Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A non-inferiority phase III trial: AIO 0207

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PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

AIO 0207: Background

- The optimal duration of combination chemotherapy with Fluoropyrimidines (FP), oxaliplatin (Ox) and Bevacizumab (Bev) in metastatic colorectal cancer (mCRC) is still unknown.
- Maintenance therapy with FP plus Bev is widely accepted standard – resulting from of chemo-only trials[1,2] and the use in standard arms of clinical trials.[3]
- Recent randomized de-escalation maintenance trials [4-7] have evaluated different regimen, but failed to define a clear standard.
- None of those trials prospectively compared de-escalation doublet vs. single vs. no maintenance.

1 Tournigand et al., J Clin Oncol 2006; 24 (3): 394–400 2 Chibaudel et al., J Clin Oncol 2009; 27: 5727–5733
3 Saltz et al., J Clin Oncol 2007; 25(24): 3572-5; 4 Koopman et al., GI Cancer Syposium 2014; #LBA388
5 Koeberle et al., J Clin Oncol 31, 2013 (suppl.); abstr. 350; 6 Diaz-Rubio et al., Oncologist 2012; 17:15-25;
7 Yalcin et al., Oncology 2013, 85: 328-35

Objectives

AIO 0207 investigates

whether after a 24-week standard induction with

any Fluoropyrimidine (FP), oxaliplatin (Ox) and bevacizumab (Bev)

→ no continuation of therapy or

→ continuation with Bev alone

are non-inferior to

→ FP plus Bev

as maintenance treatment

followed by a planned re-induction of (parts of) FP/Ox/Bev as whole treatment strategy

Main endpoints of AIO 0207

Primary endpoint

- Time to failure of strategy (TFS)[1] =

  Time from randomization (@ start of maintenance) to either

  - 2nd progression after maintenance and re-induction *or*
  - in case of no re-induction after 1st progression: use of a new drug („2nd line“), or no further treatment

Secondary endpoints include

- Progression free survival: Rand → until 1st progression (PFS1)
- Overall survival (OS)
- Toxicity (throughout maintenance treatment); Quality of life
- Biomarker and translational projects

[1]Allegra, et al., J Clin Oncol 2007; 25(24): 3572-5

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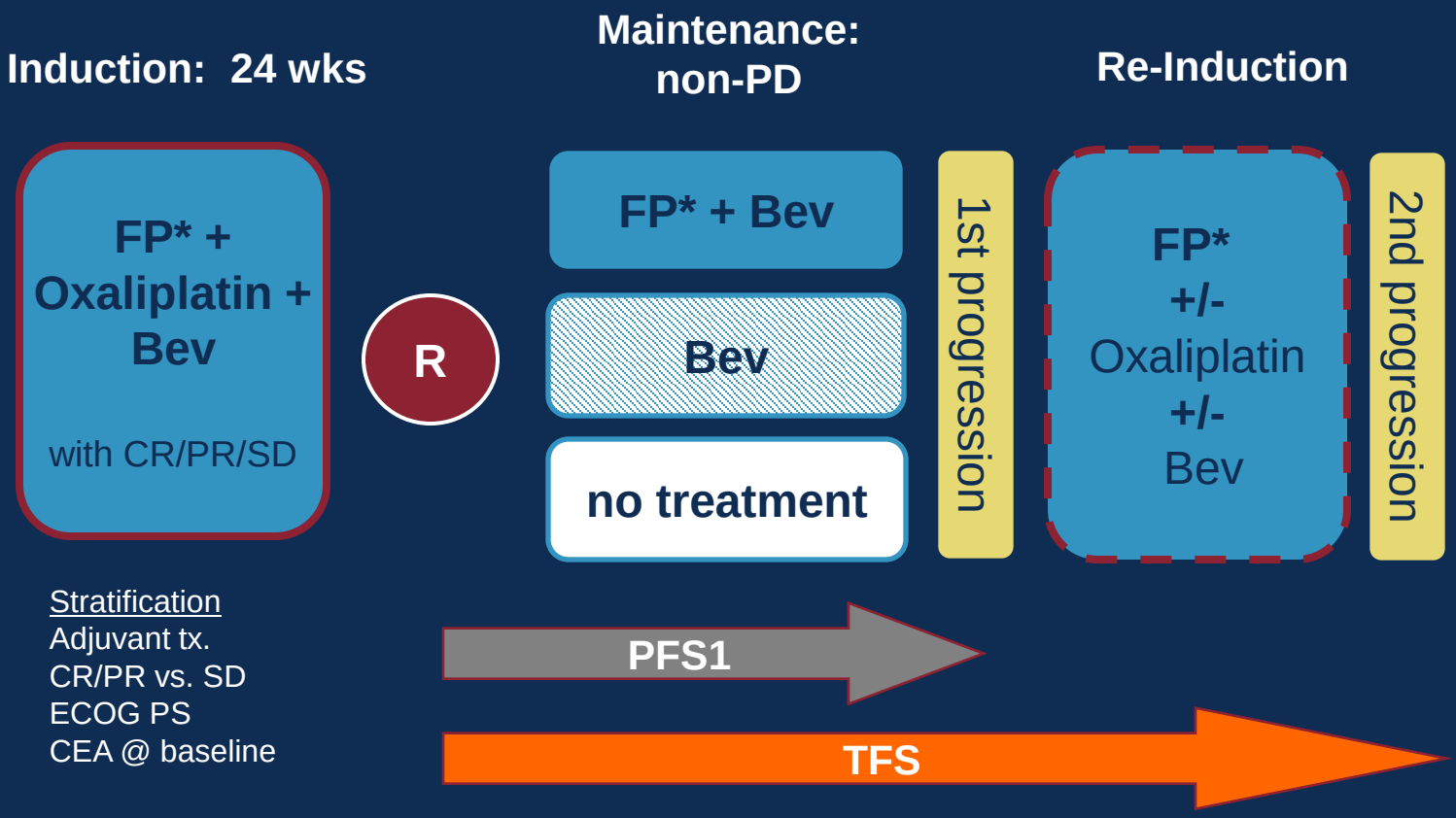
AIO 0207: Treatment algorithms



