ESMO-JSMO Joint symposium: Recent advances in the treatment of GI tract and liver cancer in the EU and Japan

1st October 2012

Colorectal cancer:
A new oral cytotoxic agent reappears

TAS-102; a Novel Oral Nucleoside Antitumor Agent for Metastatic Colorectal Cancer

Takayuki YOSHINO, MD

Department of GI oncology,
National Cancer Center Hospital East, Japan

VIENNA 2012 ESMO congress

www.esmo2012.org

Disclosure slide

I have received

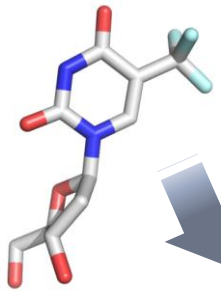
- Honoraria from Chugai, Takeda, Bristol-Myers Squibb, Yakult and Merck Serono.
- Research funding from Bayer, Taiho, Daiichi-sankyo and ImClone.
- Consulting fee from Takeda.

Mechanism of TAS-102

TPase

FTY
(*inactive form*)

TPI



F_3Thd (FTD)

F_3TMP

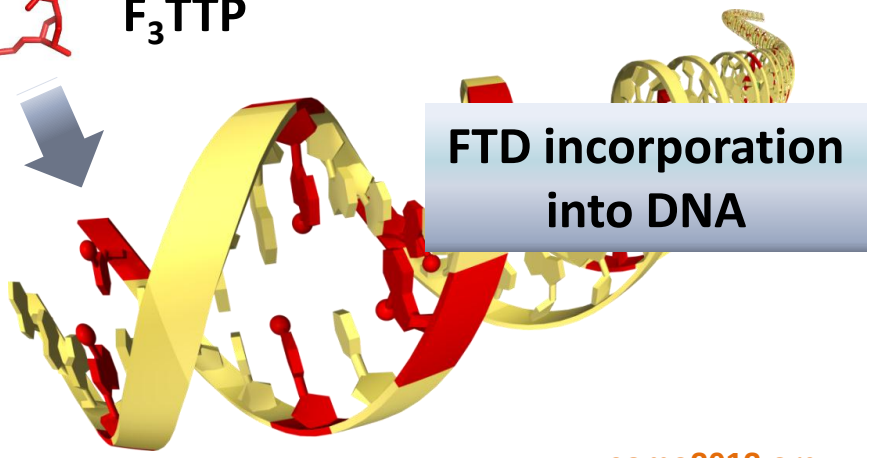
F_3TDP

F_3TTP

Inhibition of tumor growth

DNA dysfunction

FTD incorporation into DNA



TAS-102

FTD (F_3Thd) + TPI

Molar ratio = 1 : 0.5

