

P-0235

S. Stintzing¹, B. Price², L. Knight², A. McCavigan², S.M. Walker², D.P. Harkin², R.D. Kennedy², D. Neureiter³, S. Held⁴, A. Jung⁵, T. Kirchner⁵, V. Heinemann¹

¹ Department of Medicine III, University Hospital, LMU Munich, Germany; ²ALMAC Diagnostics Ltd, Craigavon, United Kingdom;

³Institute of Pathology, SALK Salzburg, Austria; ⁴ClinAssess GmbH, Leverkusen, Germany, ⁵Institute of Pathology University of Munich, Germany



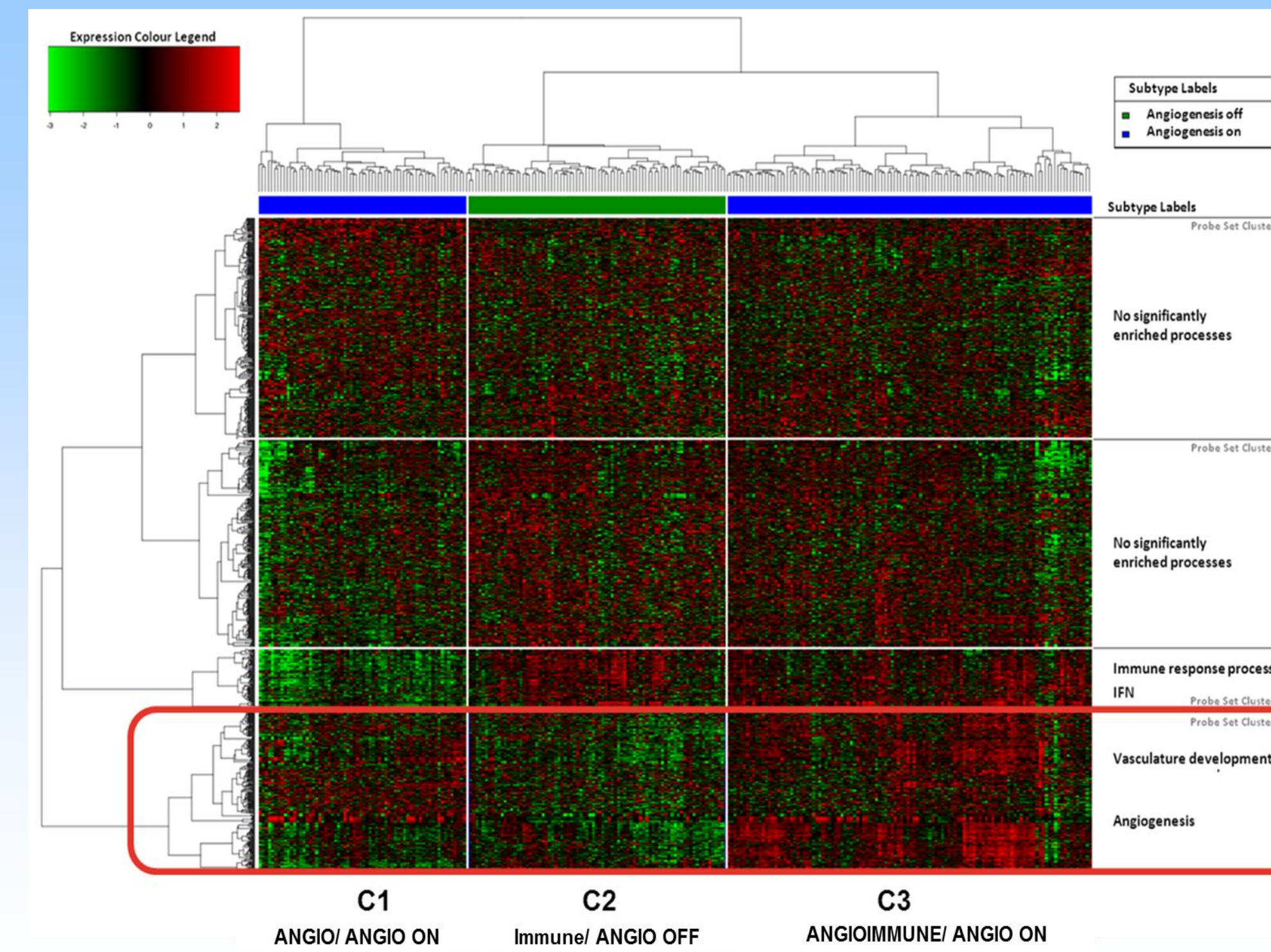
Background:

The FIRE-3 trial compared 1st-line therapy of FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wildtype (wt) mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The AADx molecular assay has previously been shown to identify a poor prognosis angiogenic subgroup across multiple cancer types including ovarian and lung cancer. Both, bevacizumab (through inhibition of VEGFR-activation) and cetuximab (through inhibition of EGFR-signaling) are expected to have anti-angiogenic effects in colorectal cancer. The predictive role of AADx in FOLFIRI plus bevacizumab or cetuximab treated in colorectal cancer patients remains unclear.

Methods:

Transcriptional profiling of 501 formalin fixed paraffin embedded pre-treatment samples from the ITT population was performed using the Almac Diagnostics Xcel™ array. Patients were classified by the AADx assay as **ANGIO ON** or **ANGIO OFF** based on a predefined score. ORRs were compared using Fischer's exact test. Progression-free survival (PFS) and Overall survival (OS) times were compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard method.

