Phase III RECOURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies.

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Conflict of Interest Disclosure

- **Research funding from Amgen, Bayer, Boehringer, Lilly, Merckserono, Novartis, Roche, Sanofi,**

TAS-102; Mechanism of Action

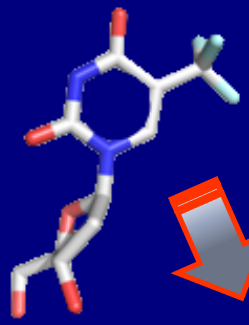


FTY

(*inactive form*)

TPase

TPI



F_3dThd (FTD)
Thymidine-based nucleoside analogue

F_3dTMP

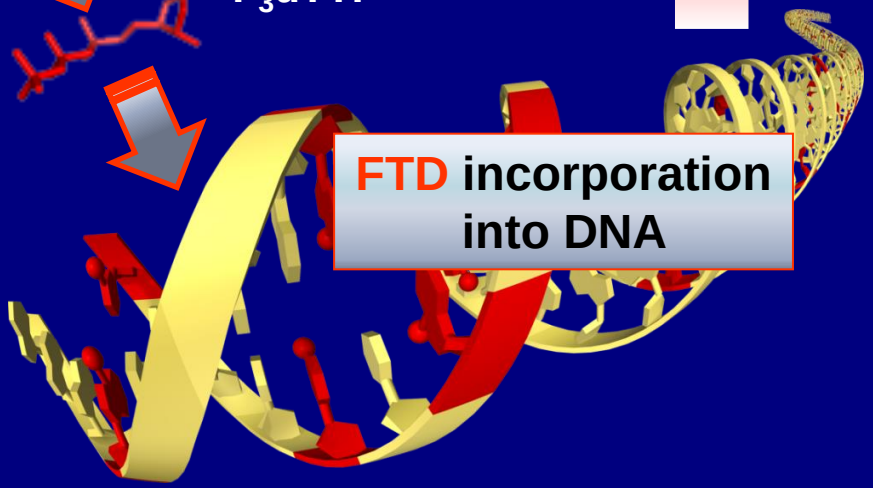
F_3dTDP

F_3dTTP

Inhibition of tumor growth

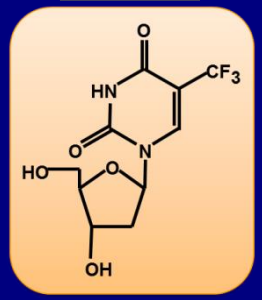
DNA dysfunction

FTD incorporation into DNA

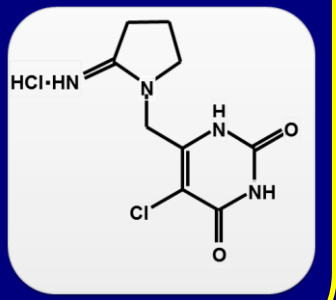


TAS-102
(Oral Combination Drug)

