Predictive assay for anti-angiogenic agents (AADx) identifies a molecular subgroup of RAS wt mCRC with low efficacy of FOLFIRI plus bevacizumab – analysis of the FIRE-3 (AIO KRK-0306) trial

P-0235

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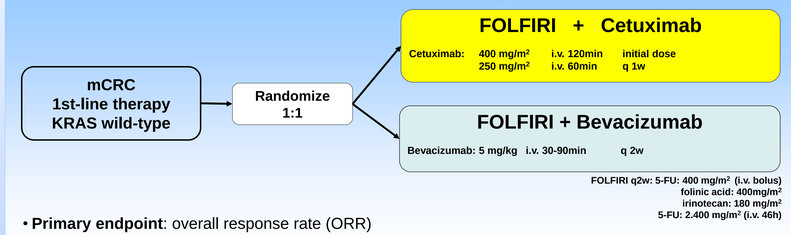
Background:

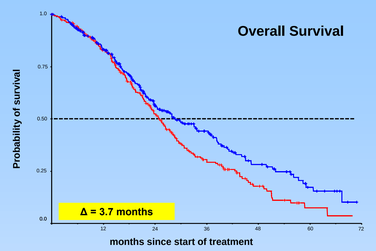
The FIRE-3 trial compared 1st-line therapy of FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wildtype (wt) mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The AADx molecular assay has previously been shown to identify a poor prognosis angiogenic subgroup 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.

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

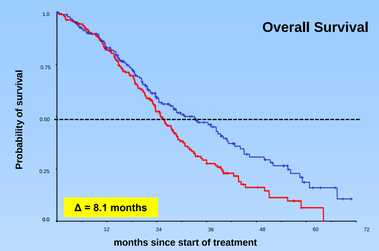
HR 0.77 (95% CI: 0.62 – 0.96)
Log-rank test p= 0.017

ITT population (N= 592)	FOLFIRI + CET	FOLFIRI + BEV	Hazard ratio	p
PFS (months)	10.0	10.3	1.06	0.547
ORR (%)	62.0%	58.0%	1.18	0.183*

p = log-rank test p; p*= one-sided Fisher´exact test

Heinemann et al Lancet Oncol 2014

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

RASwt population (N= 400)	FOLFIRI + CET	FOLFIRI + BEV	Hazard ratio	p
PFS (months)	**10.3**	**10.2**	0.97	**0.77**
ORR (%)	**65.3%**	**58.7%**	1.33	**0.18***

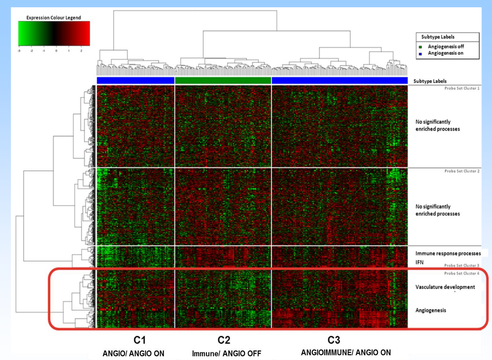
p = log-rank test p; p*= one-sided Fisher´exact test

Stintzing et al Lancet Oncol 2016

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



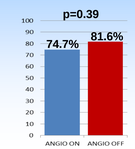
- Almac has developed the anti-angiogenic diagnostic (AADx) gene expression assay in ovarian cancer that:
  - identifies angiogenic molecular subtypes
  - Is defined by activation/ repression of genes associated with angiogenic processes
  - demonstrates prognostic performance in ovarian, colorectal 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

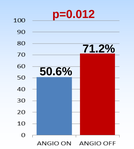
Baseline Characteristics (AADx Score Population)