*FP= any fluoropyrimidine in a standard protocol (e.g. mFOLFOX6, FOLFOX4, Cape/Ox, LV5FU2; Cape 2x1000)

Bev used in standard doses (5mg/kg q 2 wks or 7.5mg/kg q 3wks arm A; 7.5 mg/kg 3q 3 wks arm B)

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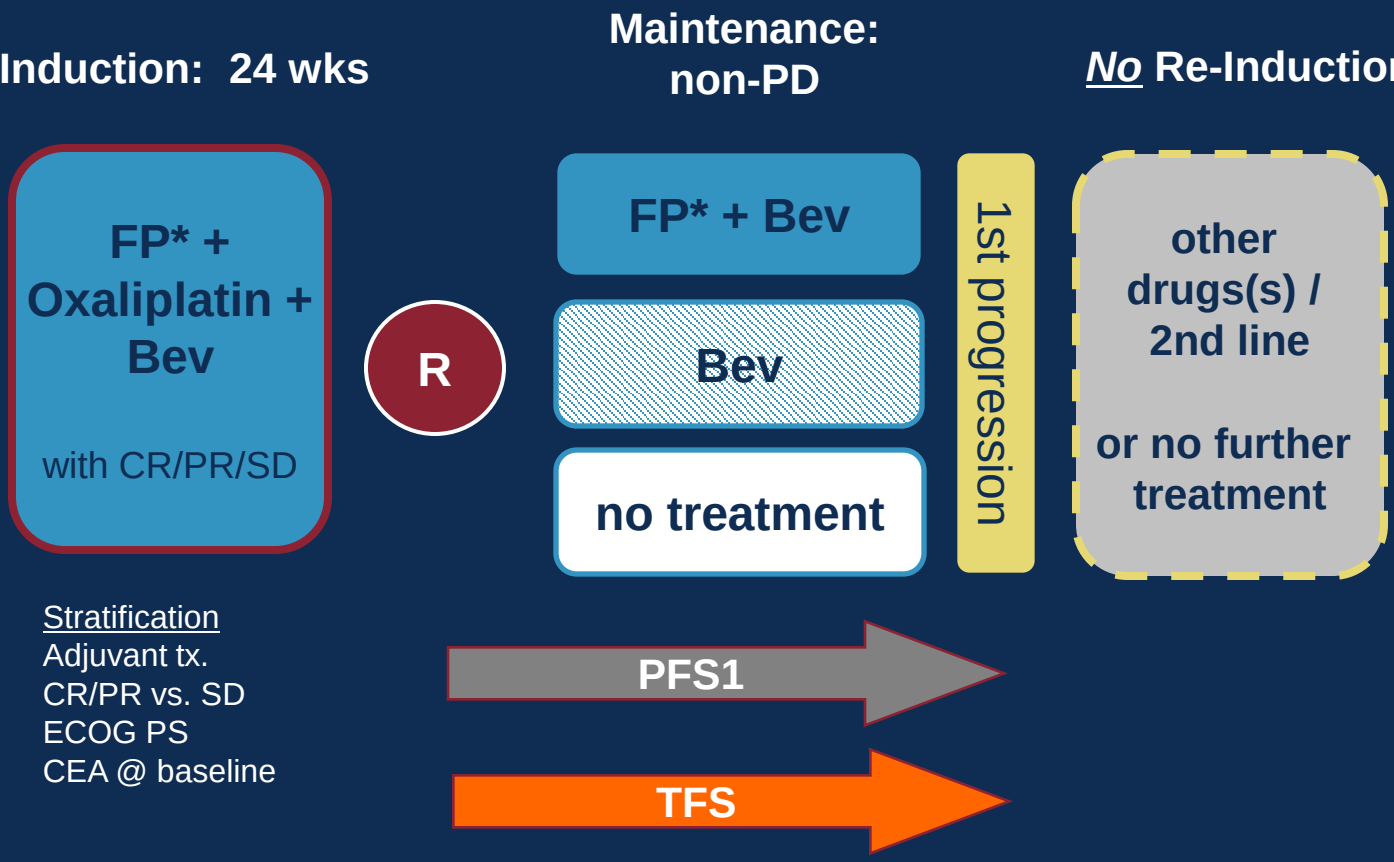