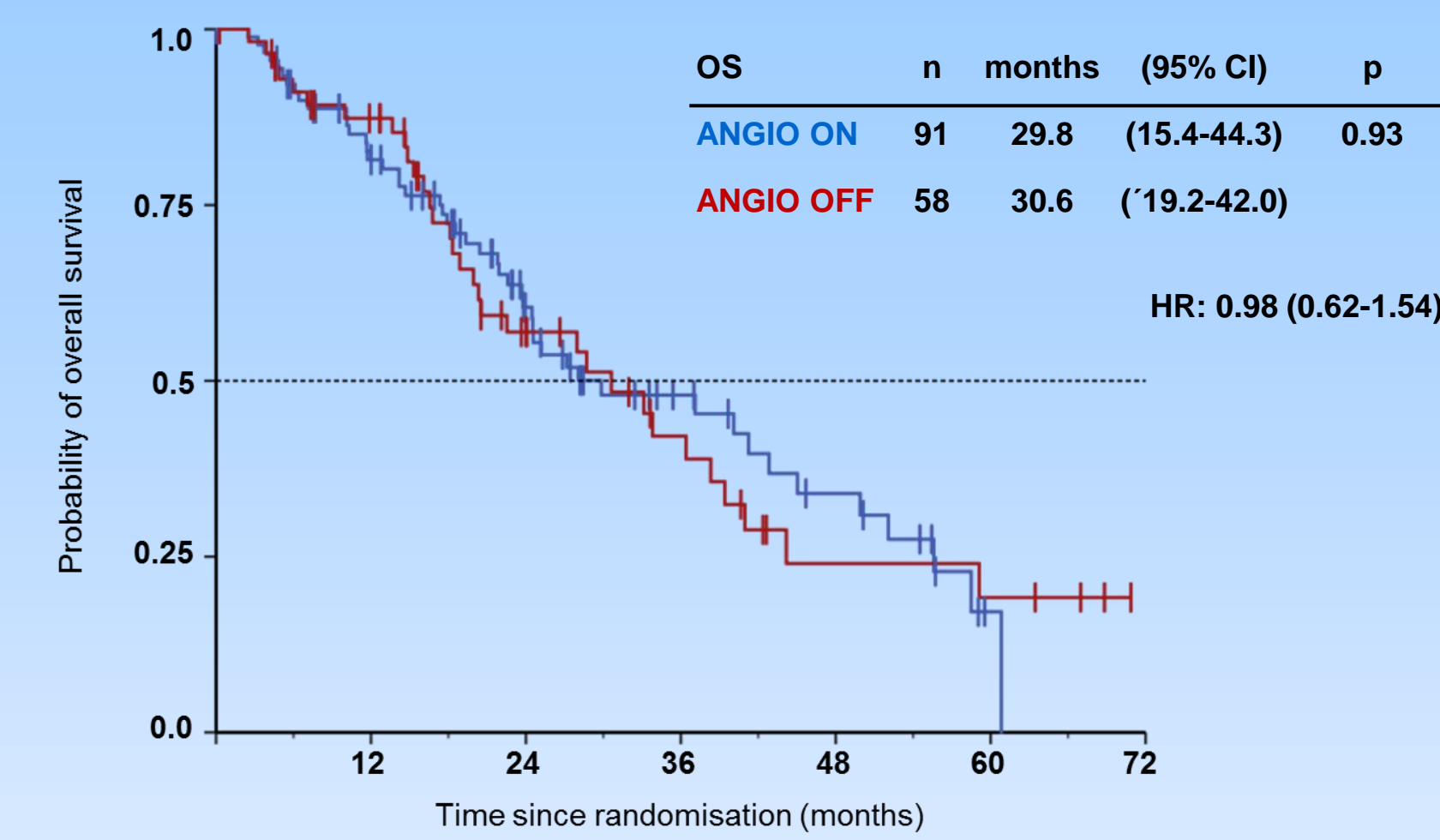
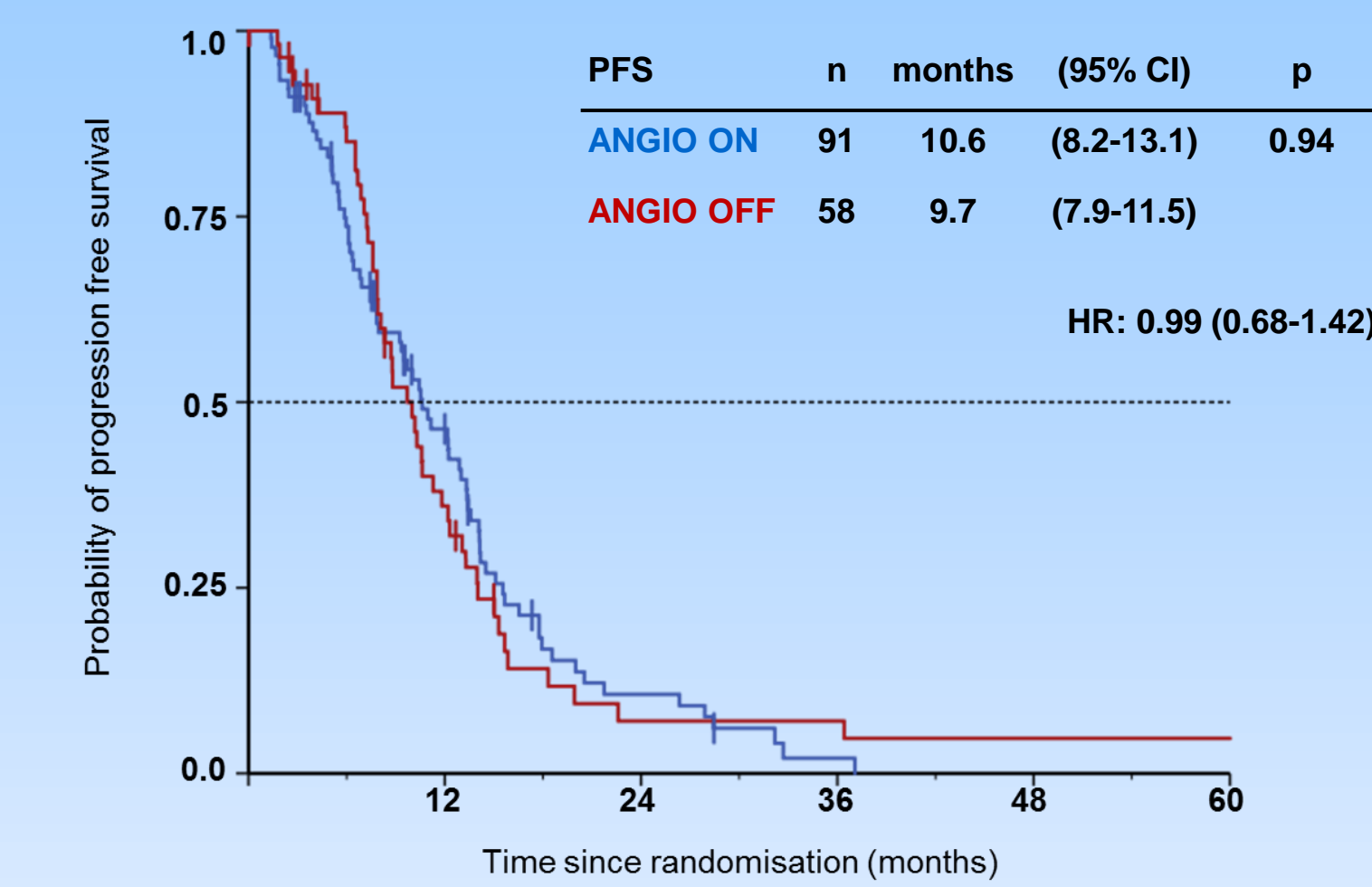
ALMAC AADx Test