FTD : Trifluorothymidine

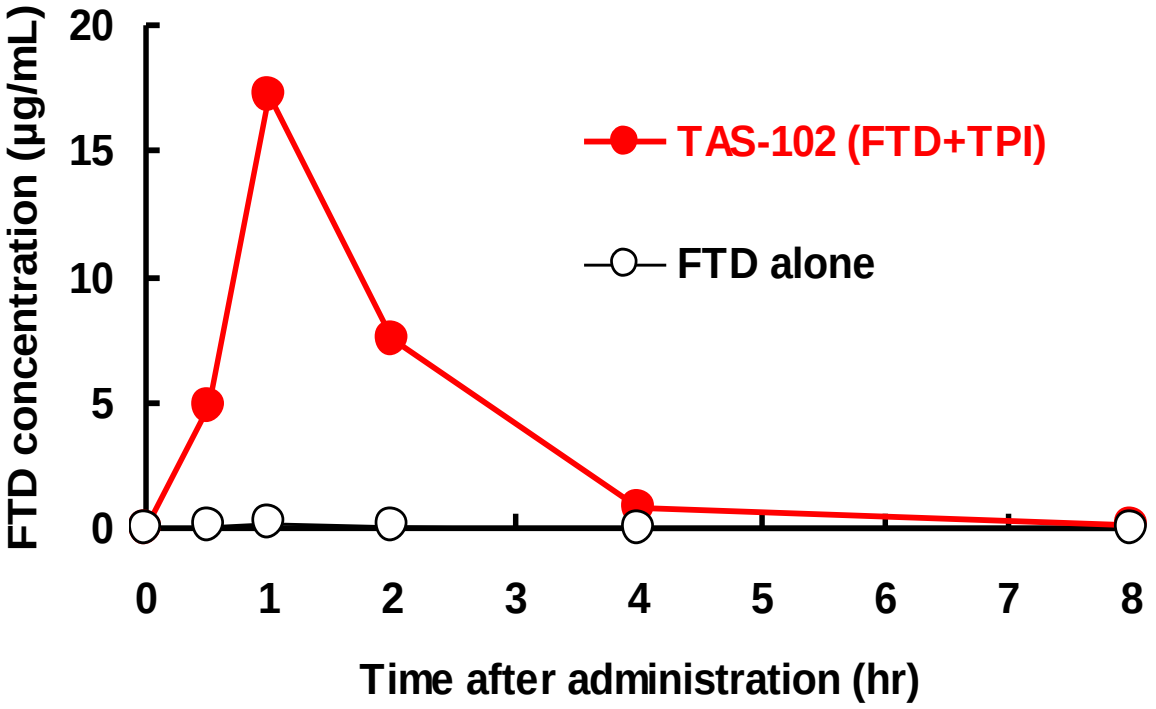
TPI : Thymidine phosphorylase inhibitor

15mg tablet 20mg tablet

VIENNA 2012 ESMO congress

www.esmo2012.org

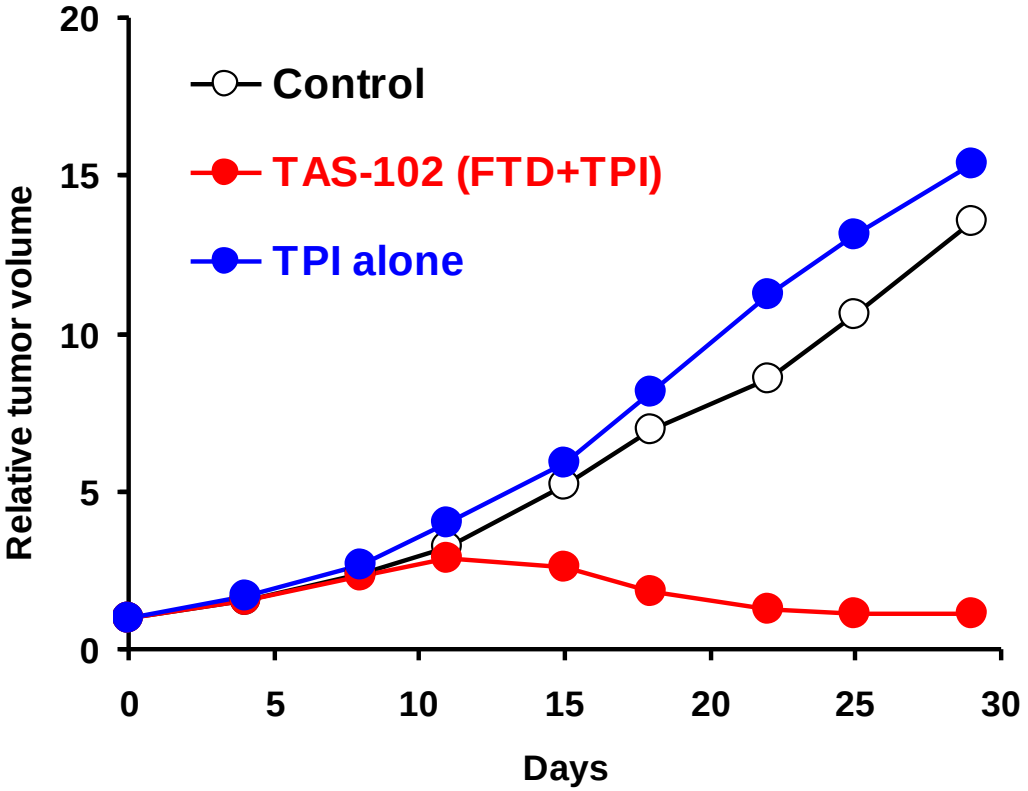
FTD concentration in plasma after oral administration of TAS-102 and FTD alone in monkey



- **TPI increased FTD exposure over 100-fold in monkey.**
- **TPI is essential in adequate FTD exposure in the oral administration of FTD in human.**

Tanaka N et al. *AACR 2012*.

Antitumor efficacy of TAS-102 and TPI

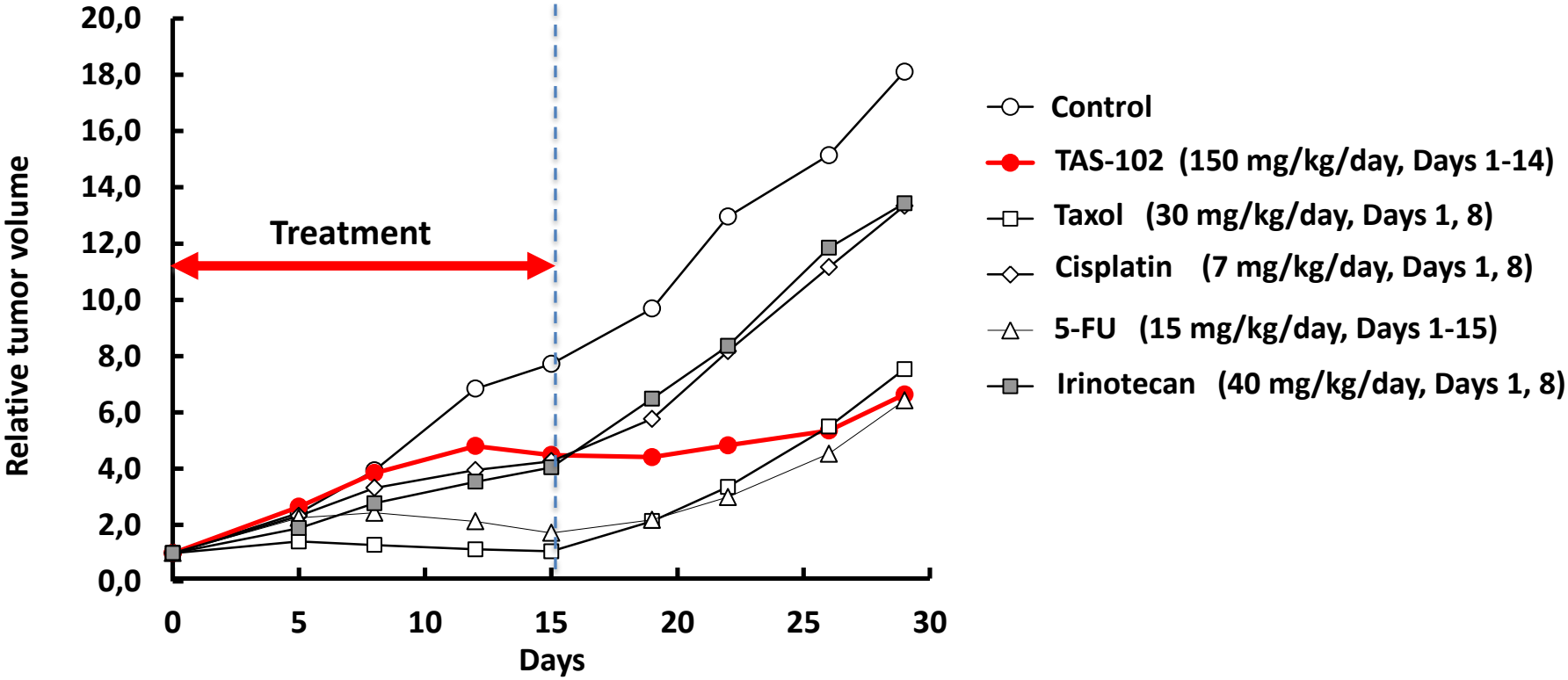


Model: Mice implanted s.c. with Human Breast Cancer MC-2 Treatment : Day 1-14
Dose: TAS-102 150mgkg/day (FTD 150 mg/kg + TPI 70.7 mg/kg), TPI 70.7 mg/kg/day

- **TPI didn't exhibit any antitumor activity in mice xenografted model.**
- **TPI is the only PK modulator of FTD, and FTD is the active component of TAS-102.**

Tanaka N et al. *AACR 2012*.

