS
3rd～	ONO-4538-12	nivolumab	PD-1	BSC (placebo)	OS

RCTs with Targeting Agents for Metastatic GC

Line	Study	Agent Tested	Molecular Target	Control Arm	Pri. End.
1st	ToGA (HER2)	trastuzumab	HER2	XP/FP	OS
	LOGiC(HER2)	lapatinib	HER2	XELOX	OS
	JACOB (HER2)	pertuzumab	HER2	XP + trastuzumab	OS
	AVAGAST	bevacizumab	VEGF	XP	OS
	EXPAND	cetuximab	EGFR	XP	PFS
	REAL-3	panitumumab	EGFR	EOX	OS
	RILOMET-1, 2	rilotumumab	cMET	ECX, XP	OS
	RAINFALL	ramucirumab	VEGFR2	XP	PFS
2nd	TyTAN (HER2)	lapatinib	HER2	weekly paclitaxel	OS
	GATSBY (HER2)	TDM-1	HER2	weekly paclitaxel	OS
	RAINBOW	ramucirumab	VEGFR2	weekly paclitaxel	OS
	GRANITE2	everolimus	HER2	weekly paclitaxel	PFS
	ENRICH	nimotuzumab	EGFR	irinotecan	OS
	REGARD	ramucirumab	VEGFR2	BSC (placebo)	OS
	GOLD	olaparib	PARP	weekly paclitaxel	OS
	BRIGHTER	BBI-608	STAT3	weekly paclitaxel	OS
	KEYNOTE 061	pembrolizumab	PD-1	weekly paclitaxel	OS
2nd / 3rd	GRANITE1	everolimus	mTOR	BSC (placebo)	OS
3rd～	ONO-4538-12	nivolumab	PD-1	BSC (placebo)	OS

Previous study-1

British Journal of Cancer (2008) 98, 316 – 322

www.bjcancer.com

A phase II study of paclitaxel and capecitabine as a first-line combination chemotherapy for advanced gastric cancer

HJ Kang[1], HM Chang[1], TW Kim[1], M-H Ryu[1], H-J Sohn[1], JH Yook[2], ST Oh[2], BS Kim[2], J-S Lee[1] and Y-K Kang*,[1]

[1]Division of Oncology, Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Clinical St

N=45
- Paclitaxel: 175mg/m2 day1
- Capecitabine: 825mg twice daily on days 1-14 q3w

ORR: 48.9% (95%CI, 30.3-63.5)
mTTP: 5.6 months (95%CI, 3.9-7.2)
mOS: 11.3 months (95%CI, 8.1-14.4)

Keywords: paclitaxel; capecitabine; advanced gastric cancer

Kang HJ et al. Br J Cancer 98: 316-322, 2008