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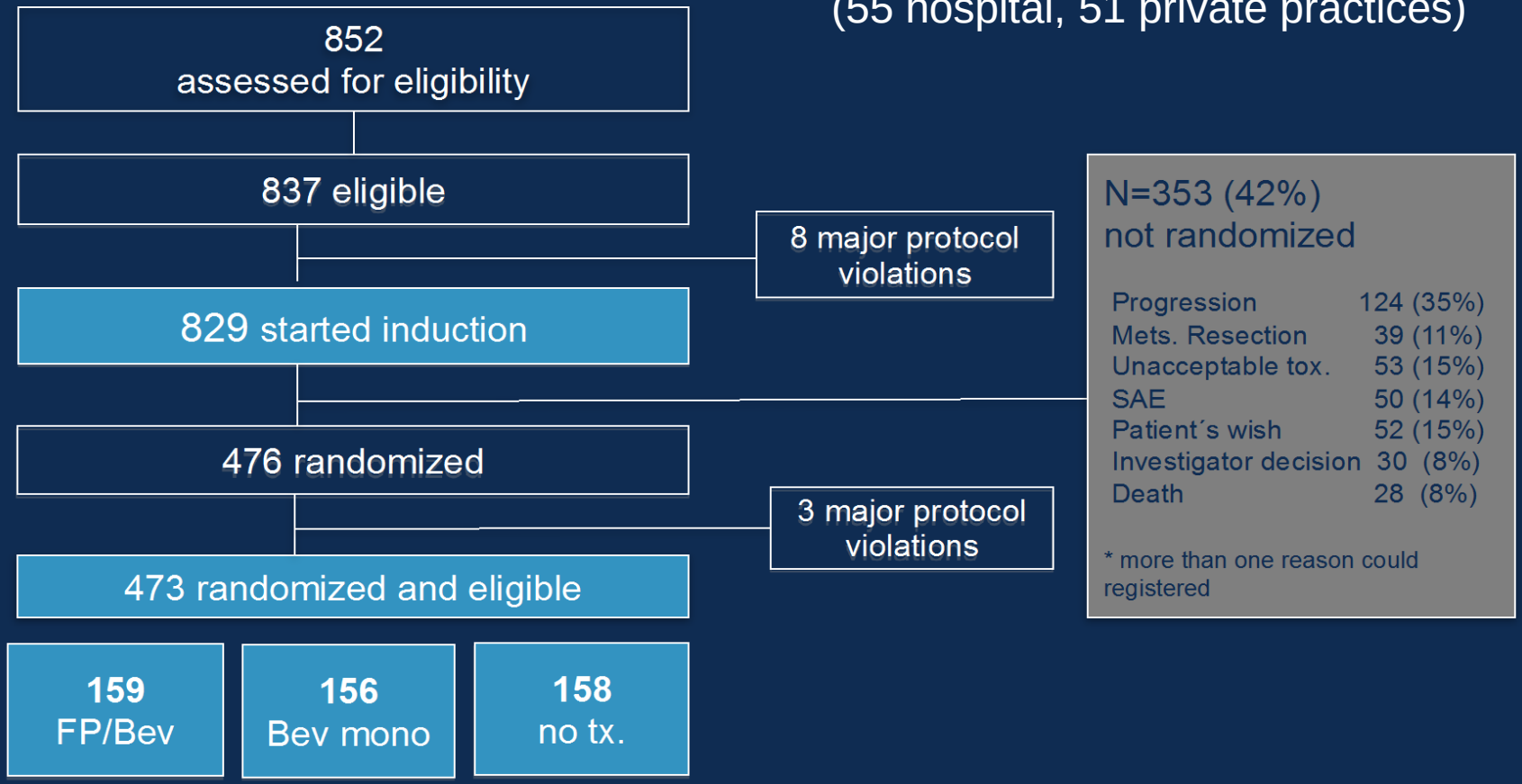
Statistical considerations

- Non-inferiority study - both experimental arms vs. standard arm (FP/Bev)
- 80% power with a one-sided alpha error of 0.0125 for each of the two pairwise comparisons → 148 events per arm needed
- Inferiority margin to be excluded by the confidence interval was set at a median TFS of 3.5 months (assuming a median of 5 months for the standard arm), corresp. to a HR of 1.43
- Time-to-event curves were compared using the logrank test, with all p values being descriptive and two-sided.