Tumor growth after termination of the drug administration

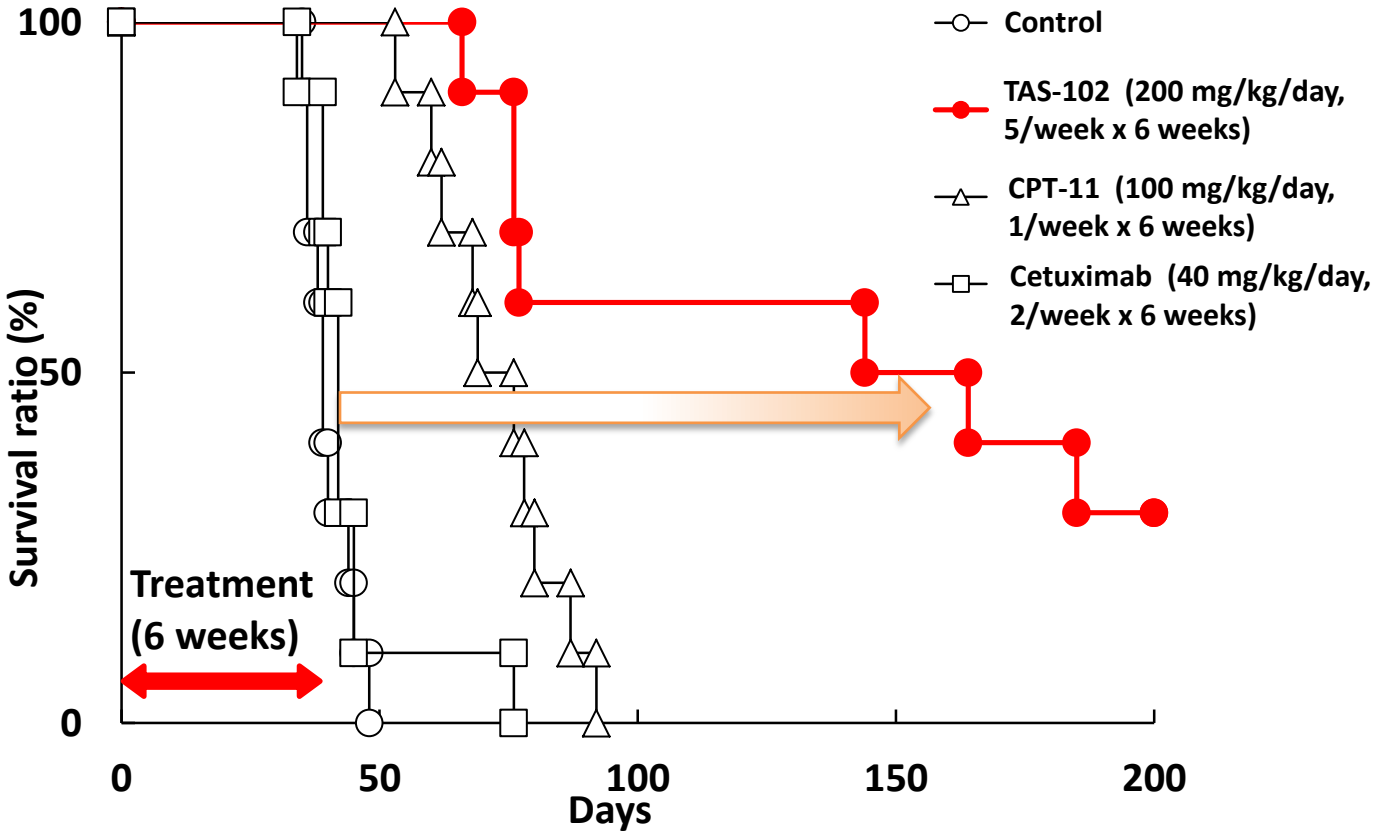


Drugs were administered to mice implanted s.c. with human colon cancer KM20C cells.

TAS-102 caused the longest delay in tumor growth following termination of drug administration. It depends on FTD accumulation in the DNA.

Tanaka N et al. *AACR 2012*.

Marked survival benefit from TAS-102 treatment



Drugs were administered for 6 weeks to mice i.p. implanted with human colon cancer KM20C cells.

FTD incorporation into DNA caused delayed tumor growth, thereby leading to markedly prolonged survival.

Tanaka N et al. *AACR 2012*.

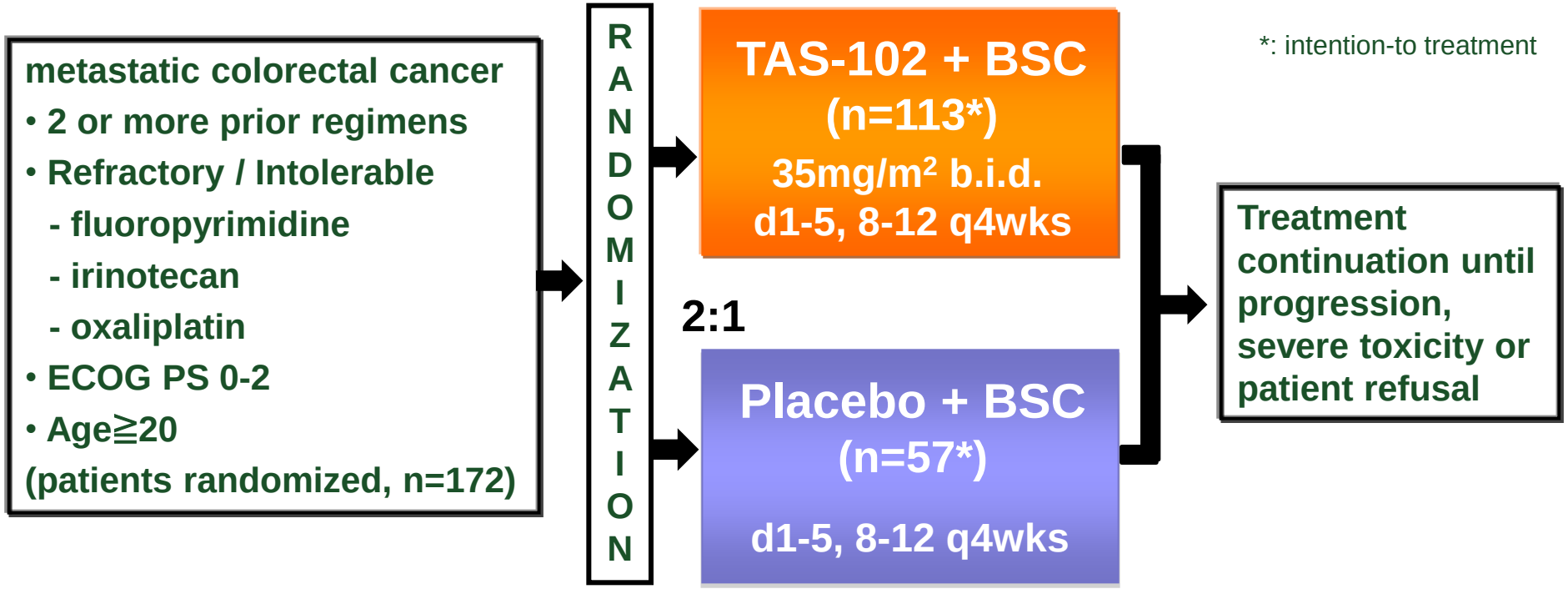
Clinical rationale for TAS-102 in mCRC: phase I experience[1,2]

- **Japanese Phase I study[1]:**
  - 21 Japanese patients with advanced solid tumor included in the study
  - 18 patients with mCRC
  - The recommended dose (RD) was determined to be 70 mg/m^2/day.
    (35mg/m^2 orally twice daily on days 1 to 5 and days 8 to 12 in a 28-day cycle)
  - The most common grade 3 or 4 toxicity was hematological toxicity.
  - In colorectal cancer patients (n=18)
    - the DCR was 50.0% including one with a partial response and 6 patients able to continue treatment over 12 weeks.
    - The median PFS and OS were 2.4 and 9.8 months, respectively.

