Challenges in salvage chemotherapy for metastatic colorectal cancer

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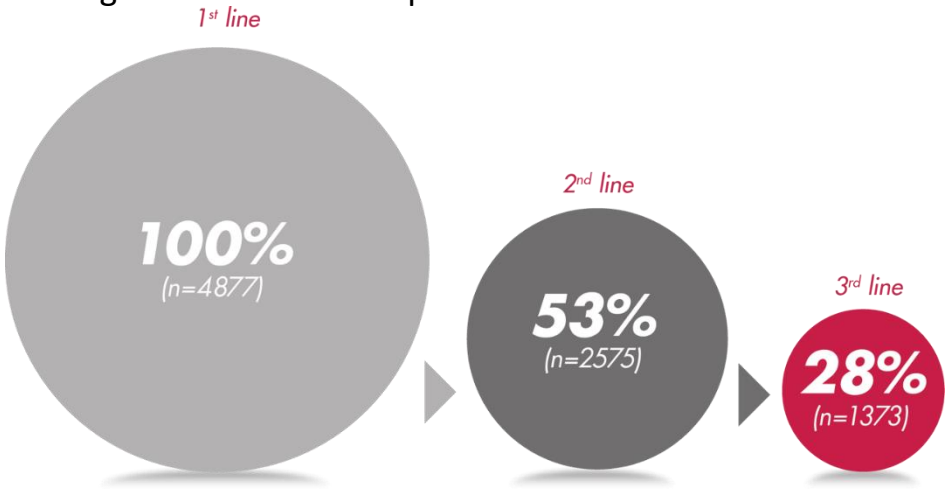
Patients deserve evidence-based treatment beyond 2nd line

Many patients are candidates for further treatment

- After 2+ lines of treatment a significant number of patients with mCRC are able and willing to receive more treatments[1]



Despite advances, the prognosis of mCRC patients pretreated with all available agents is poor and there is a high unmet need for newer treatments[3]

n=4877 patients with mCRC who received chemotherapy between Jan 2004 and March 2011 in oncology practices subscribing to a US-wide chemotherapy order entry system[2]

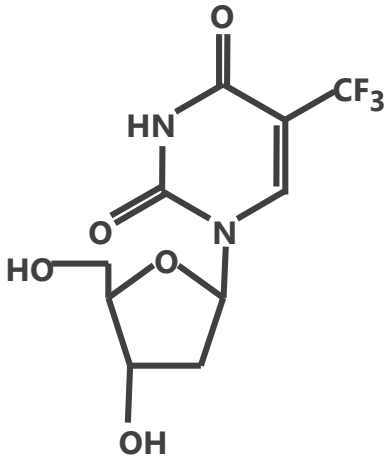
1. Chibaudel B et al. Ther Adv Med Oncol 2012;4:75-89.
2. Abrams TA et al. J Natl Cancer Inst 2014; 106(2): dji371.
3. Salvatore L et al. ExpertRev Anticancer Ther 2015;15:1283-92.

Trifluridine/tipiracil is a novel oral antitumor nucleoside

- Trifluridine (FTD) is a thymidine-based nucleoside, which is incorporated into DNA in tumor cells following phosphorylation
- Tipiracil hydrochloride (TPI), a thymidine phosphorylase inhibitor prevents degradation of FTD
  - *Employed to increase the effective in vivo FTD concentration*

Trifluridine/tipiracil

2′-deoxy-5-(trifluoromethyl)uridine (trifluridine, FTD) [1]



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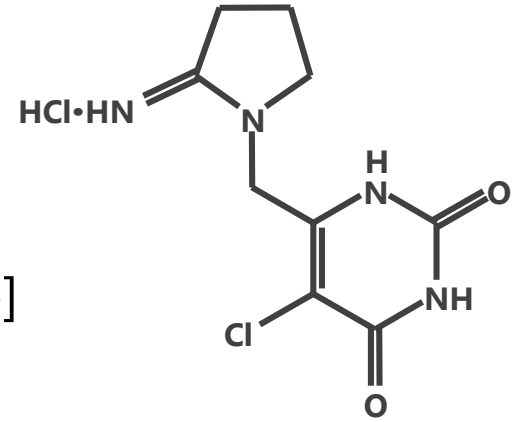
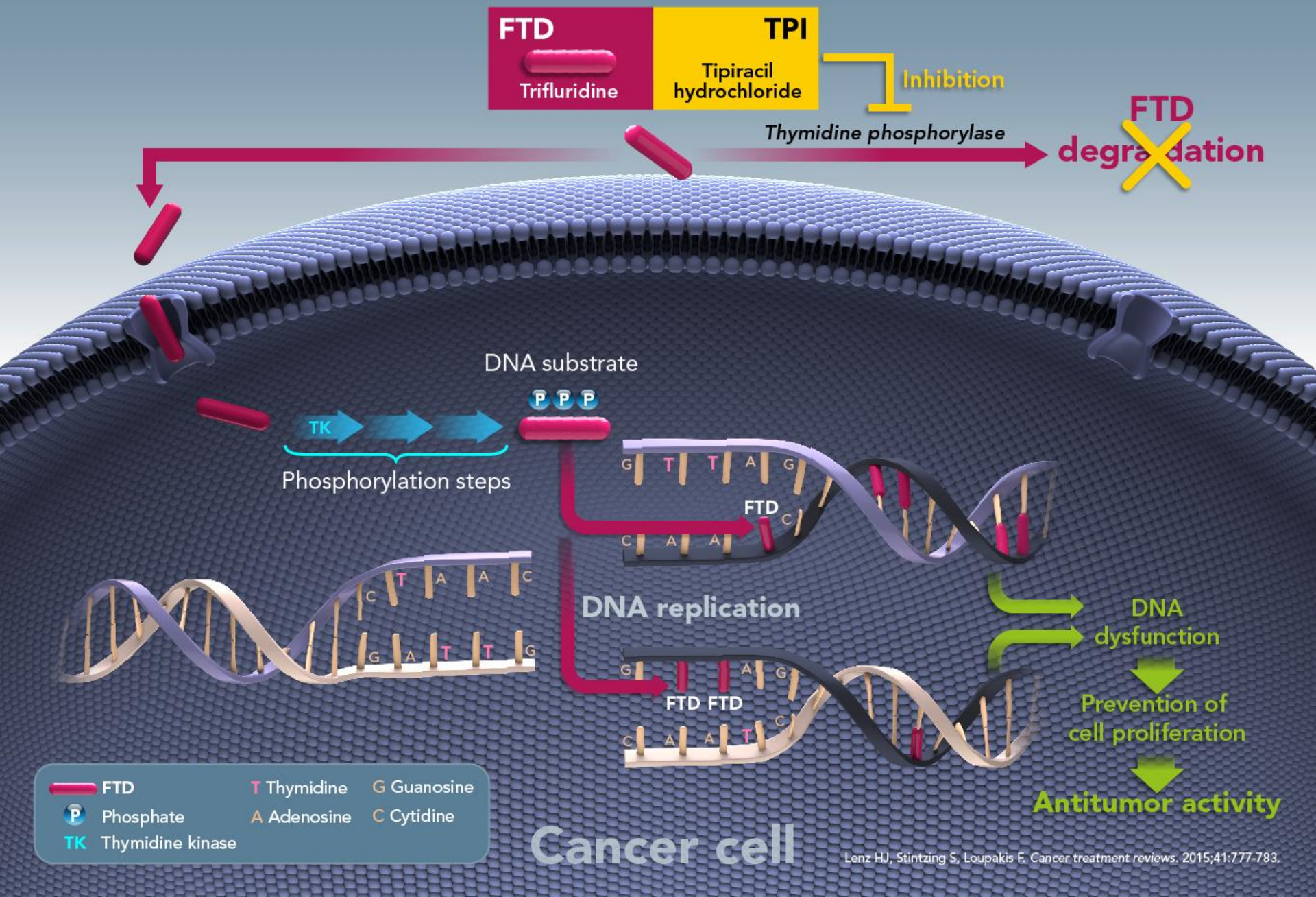
[Molar ratio]
[1:0.5]