FTD



TPI

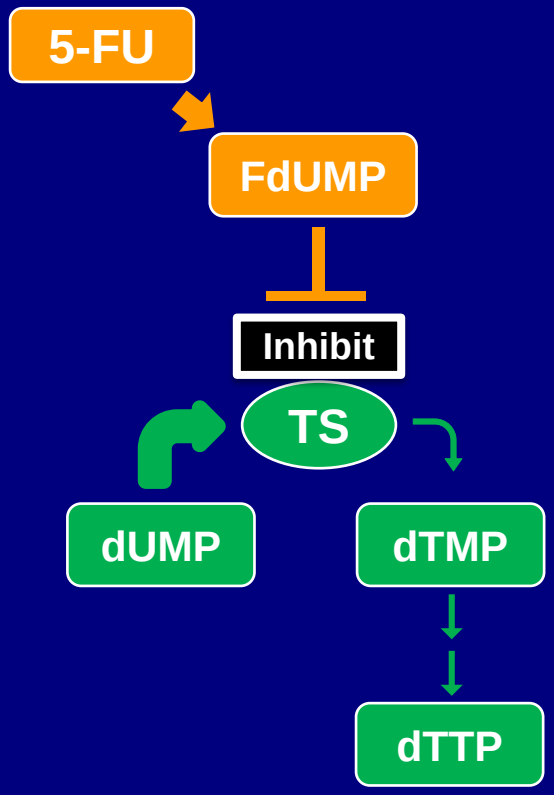


Molar ratio = 1 : 0.5

FTD: Trifluridine
TPI: Tipiracil-HCl

Differentiation between 5-FU and TAS-102

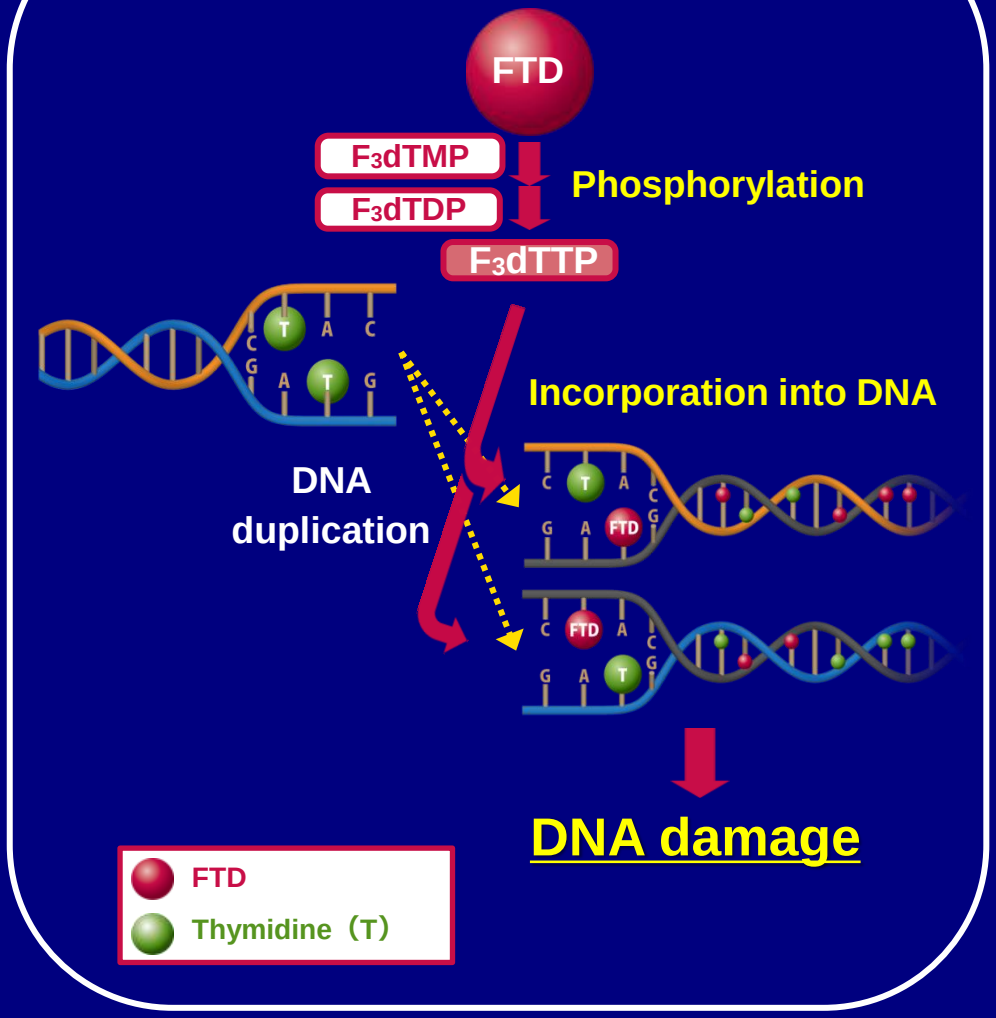
5-FU



Inhibit DNA duplication



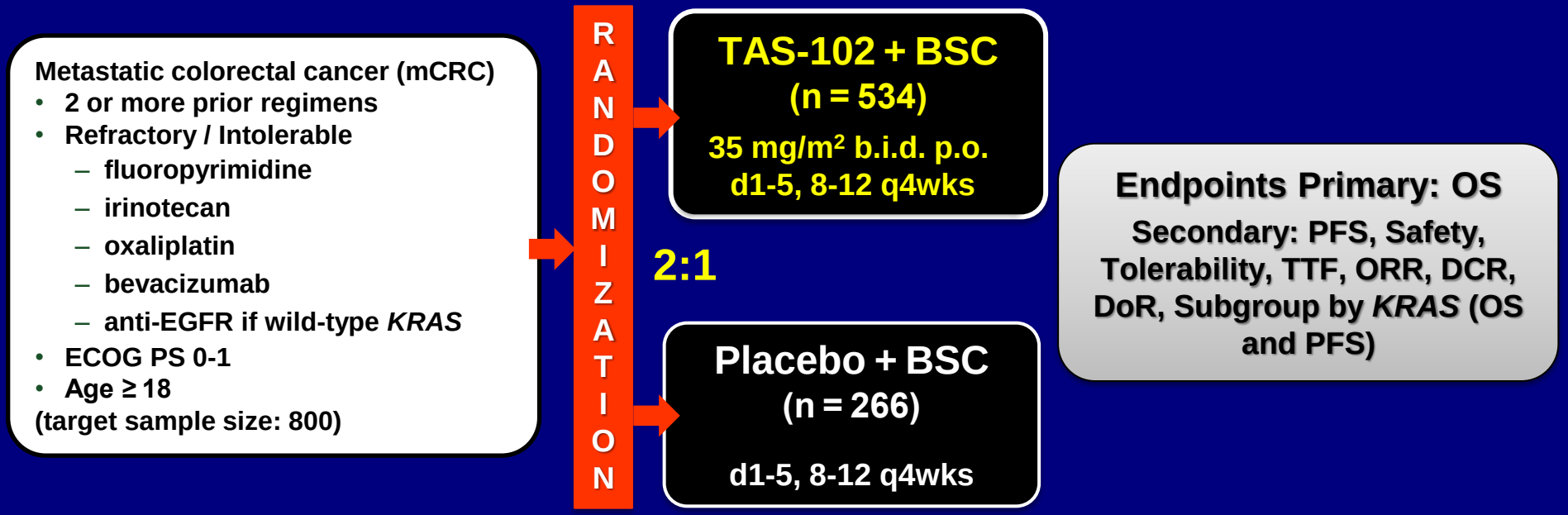
TAS-102



Global Randomized Phase III study

RECOURSE: Refractory Colorectal Cancer Study

(NCT01607957)