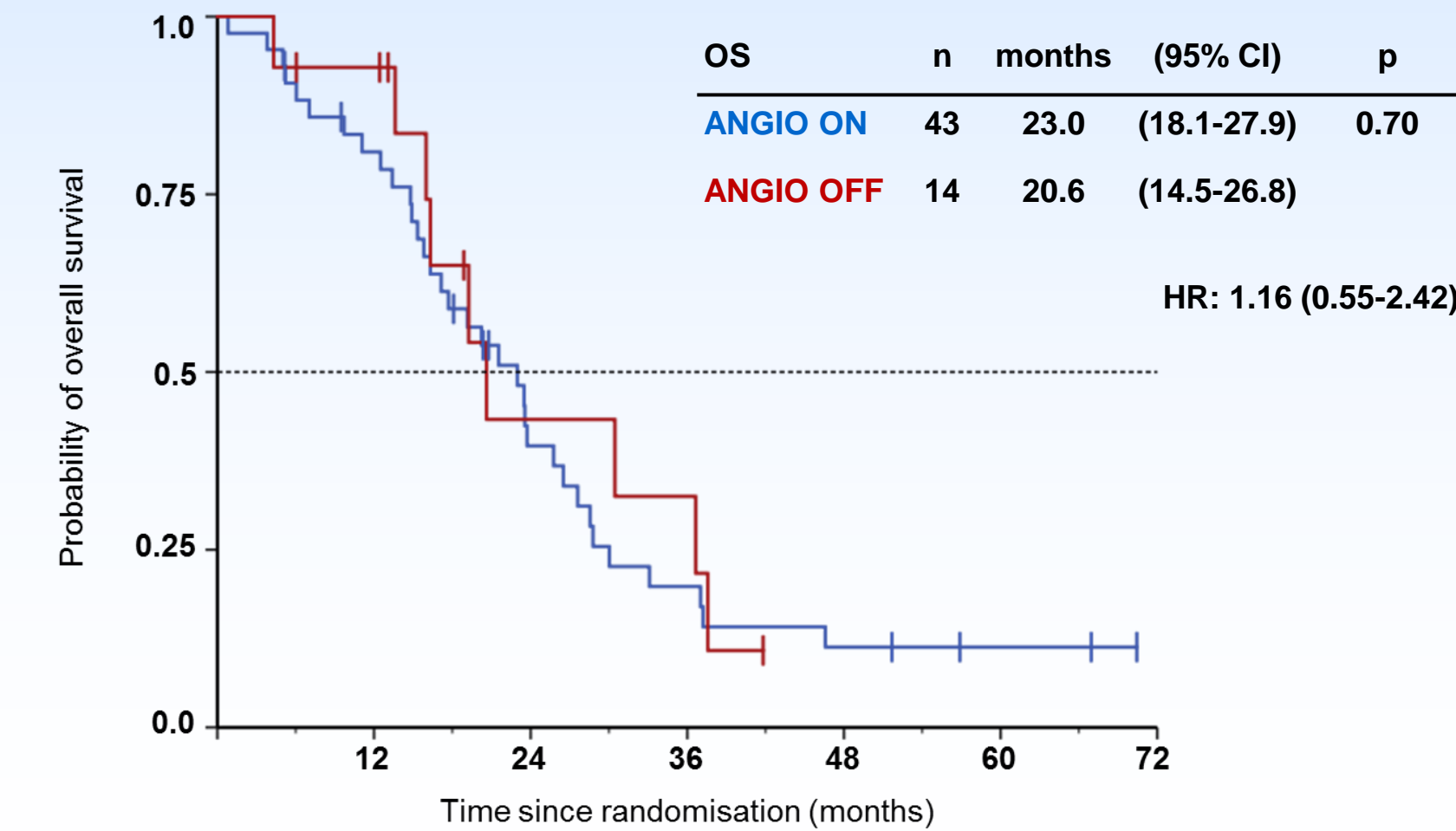
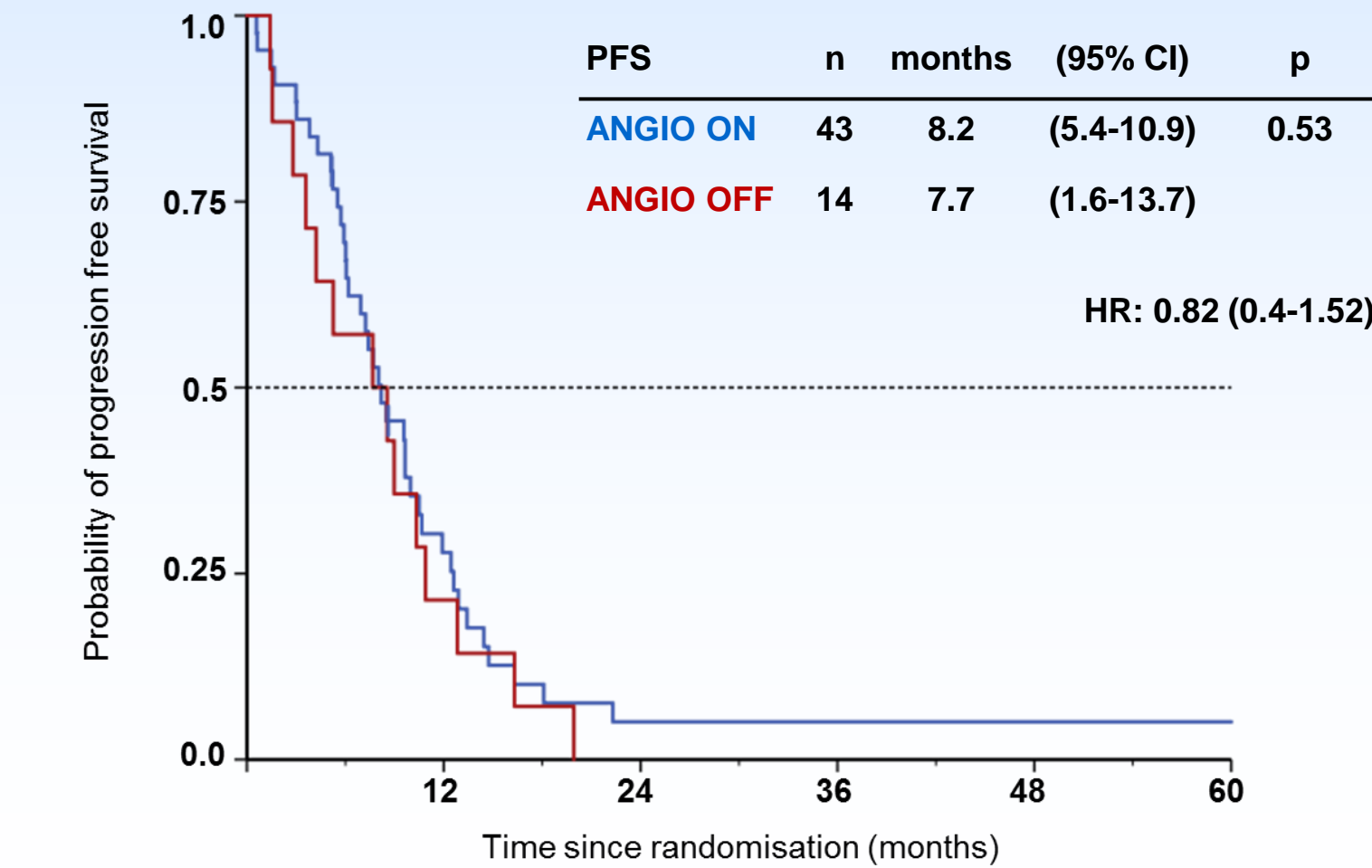
- Almac has developed the anti-angiogenic diagnostic (AADx) gene expression assay in ovarian cancer that:
 - identifies angiogenic molecular subtypes
 - Is defined by activation/ repression of genes associated with angiogenic processes
 - demonstrates prognostic performance in ovarian, colorectal and lung cancers
 - predicts response to bevacizumab in ovarian cancer
- Angiogenesis active = AADx negative = ANGIO ON (C1 and C3):**
Angiogenesis biology switched on in the patient tumour
- Angiogenesis inactive = AADx positive = ANGIO OFF (C2):**
Angiogenesis biology switched off in the patient tumour

