N.N. Blokhin's Russian Cancer Research Center

The possibilities of targeted therapy for disseminated/metastatic gastric cancer (GC)

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The material is intended for health professionals ONCO-EM-2431-2016-11-23

Information disclosure

- Natalia Sergeevna Besova, Cand.med.sci., к.м.н., senior researcher of the department of chemotherapy of RCRC
- Presentations made: Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, Roche, Novartis.
- Participation in expert councils/consultations: Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, Roche
- Participation in clinical trials: Eli Lilly, Roche, Pfizer.

Uniform standards for treatment of disseminated gastric adenocarcinoma and cardioesophageal junction are not developed

Treatment methods

<table>
<tr><th>Doublet chemotherapy</th><th>Additional therapy</th><th>Targeted therapy</th><th>X-ray therapy</th></tr>
<tr><td>Common practice</td><td>No uniform decision</td><td rowspan="4">Depending on biomarkers

(HER2: trastuzumab)</td><td rowspan="4">Only the symptoms control

(The role after radical surgery is not clearly defined)</td></tr>
<tr><td>Standard practice in Asia</td><td>Widespread in Europe and the US (also in Australia)</td></tr>
<tr><td>Fluoropyrimidines and platinum derivatives</td><td>Taxanes; Anthracyclines</td></tr>
<tr><td colspan="2">A wide variety of preferred combinations in different countries of the world</td></tr>
</table>

- The prognosis for gastric cancer of very early stages is favorable in Asian countries, but unfavorable in other countries, as well as in the late stages
- Median overall survival in most studies of the 1st line therapy - 9-11 months

ЖПС – желудочно-пищеводное соединение; HER2 – рецептор 2 человеческого эпидермального фактора роста.

Price TJ et al. *Expert Rev Gastroenterol Hepatol* 2012;6:199–208

Disseminated/metastatic gastric adenocarcinoma/cardioesophageal junction

First line therapy

Chemotherapy

mGC. Chemotherapy. 1st line standards

Efficacy of capecitabine = efficacy of the **infusion 5-FU**
The efficacy of oxaliplatin = the efficacy of cisplatin

Doublet regimens

A combination of fluoropyrimidines (5-FU **daily infusions!,** capecitabine) with platinum derivatives (cisplatin, oxaliplatin) - PF (CF), XP, XELOX, FOLFOX or irinotecan - IF, FOLFIRI

Triplet regimens

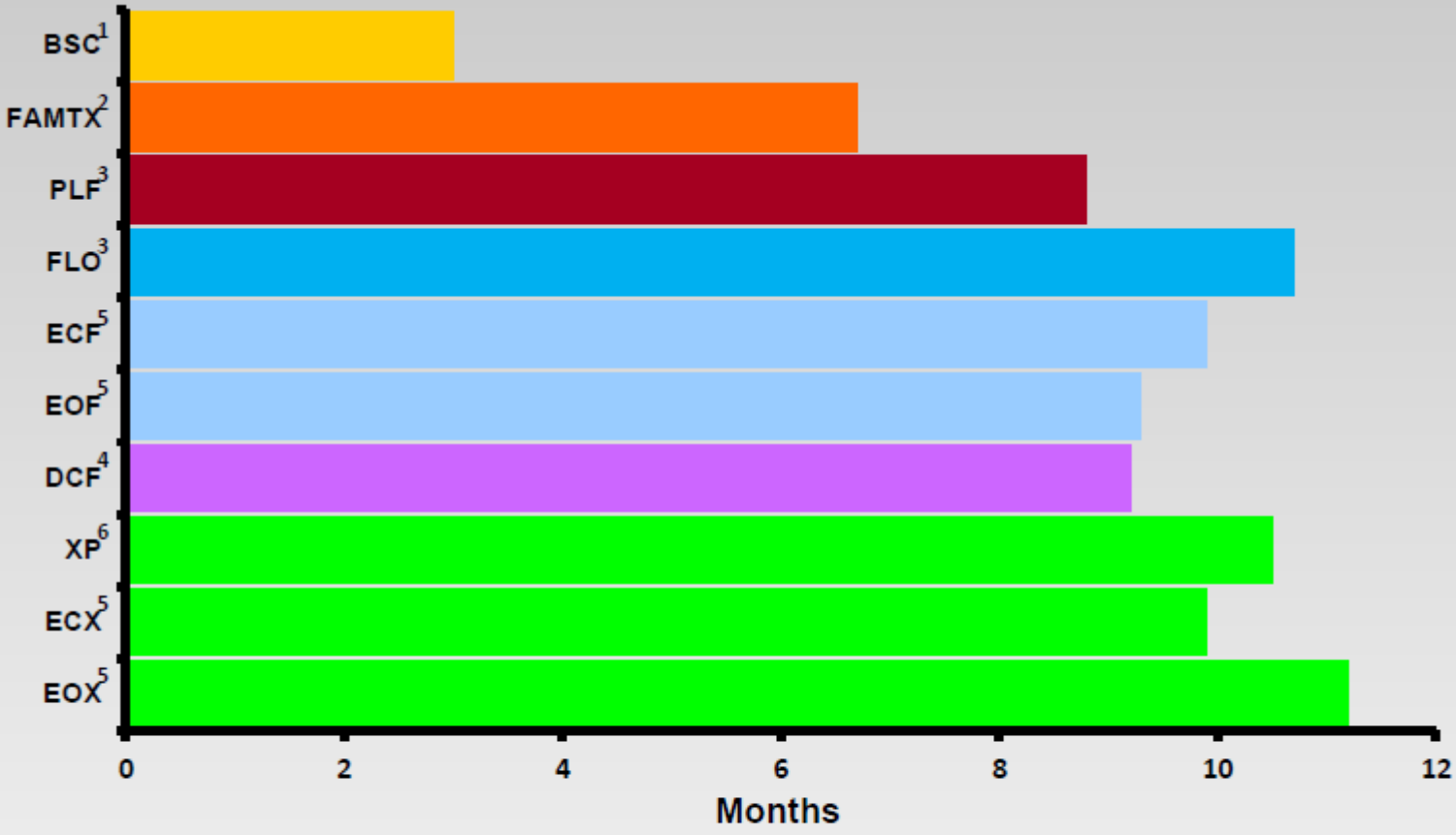
Fluoropyrimidines + platinum derivatives + anthracyclines: ECF, ECX, EOF, EOX
Docetaxel: DCF,