5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2, 4(1*H*,3*H*)-dione monohydrochloride (tipiracil hydrochloride, TPI) [0.5]



Hong DS, et al. Cancer. 2006;107:1383–90

Trifluridine/Tipiracil mode of action



Lenz HJ, Stintzing S, Loupakis F. *Cancer treatment reviews*. 2015;41:777-783.

Mechanism of action of trifluridine/tipiracil: comparison with 5-FU-based fluoropyrimidines

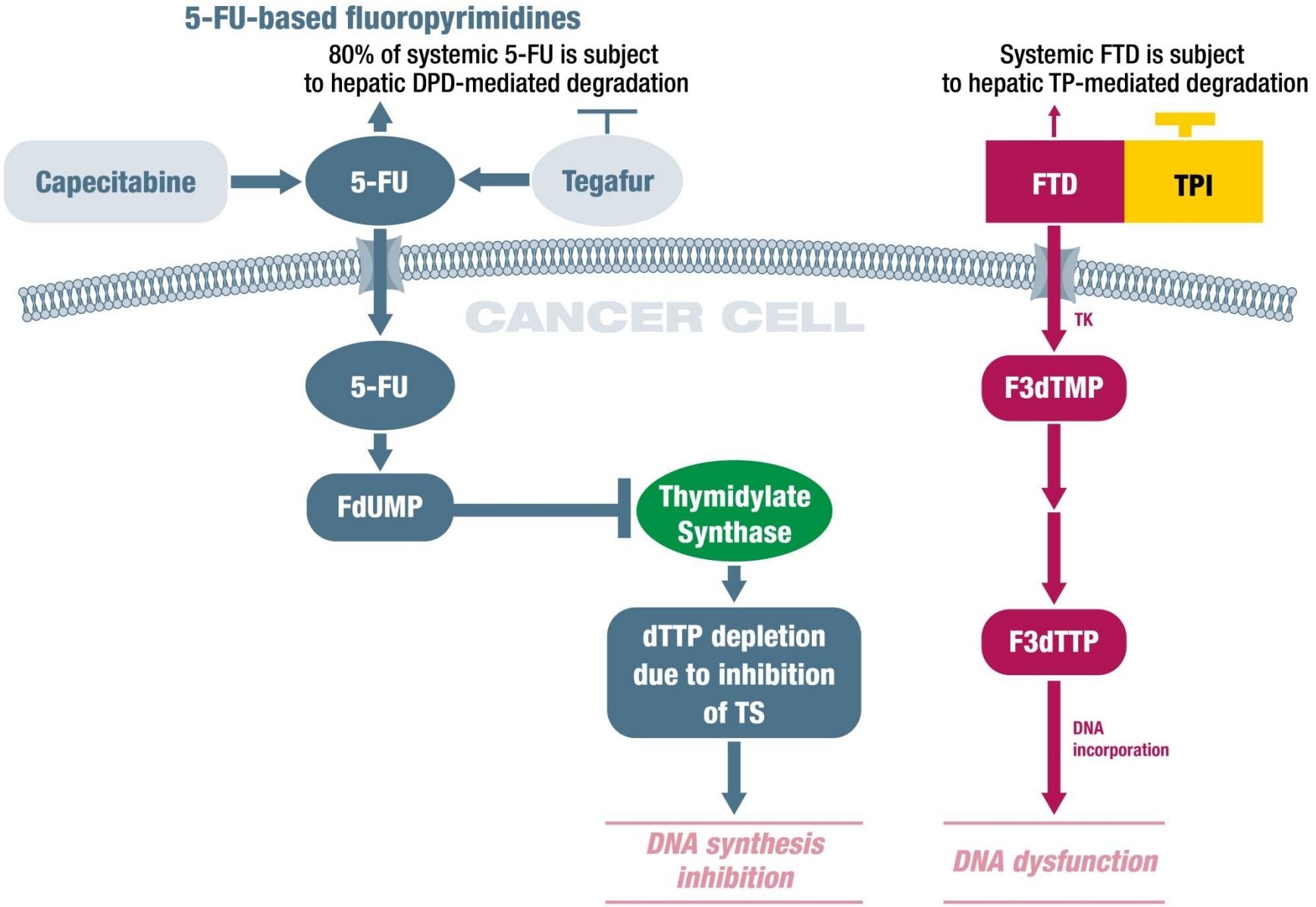


Figure adapted from H.-J. Lenz et al. *Cancer Treatment Reviews.* 2015;41:777-783.