- Treatment continuation until progression, intolerant toxicity or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

Patient Demographics and Characteristics

(Intent-to-treat population)

		TAS-102 N=534	Placebo N=266
Age, median (range)		63.0 (27-82)	63.0 (27-82)
Gender, %	Male	61.0	62.0
	Female	39.0	38.0
Race, %	White	57.3	58.3
	Asian	34.5	35.3
	Black	0.7	1.9
Geographic Region, %	Japan	33.3	33.1
	Western	66.7	66.9
	Europe	50.7	49.6
	US	12.0	13.2
	Australia	3.9	4.1
ECOG PS, %	0	56.4	55.3
	1	43.6	44.7

Patient Disease Characteristics

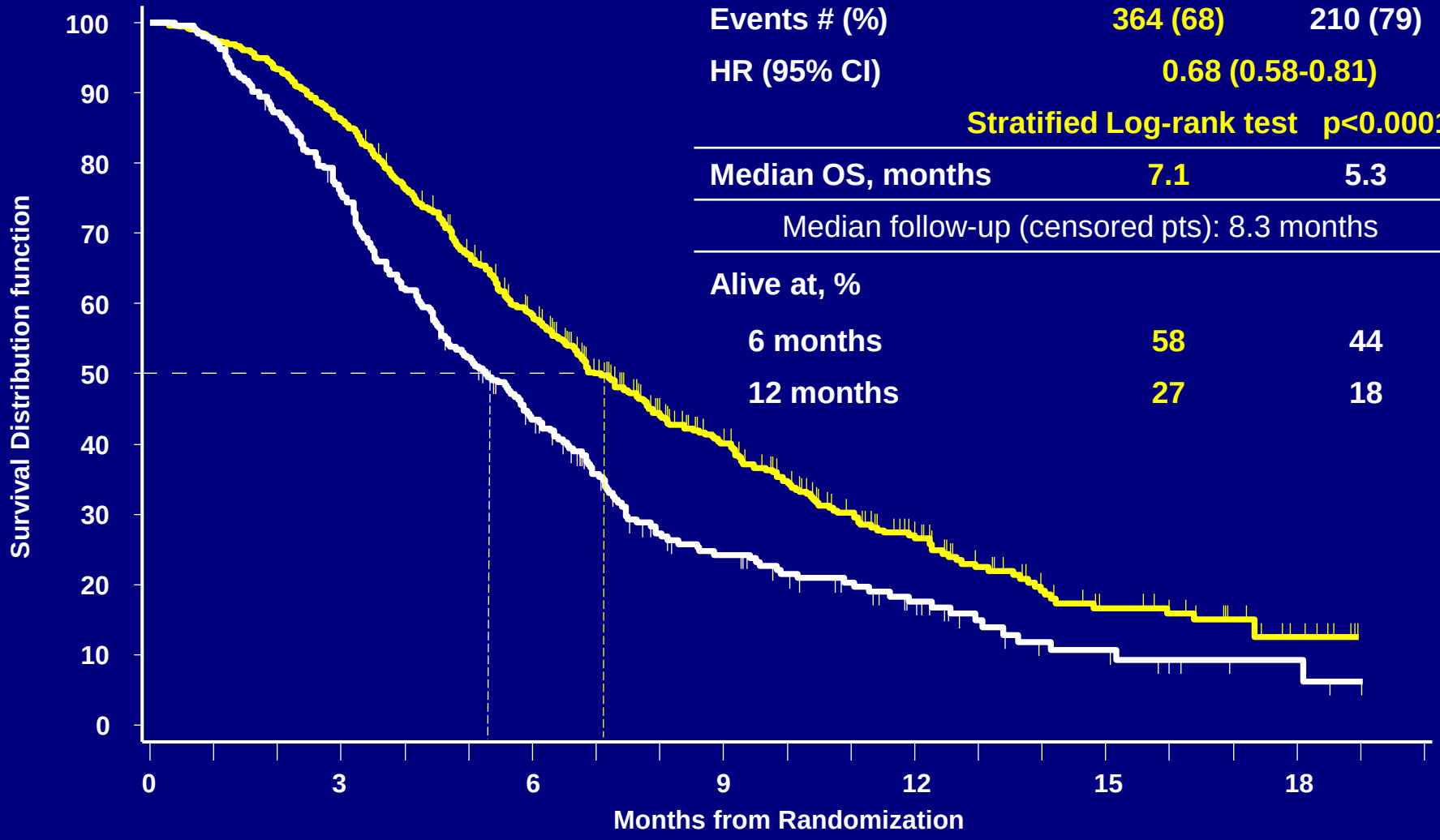
(Intent-to-treat population)

		TAS-102 N=534	Placebo N=266
Primary site, %	Colon	63.3	60.5
	Rectum	36.7	39.5
***KRAS* mutational status, %**	Wild-type	49.1	49.2
	Mutant	50.9	50.8
Time since diagnosis of metastasis, %	< 18 months	20.8	20.7
	≥ 18 months	79.2	79.3
Number of prior regimens, %	2	17.8	16.9
	3	22.3	20.3
	≥4	59.9	62.8
All prior systemic cancer therapeutic agents, %	Fluoropyrimidine	100	100
	Irinotecan	100	100
	Oxaliplatin	100	100
	Bevacizumab	100	99.6
	Anti-EGFR (if wild *KRAS**)	99.6	99.3
	Regorafenib	17.0	19.9