- **Western Phase I study[2]:**
  - 26 patients with mCRC included in the study
  - Western patients with refractory mCRC achieved the same RD as Japanese patients with a similar safety profile.

1. Doi T, Ohtsu A, Yoshino T et al. *Br J Cancer* 2012.
2. Patel M, Bendell J, Mayer RJ, et al. Abstr 3631 *ASCO* 2012.

10040030 Study Design



Evaluation with CT scan : 4, 8, 12 weeks, and every 8 weeks thereafter

- **Multicenter, randomized, double-blind, placebo-controlled, phase II**
  - **Stratification: Performance Status (0/1-2)**
- **20 centers only in Japan**
- **Recruitment Period: August 2009 - April 2010**

VIENNA 2012 ESMO congress

Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.

www.esmo2012.org

10040030 study Endpoints

Primary endpoint : Overall Survival (OS)

- Assumed OS (TAS-102/Placebo) : 9/6 months (**HR : 0.67**)
- Significance Level : one-sided 10%, Power : 80 %
- Enroll period : 12 months, Follow-up period : 12 months
- 162 patients randomly assigned in a 2:1 ratio to observe 121 events
- Primary Analysis : Stratified logrank test adjusted by ECOG PS (0/1-2)

Secondary endpoints : PFS, TTF, DCR, Response Rate (RR), Duration of Response, Safety, Efficacy depends on *KRAS* status

Tertiary endpoints: Biomarkers (TK1, TP)

VIENNA 2012 ESMO congress

Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.

Patient eligibility: key inclusion criteria

- Histological or cytological documentation of the colon or rectum cancer
- 2 or more prior chemotherapy for mCRC
- Refractory / intolerable to standard therapies, which had to include:
  - Fluoropyrimidine, Oxaliplatin, Irinotecan
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.0
- Age ≥20 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, life expectancy ≥ 12 weeks
- Adequate bone marrow, liver and renal function
- Signed informed consent

Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.

Patient demographics

		TAS-102 (N=112)	Placebo (N=57)
Age, median years (range)		63 (28-80)	62 (39-79)
Sex, %	Male	57	49
	Female	43	51
Race, %	Asian (Japan)	100	100
ECOG PS, %	0	64	61
	1	33	37
	2	3	2

Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.

Baseline disease characteristics

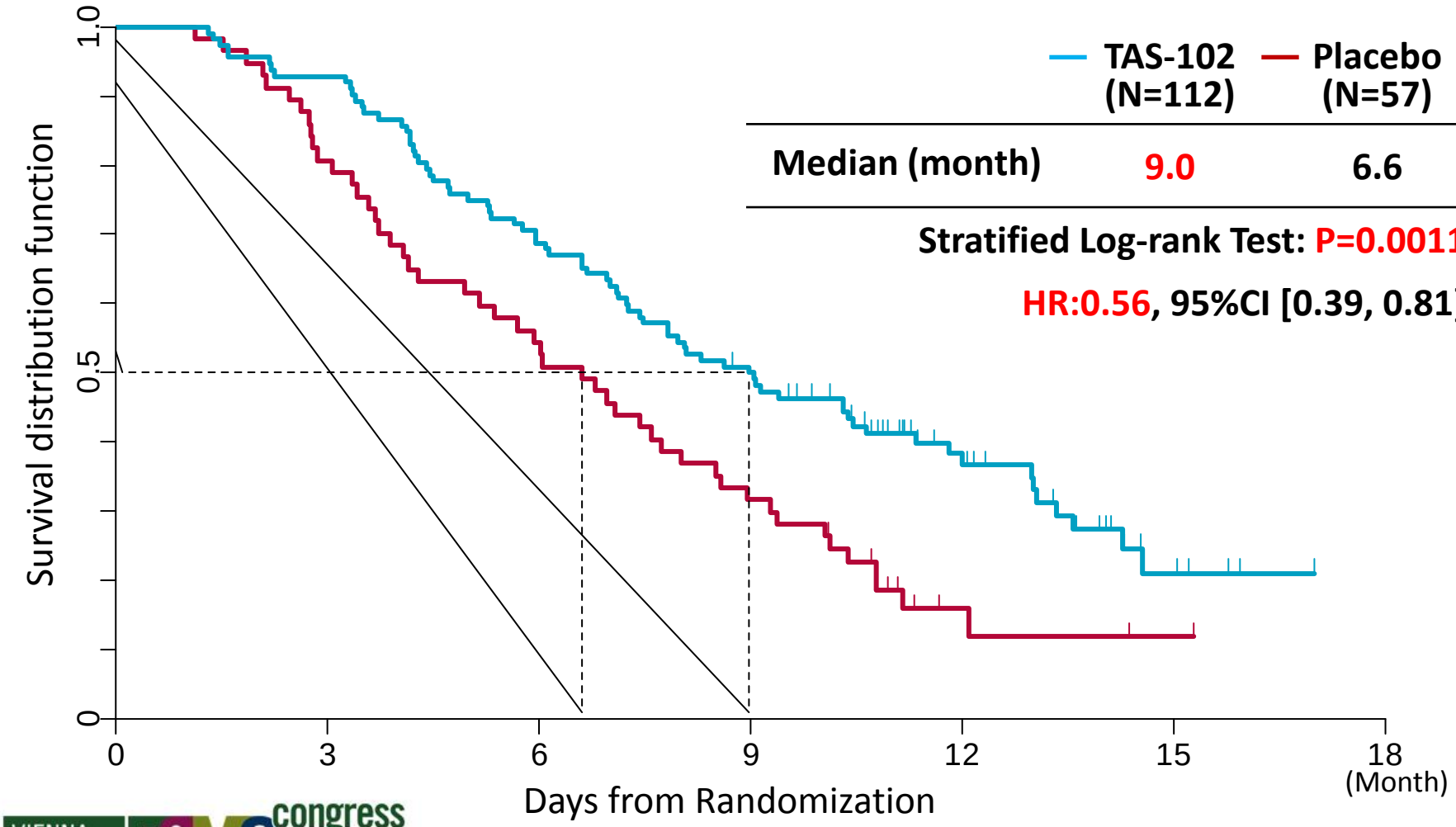
		TAS-102 N=112	Placebo N=57
Primary site of disease, %	Colon	56	63
	Rectum	44	37
KRAS mutation, %*	No	55	48
	Yes	45	52
Histology, %	Adenocarcinoma	100	100
Number of prior lines of therapy for metastatic disease, %	2	15	23
	≥3	85	77
Prior bevacizumab, %		78	82
Prior anti-EGFR, %		63	63
Prior anti-EGFR for *KRAS* wild-type, %		91	96