5-FU: 5-fluorouracil; **DPD:** dihydropyrimidine dehydrogenase; **dTTP:** thymidine triphosphate; **F3dTMP:** trifluoromethyl deoxyuridine 5'-monophosphate; **F3dTTP:** trifluoromethyl deoxyuridine 5'-triphosphate; **FdUMP:** fluorodeoxyuridine monophosphate; **FTD:** trifluorothymidine (trifluridine); **TK:** thymidine kinase; **TP:** thymidine phosphorylase; **TPI:** tipiracil hydrochloride; **TS:** thymidylate synthase.

RECOURSE: Refractory Colorectal Cancer Study

- Multicentre, randomised, double-blind, placebo-controlled, phase III study
  - *Stratification: KRAS status, time from diagnosis of metastatic disease, geographical region*
- Treatment continuation until progression, intolerant toxicity or patient refusal
- Sites: 13 countries, 101 sites

mCRC
- Patients previously received 2 or more prior regimens
  - Refractory / Intolerable
  - Fluoropyrimidine
  - Irinotecan
  - Oxaliplatin
  - Bevacizumab
  - Anti-EGFR if wild-type *KRAS*
- Known *KRAS* status
- ECOG PS 0-1
- Not previously treated with trifluridine/tipiracil

RANDOMIZATION

2:1

Trifluridine/tipiracil + BSC
(N=534)
35 mg/m^2 BID PO
d1-5, 8-12 q4wks

Placebo + BSC
(N=266)
BID PO
d1-5, 8-12 q4

Endpoints
- Primary: OS
- Secondary: PFS, Safety, Tolerability, Time to ECOG PS≥2, ORR, DCR, DoR, Subgroup by *KRAS* (OS and PFS)

Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015;372:1909-1919.

RECOURSE: Baseline Demographics and Disease Characteristics

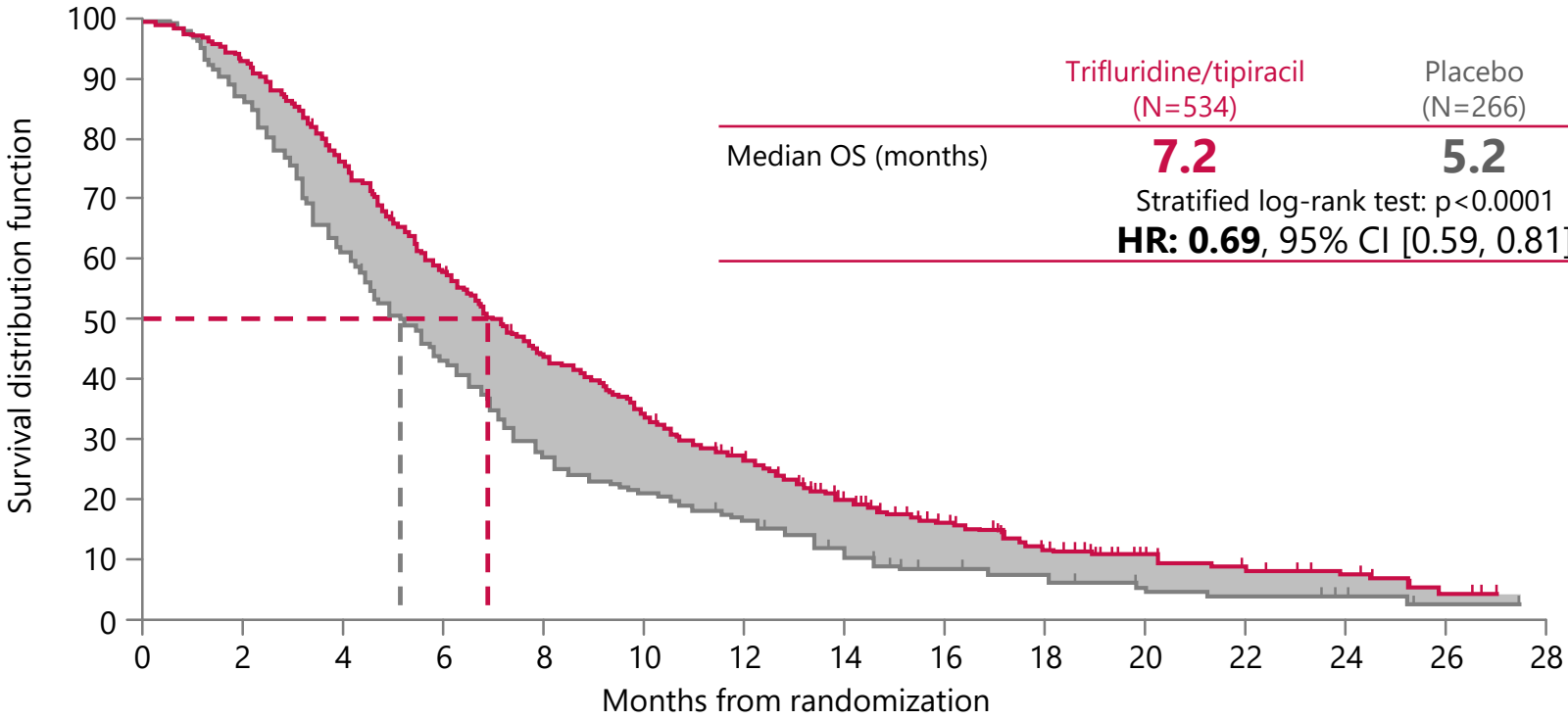
		Trifluridine/tipiracil (N=534)	Placebo (N=266)
Age in years, median (range)		63 (27-82)	63 (27-82)
Gender, %	Male	61	62
Race, %	White	57	58
	Asian	34	35
	Black	<1	2
Geographic region, %	Japan	33	33
	US, Europe, Australia	67	67
ECOG PS, %	0	56	55
	1	44	45
Primary site, %	Colon	63	61
	Rectum	37	39
KRAS mutational status, %	Wild-type	49	49
	Mutant	51	51
Time since diagnosis of metastasis,%	<18 months	21	21
	≥18 months	79	79
Number of prior regimens %	2	18	17
	3	22	20
	≥4	60	63
All prior systemic cancer therapeutic agents, %	Fluoropyrimidine	100	100
	Irinotecan	100	100
	Oxaliplatin	100	100
	Bevacizumab	100	>99
	Anti-EGFR mAntibody	52	54
	Regorafenib	17	20
Refractory to fluoropyrimidine (as part of any prior regimen), %		**98**	**>99**

Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015;372:1909-1919.

