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Final Analysis of the Greek cohort of the AGENT Phase III study "Arfolitixorin in Metastatic Colorectal Cancer"

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BACKGROUND The AGENT trial, a pivotal international randomized phase III study (NCT03750786; Tabernero et al., 2024), investigated arfolitixorin in metastatic colorectal cancer (mCRC). This study presents the final analysis focusing on the Greek patient subpopulation.

METHODS Patients with mCRC were randomized to receive arfolitixorin (Arm A: 120 mg/m2 given as two intravenous bolus doses) or leucovorin (Arm B: 400 mg/m2 as a single intravenous infusion), both in combination with 5-FU, oxaliplatin, and bevacizumab. Response assessments were conducted every 8 weeks by blinded independent central review (BICR), and toxicity was reported according to MedDRA Version 22.1. The primary endpoint was ORR per RECIST v1.1 by BICR. Key secondary endpoints included PFS, DoR, OS, and safety.

DISCUSSION The AGENT trial did not demonstrate the clinical superiority of arfolitixorin over leucovorin in first-line therapy for mCRC. Nonetheless, this analysis suggests potential benefits associated with arfolitixorin in the Greek population, possibly influenced by regional and genetic factors. Limitations, including the small sample size, warrant a cautious interpretation of these findings.

RESULTS A total of 59 patients were included, with 24 in Arm A (arfolitixorin) and 35 in Arm B (leucovorin). Patients characteristics are shown in Table 1. Grade ≥3 drug-related AE rates were similar between arms, with fatigue (53.4%), hematologic toxicity (53.4%), nausea (50%), and sensory neuropathy (27.6%) being the most frequently reported. However, only one patient discontinued treatment in Arm A compared to three in Arm B. Notably, efficacy and survival outcomes in this Greek analysis were inversely proportional to those of the overall study population, highlighting potential regional variations.

Table 1. Patient clinicopathologic characteristics

Parameter	Arfolitixorin N=24	Leucovorin N=35	All N=59
Female gender	11 (45.8%)	12 (34.3%)	23 (39.0%)
Age (mean)	62.8	64.5	63.8
Race Caucasian	24 (100%)	35 (100%)	59 (100%)
Left colon	15 (62.5%)	16 (45.7%)	31 (52.5%)
Right colon	4 (16.7%)	10 (28.6%)	14 (23.7%)
Rectal cancer	5 (20.8%)	9 (25.7%)	14 (23.7%)
BRAF mut	2 (10.5 %)	1 (3.3%)	3 (6.1%)
KRAS mut	9(42.9%)	21 (63.6%)	30 (55.6%)
NRAS mut	2 (10.0%)	2 (6.5%)	4 (7.8%)
Liver metastasis	17 (70.8%)	27 (77.1%)	44 (74.6%)
Lung metastasis	4 (16.7%)	16 (45.7%)	20 (33.9%)
Median PFS (95% CI) *	13.1 (7.4, 22.1)	7.6 (6.9, 11.4)	HR 0.554(0.261, 1.176)
Median OS (95% CI) *	NR$ (20.1, NR$)	28.6 (15.9, NR$)	HR 0.732(0.325, 1.649)
Partial Response (PR)	10 (41.7%)	13 (37.1%)	
Stable Disease (SD)	12 (50.0%)	15 (42.9%)	
Progressive Disease (PD)	2 (8.3%)	2 (5.7%)	
Not evaluable	-	5 (14.3%)	
Overall Response Rate [95% CI]] **	10(41.7%) [22.1%, 63.4%]	13(37.1%) [21.5%, 55.1%]	Risk Difference (95%CI): 0.05(-0.21, 0.30) ***
Median Duration of Response in months# (95% CI) *	18.6 (5.3, NR$)	9.9 (5.1, 14.8)	

* Based on Kaplan-Meier product limit estimates method. ** Intention-to-treat Analysis Set confidence interval. ***: Mantel-Haenszel estimate of the common risk difference and 95% two-sided. # by Blinded Independent Central Review. Abbreviations: N: number of patients; CI: confidence interval; NR: not reached

Figure 1. Confirmed best Overall, Response by BICR per RECIST 1.1

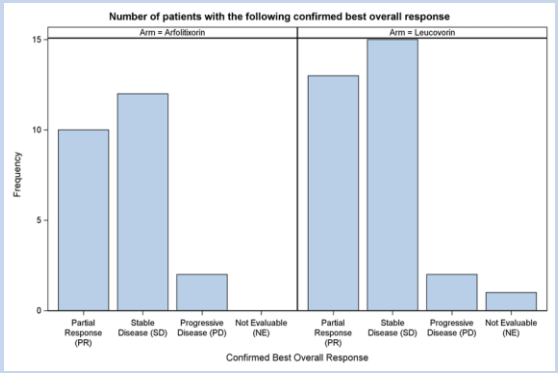
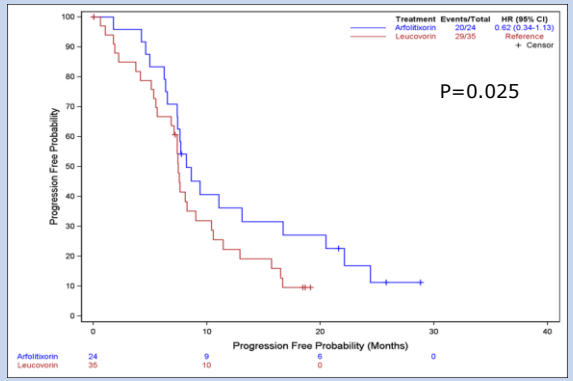


Figure 2. Kaplan Meier curves for PFS by BICR



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