Survival According to AADx Score in Patients Treated with FOLFIRI + Cetuximab

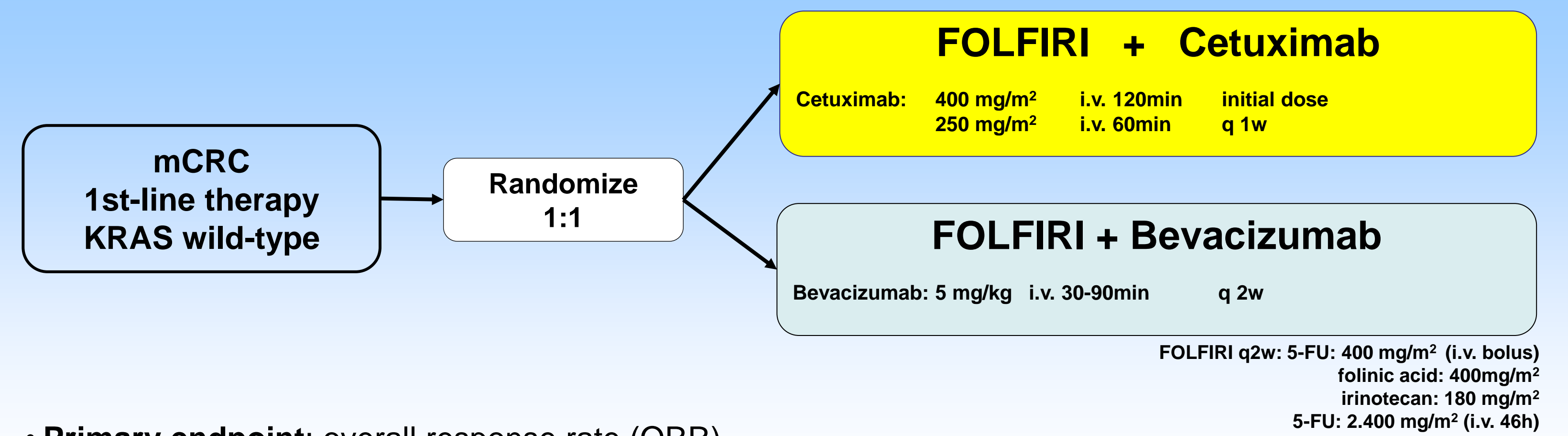
RAS wild-type subpopulation



RAS mutant subpopulation

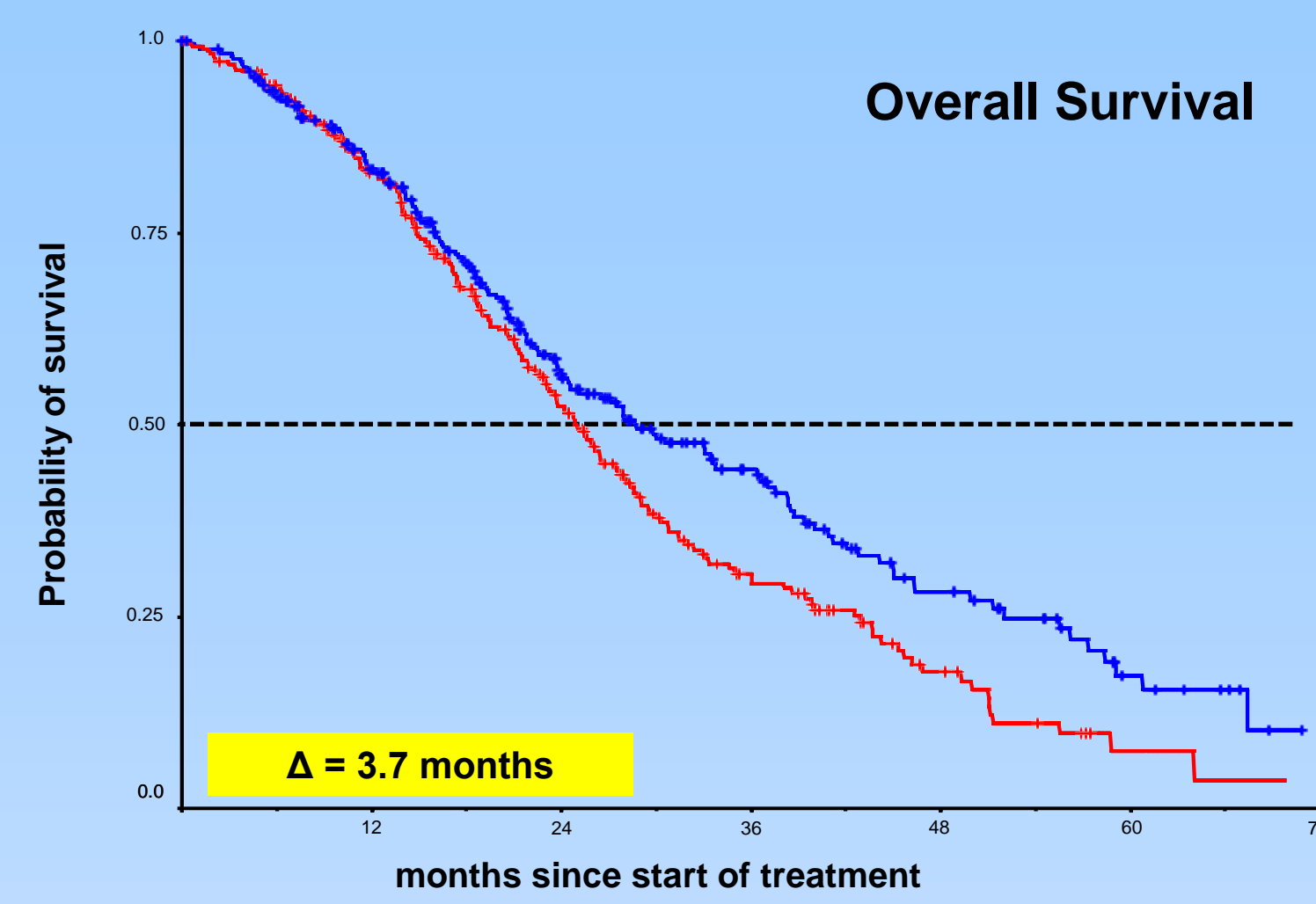


FIRE-3 Study Design



- Primary endpoint: overall response rate (ORR)
- Amendment October 2008 to include only KRAS wild-type patients