RECOURSE: Updated overall survival

Carried out at 89% of events (138 additional events)

- **2-month improvement in OS and 31% reduction in risk of death (HR=0.69)**
- **Improvement in 1yr survival was preserved in this updated analysis**



	Trifluridine/tipiracil (N=534)	Placebo (N=266)
Median OS (months)	**7.2**	**5.2**

Stratified log-rank test: p<0.0001

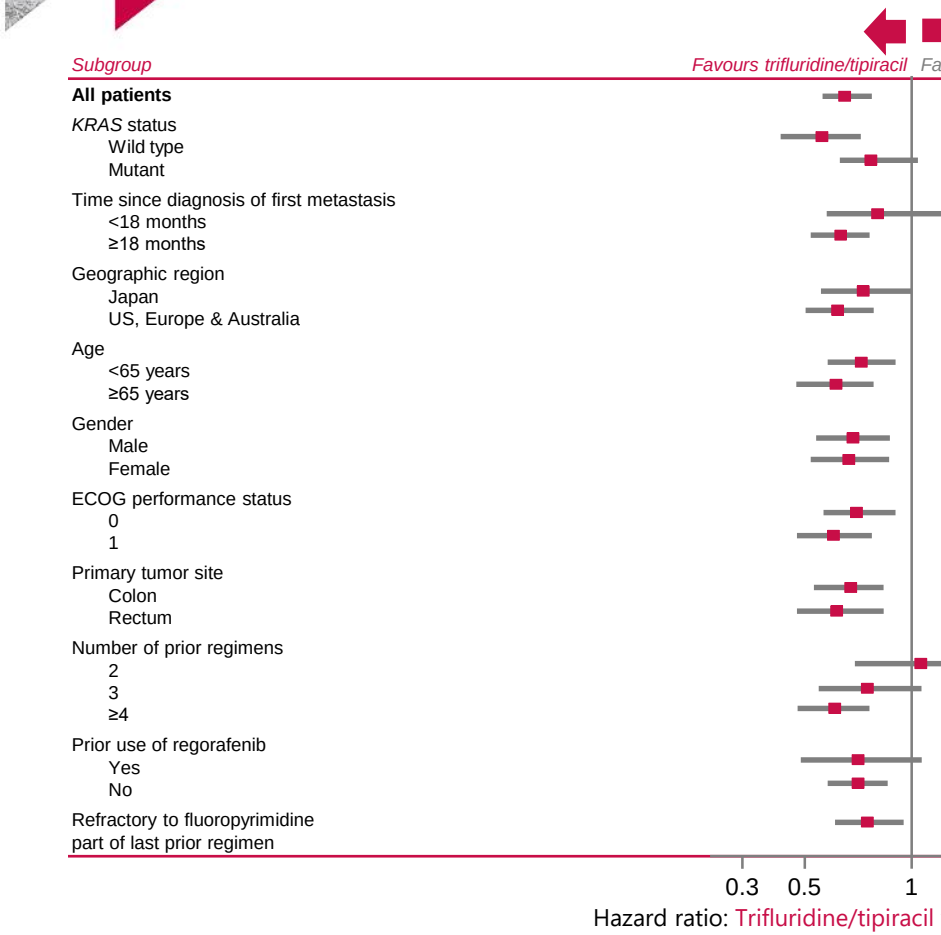
HR: 0.69, 95% CI [0.59, 0.81]

No. at Risk:

Trifluridine/tipiracil	534	499	406	308	231	180	137	95	59	38	20	14	10	4	0
Placebo	266	232	163	114	71	56	43	27	16	14	8	6	4	1	0

