Treatment strategies for advanced or metastatic colorectal cancer

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

1. The first-line chemotherapy for advanced colorectal cancer

2. New options of targeted-drugs

3. The second-line and cross-line treatment for advanced colorectal cancer

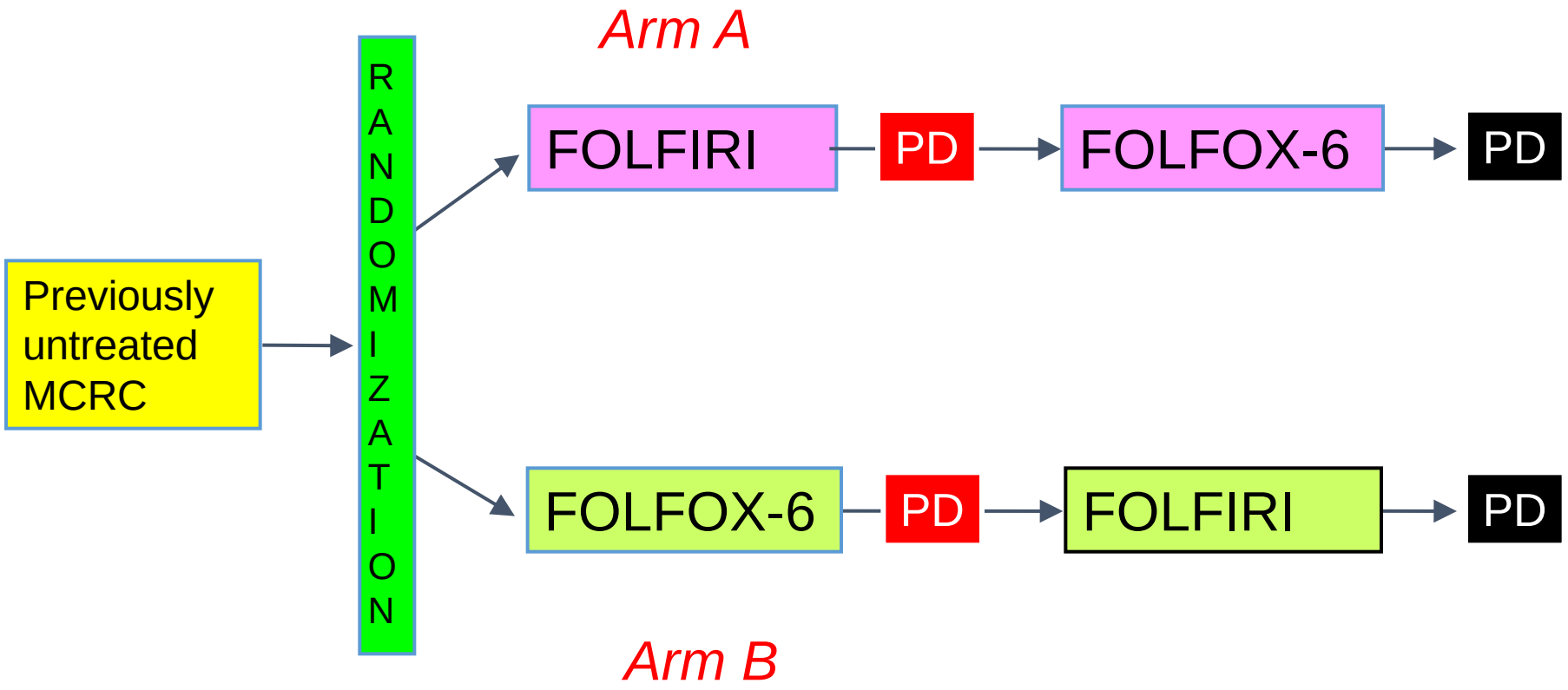
Phase III clinical trials of first-line mCRC using Irinotecan combined with 5-FU/LV

Author	Protocol	RR (%)	PFS (mos)	OS (mos)
Saltz,	FU/ LV bolus (Mayo)	21	4.3	12.6
NEJM 9/2000	FU/ LV bolus + Irinotecan (IFL)	39	7.0	14.8
#457	p-value	<0.001	0.004	0.04
Douillard,	FU/ LV inf.	31	4.4	14.1
Lancet 3/2000	FU/ LV inf. + Irinotecan	49	6.7	17.4
#338	p-value	<0.001	<0.001	0.031
Koehne,	FU/ LV inf.	31.5	6.4	16.9
ASCO 2003	FU/ LV inf. + Irinotecan	54.2	8.5	20.1
#430	p-value	<0.0001	0.0001	n.s.

Phase III clinical trials of first-line mCRC using Oxaliplatin combined with 5-FU/LV

Author	Protocol	RR (%)	PFS (mos)	OS (mos)
Giacchetti,	FU/LV inf.	16	6.1	19.9
JCO 1/ 2000	FU/LV inf. + Oxaliplatin	53	8.7	19.4
#200	p-value	<0.0001	0.048	n.s.
De Gramont,	FU/LV inf.	22.3	6.2	14.7
JCO 8/ 2000	FU/LV inf. + Oxalipl. FOLFOX4	50.7	9.0	16.2
#420	p-value	0.0001	<0.0001	n.s.
Grothey,	FU/ LV Bolus (Mayo)	22.6	5.3	16.1
ASCO 2002	FU/ LV inf. + Oxaliplatin	49.1	7.8	19.7
#252	p-value	<0.0001	0.0001	n.s.