Study conduct

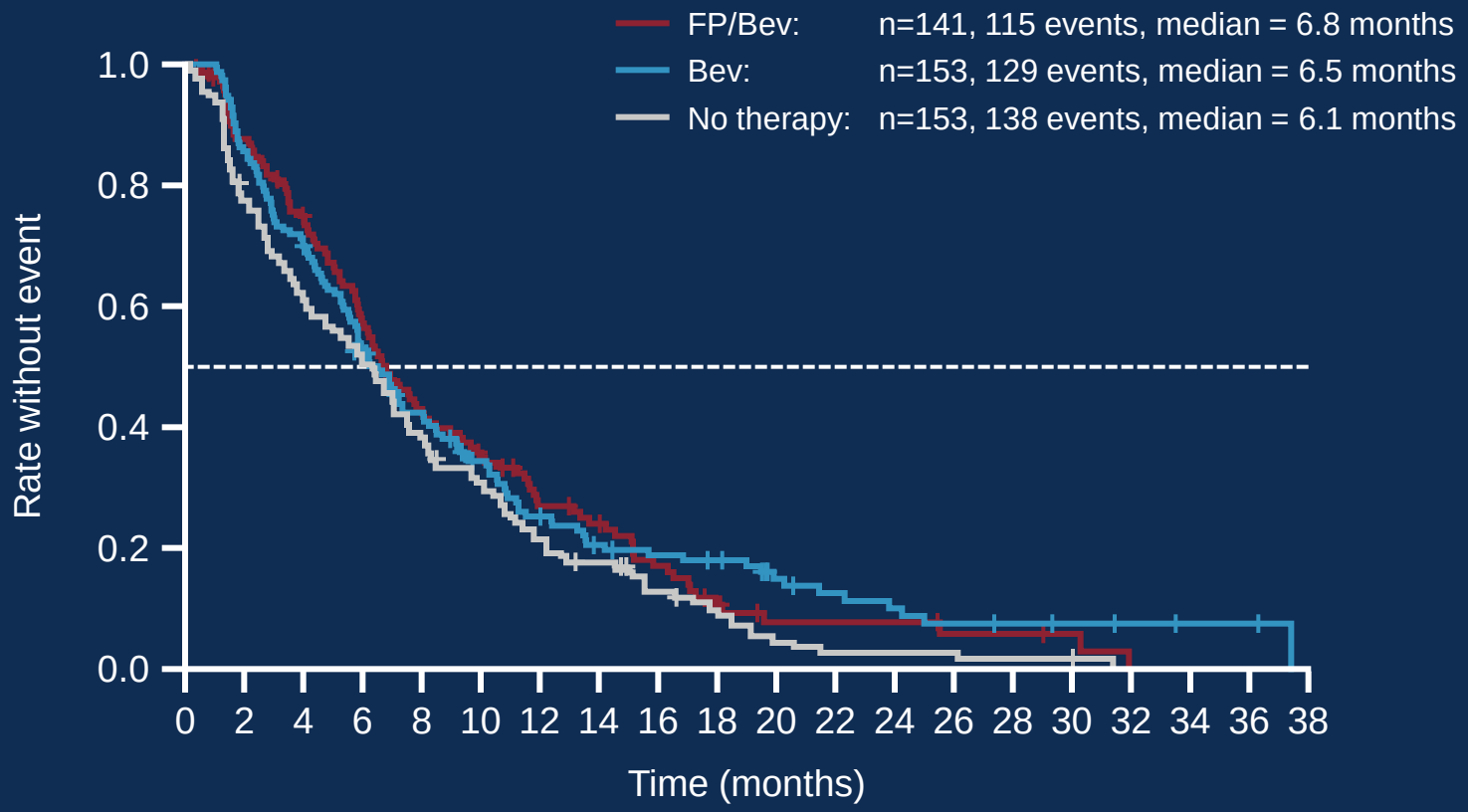
AIO sponsored phase III trial
106 sites in Germany
(55 hospital, 51 private practices)



Accrual: Sept 2009-Feb 2013; Cut-off data 14 Apr 2014 (updated from abstract)