*: *KRAS* mutational status assessed for 99 (88%) pts in the TAS-102 group and for 50 (88%) pts in the placebo group

Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.
www.esmo2012.org

Overall survival (primary endpoint)

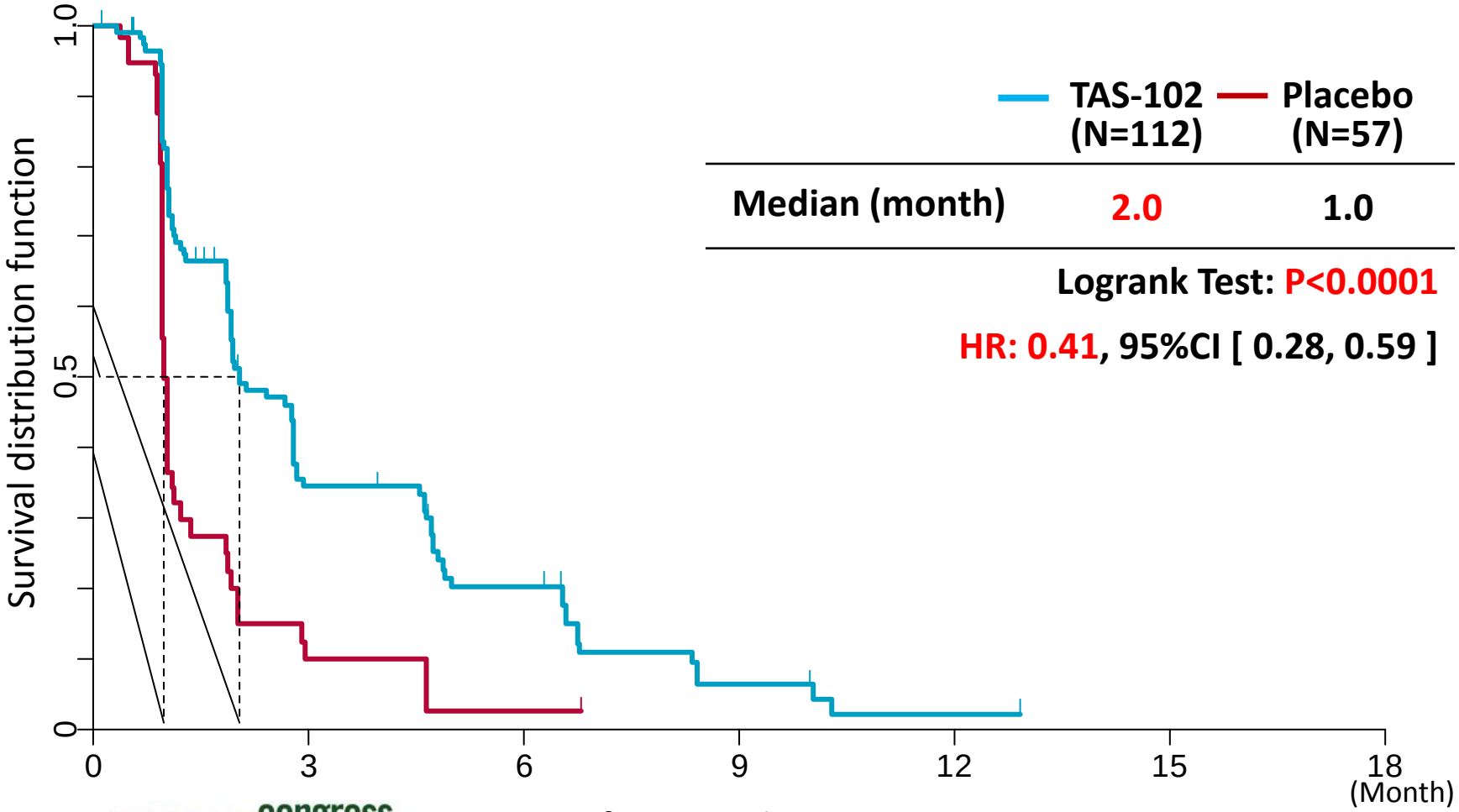
TAS-102 significantly improves OS compared to placebo



Progression-Free Survival

Independent Review Committee Assessment, RECIST v1.0

TAS-102 significantly improves PFS compared to placebo



	TAS-102 (N=112)	Placebo (N=57)
Median (month)	2.0	1.0

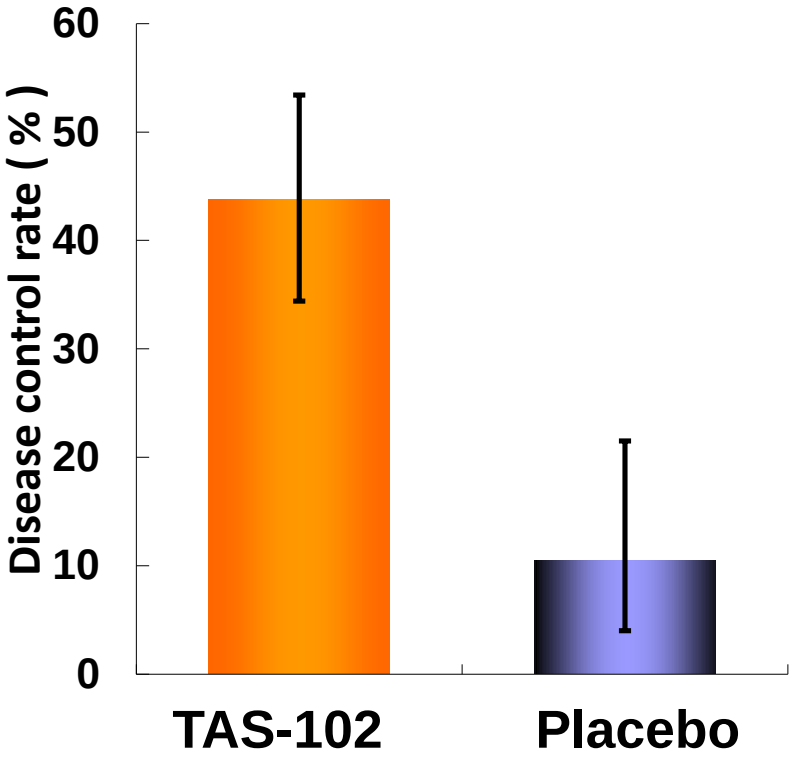
Logrank Test: P<0.0001

HR: 0.41, 95%CI [0.28, 0.59]