Characteristic	RASwt population (n= 400) FOLFIRI Cetuximab (n= 199)	RASwt population (n= 400) FOLFIRI Bevacizumab (n=201)	total (n= 400)	AADx-Score RAS wild-type (n= 312) FOLFIRI Cetuximab (n= 149)	AADx-Score RAS wild-type (n= 312) FOLFIRI Bevacizumab (n=163)	total (n= 312)	AADx-Score RAS mutant (n= 119) FOLFIRI Cetuximab (n= 57)	AADx-Score RAS mutant (n= 119) FOLFIRI Bevacizumab (n=62)	total (n= 119)
Sex -male, % (n) -female, % (n)	73% (146) 27% (53)	66% (133) 34% (68)	70% (279) 30% (121)	74% (110) 26% (39)	65% (106) 35% (57)	69% (216) 31% (96)	54% (31) 46% (26)	73% (45) 27% (17)	64% (76) 36% (43)
Age -Median, years	64	65	64	64	65	64	65	63	65
ECOG % (n) -0 -1 -2	54% (107) 45% (89) 1% (3)	54% (109) 44% (89) 2% (3)	54% (216) 45% (178) 1% (6)	53% (79) 46% (69) 0.7% (1)	51% (84) 47% (76) 2% (3)	52% (163) 47% (145) 1% (4)	40% (23) 51% (29) 9% (5)	55% (34) 42% (26) 3% (2)	48% (57) 46% (55) 6% (7)
Site of primary, % (n) -right colon -left colon -unknown	20% (39) 80% (159) 0.5% (1)	26% (52) 74% (149)	23% (91) 77%(308) 0.3% (1)	20% (31) 80% (121)	25% (40) 75% (123)	23% (71) 77% (241)	35% (20) 65% (37)	31% (19) 69% (43)	33% (39) 67% (80)
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 -≥2 sites -unknown	43% (85) 56% (72) 1% (2)	41% (82) 59% (118) 0.5% (1)	42% (167) 48% (190) 1% (3)	44% (66) 56% (83) 0% (0)	44% (71) 56% (92) 0% (0)	44% (137) 56% (175) 0% (0)	39% (22) 61% (35) 0% (0)	48% (30) 52% (32) 0% (0)	44% (52) 56% (67) 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 Intermediate Poor	8% (15) 43% (86) 47% (94)	10% (21) 48% (96) 41% (83)	9% (36) 46%(182) 44% (177)	6% (9) 42% (62) 52% (78)	12% (19) 46% (76) 42% (68)	9% (28) 44% (138) 47% (146)	17% (10) 53% (30) 30% (17)	11% (7) 47% (29) 41% (26)	14% (17) 50% (59) 36% (43)
Primary resected, % (N)	81% (162)	88% (175)	84% (337)	89% (132)	90% (147)	89% (279)	95% (54)	87% (54)	91% (108)

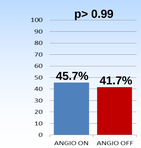
Overall Response Rates According to AADx Score (ORR)

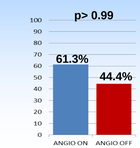
RAS wild-type subpopulation





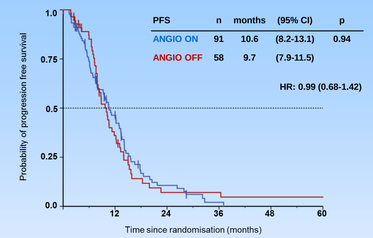
RAS mutant subpopulation

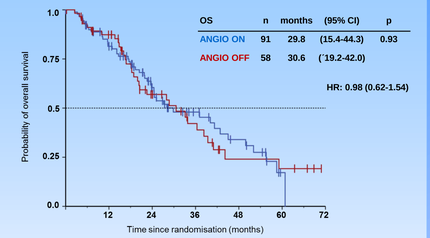




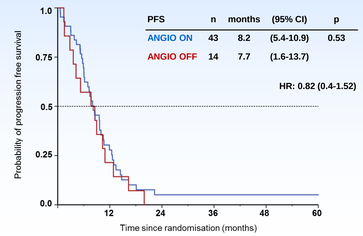
Survival According to AADx Score in Patients Treated with FOLFIRI + Cetuximab

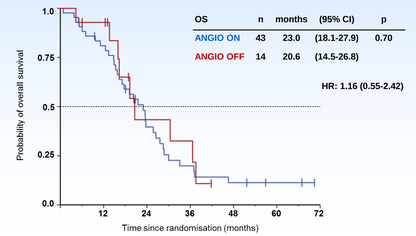
RAS wild-type subpopulation





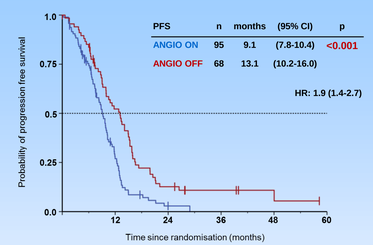
RAS mutant subpopulation

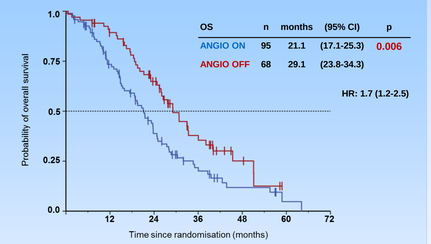




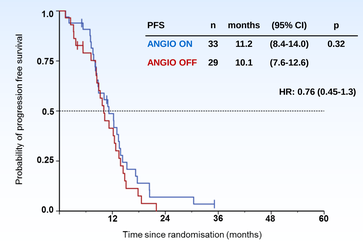
Survival According to AADx Score in Patients Treated with FOLFIRI + Bevacizumab

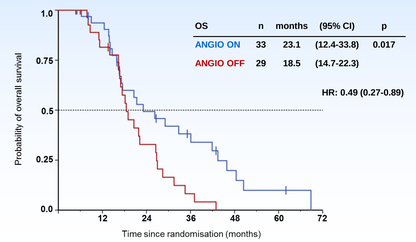
RAS wild-type subpopulation





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.