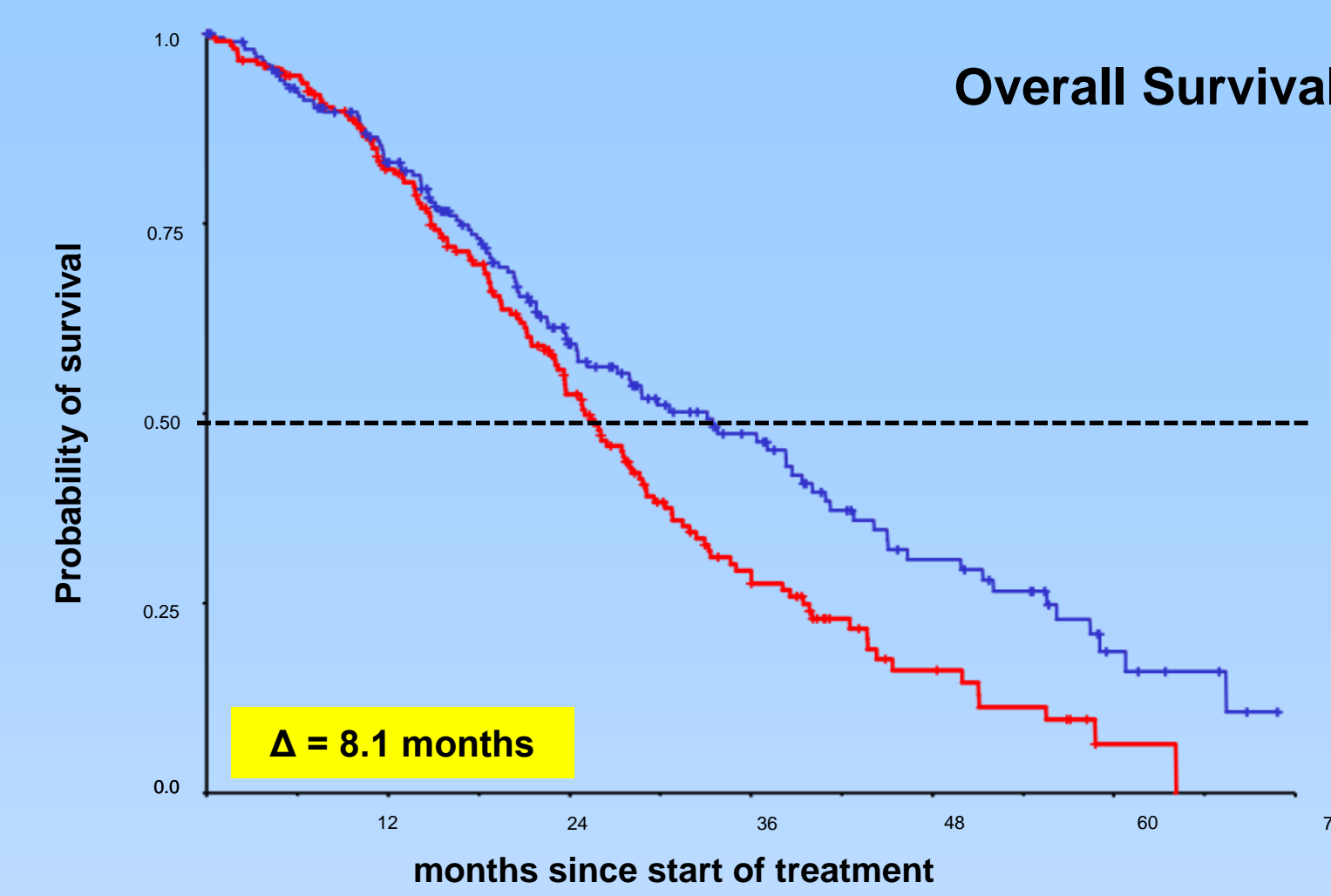
KRAS exon 2 wild-type (ITT; n= 592)



	Events n/N (%)	Median months	95% CI
FOLFIRI + Cetuximab	158/297 (53.2%)	28.7	24.0 – 36.6
FOLFIRI + Bevacizumab	185/295 (62.7%)	25.0	22.7 – 27.6

HR 0.77 (95% CI: 0.62 – 0.96)
Log-rank test p= 0.017

RAS wild-type (n=400)



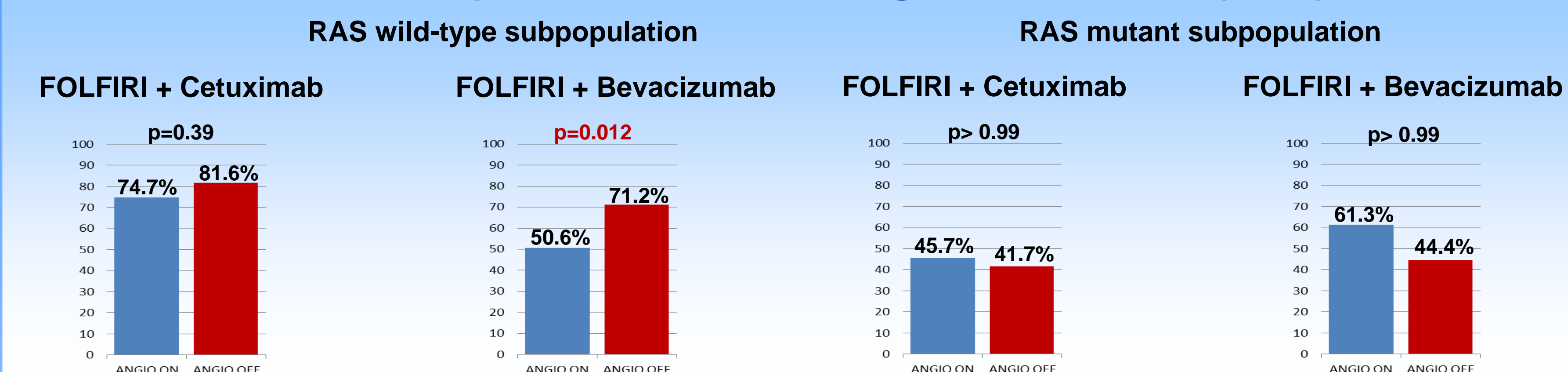
	Events n/N (%)	Median months	95% CI
FOLFIRI + Cetuximab	107/199 (53.8%)	33.1	24.5 – 39.4
FOLFIRI + Bevacizumab	133/200 (66.2%)	25.0	23.0 – 28.1