*Based on historical patient record

Overall Survival

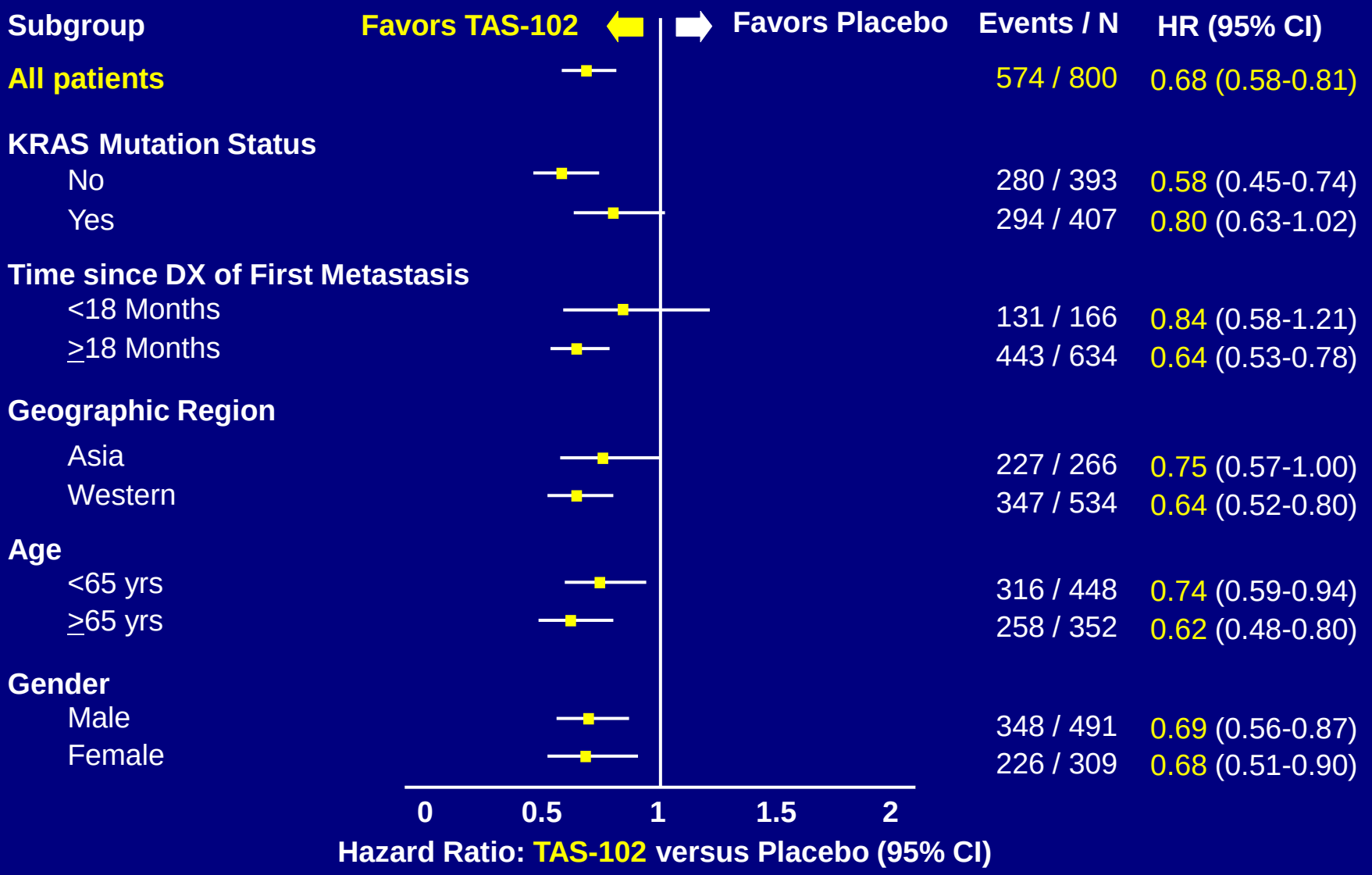
	TAS-102 N=534	Placebo N=266
Events # (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81)	
	Stratified Log-rank test	p<0.0001
Median OS, months	7.1	5.3
Median follow-up (censored pts): 8.3 months		
Alive at, %		
6 months	58	44
12 months	27	18