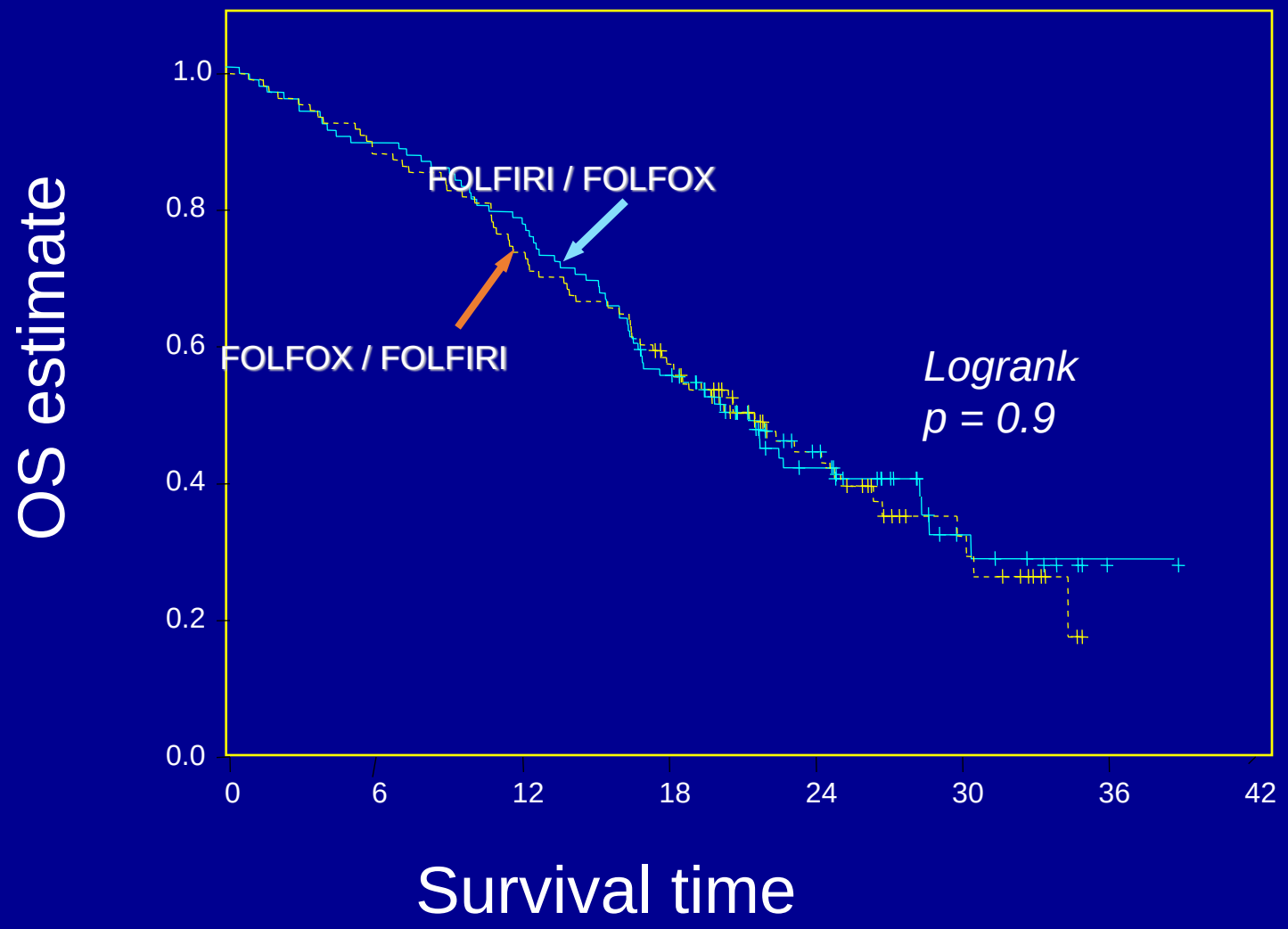
Tournigand Study



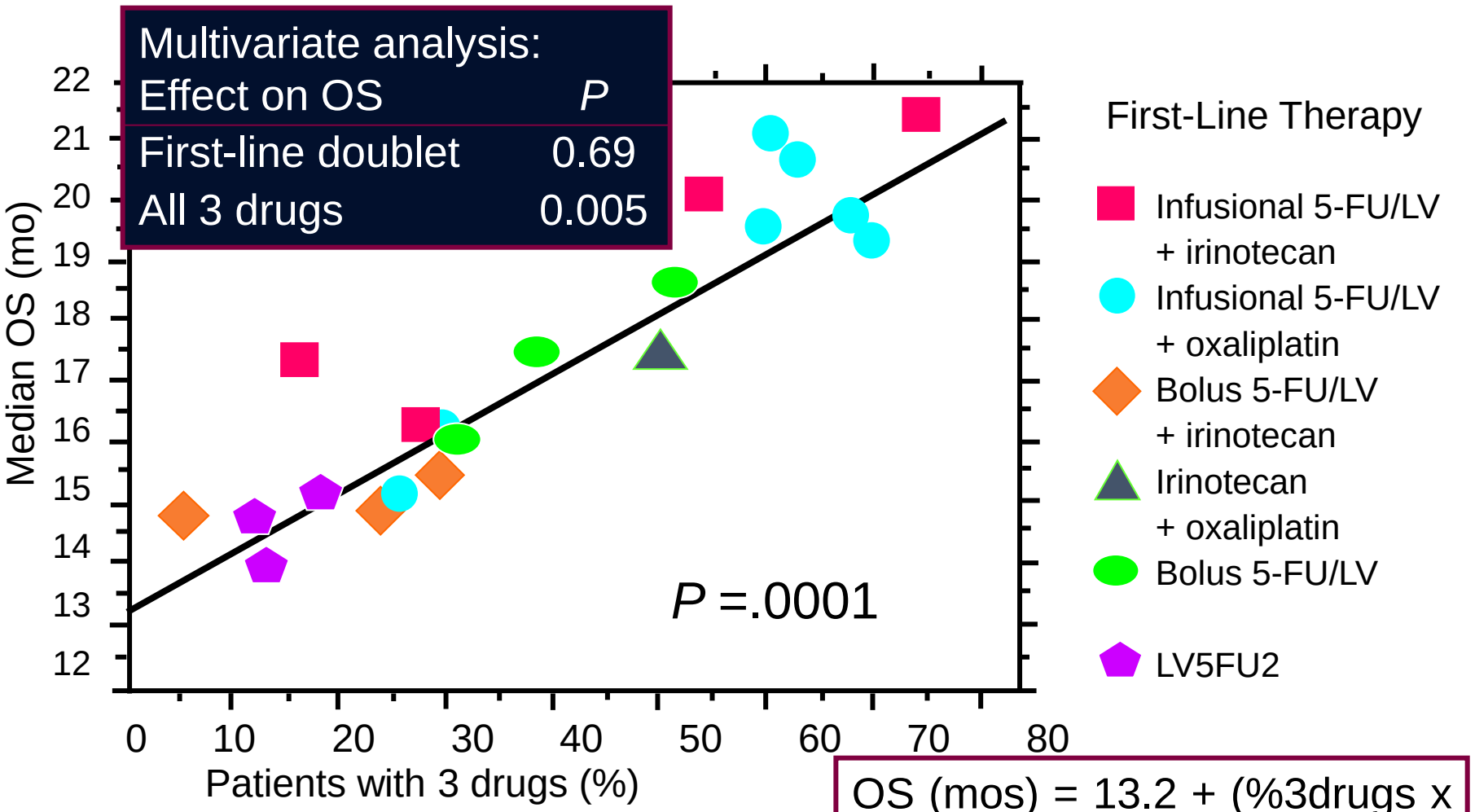
PD = progressive disease.