E. Van Cutsem et al. *European Journal of Cancer* ;90.2018.63-72

RECOURSE: OS Subgroup Analyses



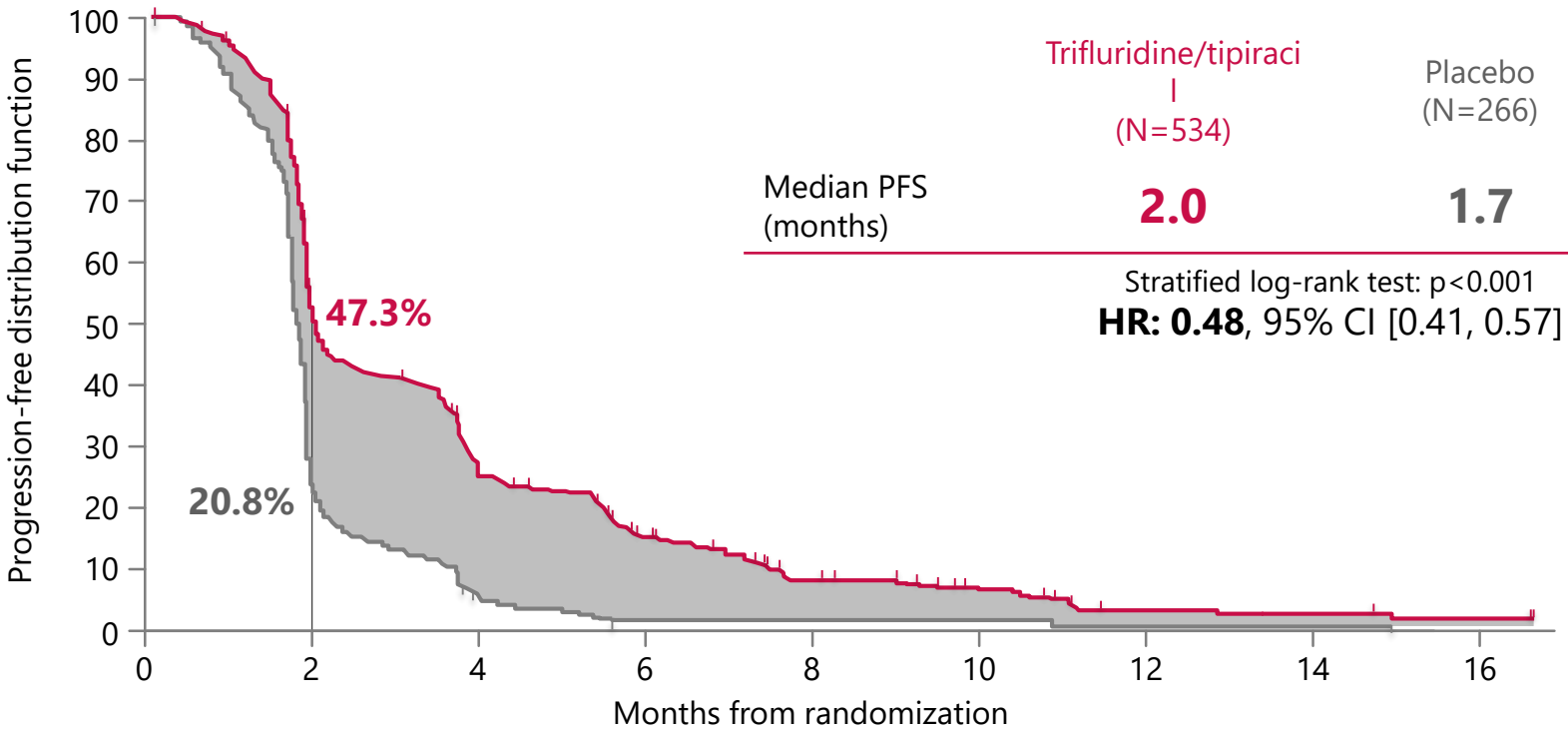
Subgroup	Events / N	HR	(95% CI)
All patients	**574 / 800**	**0.68**	**(0.58-0.81)**
KRAS status			
Wild type	280 / 393	**0.58**	(0.45-0.74)
Mutant	294 / 407	**0.80**	(0.63-1.02)
Time since diagnosis of first metastasis			
<18 months	131 / 166	**0.84**	(0.58-1.21)
≥18 months	443 / 634	**0.64**	(0.53-0.78)
Geographic region			
Japan	227 / 266	**0.75**	(0.57-1.00)
US, Europe & Australia	347 / 534	**0.64**	(0.52-0.80)
Age			
<65 years	316 / 448	**0.74**	(0.59-0.94)
≥65 years	258 / 352	**0.62**	(0.48-0.80)
Gender			
Male	348 / 491	**0.69**	(0.56-0.87)
Female	226 / 309	**0.68**	(0.51-0.90)
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)
Rectum	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			
Yes	94 / 144	**0.69**	(0.45-1.05)
No	480 / 656	**0.69**	(0.57-0.83)
Refractory to fluoropyrimidine part of last prior regimen	329 / 455	**0.75**	(0.59-0.94)

Most patients benefit from trifluridine/tipiracil treatment

Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015;372:1909-1919.

RECOURSE: PFS

52% reduction in risk of progression (HR=0.48)



	Trifluridine/tipiracil (N=534)	Placebo (N=266)
Median PFS (months)	**2.0**	**1.7**

Stratified log-rank test: p<0.001

HR: 0.48, 95% CI [0.41, 0.57]

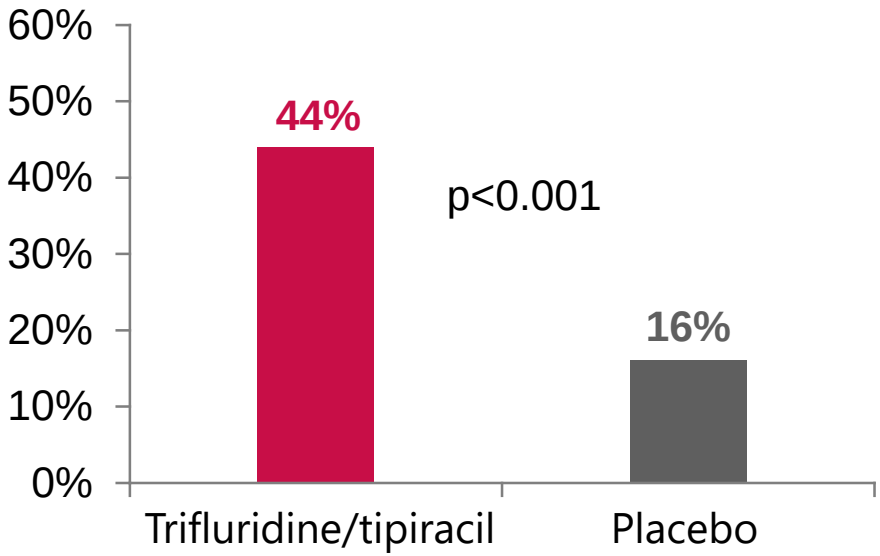
No. at Risk:									
Trifluridine/tipiracil	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

CT scan performed every 8 weeks from month 2

Mayer RJ, Van Cutsem E, *et al. N Engl J Med*. 2015;372:1909-1919.