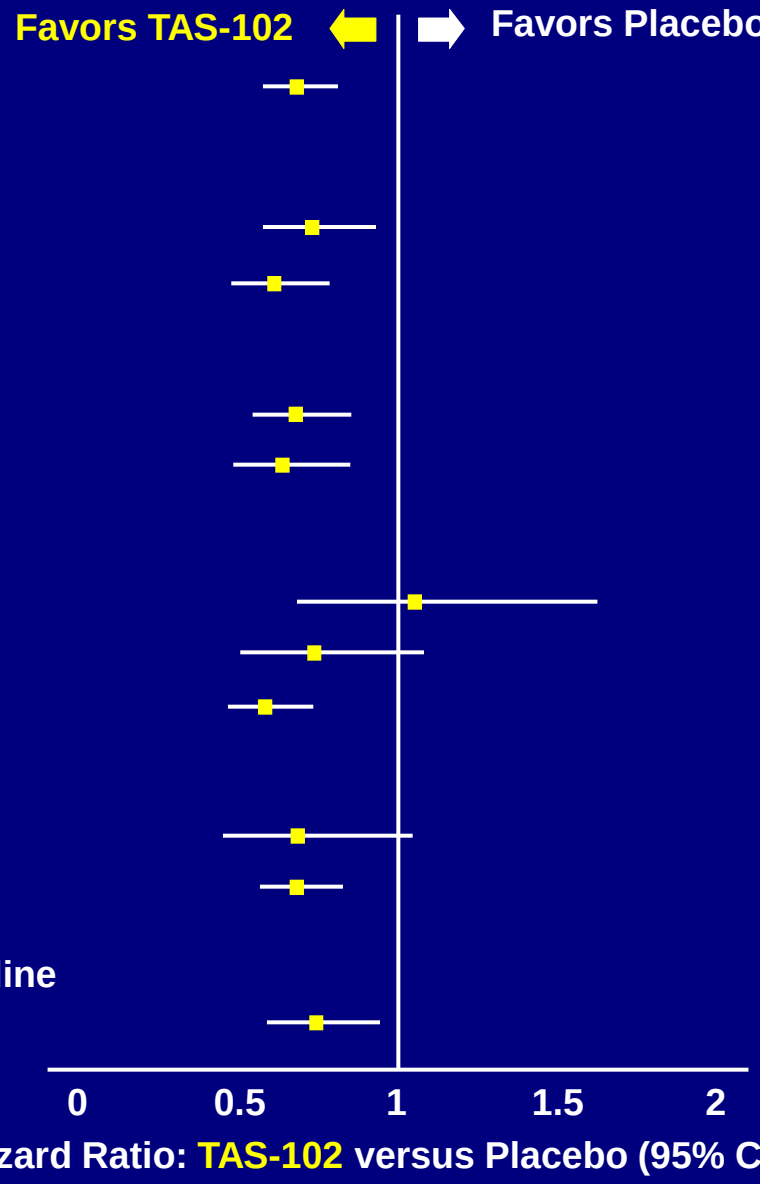
N at Risk:

TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

OS Subgroup Analyses (1)



OS Subgroup Analyses (2)



Subgroup	Events / N	HR (95% CI)
All patients	574 / 800	0.68 (0.58-0.81)
ECOG Performance Status		
0	298 / 448	0.73 (0.58-0.93)
1	276 / 352	0.61 (0.48-0.79)
Primary Tumor Site		
Colon	361 / 499	0.68 (0.55-0.85)
Rectal	213 / 301	0.64 (0.48-0.85)
Number of Prior Regimens		
2	106 / 140	1.05 (0.68-1.63)
3	137 / 173	0.74 (0.51-1.08)
≥4	331 / 487	0.59 (0.47-0.73)
Prior Use of Regorafenib		
Use	94 / 144	0.69 (0.45-1.05)
Not Use	480 / 656	0.69 (0.57-0.83)
Refractory to Fluoropyrimidine		
Part of last prior regimen	329 / 455	0.75 (0.59-0.94)

OS Multivariate Analysis

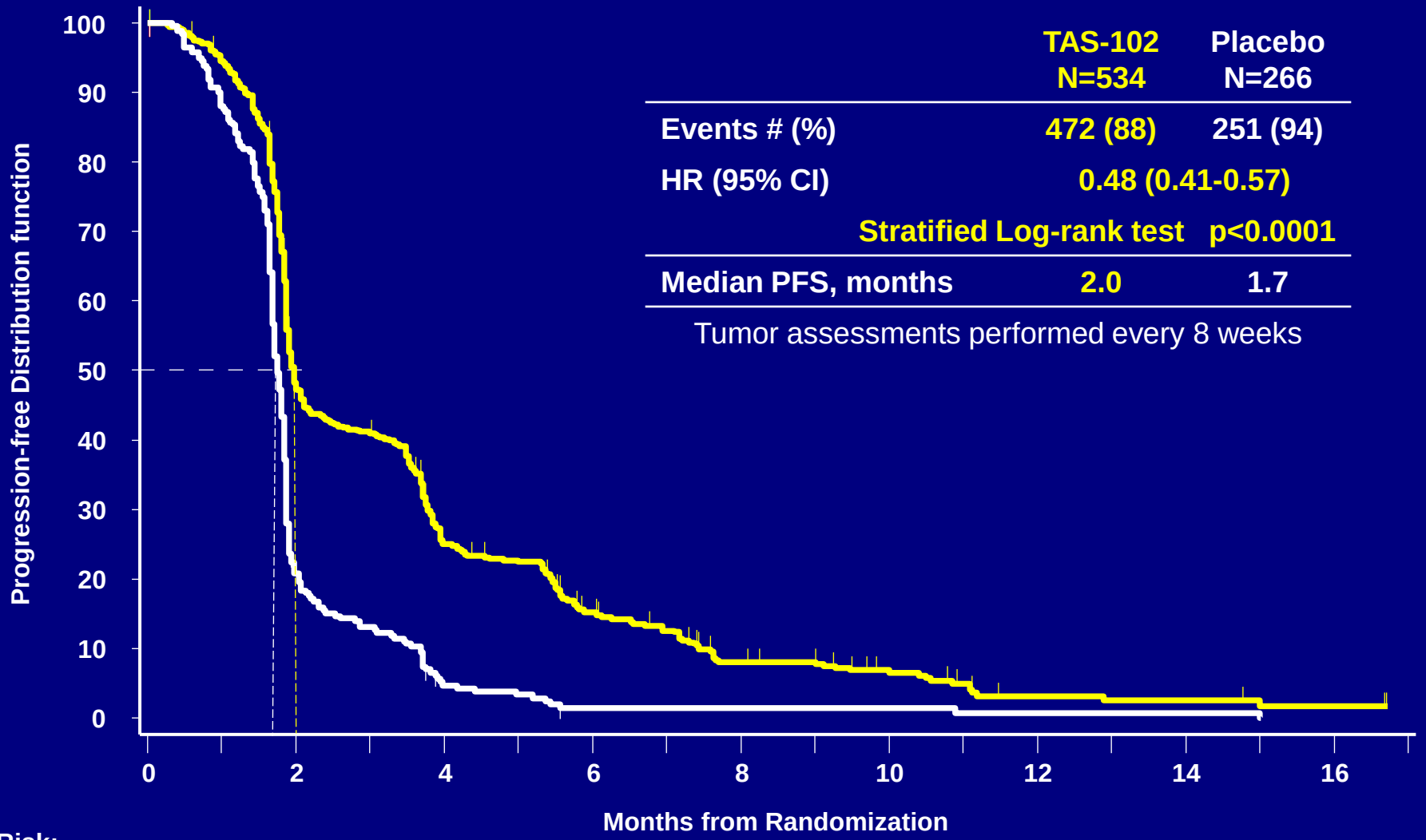
- Multivariate Cox Regression model with all predefined covariates
  - No predictive factors identified – all interaction p-values >0.20
  - Statistically significant prognostic factors ($p < 0.05$) in final model based on stepwise selection:
    - Time since diagnosis of 1st metastasis
    - ECOG performance status
    - # of metastatic sites
  - Similar treatment effect after adjusting for covariates
    - Multivariate HR (95% CI): 0.69 (0.58, 0.81) p<0.0001
    - Univariate HR (95% CI): 0.68 (0.58, 0.81) p<0.0001 *