Docetaxel 40 mg / m² + cisplatin 40 mg / m² every 2 weeks +
5-FU 2000 mg / m² / folic acid 200 mg / m² - weekly
OE = 46,6%, MTTP – 8,1 months, MOS – 15,1 months
(Lorenzen S et al. Ann Oncol 2007;18(10):1673-1679)

FLOT
Docetaxel 50 mg/m²+ mFOLFOX – every 2 weeks
OE = 53% MTTP– 5,3 months
MOS – 11,3 months
(Al-Batran SE et al. Ann Oncol 2008;19(11):1882-1887)

TEF
Docetaxel 50 mg/m² + oxaliplatin 85 mg/m² + leucovorin 400 mg/m² + 5-FU + 2,400 mg/m² every 2 weeks
OE = 47% MTTP – 7,7 months MOS – 14,6 months
(Van Cutsem E., Boni C., Tabernero J, et al Ann Oncol.2015;26:149-156)

mGC. 1st line chemotherapy. Median overall survival of patients



1. Murad AM, et al. *Cancer.* 1993;72(1):37-41. 2. Vanhoefer U, et al. *J Clin Oncol.* 2000;18(14):2648-2657.
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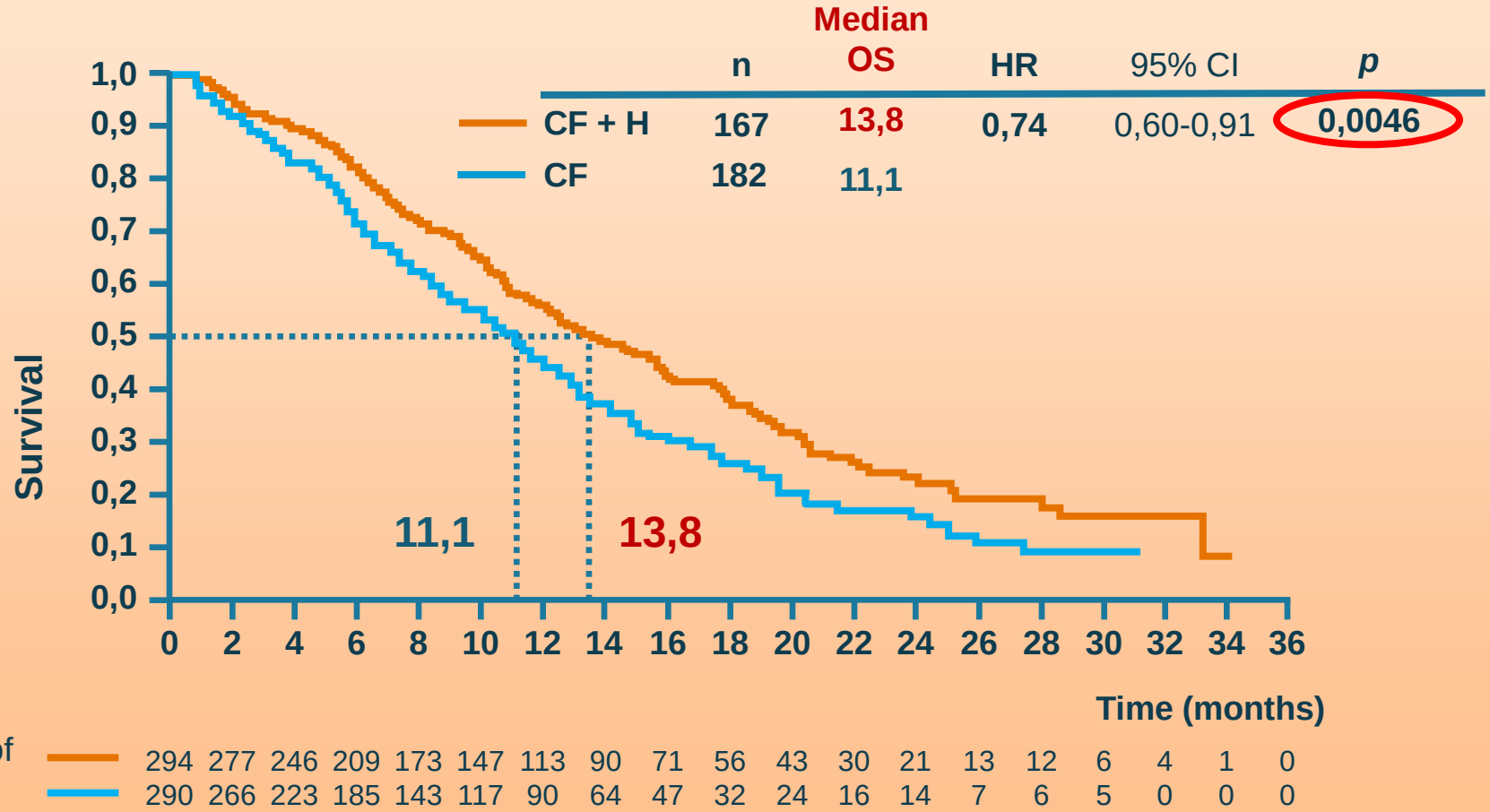
5. Cunningham D, et al. *N Engl J Med.* 2008;358(1):36-46. 6. Kang YK, et al. *Ann Oncol.* 2009;20(4):666-673.