RECOURSE: Overall Response Rate and Disease Control Rate

Disease Control Rate



Response Rate

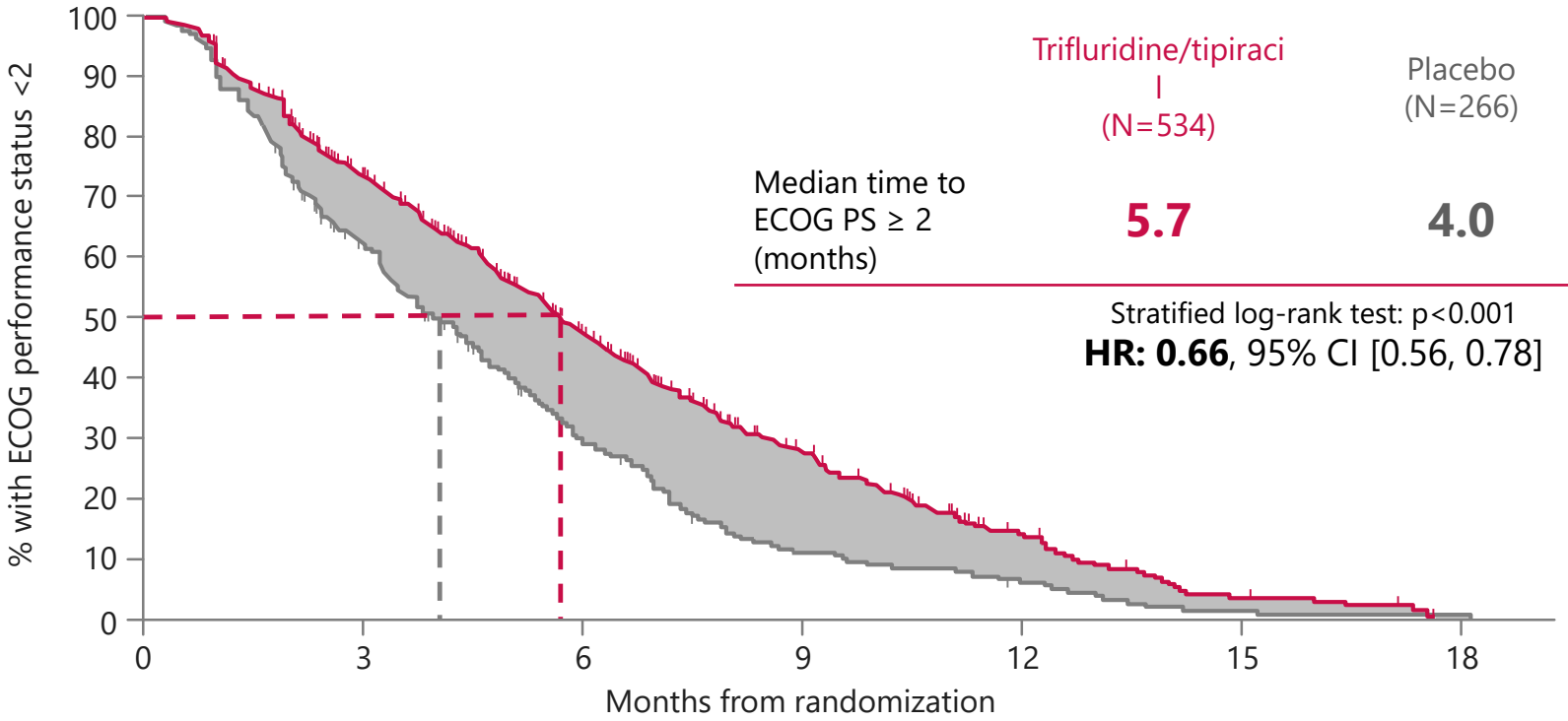
	Trifluridine/ tipiracil N=502 %	Placebo N=258 %
CR	0	0.4
PR	1.6	0
SD	42.4	15.9
ORR (%)	1.6	0.4

Significant improvement in disease control achieved

Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015;372:1909-1919.

RECOURSE: Time to ECOG Performance Status ≥2

Patients stay in PS 0–1 significantly longer (5.7 vs. 4.0 months)



	Trifluridine/tipiracil (N=534)	Placebo (N=266)
Median time to ECOG PS ≥ 2 (months)	**5.7**	**4.0**

Stratified log-rank test: p<0.001

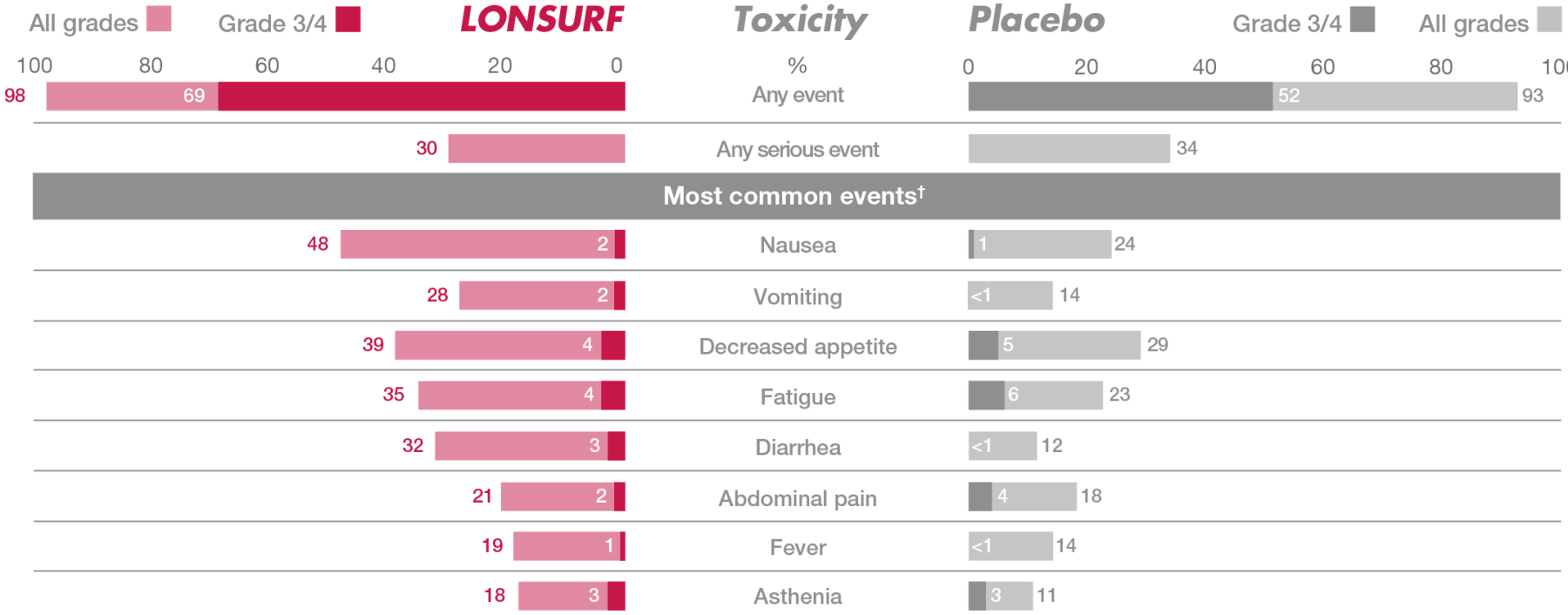
HR: 0.66, 95% CI [0.56, 0.78]

No. at Risk:

Trifluridine/tipiracil	534	352	188	84	28	7	0
Placebo	266	134	57	21	11	3	1

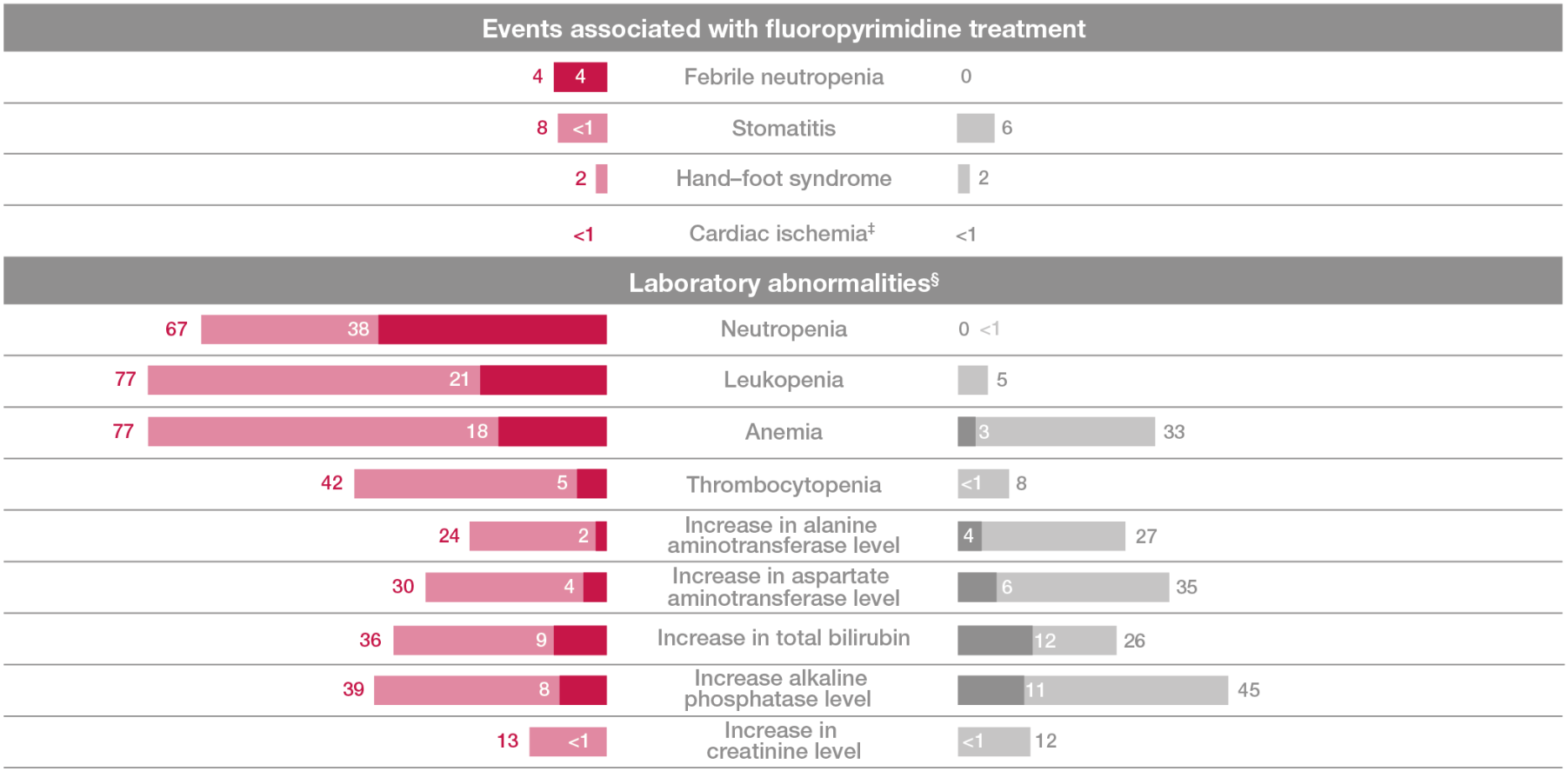
Mayer RJ, Van Cutsem E, *et al. N Engl J Med*. 2015;372:1909-1919.

Trifluridine/tipiracil non-haematologic adverse event[1,2]



1. Trifluridine/tipiracil Summary of Product Characteristics
2. Mayer RJ et al. N Engl J Med 2015;372:1909-19.

Trifluridine/tipiracil haematologic adverse event [1,2]



1. Trifluridine/tipiracil Summary of Product Characteristics
2. Mayer RJ et al. N Engl J Med 2015;372:1909-19.

‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischemia
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one postbaseline measurement during treatment. Denominators are provided in the publication

RECOURSE: Overview of adverse events and dosing modifications

- **4%** of the patients receiving trifluridine/tipiracil and 2% of the patients receiving placebo had to withdraw due to adverse events
- **14%** of patients taking trifluridine/tipiracil required a dose reduction
- **42%** of patients in each group received an additional line of therapy
- **53%** of patients experienced a delay in their dosing schedule during the trial

Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015;372:1909-1919.