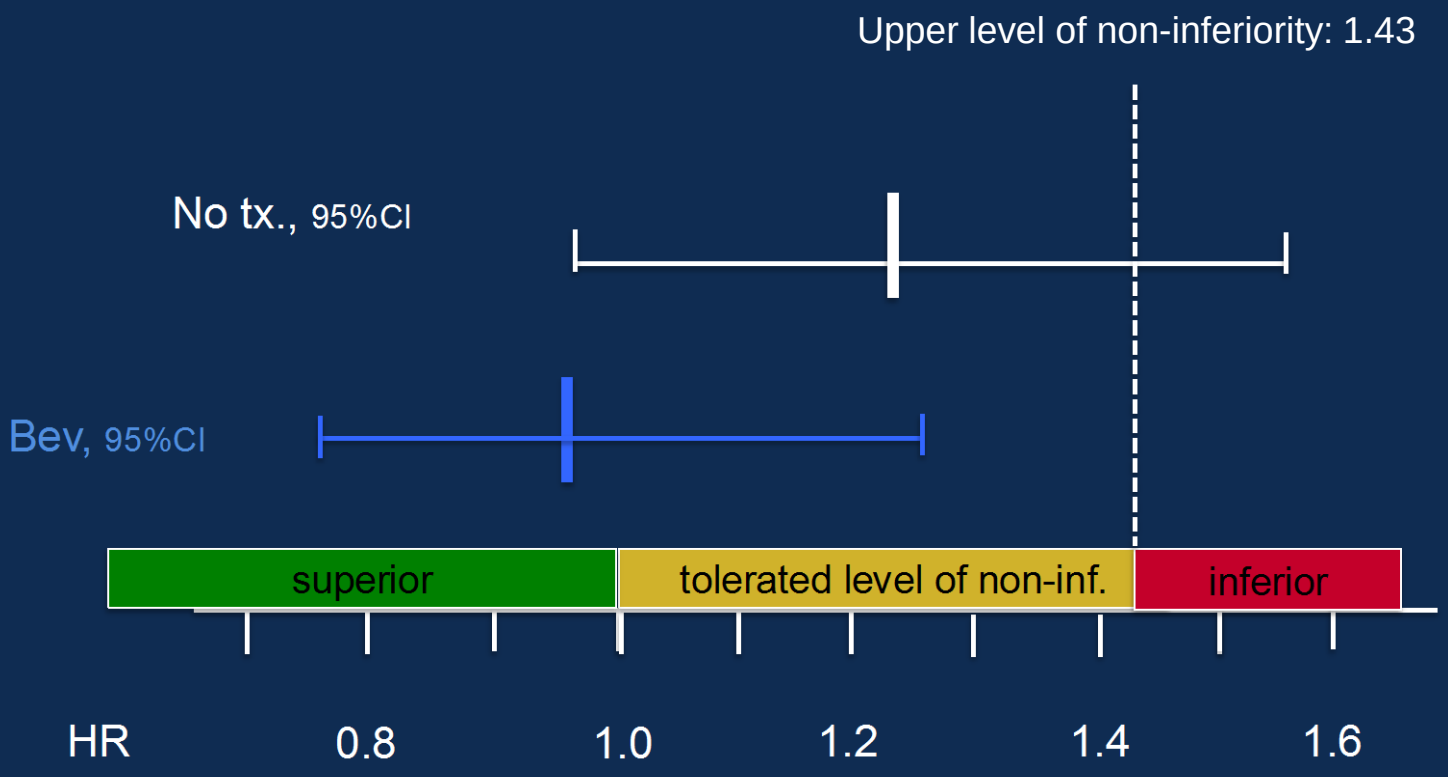
This data set: Median duration of follow-up: 21.3 months; 95% of the randomized patients had completed maintenance treatment