Disseminated/metastatic gastric adenocarcinoma/cardioesophageal junction

First line therapy

Targeted therapy

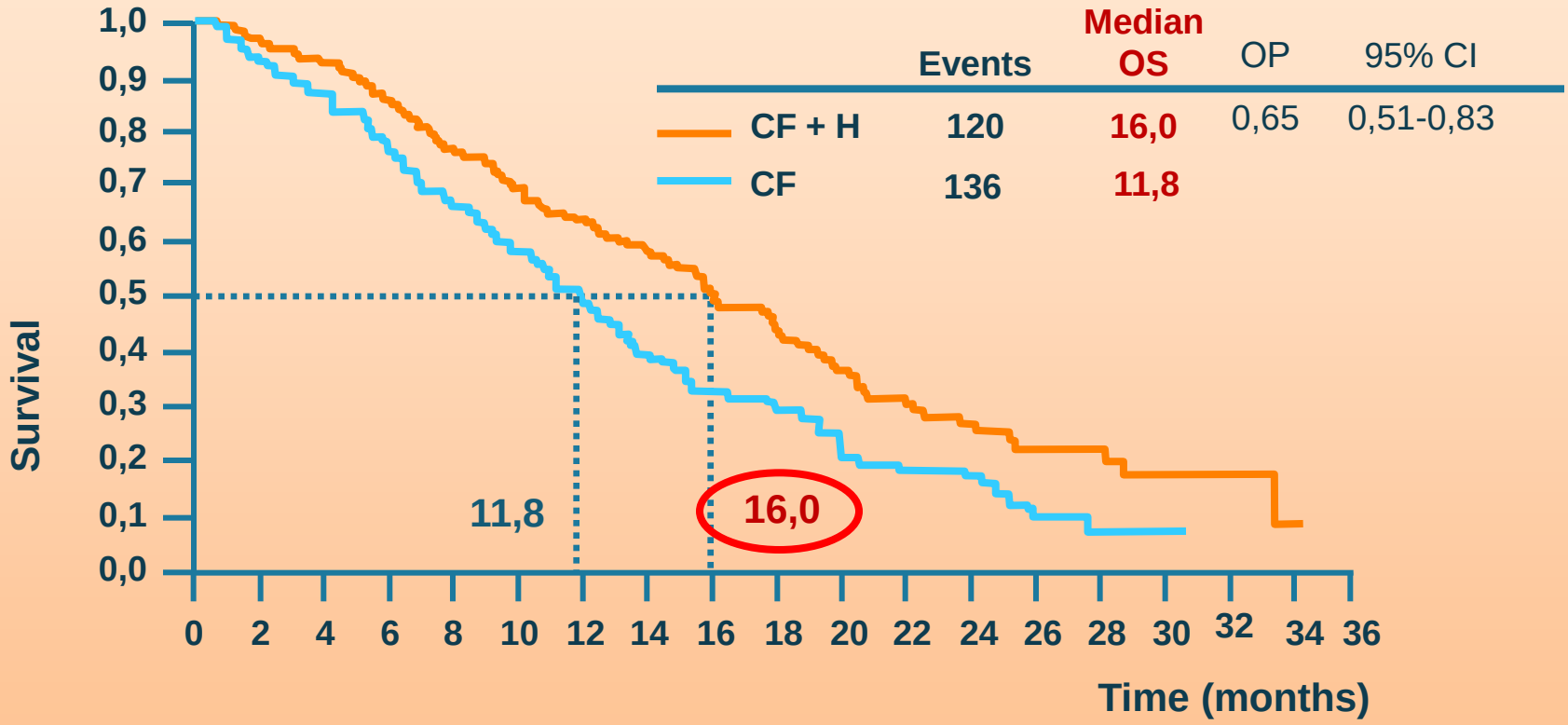
HER2 +mGC. Hyperexpression of HER2 in 7-32% (average in 19%) of cases.
TOGA. Cisplatin + fluoropyrimidine ± Trastuzumab
The main objective - improvement of OS achieved



CI: confidence interval; **H:** trastuzumab; **F**: fluoropyrimidine ; **C:** cisplatin