Overall response and disease control rates

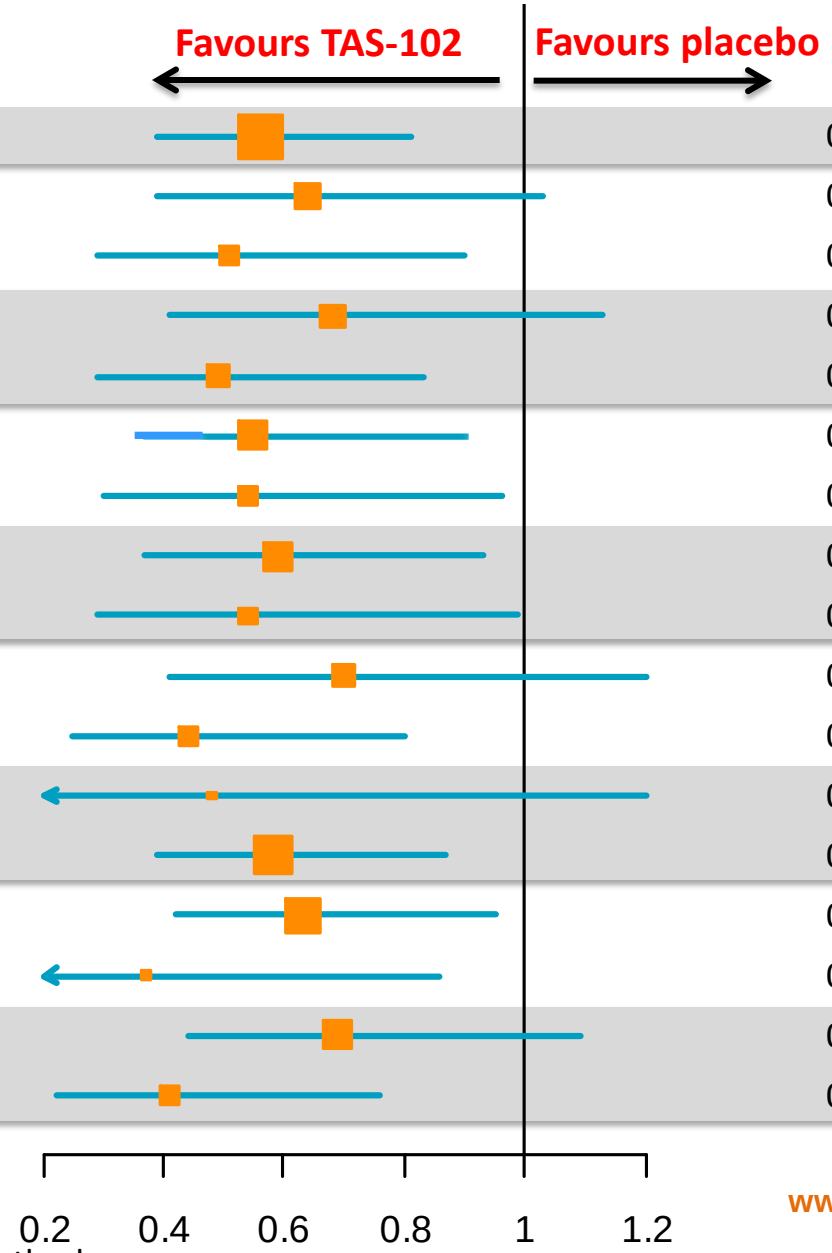
Independent Review Committee Assessment, RECIST v1.0

Best response, %	TAS-102 N=112	Placebo N=57
CR	0	0
PR	0.9	0
SD	42.9	10.5
PD	47.3	77.2
NE	8.9	12.3
DCR	43.8	10.5
	p<0.0001	



Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28.