TFS: All arms

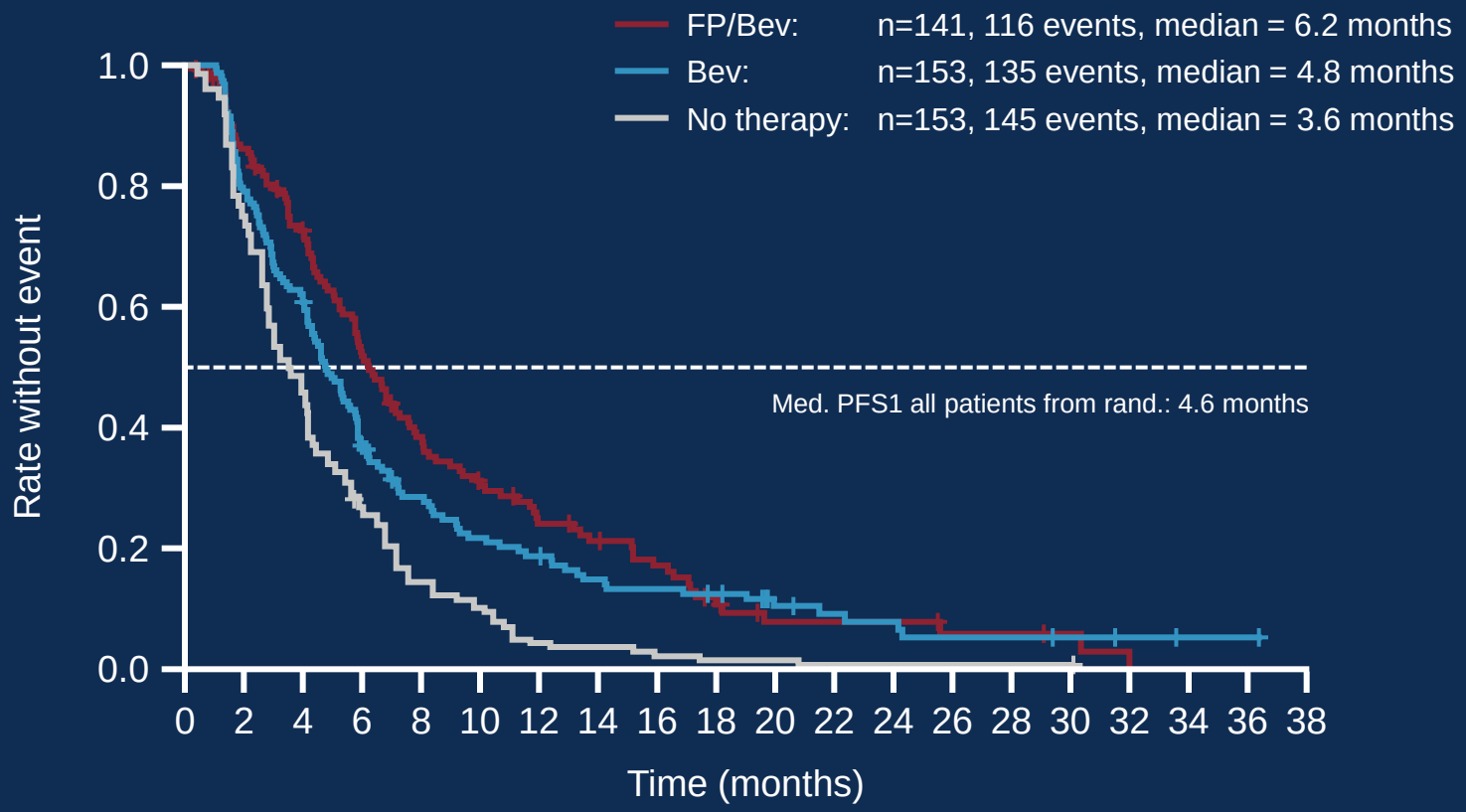


Log rank test: p=0.099

Non-inferiority testing, vs. FP/Bev

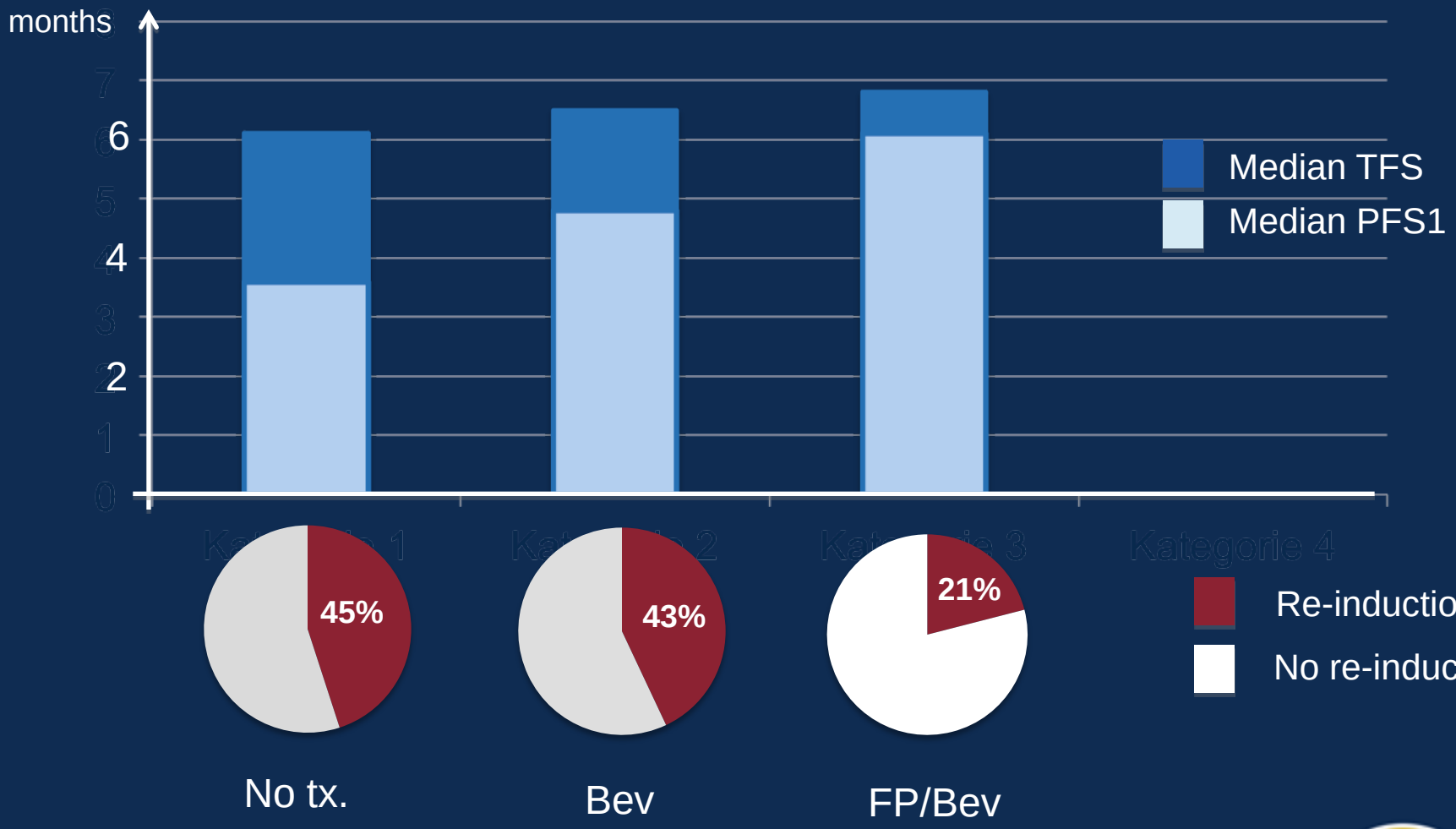


PFS1 from start of maintenance

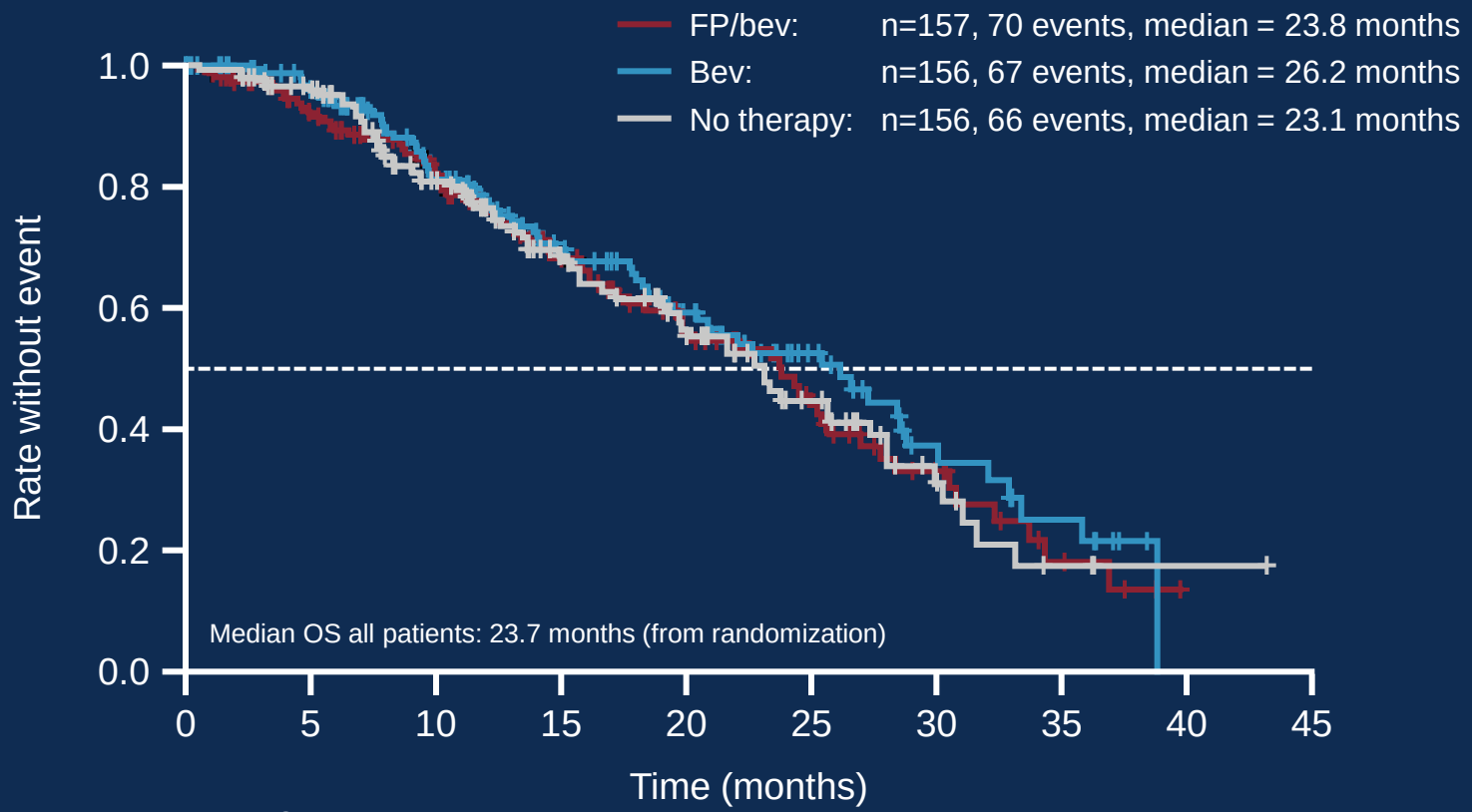


B vs A: HR=1.21; 95% CI: 0.95-1.56; log rank p=0.13
C vs A: HR=2.06; 95% CI: 1.60-2.66; log rank p<0.001
C vs B: HR=1.57; 95% CI: 1.24-1.99; log rank p<0.001
Log rank test: p<0.0001

Re-induction rates and PFS1/TFS



OS from start of maintenance



N=473
Interim analysis: 203 events
Log rank p=0.70

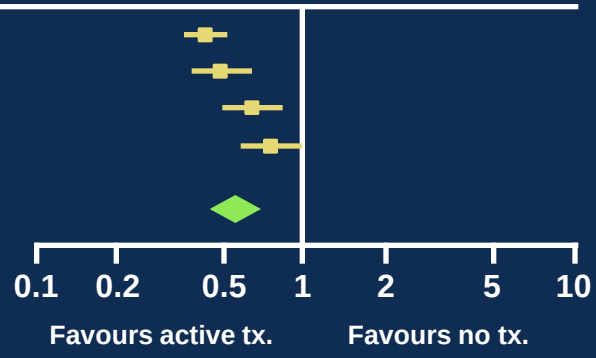
Maintenance trials: combined analysis

PFS

Study or subgroup		Log [Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
CAIRO3	cape/bev	–0.84397007	0.09065533	27.4%	0.43 [0.36, 0.51]
AIO 0207	FP/bev	–0.71334989	0.12971368	24.1%	0.49 [0.38, 0.63]
AIO	bev	–0.4462871	0.12595133	24.5%	0.64 [0.50, 0.82]
SAKK4106	bev	–0.28768207	0.13114787	24.0%	0.75 [0.58, 0.97]
Total (95% CI)				100.0%	0.56 [0.43, 0.72]