Bang and coauth.; The Lancet 2010; 376: 687-97

TOGA. Maximum patient survival achieved at HER2 status
IHC2+/FISH+ or IHC3+

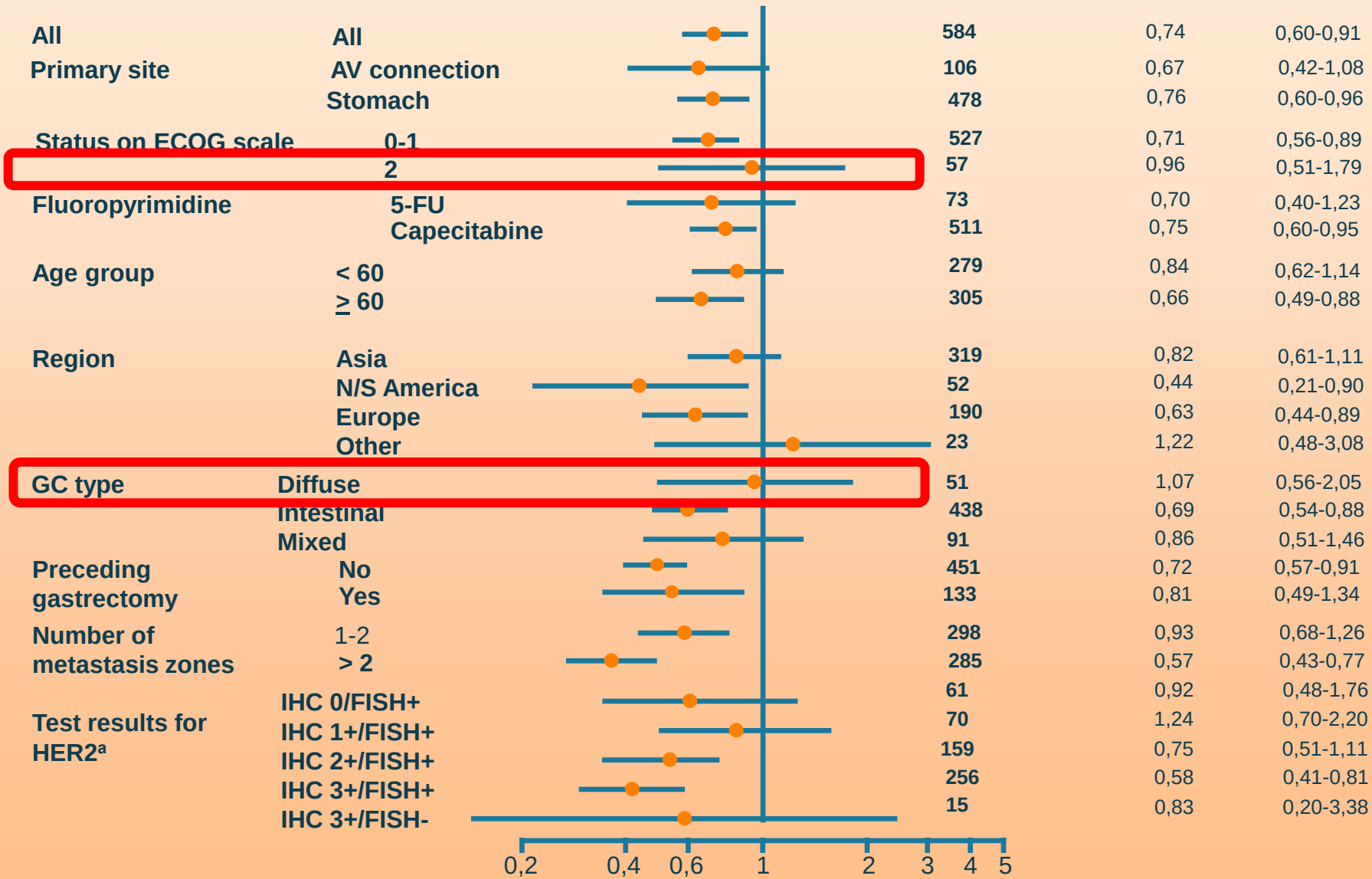


Number of patients

	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

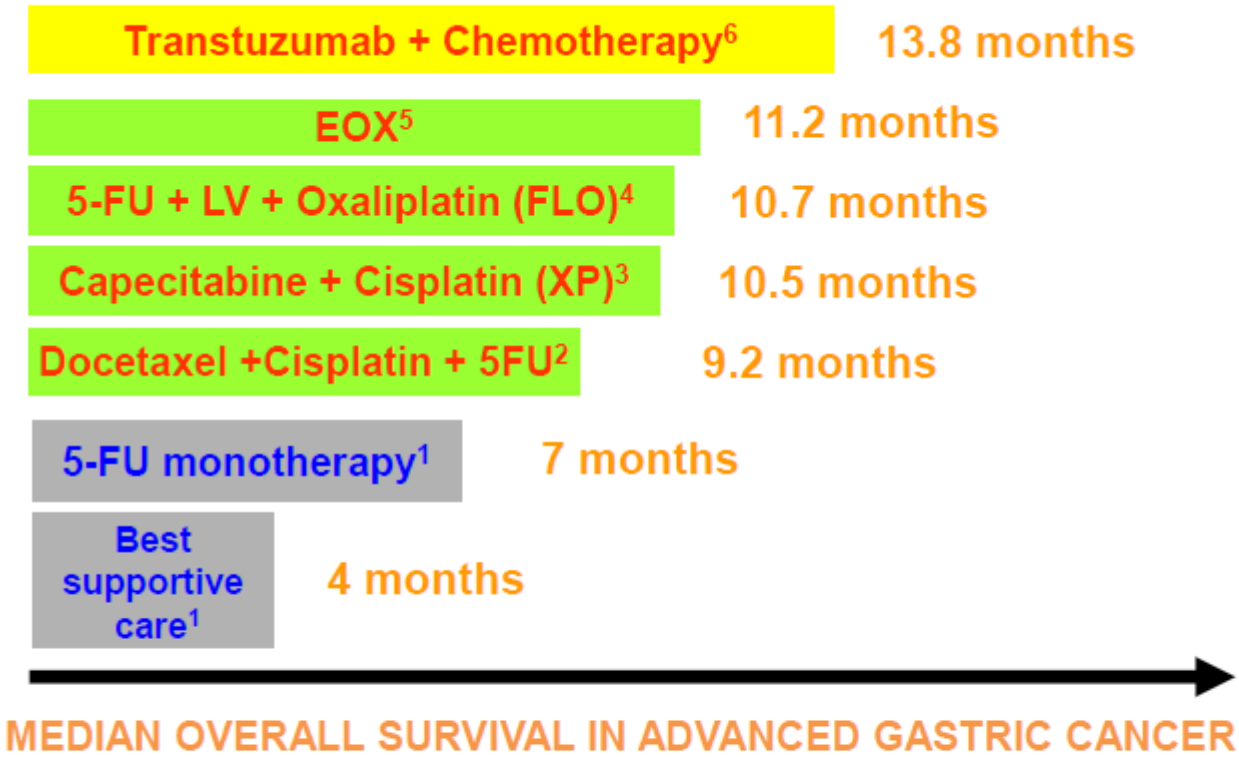
Bang and coauth.; The Lancet 2010; 376: 687-97

Overall survival by subgroups



Bang u coaвm.; The Lancet 2010; 376: 687-97

Progress in treatment of patients with disseminated gastric adenocarcinoma/cardioesophageal junction: increase of median life expectancy by 3 times



1. Wagner A, et al. JCO 2003, 2. van Cutsen E, et al. JCO 2006. 3.Kang YK et al, Ann Oncol 2009. 4. Al Batran SE, et al. JCO 2009. 5. Cunningham D, et al. NEJM 2007. 6.van Cutsen E, et al. ASCO 2009.

HER2+mGC/CEJ. Current research
III phase research

	n	Regimen	Main aim
mGC/CEJ 1 line	780	Group A: Pertuz + T/CisPt/fluoropyrimidine Group B: Placebo + T/CisPt/fluoropyrimidine	OS
mGC/CEJ 1 line	400	Group A: T 6mg/kg /3 weeks + Cape/CisPt Group B: T 10mg/kg /3 weeks+ Cape/CisPt	OS
Oesophageal cancer/CEJ neoadjuvant	480	Group A: LT + Carbo/Pac/T Group B: LT + Carbo/Pac	RVS