HR 0.697 (95% CI: 0.54 – 0.90)
Log-rank test p= 0.059

Baseline Characteristics (AADx Score Population)

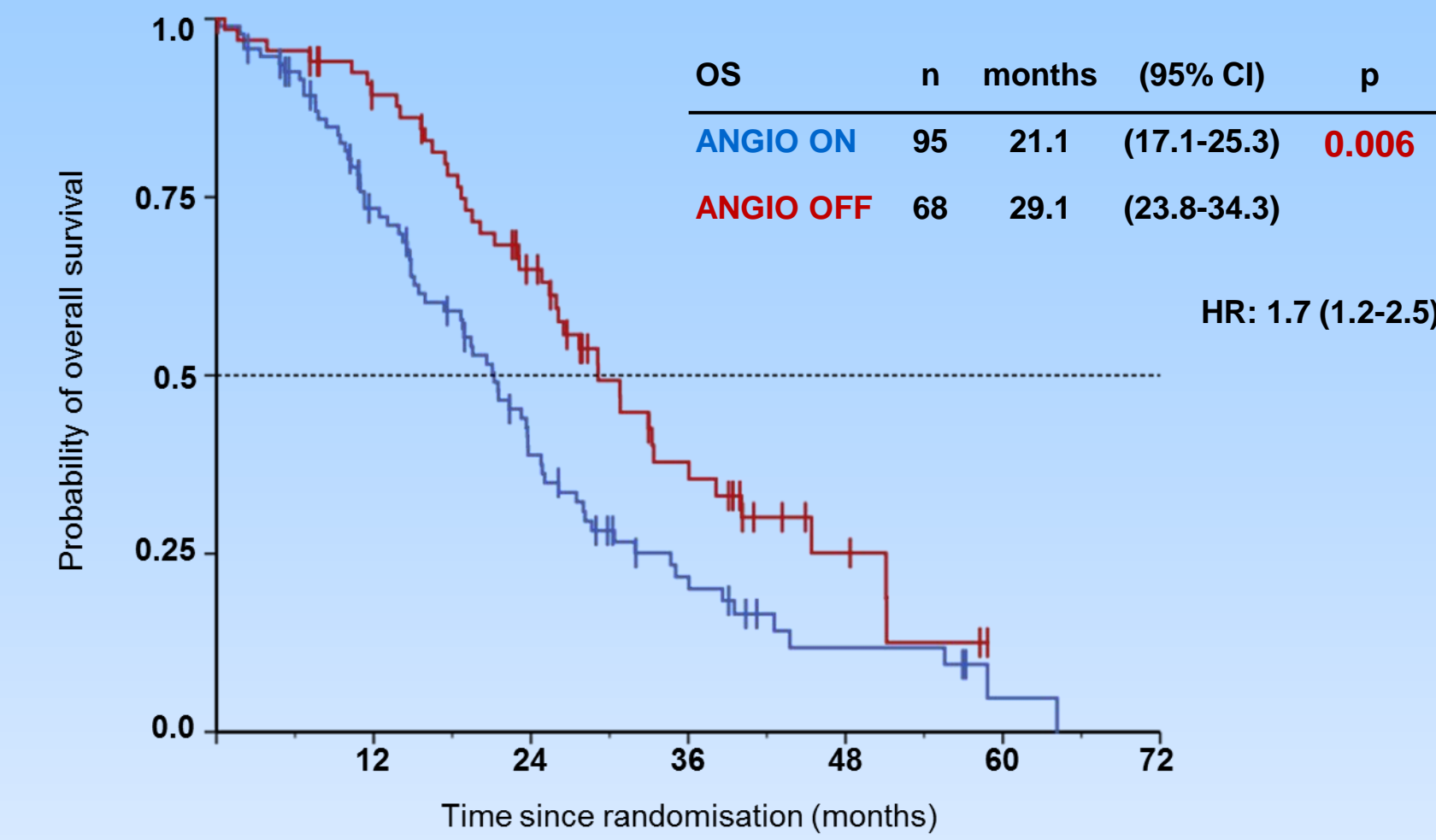
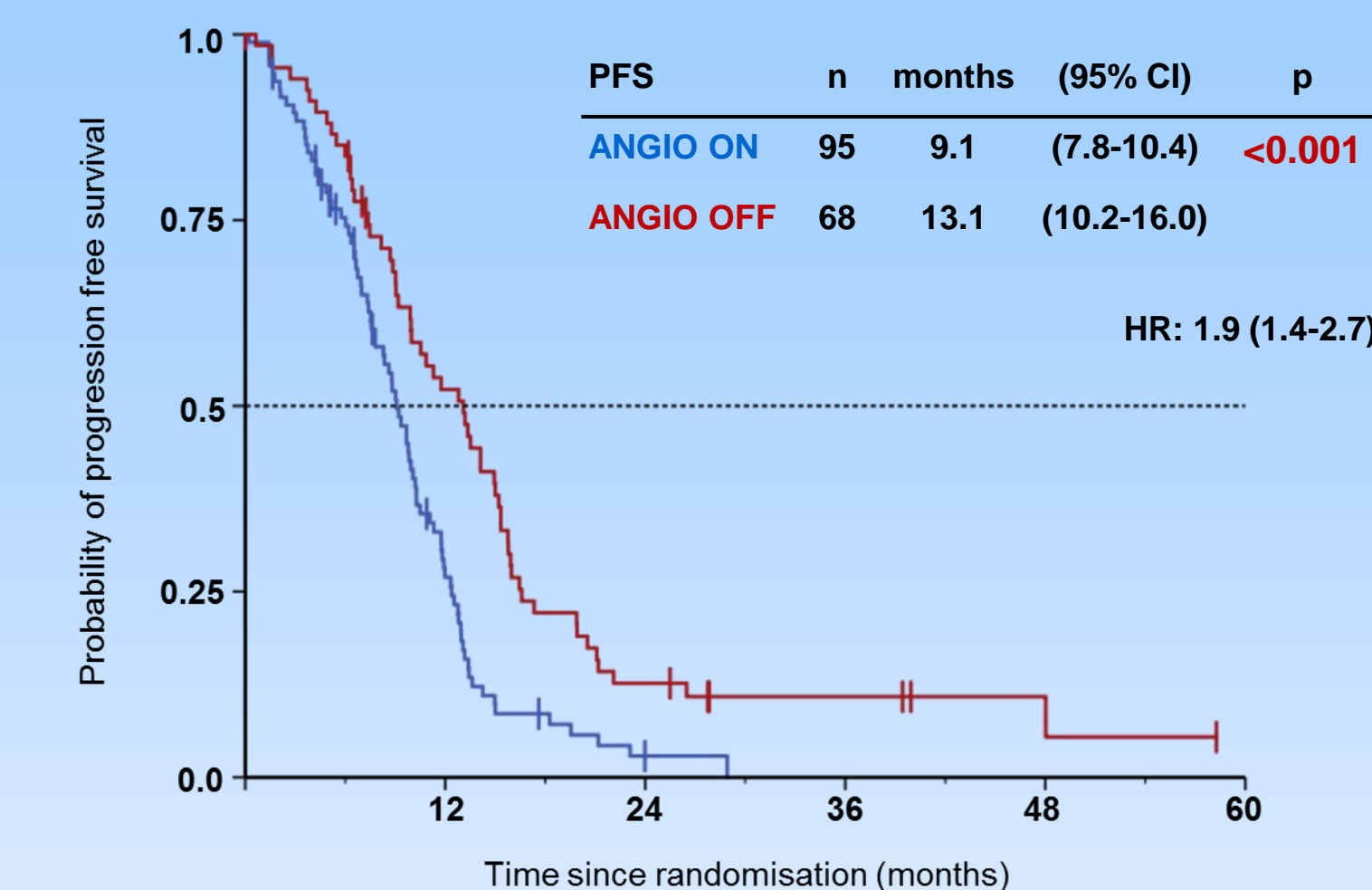
Characteristic	RASwt population (n= 400)			AADx-Score RAS wild-type (n= 312)			AADx-Score RAS mutant (n= 119)		
	FOLFIRI Cetuximab (n= 199)	FOLFIRI Bevacizumab (n=201)	total (n= 400)	FOLFIRI Cetuximab (n= 149)	FOLFIRI Bevacizumab (n=163)	total (n= 312)	FOLFIRI Cetuximab (n= 57)	FOLFIRI Bevacizumab (n=62)	total (n= 119)
Sex									
-male, % (n)	73% (146)	66% (133)	70% (279)	74% (110)	65% (106)	69% (216)	54% (31)	73% (45)	64% (76)
-female, % (n)	27% (53)	34% (68)	30% (121)	26% (39)	35% (57)	31% (96)	46% (26)	27% (17)	36% (43)
Age									
-Median, years	64	65	64	64	65	64	65	63	65
ECOG % (n)									
-0	54% (107)	54% (109)	54% (216)	53% (79)	51% (84)	52% (163)	40% (23)	55% (34)	48% (57)
-1	45% (89)	44% (89)	45% (178)	47% (76)	46% (69)	47% (145)	51% (29)	42% (26)	46% (55)
-2	1% (3)	2% (3)	1% (6)	0.7% (1)	2% (3)	1% (4)	9% (5)	3% (2)	6% (7)
Site of primary, % (n)									
-right colon	20% (39)	26% (52)	23% (91)	20% (31)	25% (40)	23% (71)	35% (20)	31% (19)	33% (39)