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 14.92$, df = 3 (P = 0.002); I^2=80%

Test for overall effect: Z = 4.42 (P < 0.00001)

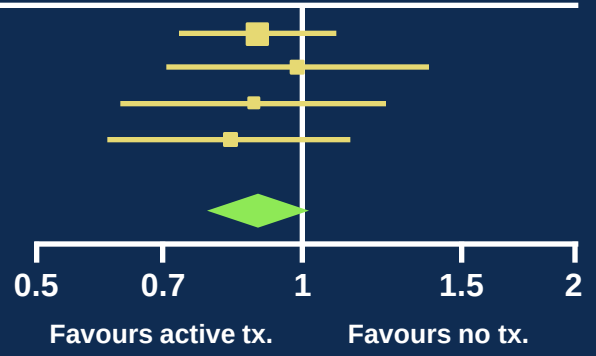


OS

Study or subgroup		Log [Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
CAIRO3	cape/bev	–0.11653382	0.10111254	47.1%	0.89 [0.73, 1.09]
AIO 0207	FP/bev	–0.01005034	0.16961535	16.8%	0.99 [0.71, 1.38]
AIO	bev	–0.12783337	0.1705144	16.6%	0.88 [0.63, 1.23]
SAKK4106	bev	–0.18632958	0.15712878	19.5%	0.83 [0.61, 1.13]
Total (95% CI)				100.0%	0.89 [0.78, 1.02]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.59$, df = 3 (P = 0.90); I^2=0%

Test for overall effect: Z = 1.64 (P = 0.10)



Summary

- Using a TFS strategy, including suggestion for an immediate re-induction, following 6 months with FP/Ox/Bev
  - Maintenance with Bev is non-inferior to FP/Bev
  - Non-inferiority can not be concluded for no active treatment
- Re-induction rates were much lower than expected: 37% overall, decreasing with maintenance intensity
- PFS1 improves with treatment intensity: FP/Bev is better than Bev alone, and this is better than no treatment.
- Preliminary OS showed no difference between treatment arms.

Conclusions

- In the clinical routine, an *immediate re-induction strategy* – following a 6 mos. induction treatment with FP/Ox/Bev and failure of any de-escalation maintenance - is rarely used even in the defined setting of a clinical trial.
- If time to 1st progression (PFS1) should be prolonged, FP plus Bev is the best treatment option.
- In future, “moderately active” maintenance regimen without symptomatic toxicity may improve outcome and should be further evaluated → next AIO phase III project.

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- Patients and their families
- Investigators, study coordinators, nurses, all staff
- AIO study team

AIO 0207 study team

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