T = Trastuzumab

Disseminated/metastatic gastric adenocarcinoma/cardioesophageal junction

Second line therapy

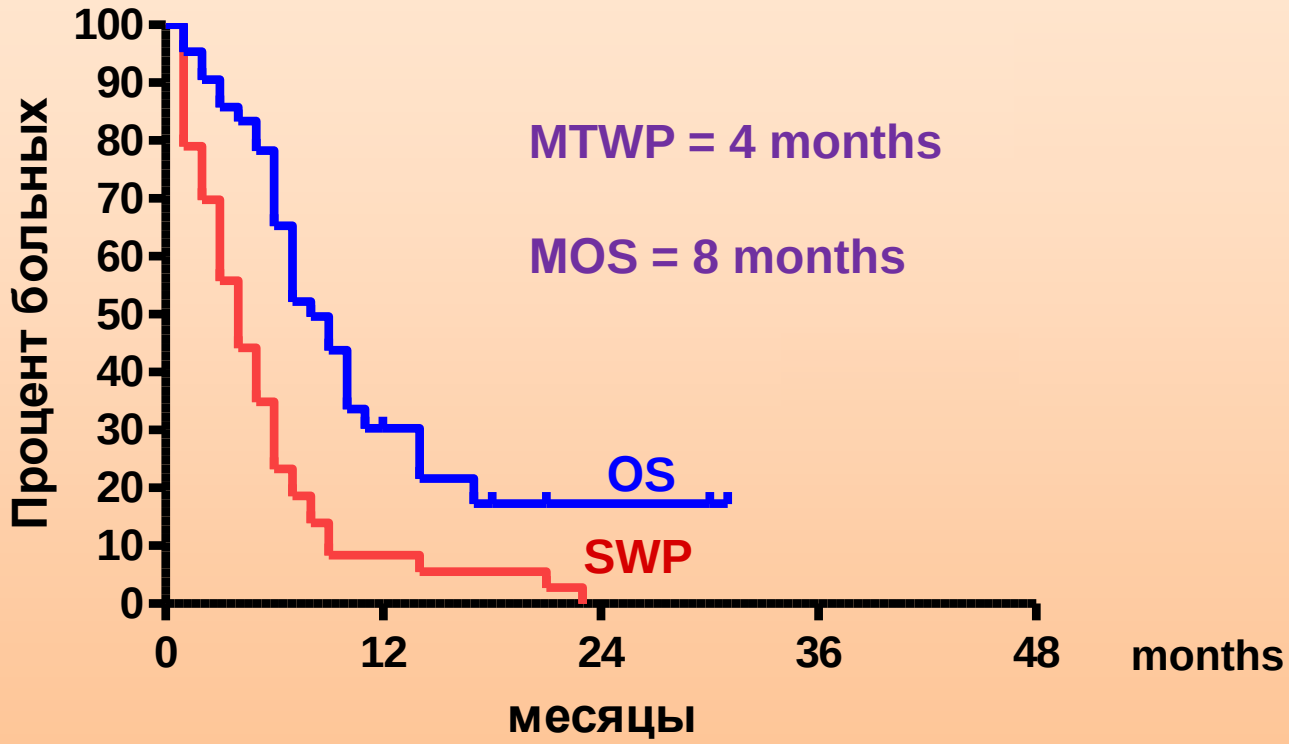
Chemotherapy

mGC/CEJ. Second-line chemotherapy while resistance to a combination of fluoropyrimidines with platinum derivatives (CF / CX / XELOX). Randomized trials

Author	n	Drugs, dozes in mg/m²	MOS, months	HR (95%CI)	p
Thuss-Patience et al., EJC 2011	40	Irinotecan 250-300 /3 week	4.0	0.48 (0.25-0.92)	0.012
		BSC	2.4		
Ford et al., Lancet Oncol 2014	168	Docetaxel 75 /3 week	5.2	0.67	0.01
		BSC	3.6		
Park, et al JCO 2012	193	Doc 60 /3week or Iri 150 /2week	5.3	0.65	0.007
		BSC	3.7		
Cunningham et al. ASCO GI 2011		**Docetaxel 75 /3 week**	7.3		
		Irinotecan 300 /3 week	7.8		
Park et al. ASCO 2011		**Docetaxel 60 /3 week**	5.2		
		Irinotecan 180 /2 week	6.5		
Hironaka, et al. JCO 2013; 31(35):4438-4444	108	Paclitaxel 80 1,8,15d /4 week	9.5	1.13 (0.86-1.49)	0.38
	111	Irinotecan 180 1,15 d /4 week	8.4		

mGC. 2nd line. Irinotecan + capecitabine *(n=43)* after the combination of docetaxel with platinum derivatives and 5-FU. General and non-progressive survival

(Gorbunova V.A., Besova N.S., Trusilova E.V.)



Drug	Irino	Docet	Doc/Iri	Pacli	Xeliri
n	21	84	20	335	43
MOB, mon.	4,0	5,4	5,3	7,4	8,0

Disseminated/metastatic gastric adenocarcinoma/cardioesophageal junction

Second line therapy

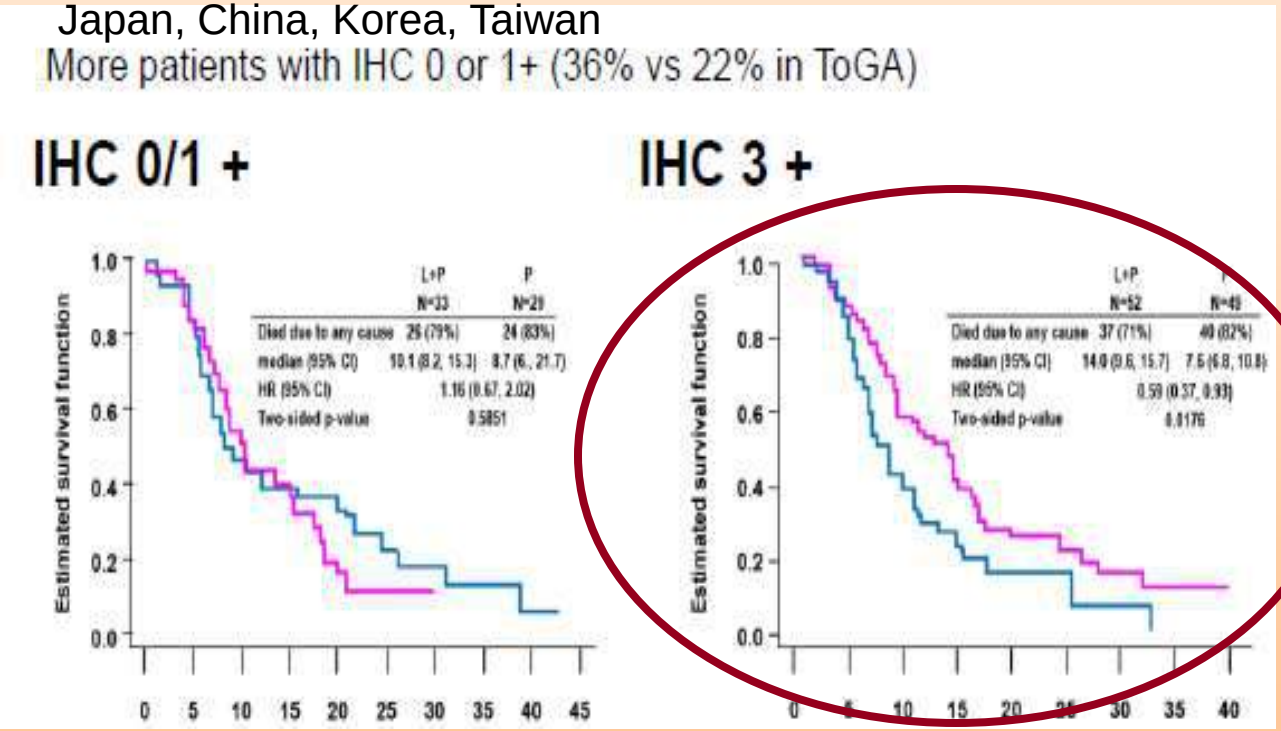
Targeted therapy

HER2+mGC. TyTAN. 2nd line treatment after Herceptin: Paclitaxel ± lapatinib.