Tournigand et al. *J Clin Oncol*. 2004;22:229.

Overal Survival



Concept of “All-3-Drugs” - Update 2005
11 Phase III Trials, 5768 Patients



OS (mos) = 13.2 + (%3drugs x 0.1), R^2 = 0.85

Grothey & Sargent, JCO 2005

Summary:

1. Patients appropriate for intensive therapy, FOLFIRI, FOLFOX, XELOX all can be chosen as the first-line therapy.

2. Patients not appropriate for intensive therapy, 5-FU/LV or Capecitabine monotherapy can be chosen as the first-line therapy.

In this case:

FOLFOX and Cape are appropriate for the first-line treatment.

- So far:
  - 4 mos. FOLFOX/Bev → 9 mos. Cape/Bev (= 13 in total)
  - 7 mos. FOLFIRI/Aflibercept (with some interruptions), stable disease
  - 4 mos. Panitumumab single agent → some response, then progression
- What now?
  - FOLFOX (Re-Induction) → Regorafenib ?
  - Regorafenib → FOLFOX (Re-Induction)
  - How to integrate TAS 102 ?

To patients not appropriate for intensive therapy, infusional 5-FU is still one of the standard options.

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Treatment of metastatic disease

Maintenance treatment

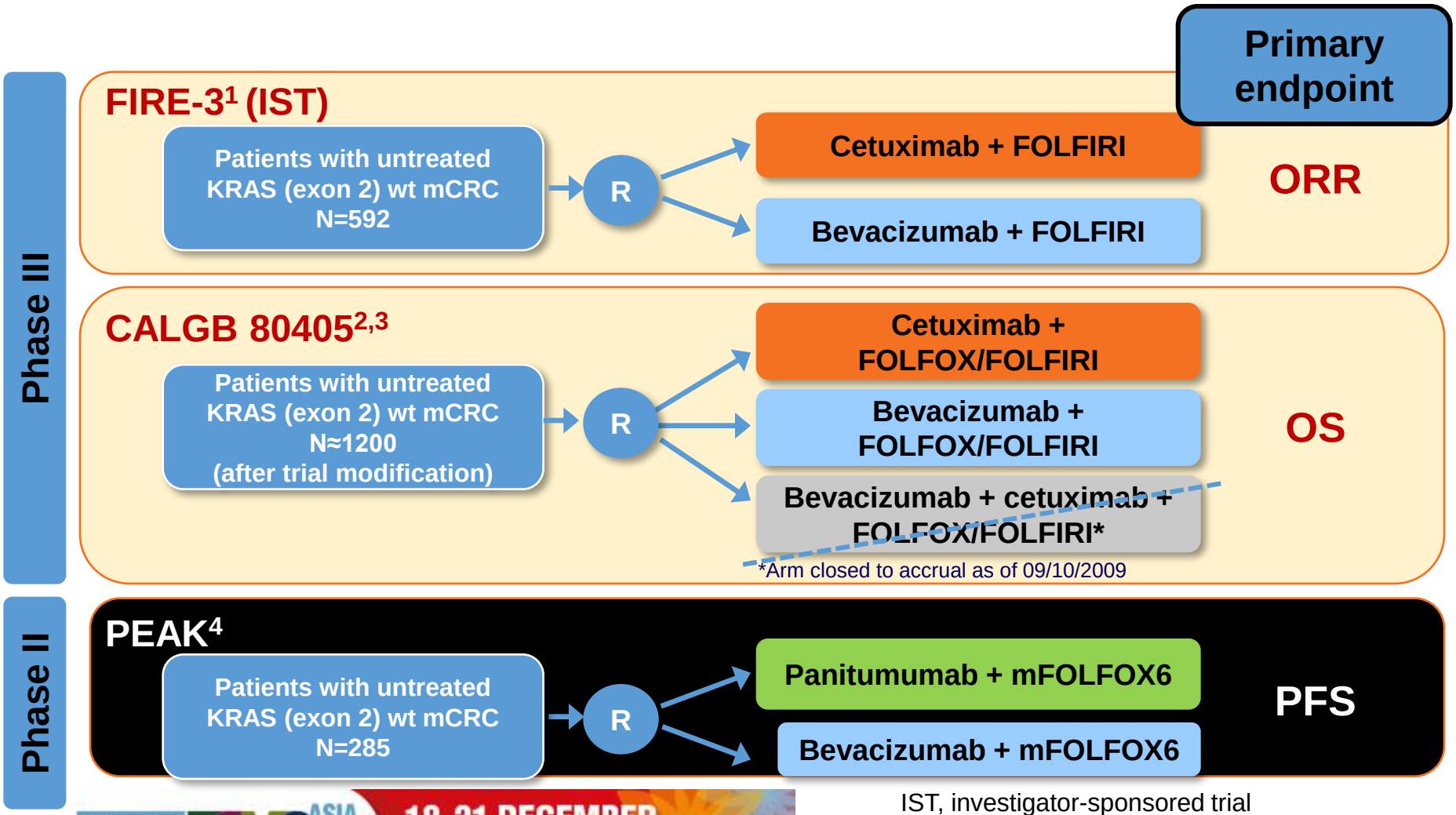
- Patients receiving FOLFOX or CAPOX as induction therapy should be allocated to maintenance therapy after 6–8 cycles.
- Patients receiving FOLFIRI as induction should continue for (at least) as long as tumour shrinkage continues/disease stabilisation is maintained.
- In the case of patients receiving induction therapy with single-agent 5-FU/capecitabine or capecitabine plus bevacizumab induction therapy should be maintained until progression
- Optimal maintenance treatment after a bevacizumab-containing induction is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab monotherapy as maintenance is not recommended.
- Individualisation and discussion with the patient is essential.
- Induction therapy should be re-introduced throughout the whole treatment strategy

Targeted-drug therapy for advanced colorectal cancer

- Anti-angiogenic monoclonal anti-body：
  - Bevacizumab
  - Aflibercept

- Epidermal growth factor receptor anti-body：
  - Cetuximab
  - Panitumumab
  - Regorafenib