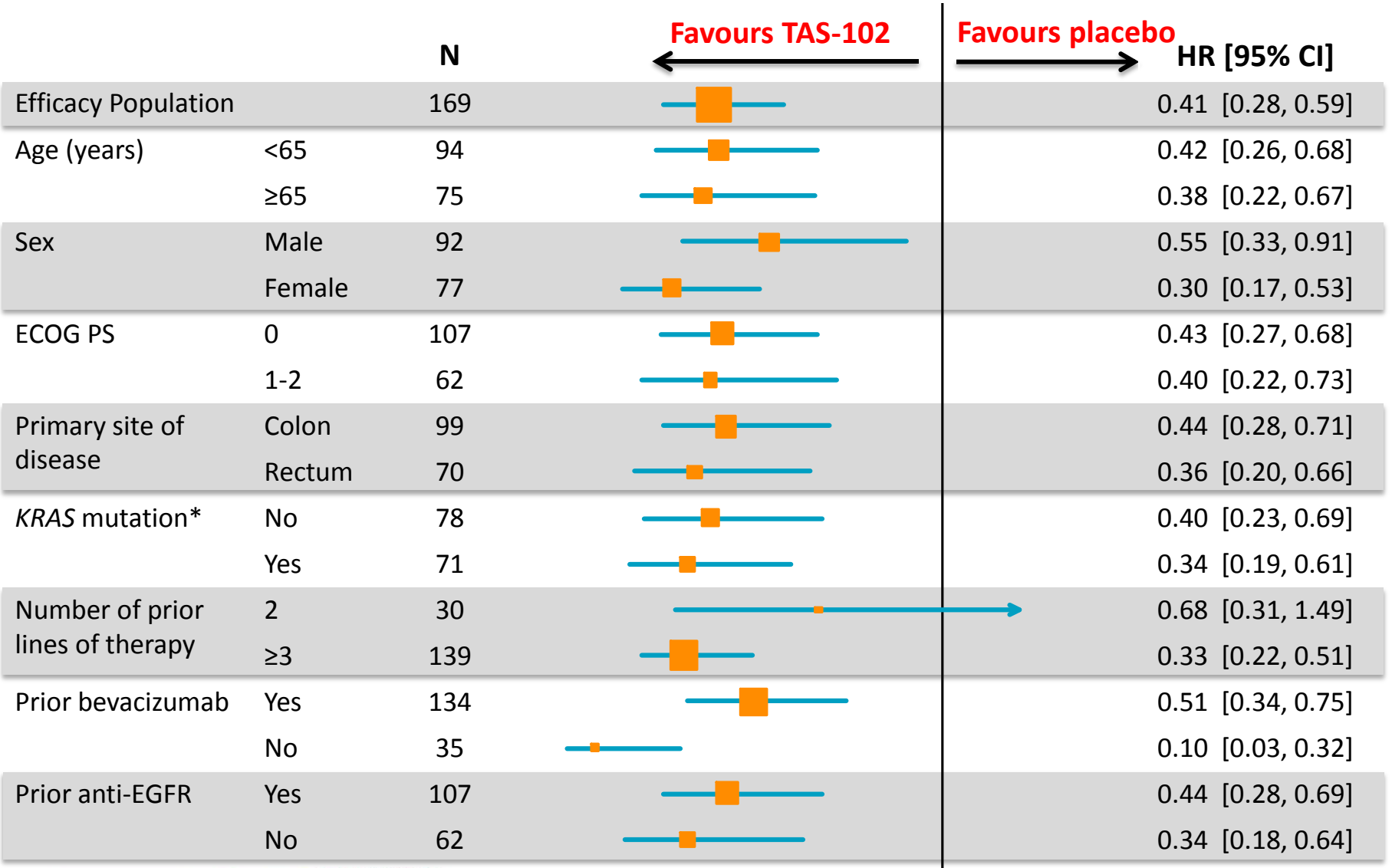
Subgroup analysis of overall survival



		N	HR [95% CI]
Efficacy Population		169	0.56 [0.39, 0.81]
Age (years)	<65	94	0.64 [0.39, 1.03]
	≥65	75	0.51 [0.29, 0.90]
Sex	Male	92	0.68 [0.41, 1.13]
	Female	77	0.49 [0.29, 0.83]
ECOG PS	0	107	0.55 [0.34, 0.89]
	1-2	62	0.54 [0.30, 0.96]
Primary site of disease	Colon	99	0.59 [0.37, 0.93]
	Rectum	70	0.54 [0.29, 0.99]
KRAS mutation*	No	78	0.70 [0.41, 1.20]
	Yes	71	0.44 [0.25, 0.80]
Number of prior lines of therapy	2	30	0.48 [0.19, 1.20]
	≥3	139	0.58 [0.39, 0.87]
Prior bevacizumab	Yes	134	0.63 [0.42, 0.95]
	No	35	0.37 [0.16, 0.86]
Prior anti-EGFR	Yes	107	0.69 [0.44, 1.09]
	No	62	0.41 [0.22, 0.76]

*: Centrally tested by the ARMS-Scorpion method

Subgroup analysis of progression-free survival



VIENNA 2012 ESMO congress

www.esmo2012.org

*: Centrally tested by the ARMS-Scorpion method

Most frequent drug-related adverse events (>5% at grade 3 or greater)

	TAS-102 (N = 113)			Placebo (N = 57)		
	Any grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Any grade N (%)	Grade 3 N (%)	Grade 4 N (%)
Neutropenia	81 (71.7)	36(31.9)	21(18.6)	1 (1.8)	0	0
Leukopenia	85 (75.2)	29(25.7)	3 (2.7)	2 (3.5)	0	0
Anemia	72 (63.7)	12(10.6)	6 (5.3)	7 (12.3)	0	0
Lymphopenia	36 (31.9)	8 (7.1)	2 (1.8)	5 (8.8)	1 (1.8)	0
Fatigue	61 (54.0)	7 (6.2)	0	16 (28.1)	0	0
Diarrhea	39 (34.5)	6 (5.3)	0	8 (14.0)	0	0
Drug-related AEs leading to permanent discontinuation	4 (3.5)			1 (1.8)		
Drug-related grade 5 AEs	0			0		

No treatment-related death was observed

KRAS subgroup analysis

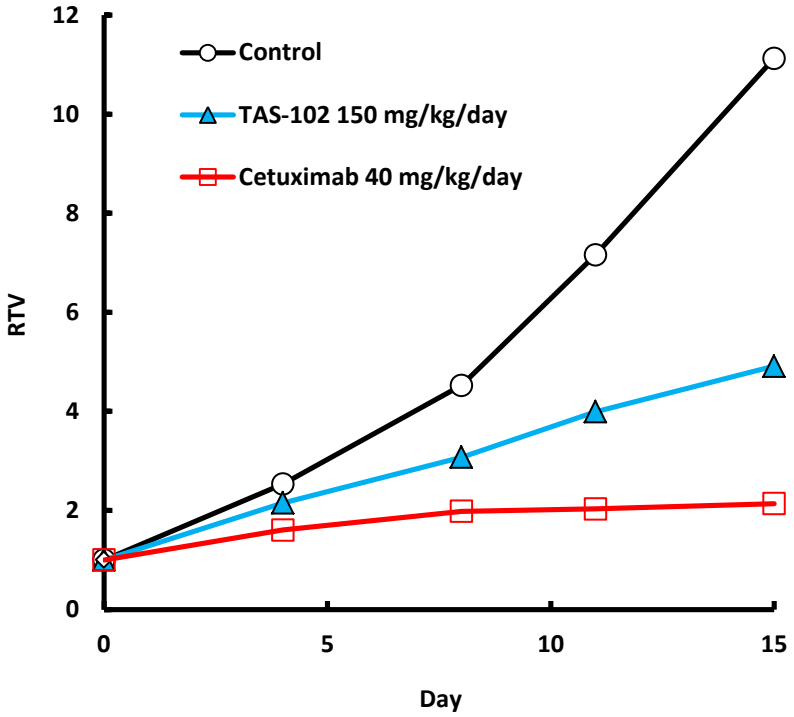
***KRAS* status was centrally evaluated by ARMS-Scorpion method in 149 patients.**

		TAS-102 N=99	Placebo N=50	HR (95% CI)
KRAS mutation, %	No	55	48	NA
	Yes	45	52	NA
Median OS, months	*KRAS* wild-type	7.2	7.0	0.70 (0.41-1.20)
	KRAS mutant	13.0	6.9	0.44 (0.25-0.80)
Median PFS, months	*KRAS* wild-type	1.9	1.0	0.40 (0.23, 0.69)
	KRAS mutant	2.8	1.0	0.34 (0.19, 0.61)

- **TAS-102 could be effective irrespective of *KRAS* mutational status, although the drug seemed to have more of an effect on overall survival in patients with *KRAS* mutations**
- **Because this subgroup analysis was based on a small number of patients, further investigation in future clinical studies with large sample sizes are necessary**

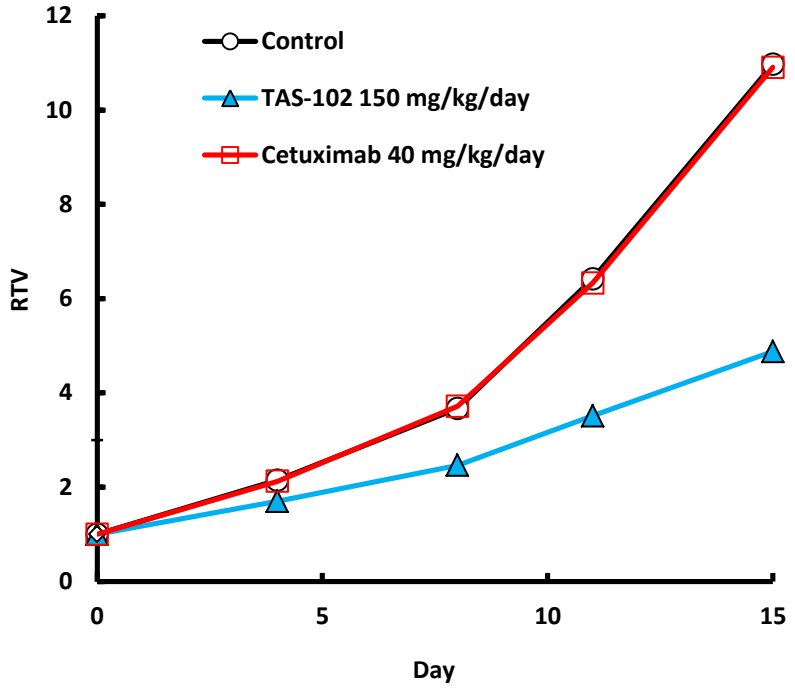
Antitumor efficacy of TAS-102 against human colon cancer cell line xenograft model

KRAS wild-type



Cell line : COL-1

KRAS mutant



Cell line : HCT-116

Model: Mice implanted s.c. with Human Colon Cancer Cell Lines,
Treatment TAS-102 (Day 1-14, p.o.), Cetuximab (Day 1,4,8,11, i.p.)