Significant improvement of overall survival in only one subgroup of patients: with IHC 3+

Japan, China, Korea, Taiwan

More patients with IHC 0 or 1+ (36% vs 22% in ToGA)

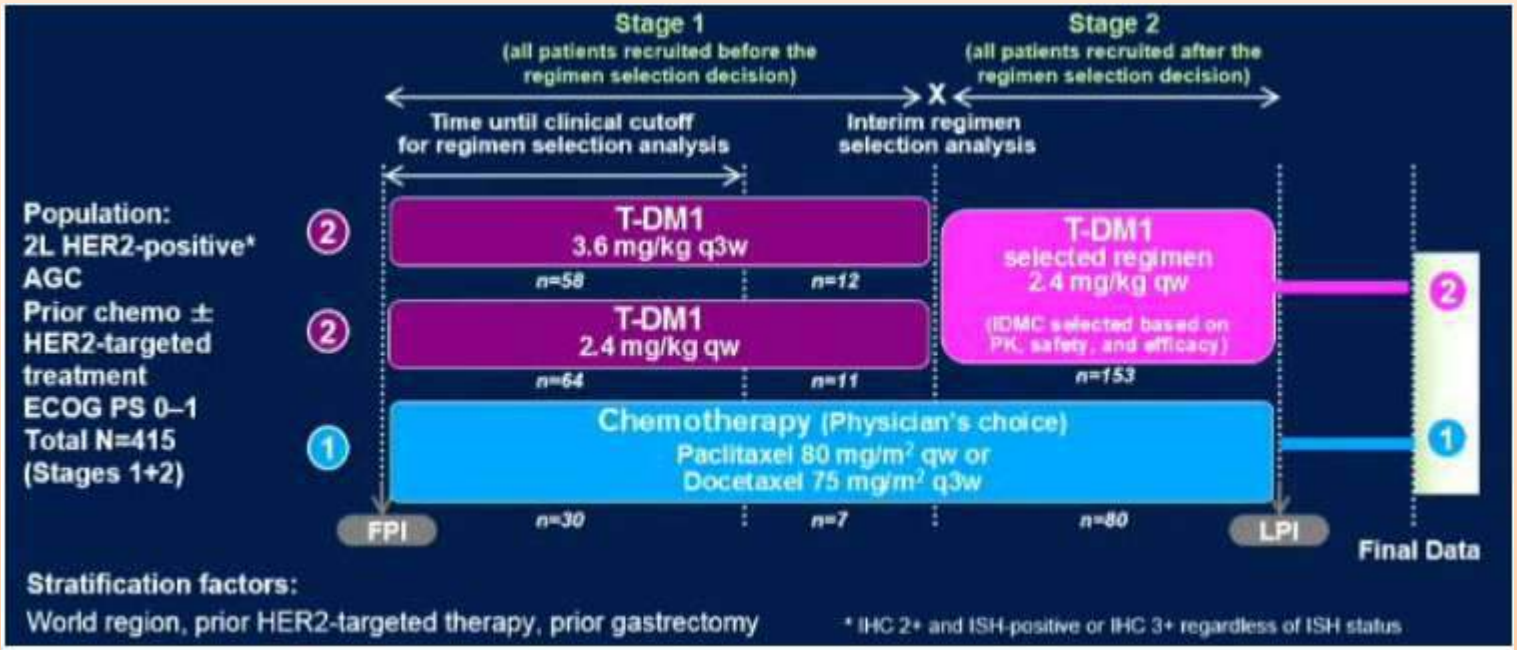


While G/CEJ adenocarcinoma metastasizing after herceptin treatment, a repeated biopsy with HER2-status examination is needed

Bang, et al. 2013 ASCO-GI

HER+mGC/CEJ. 2nd line . GATSBY: T-DM1 vs taxanes

(Kang YK PC et al., ASCO GI, 2016)



- Primary Endpoint: OS

effectiveness parameter	T-DM1 n=201	taxanes n=102	HR	p
MOS	7.9 months	8.6 months	1.15	0.8558
MTWP	2.7 months	2.9 months	1.13	0.3080
OE	20.6%	19.6%	0.98	0.8406