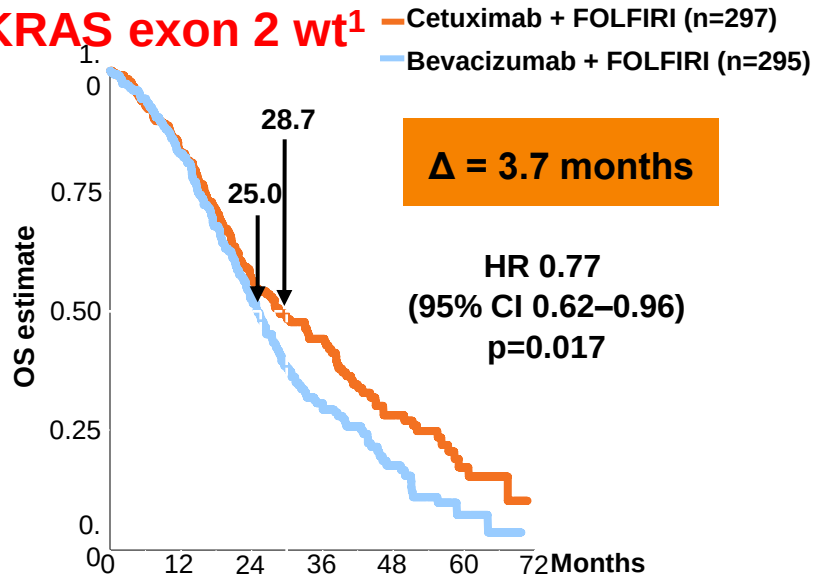
What is the optimal 1st line therapy? Evidence from head-to-head trials

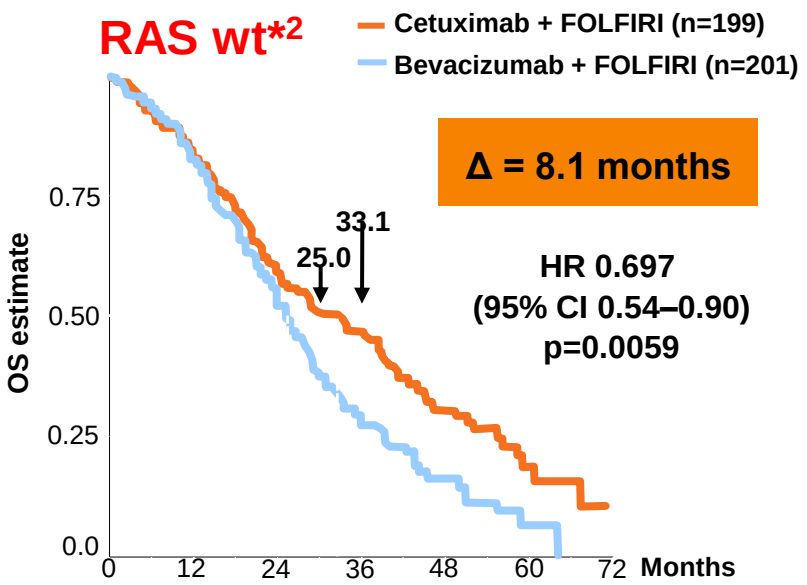


IST, investigator-sponsored trial

1. Heinemann V, et al. ASCO 2013 (Abstract No. LBA3506); 2. Naughton MJ, et al. ASCO 2013 (Abstract No. 3611); 3. NCT00265850; 4. Schwartzberg LS, et al. ASCO GI 2013 (Abstract No. 446)

FIRE-3: Greater selection of patients further improves the benefit with cetuximab





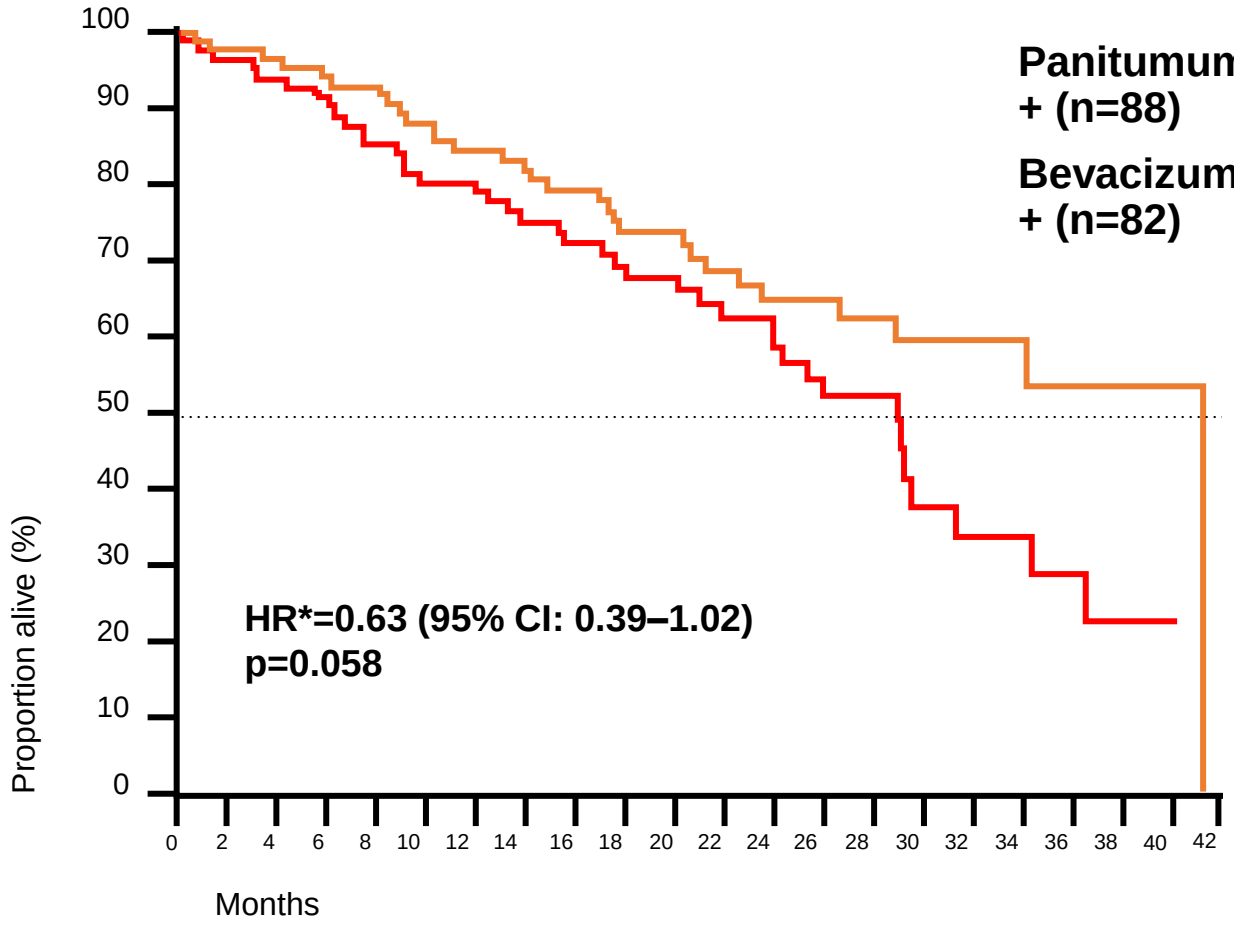
	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI	OR (95% CI)	p value
KRAS exon 2 wt (ITT),	592			
ORR, % (95% CI)	62.0 (56.2–67.5)	58.0 (52.1–63.7)	1.18 (0.85–1.64)	0.183†
RAS wt*, n	342			
ORR, % (95% CI)	65.3 (58.3–51.6)	58.7 (51.6–65.6)	1.33 (0.88–1.99)	0.18‡