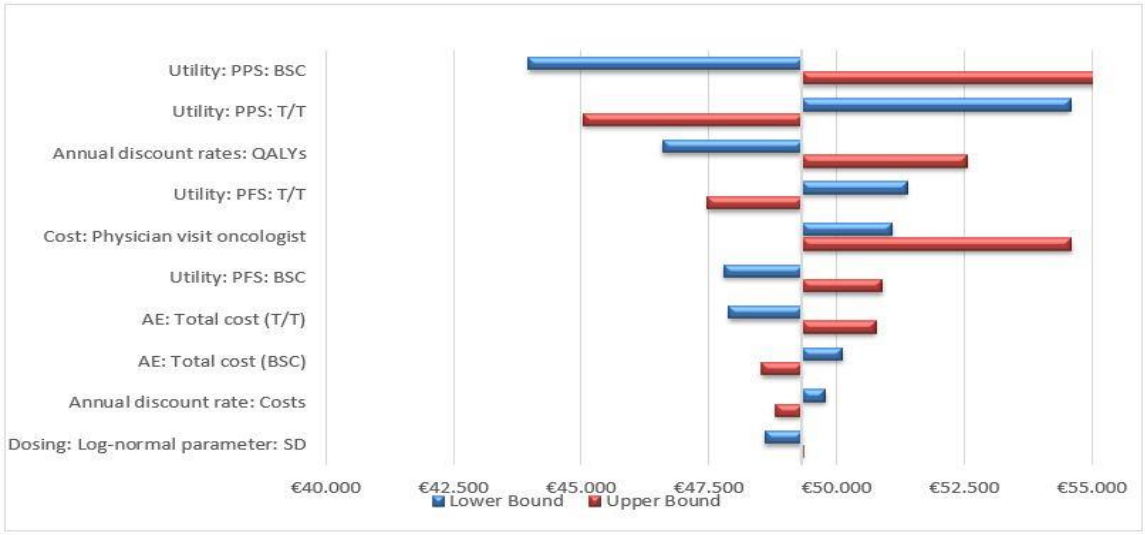
PRECONNECT TRIAL

Real World Data

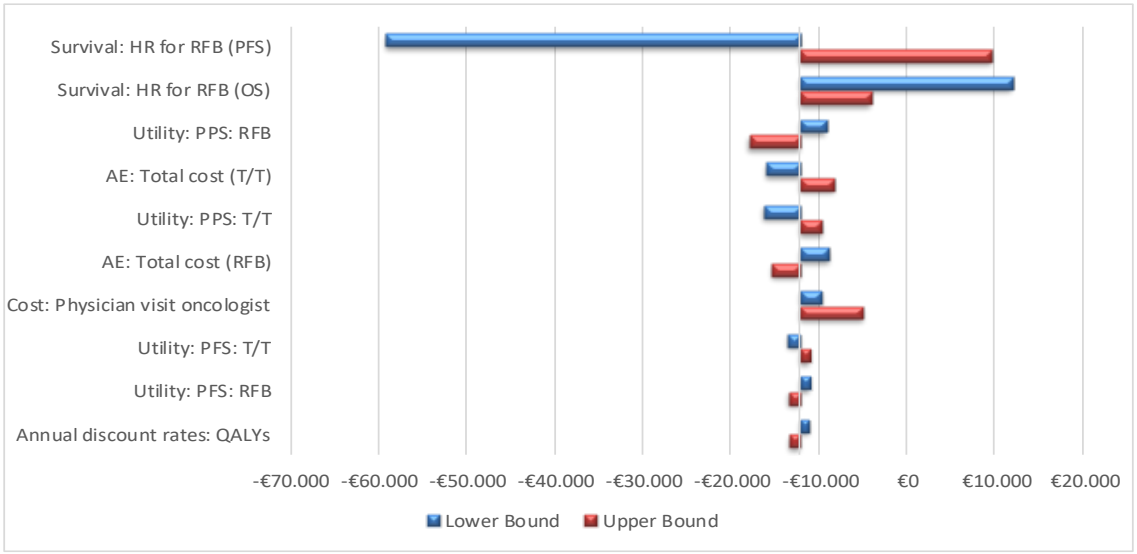
- PFS TAS-102 2.8 months (95% CI, 2.7-3.3).
- ORR 2.4% (95% CI, 1.2%-4.2%) and disease control rate was 36.8% (95% CI, 32.4%-41.4%). T
- The **median time to deterioration** to ECOG performance status ≥2 was **8.7 months** (range, 0.2-11.0).

Falcone A et al WCGI 2018

COST EFFECTIVENESS STUDY IN GREECE



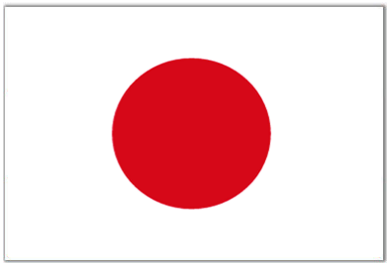
TAS102 vs. BCC



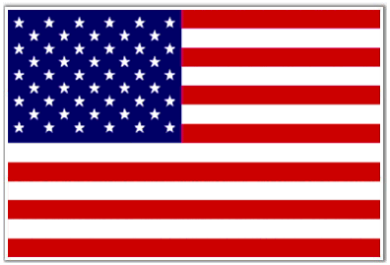
TAS102 vs. REGORAFENIB

Change the story of pre-treated mCRC

Trifluridine/tipiracil approved:



Japan
May 2014



FDA
September 2015

EMA
April 2016

*Trifluridine/tipiracil is indicated for the treatment of **adult patients with metastatic colorectal cancer (mCRC)** who have been **previously treated with, or are not considered candidates for**, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan based chemotherapies, anti-VEGF agents, and anti-EGFR agents (EMA SmPC)*

Trifluridine/tipiracil Summary of Product Characteristics.

Treatment algorithm recommended by the 2016 ESMO consensus guidelines for the management of fit patients with mCRC

	RAS wt		*RAS mt*		*BRAF mt*	
First-line	EGFR antibody + CT doublet	Bevacizumab + CT triplet or CT doublet or FP	Bevacizumab + CT triplet or CT doublet	CT triplet	Bevacizumab + CT triplet or CT doublet	CT triplet
Maintenance	FP + bevacizumab or pause		FP + bevacizumab or pause		FP + bevacizumab or pause	
	First progression					
Second-line	Anti–VEGF + CT doublet	EGFR antibody + CT doublet	Anti–VEGF + CT doublet		Anti–VEGF + CT doublet	
	Second progression					
Third-line	**Trifluridine/tipiracil** or Regorafenib or If not yet pretreated with an EGFR antibody: EGFR antibody monotherapy or with CT doublet or with irinotecan		**Trifluridine/tipiracil** or Regorafenib		**Trifluridine/tipiracil** or Regorafenib	

Reintroduction[1,3]
No progression of mCRC while on therapy. Treatment was either of a set duration (eg, adjuvant) or was stopped for a planned break (eg, to reduce or manage adverse events).

≠

Rechallenge[4]
Reintroduction, after an intervening treatment, of the same therapy to which the tumor has already been proven to be resistant. The disease is challenged with the same regimen/agent in later-line treatment.

Van Cutsem E et al. Ann Oncol. 2016;27(8):1386-1422.

Concluding remarks

Trifluridine/tipiracil is a new treatment for pre-treated mCRC patients

- The following benefits were observed in a phase III trial of trifluridine/tipiracil versus placebo:
  - Clinically relevant and statistically significant improvement in OS
    - ***32% reduction in risk of death (HR=0.68)***
  - Clinically relevant and statistically significant improvement in PFS
    - ***52% reduction in the risk of progression***
  - 44% of patients treated with trifluridine/tipiracil had their disease controlled (vs 16%)
  - Patients stay in PS 0–1 significantly longer (5.7 vs. 4.0 months)
  - Well-tolerated with minimal non-hematological toxicity
- Oral dosing, easy to take outside of the hospital