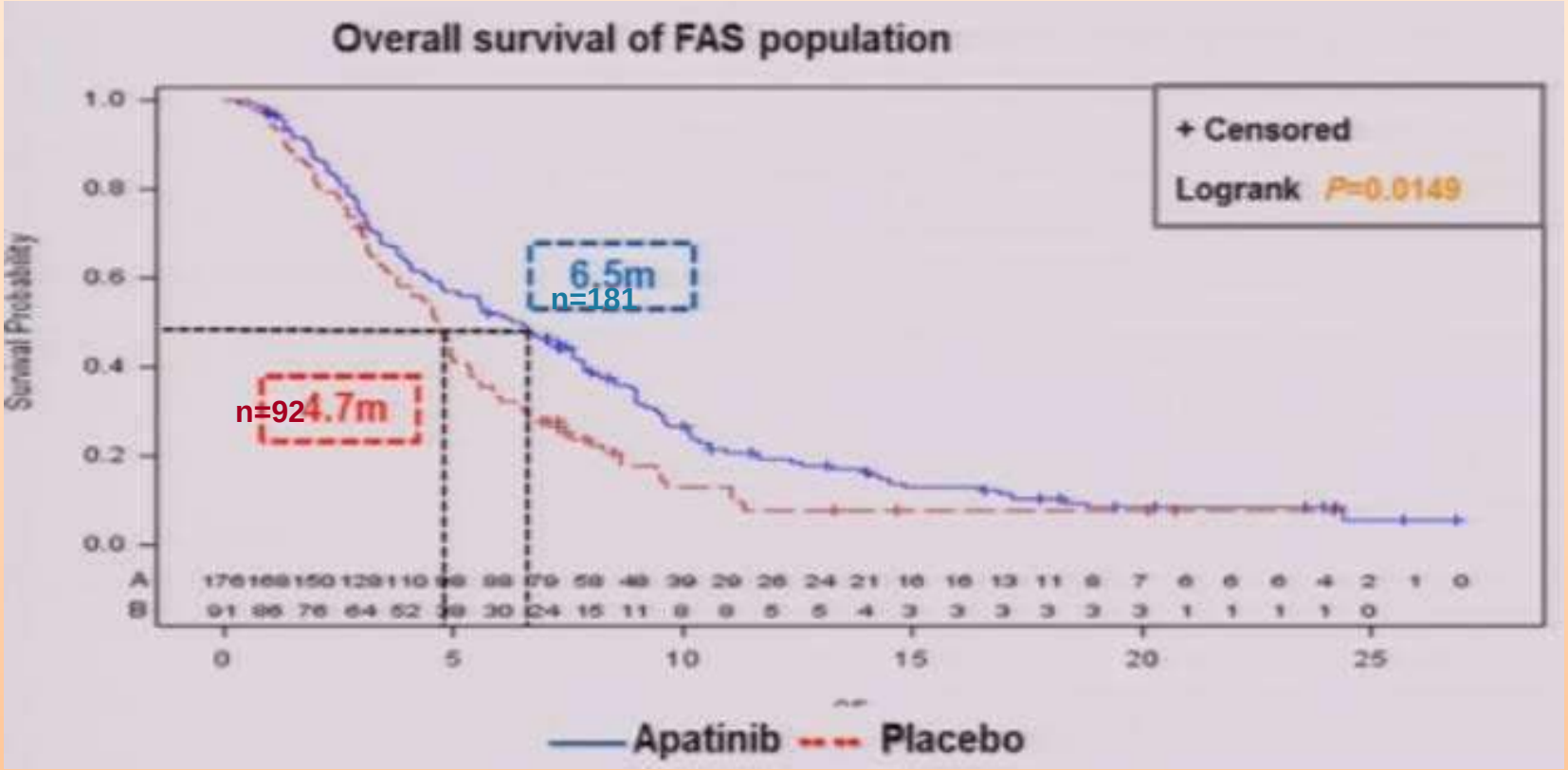
Randomized clinical trials to evaluate the effectiveness of targeted therapy for disseminated gastric adenocarcinoma/CEJ

	CS	Target	N	Main criterion	Treatment	MOS (mon.)	*p*	ОЭ (%)
1st line		**MET+ HER2-**		**OS while MET IHC2+/3+**	**mFOLFOX6 ± Onartuzumab**	*Current trial*		
2nd line	GRANITE[1]	mTOR	656	OS	Placebo everolimus	4,34 5,39	незначим.	2 5
	COG[2]	EGFR	450	OS	Placebo gefitinib	3,67 3,73	незначим.	0 3
	GRANITE-2	mTOR			Paclitaxel ± Everolimus	*Current trial*		
3rd line		VEGFR	273	OS	Placebo Apatinib	4.7 6.5 *(for fas population)*	0.0149	

CT - chemotherapy;
EGFR – epidermal growth factor receptor;
mTOR – mammalian target of rapamycin;
OE – objective effect;
OS – general survival;
SWP – survival without progression.

1. Ohtsu A et al. *J Clin Oncol* 2013;31:3935–3943
2. Dutton SJ et al. *Lancet Oncol* 2014;15:894–904

Apatinib is a multitarget multikinase TKIninhibitor that is active against VEGFR.
Apatinib (850 mg daily) vs BSC in 3L treatment of mGC



Qin S. *J Clin Oncol. 2014;32(5s):Abstract 4003.*

Phase	Disease status	Regimen	n	MTWP, months	MOS	Literature
II Line 3	MTS, 2 line, refractoriness to Trast	Afatinib	13	6.6	—	Janjigian. ASCO GI 2014, A 52

Заключение

Of the many targeted therapy drugs that have undergone Phase III clinical trials, for the treatment of patients with disseminated gastric adenocarcinoma or cardioesophageal junction there are recommended

- Trastuzumab in combination with chemotherapy -
In the first line treatment of HER2 positive stomach cancer / CEJ

…Research continues

Практические рекомендации по лекарственному лечению рака желудка. Версия 2015 RUSSCO

Thank you for your attention