- Overall survival (OS) data are based on an event rate of 59%
- The FIRE-3 study did not meet its primary endpoint of significantly improving overall response rate (ORR) in patients with KRAS (exon 2) wt mCRC based on investigators' read
- The study design, cross-over treatment in 2nd line and other study attributes are needed to better understand the data
- The study was financially supported by Merck Serono GmbH
- Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or

*Including KRAS exon 2, 3, 4 and NRAS exon 2, 3, 4;
†One-sided Fisher's exact test; ‡two-sided Fisher's exact test
Adapted from 1. Heinemann V, et al. ASCO 2013 (Abstract No. LBA3506) and 2. . Stintzing S, et al. 2014 ESCO Abstract LBA11

PEAK study: Overall survival
Panitumumab vs. Bevacizumab in RAS wt mCRC: WT RAS (exon 2,3,4 KRAS/NRAS)

mFOLFOX6 +	Events n (%)	Median (95% CI) months
Panitumumab + (n=88)	30 (34)	41.3 (28.8–41.3)
Bevacizumab + (n=82)	40 (49)	28.9 (23.9–31.3)

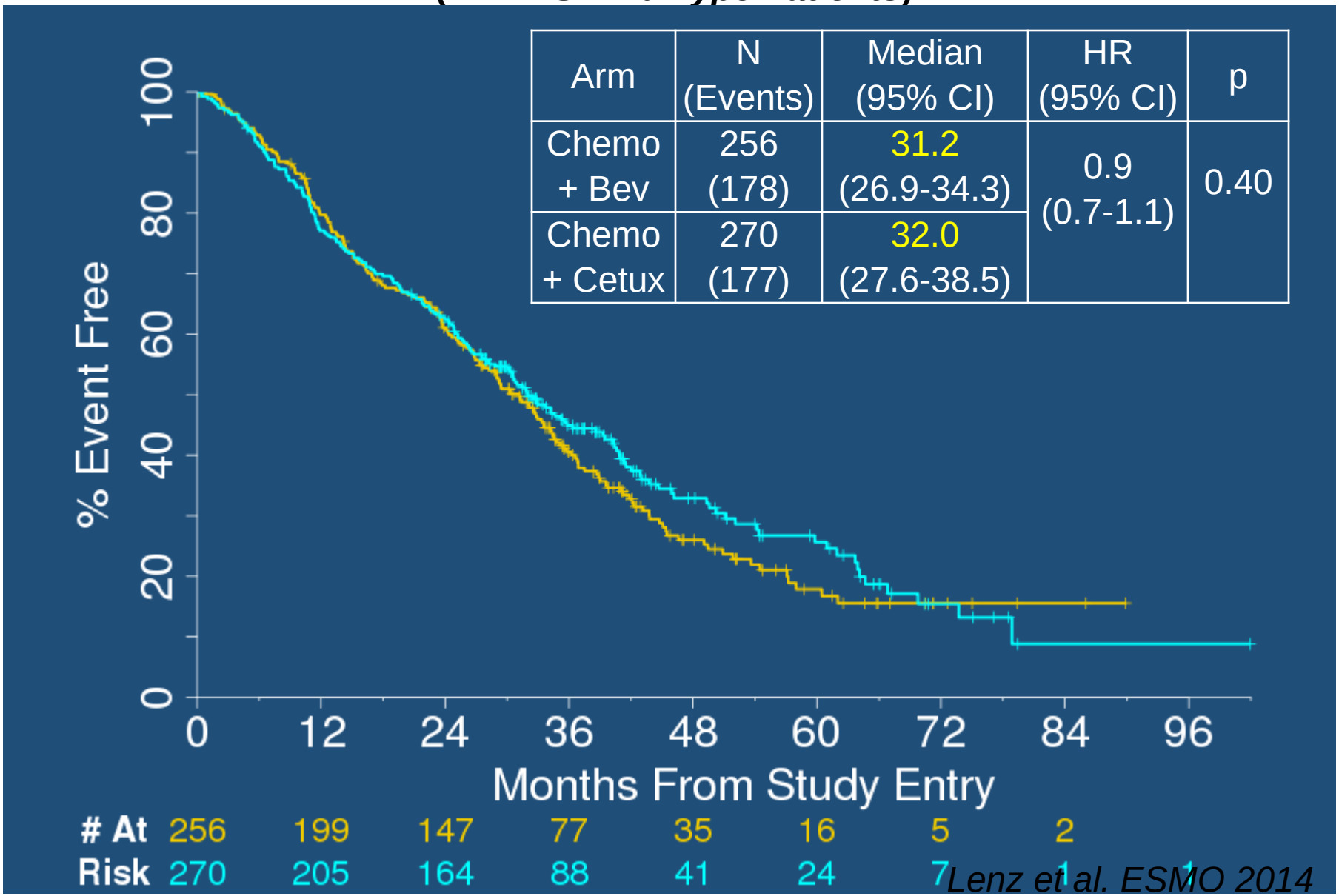


Schwartzberg L, et al. JCO 2014

CALGB/SWOG 80405 Study: Overall Survival By Arm

(*All RAS Wild Type Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	256 (178)	31.2 (26.9-34.3)	0.9 (0.7-1.1)	0.40
Chemo + Cetux	270 (177)	32.0 (27.6-38.5)		



Lenz et al. ESMO 2014

Treatment of metastatic disease

Fit patients with „disease control“ as goal

- The unanimous recommendation….was that they **should receive chemotherapy (single-agent/doublet) plus bevacizumab first-line, with EGFR antibody therapy as an option** for patients with *RAS* wild-type disease.
- Patients should be re-evaluated every 2–3 months. Where there is evidence of good disease control, patients should continue on therapy and if after two re-evaluations, **active maintenance** should be preferrably considered.