*Stratified log rank test

Post-study Chemotherapy
(Intent-to-treat population)

	TAS-102 N=534	Placebo N=266
Any systemic therapy, %	41.6	42.5
Agent		
Fluoropyrimidine-based	16.1	18.0
Irinotecan-based	6.9	4.1
Oxaliplatin-based	7.3	10.2
Bevacizumab	4.1	4.5
Aflibercept	1.1	0
Cetuximab/Panitumumab	6.6	2.3
Regorafenib	15.7	15.4

Progression-free Survival



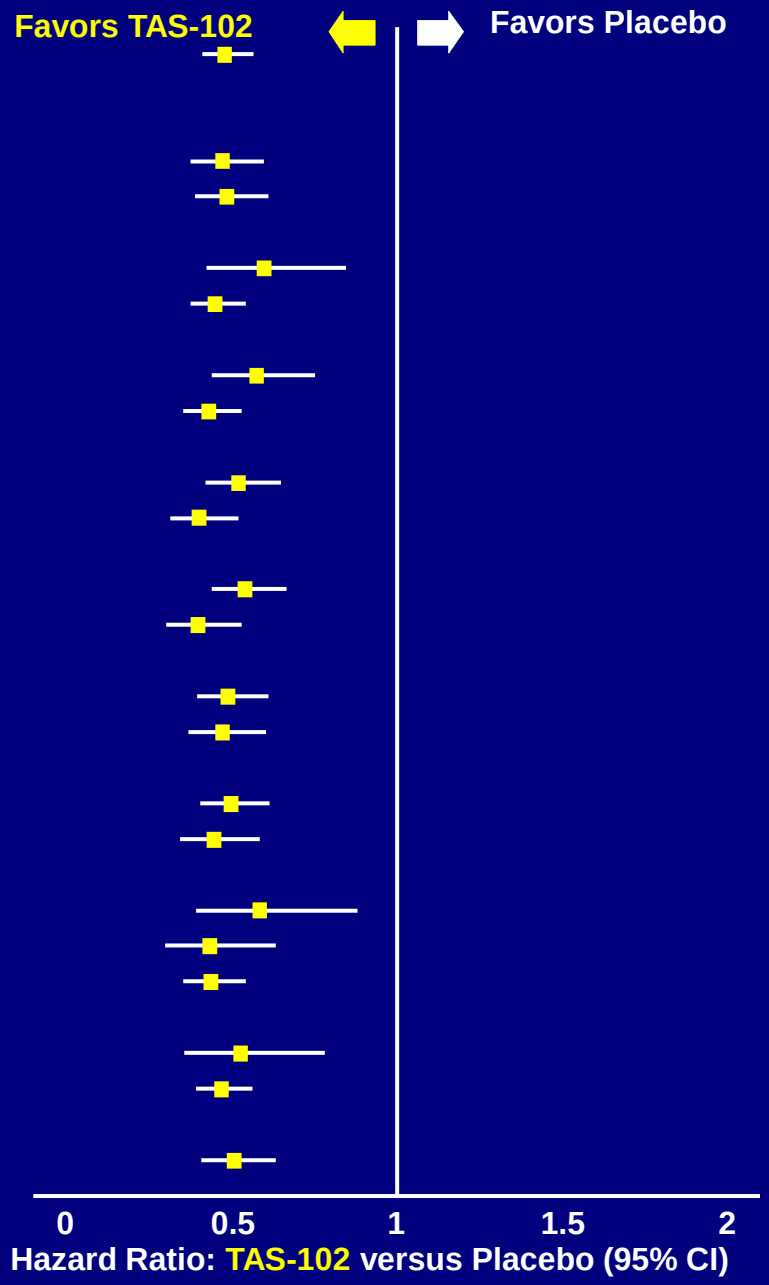
	TAS-102 N=534	Placebo N=266
Events # (%)	472 (88)	251 (94)
HR (95% CI)	0.48 (0.41-0.57)	
	Stratified Log-rank test	p<0.0001
Median PFS, months	2.0	1.7