Key Clinical trials in mCRC

Clinical trial	Phase	Regimen	N	PFS (M)	HR (PFS)	OS (M)	HR (OS)	P value (OS)
10040030 study (IRC *) [1]	rPII	TAS-102+BSC Placebo+BSC	112 57	2.0 1.0	0.41	9.0 6.6	0.56	0.0011
NCIC CTG CO. 17 (KRAS wild-type)[2]	PIII	Cetuximab+BSC BSC	117 113	3.7 1.9	0.40	9.5 4.8	0.55	<0.001
20020408 study (KRAS wild-type) [3]	PIII	Panitumumab+BSC BSC	124 119	2.9 § 1.7 §	0.45	8.1 7.6	0.99	-
CORRECT study [4, 5]	PIII	Regorafenib+BSC Placebo+BSC	505 255	1.9 1.7	0.49	6.4 5.0	0.77	0.0052

* IRC : Independent Review Committee

§ month = week × 7 / 30

1 Yoshino T et al. *Lancet Oncology* 2012; published online Aug 28
2 Karapetis CS, et al. *N Engl J Med* 2008
3 Amado RG, et al, *J Clin Oncol* 2008
4 Grothey A et al. *ASCO-GI 2012*
5 Van Cutsem E et al. *ASCO 2012*

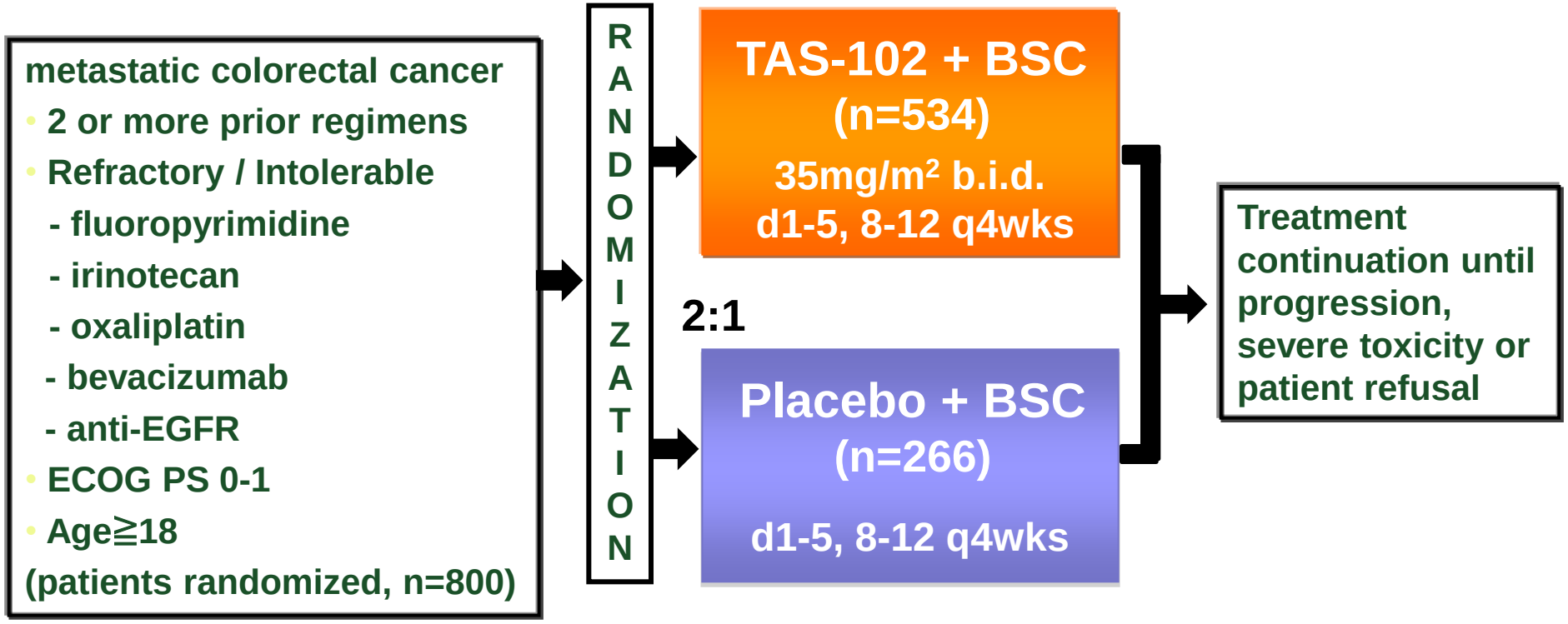
Summary of 10040030 study results

- The study met its primary endpoint
- TAS-102 *vs.* placebo:
  - OS: 9.0 *vs.* 6.6 months, HR=0.56, p=0.0011
  - PFS (IRC): 2.0 *vs*.1.0 months, HR=0.41, p<0.0001
  - DCR (PR + SD): 43.8% *vs.* 10.5%, p<0.0001
- Subgroup analyses:
  - TAS-102 showed OS and PFS benefit across subgroups including *KRAS* .
- No new or unexpected safety findings:
  - Most frequent grade 3 and 4 events related to TAS-102 were neutropenia, leukopenia, anemia, lymphopenia, fatigue and diarrhea

Conclusions

- TAS-102 significantly improved OS compared with placebo
- TAS-102 was well tolerated and no treatment-related death was observed
- TAS-102 has promising efficacy with an easily manageable safety profile in patients with mCRC who are refractory or intolerant to standard chemotherapies with fluoropyrimidine, irinotecan and oxaliplatin
- An international phase III study (RECOURSE) is in progress

Ongoing RECOURSE Phase 3 Study



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Global trial: 13 countries, 122 centers
- Recruitment Period: June 2012 - June 2014

NCT01607957

Thank you for your kind attention

The 10040030 study was sponsored by Taiho Pharmaceutical CO., Ltd., Japan