Treatment of metastatic disease

Fit patients with cytoreduction or shrinkage as a goal

- For potentially resectable patients…with *RAS* wild-type tumours, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice and those with *RAS* mutant tumours should receive a cytotoxic triplet ± bevacizumab or cytotoxic doublet plus bevacizumab are the preferred options.
- If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage, patients should be recommended for potentially curative surgery with a view to eliminating all evidence of disease (R0 resection and/or ablative strategy).
- If no response is evident at first evaluation, it is suggested that the cytotoxic doublet is changed in order to maximise the chance of resection.

Summary:

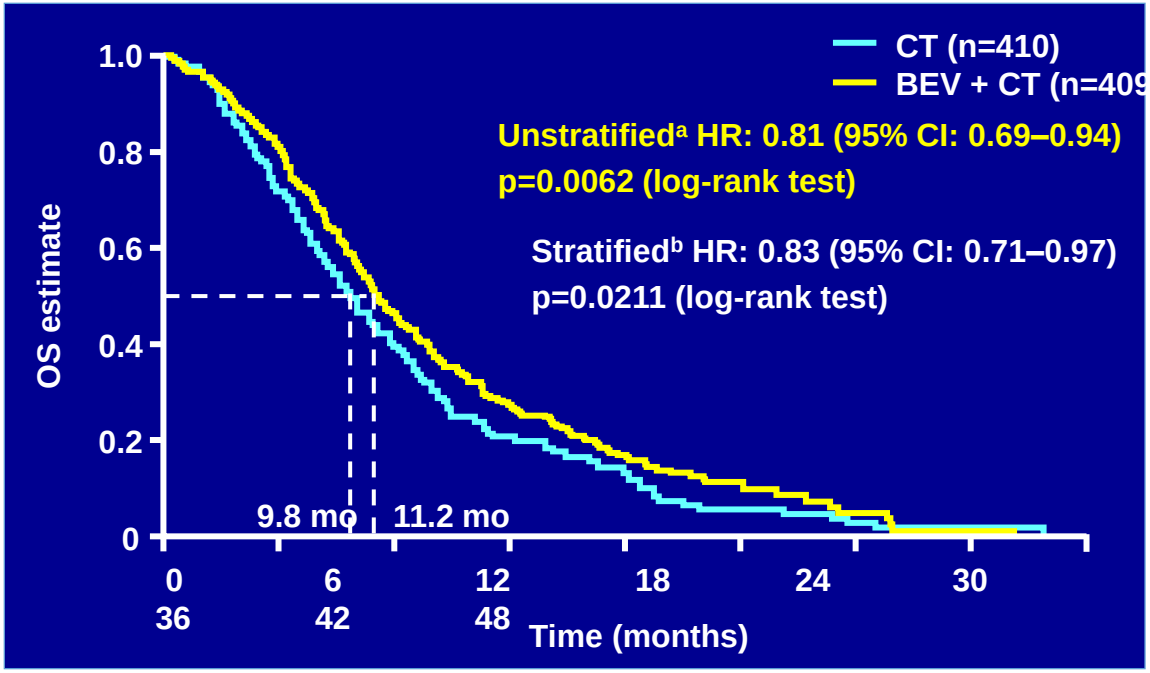
1 Cetuximab combined with chemotherapy can improve ORR and prolong OS in first-line treatment for the RAS wide type patients.

2 Bevacizumab combined with chemotherapy can prolong PFS in first-line treatment.

VEGF Inhibition in 2nd or later line therapy

	2nd line VEGF				„Last“ line multi VEGF TKI
	TML 18147	E3200	VELOUR	RAISE	CORRECT
Bev in 1st line	all pts.	no pts	yes / no	All pts.	all pts (+ EGFR if KRASwt)
2nd line Chemotherapy	FOLFIRI or FOLFOX	FOLFOX	FOLFIRI	FOLFIRI	Last line BSC
VEGF inhibitor	bevacizumab	bevacizumab	aflibercept	Ramucirumab	regorafenib
OS	11.2 v 9.8 mo HR 0.81 p=0.0062	12.9 v 10.8 mo HR 0.75 p=0.0011	13.5 v 12.1 mo HR 0.82 p=0.003	11.7 vs. 13.3 mo HR 0.84 P=0.022	6.4 vs. 5.0 mo HR 0.77 P=0.0052

TML 18147 Study



Overall survival composite from 1st and 2nd line treatment

22.5 - 9.8 = 12.7 mo

1st line (CTx+Bev)

23.9 – 11.2 = 12.7 mo

9.8 mo

2nd line (CTx ± Bev)