Tumor assessments performed every 8 weeks

N at Risk:

TAS-102	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

PFS Subgroup Analyses



Subgroup	Events / N	HR (95% CI)
All patients	723 / 800	0.48 (0.41-0.57)
KRAS Mutation Status		
No	355 / 393	0.48 (0.38-0.60)
Yes	368 / 407	0.49 (0.39-0.61)
Time since DX of First Metastasis		
<18 Months	159 / 166	0.60 (0.43-0.85)
≥18 Months	564 / 634	0.45 (0.38-0.54)
Geographic Region		
Asia	258 / 266	0.58 (0.44-0.75)
Western	465 / 534	0.43 (0.35-0.53)
Age		
<65 yrs	405 / 448	0.52 (0.42-0.65)
≥65 yrs	318 / 352	0.41 (0.32-0.52)
Gender		
Male	448 / 491	0.54 (0.44-0.67)
Female	275 / 309	0.40 (0.30-0.53)
ECOG Performance Status		
0	404 / 448	0.49 (0.40-0.61)
1	319 / 352	0.47 (0.37-0.61)
Primary Tumor Site		
Colon	445 / 499	0.50 (0.41-0.62)
Rectal	278 / 301	0.45 (0.34-0.59)
Number of Prior Regimens		
2	133 / 140	0.59 (0.39-0.88)
3	162 / 173	0.44 (0.30-0.63)
≥4	428 / 487	0.44 (0.36-0.54)
Prior Use of Regorafenib		
Use	121 / 144	0.53 (0.36-0.78)
Not Use	602 / 656	0.47 (0.39-0.56)
Refractory to Fluoropyrimidine		
Part of last prior regimen	420 / 455	0.51 (0.41-0.63)

Non-Hematologic Adverse Events Occurring in >10% of Patients
(as-treated population)

Non-Hema Adverse events, %	TAS-102 (N=533)			Placebo (N=265)		
	All Gr.	Gr. 3	Gr. 4	All Gr.	Gr. 3	Gr. 4
Nausea	48.4	1.9	0	23.8	1.1	0
Decreased appetite	39.0	3.6	0	29.4	4.9	0
Fatigue	35.3	3.9	0	23.4	5.7	0
Diarrhea	31.9	2.8	0.2	12.5	0.4	0
Vomiting	27.8	2.1	0	14.3	0.4	0
Pyrexia	18.4	0.9	0.2	14.0	0.4	0
Asthenia	18.2	3.4	0	11.3	3.0	0
Constipation	15.2	0.2	0	15.1	1.1	0
Abdominal pain	14.8	2.1	0	13.6	3.4	0
Cough	10.7	0.4	0	11.3	0.8	0
Dyspnoea	10.5	2.1	0.4	12.8	2.3	0
Oedema peripheral	9.9	0.2	0	10.2	0.8	0
Weight decreased	7.7	0	0	10.2	0	0

One treatment-related death was observed in TAS-102

Laboratory Abnormalities
(as-treated population)

Lab abnormalities, %	TAS-102 (N=533)			Placebo (N=265)		
	All Gr.	Gr. 3	Gr. 4	All Gr.	Gr. 3	Gr. 4
Hematology						
Anemia	76.5	18.2	0*	33.1	3.0	0
Neutropenia[#]	66.9	26.5	11.4	0.8	0	0
Thrombocytopenia	42.2	4.5	0.6	8.0	0	0.4
Liver function						
ALT	24.0	1.7	0.2	26.6	3.0	0.8
AST	29.6	4.0	0.4	34.7	5.0	1.1
Total Bilirubin	35.9	7.4	1.1	26.3	8.8	3.1
Renal function						
Creatinine	13.5	0.9	0	12.2	0.4	0.4