-left colon	80% (159)	74% (149)	77% (308)	80% (121)	75% (123)	77% (241)	65% (37)	69% (43)	67% (80)
-unknown	0.5% (1)	0.5% (1)	1% (3)	0.3% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
BRAF mutant, % (n)	11% (22)	12% (24)	12% (46)	13%(19)	12% (20)	13% (39)	0% (0)	0% (0)	0% (0)
Metastatic sites, % (n)									
-1 site	43% (85)	41% (82)	42% (167)	44% (66)	44% (71)	44% (137)	39% (22)	48% (30)	44% (52)
-2 sites	56% (111)	58% (116)	58% (230)	56% (83)	56% (92)	56% (175)	61% (35)	52% (32)	56% (67)
-unknown	1% (2)	0.5% (1)	1% (3)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Liver limited disease, % (n)	36% (71)	31% (62)	33% (133)	38% (57)	25% (40)	31% (97)	33% (19)	40% (25)	37% (44)
Prior adjuvant treatment, % (n)	19% (37)	19% (38)	19% (75)	17% (26)	18% (29)	18% (55)	21% (12)	21% (13)	21% (25)
Koehne Score									
Good	8% (15)	10% (21)	9% (36)	6% (9)	12% (19)	9% (28)	17% (10)	11% (7)	14% (17)
Intermediate	43% (86)	48% (96)	46%(182)	42% (62)	46% (76)	44% (138)	47% (29)	47% (29)	50% (59)
Poor	47% (94)	41% (83)	44% (177)	52% (78)	42% (68)	47% (146)	30% (17)	41% (26)	36% (43)
Primary resected, % (N)	81% (162)	88% (175)	84% (337)	89% (132)	90% (147)	89% (279)	95% (54)	87% (54)	91% (108)