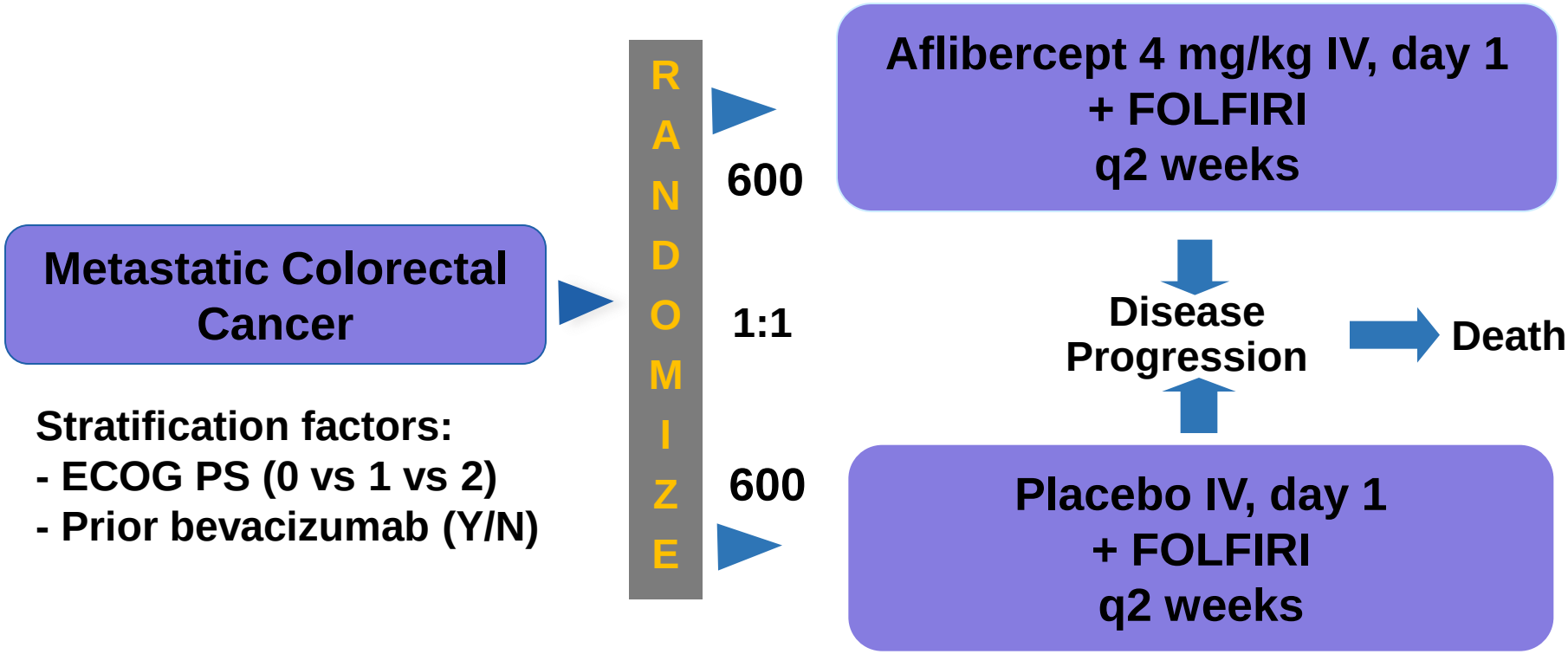
11.2 mo

22.5 mo

∂ 1.4 mo

23.9 mo

VELOUR Study

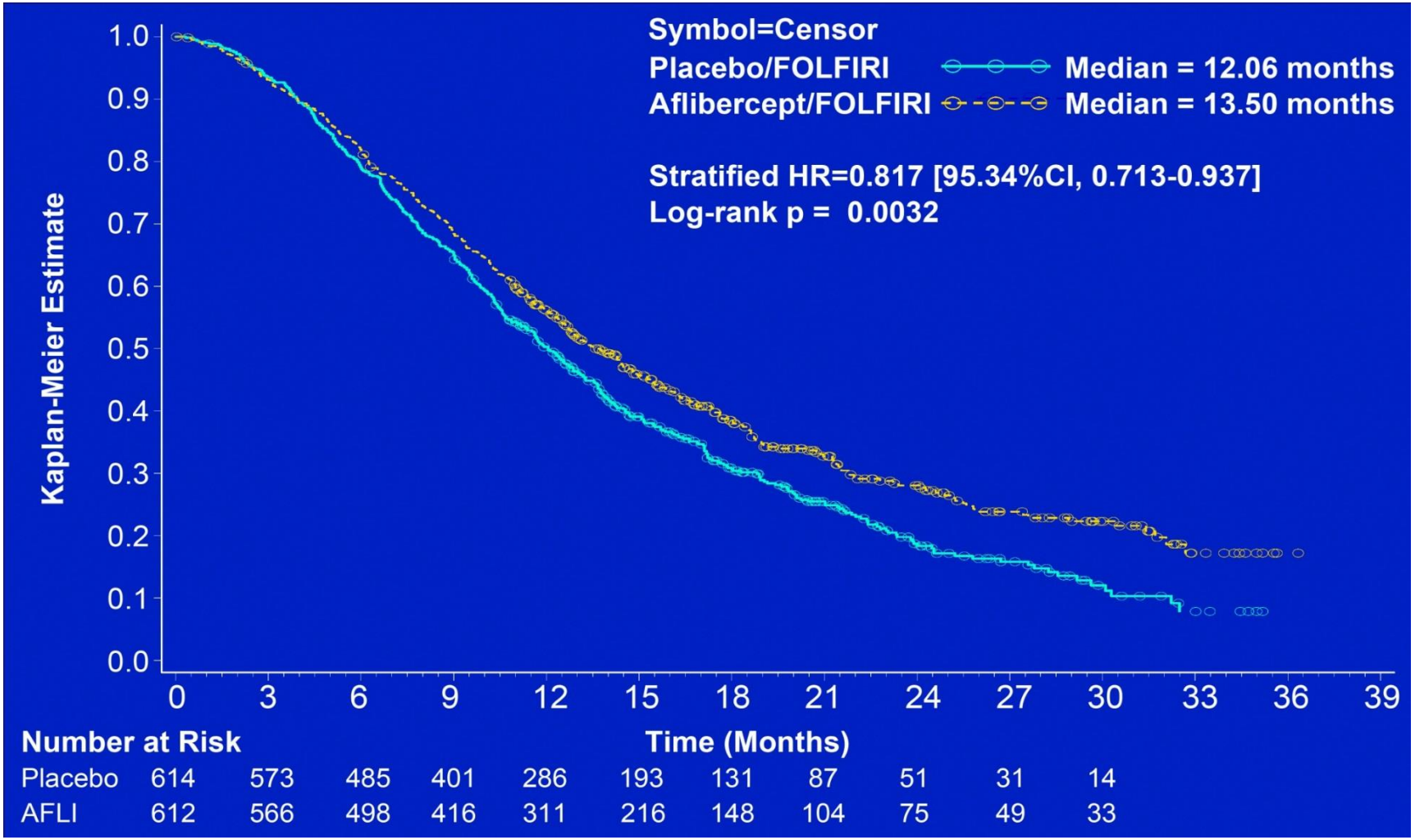


Stratification factors:
- ECOG PS (0 vs 1 vs 2)
- Prior bevacizumab (Y/N)

DMC review every 6 months

Primary Endpoint: Overall Survival

Overall Survival - ITT Population



Cut-off date = February 7, 2011; Median follow-up = 22.28 months

Summary:

1. VEGF antibodies show OS advantage in second-line treatment.

2.TML 18147 show that Bevacizumab can be used continuously after first-line treatment by Bevacizumab.

3. Aflibercept prolong OS in second-line treatment even in patients exposured to Beva.

In this patient case:

Aflibercept is an appropriate choice in second-line treatment.