*One case of grade 4 was reported in AE

[#]Frequency of G-CSF usage; 9.4% in TAS-102 and 0% in placebo

Adverse Events of Special Interest

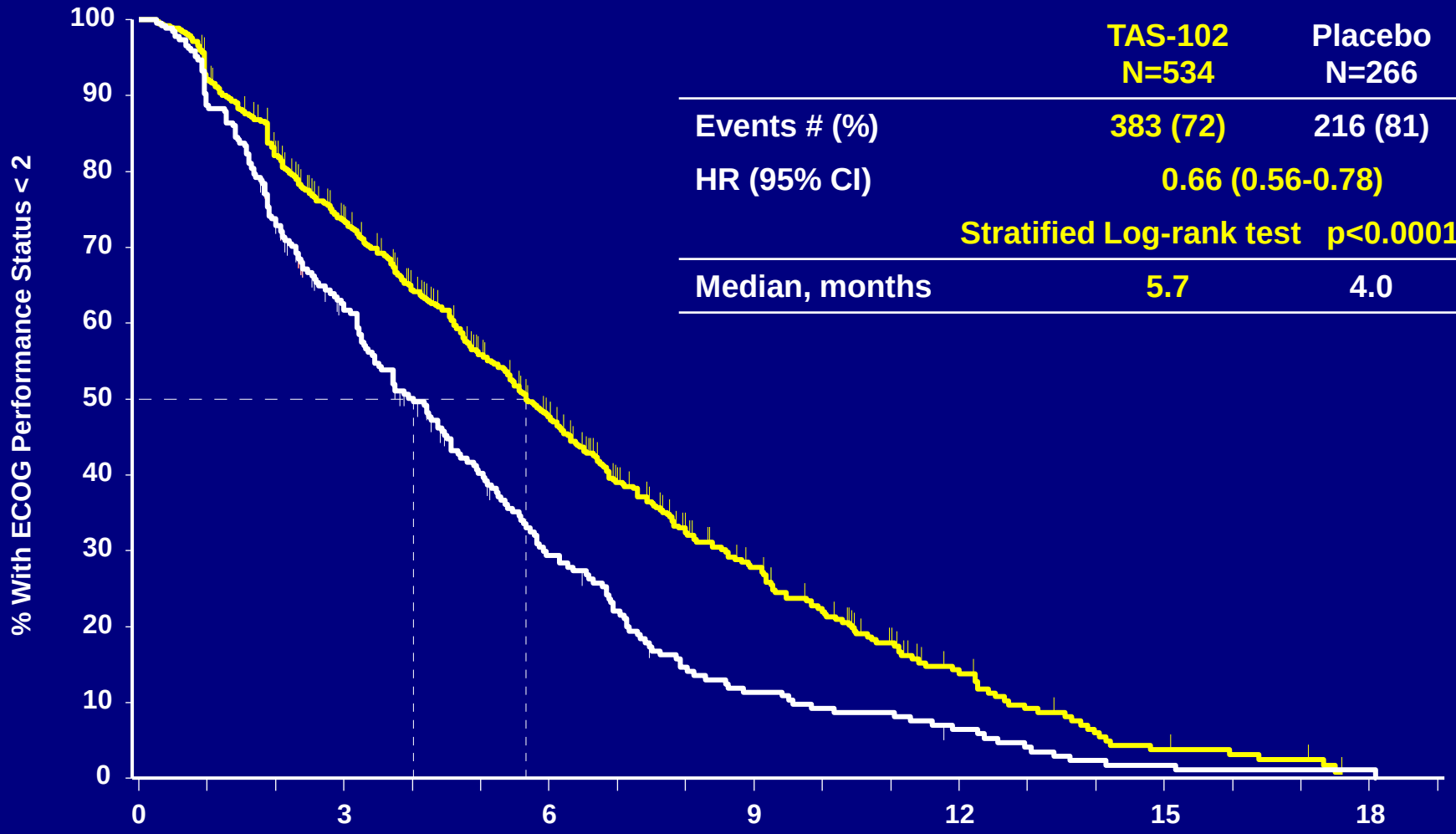
(as-treated population)

Adverse events, %	TAS-102 (N=533)			Placebo (N=265)		
	All Gr.	Gr. 3	Gr. 4	All Gr.	Gr. 3	Gr. 4
Febrile neutropenia	3.8	2.8	0.9	0	0	0
Stomatitis	7.9	0.4	0	6.0	0	0
Hand-foot syndrome	2.3	0	0	2.3	0	0
Alopecia	6.8	0	0	1.1	0	0
Proteinurea	4.1	0	0	1.9	0	0
Cardiac ischaemia events, %	**0.4**	**0.2**	**0**	**0.4**	**0**	**0.4**
Thromboembolic events, %	**3.9**	**1.7**	**0.2**	**2.3**	**1.1**	**0.4**
Pulmonary embolism	1.7	1.3	0.2	0	0	0

- SAEs were observed 29.6% in TAS-102 and 33.6% in placebo
- Primary reason for discontinuation due to AE was 3.6% in TAS-102 and 1.5% in placebo

Time to ECOG PS≥2

(Intent-to-treat population)



	TAS-102 N=534	Placebo N=266
Events # (%)	383 (72)	216 (81)
HR (95% CI)	0.66 (0.56-0.78)	
	Stratified Log-rank test	p<0.0001
Median, months	5.7	4.0

N at Risk:

TAS-102	534	352	188	84	28	7	0
Placebo	266	134	57	21	11	3	1

Conclusions

- TAS-102 demonstrated a clinically relevant improvement in OS and PFS compared with placebo in mCRC pts refractory / intolerant to standard therapies
  - Improved OS benefit was statistically significant or trended favorably for TAS-102 across all stratification factors and predefined subgroups
  - Consistent with OS results, PFS improvement for TAS-102 was statistically significant across all stratification factors and predefined subgroups
  - OS benefit was maintained irrespective of regorafenib use
- TAS-102 was well tolerated
  - The most frequently observed toxicities were gastrointestinal and hematologic, the rate of febrile neutropenia was 3.8%
  - A statistically significant prolongation of time to ECOG performance status $\geq$2 was observed

Thanks to the Patients, Their Families and Study Team/Participants

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