Overall Response Rates According to AADx Score (ORR)

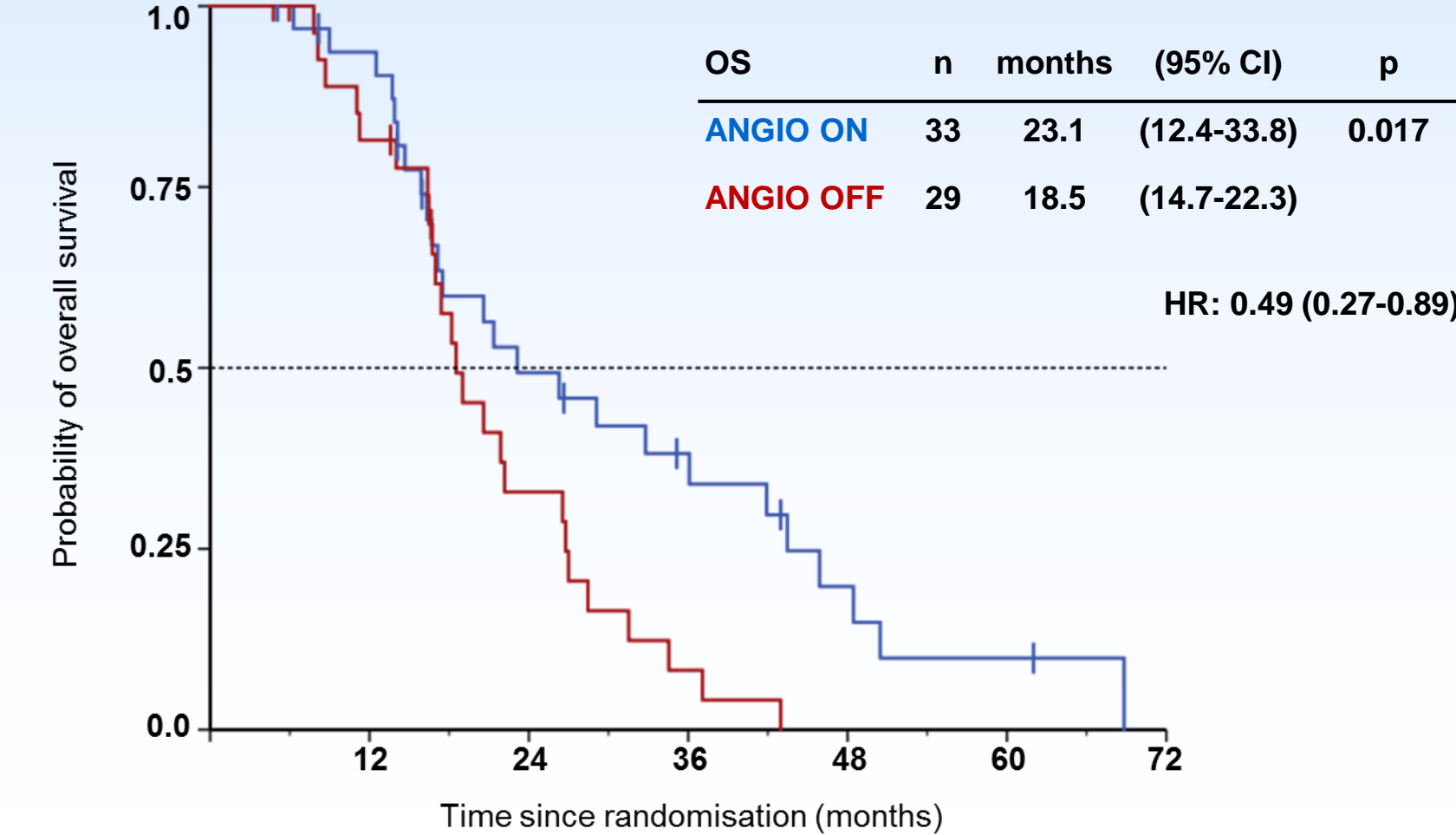
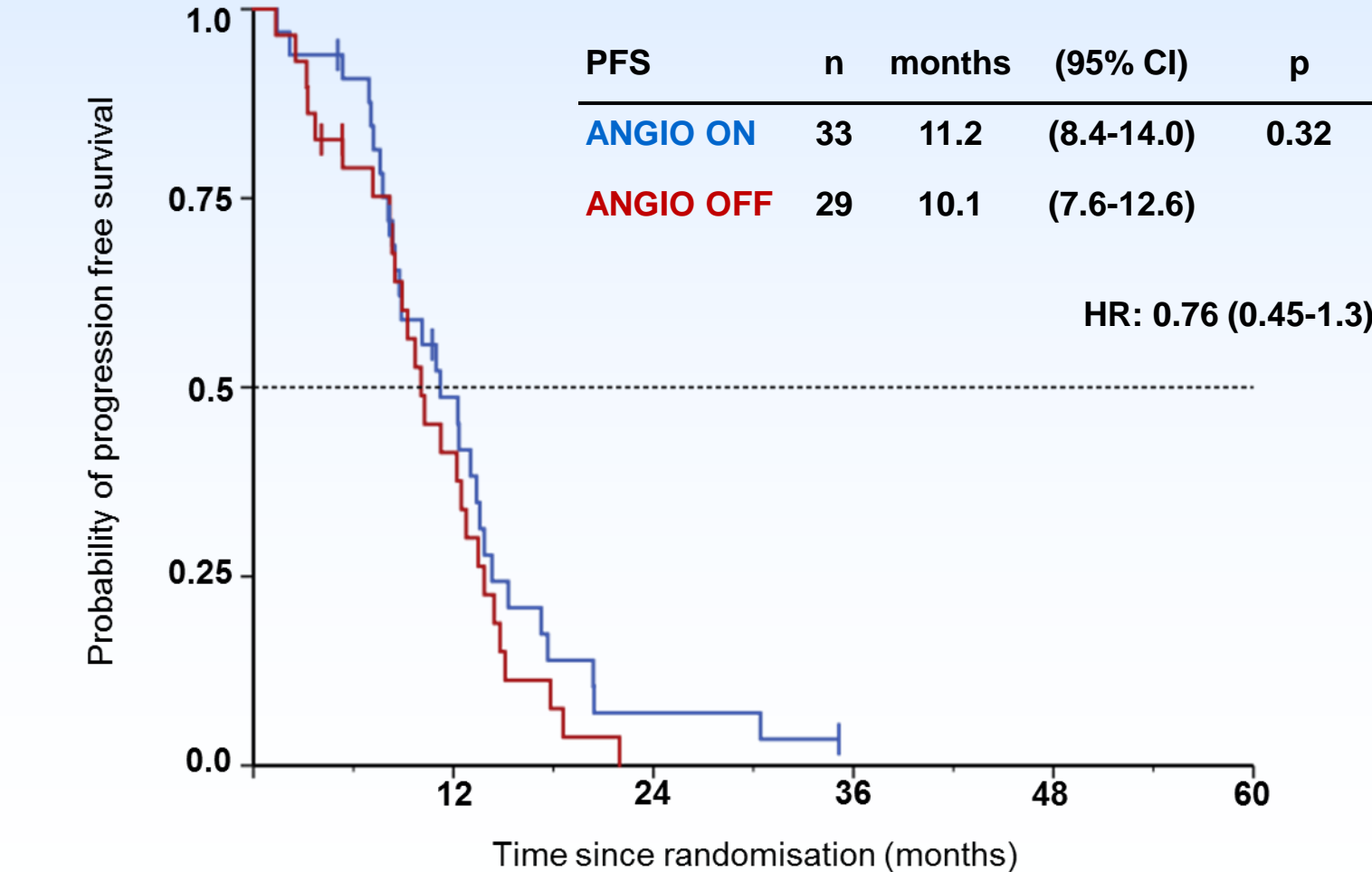


Survival According to AADx Score in Patients Treated with FOLFIRI + Bevacizumab

RAS wild-type subpopulation



RAS mutant subpopulation



Conclusions

The data suggests that the AADx assay interacts with RAS mutation and may define RAS wild-type mCRC patients that respond differently to cetuximab or bevacizumab in combination with FOLFIRI. One potential explanation of the data is that Cetuximab is a more effective treatment for the poor prognosis ANGIO ON subtype.