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  - 7 mos. FOLFIRI/Aflibercept (with some interruptions), stable disease
  - 4 mos. Panitumumab single agent → some response, then progression
- What now?
  - FOLFOX (Re-Induction) → Regorafenib ?
  - Regorafenib → FOLFOX (Re-Induction)
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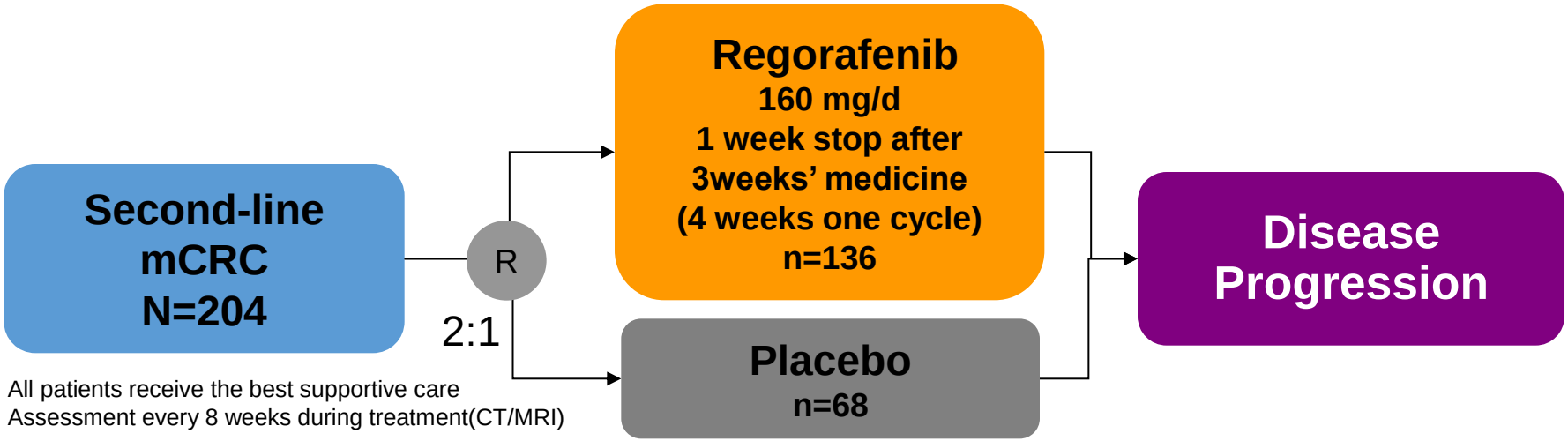
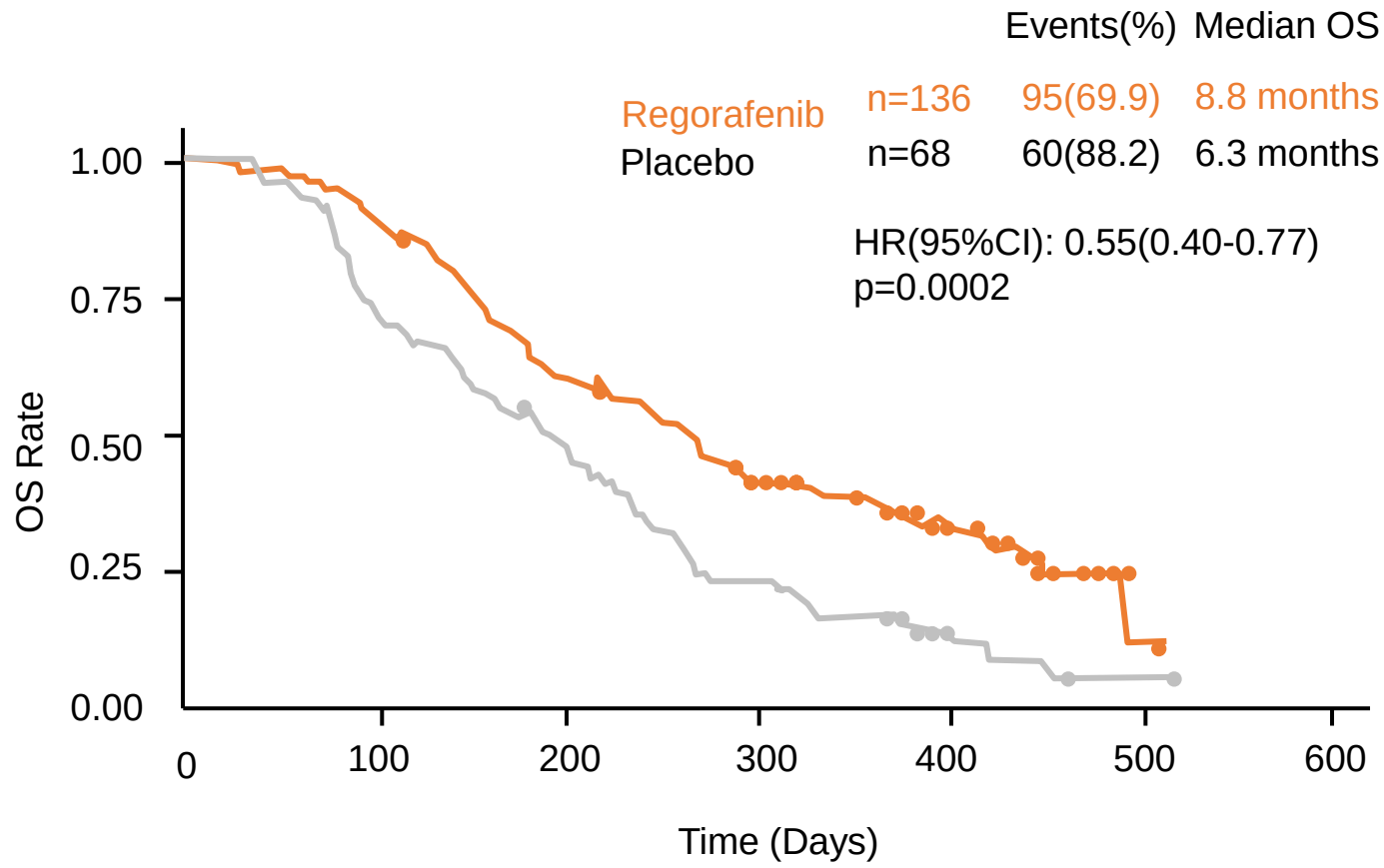
Regorafenib shows OS advantage in CONCUR study.

CONCUR: Study Design



- Primary Endpoint: OS
- Secondary Endpoints: PFS, ORR, DCR
- Stratification factor :
  - Metastasis: Single vs. Multiple organs
  - Since mCRC diagnosis : ≥ 18 vs. < 18 mo
- Analysis of sub groups in the treatment plan according to the past targeted therapy(Anti-EGFR, Anti-VEGF)

CONCUR：Primary Endpoint：OS



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Treatment of metastatic disease

Third and further line therapy

- Regorafenib is recommended in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies
  - Regorafenib is superior to placebo in terms of overall survival, although there are safety / toxicity concerns in frail patients.
- TAS 102 is a (potential) new option for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies

Thank you!