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LBA22 Negative hyper-selection of RAS wild-type (wt) metastatic colorectal cancer (mCRC) patients randomized to first-line FOLFOX plus panitumumab (Pan) followed by maintenance therapy with either 5FU/LV plus pan or single-agent pan: Translational analyses of the VALENTINO study

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Background: RAS wt unresectable mCRC pts were randomized to FOLFOX + Pan (8 cycles) followed by maintenance with Pan (arm B) or Pan + 5FU/LV (arm A). A pre-specified translational endpoint was the evaluation of PRESSING panel, that groups rare genomic markers beyond RAS/BRAFto predict anti-EGFR resistance in addition to primary tumor location (PTL) (Cremolini, Ann Oncol '17).

Methods: Primary endpoint was PFS. A sample size of 224 pts had 90% power to detect 50% 10-month PFS in arm A, max 15% less in arm B, significance level 0.1 (non-inferiority margin of arm B vs A: 1.515). PRESSING panel analyses: ISH for HER2/METamplification, IHC +/- RNA-seq for ALK/ROS/TRKs/RETfusions, NGS (Hotspot Cancer Panel, Ion Torrent®) for HER2/PI3K/PTEN/low % RAS mutations, PCR for MSI.

Results: 229 pts randomized (117 arm A/112 arm B). At updated median follow-up of 18 mos, the upper boundary of 1-sided 90% CI of HR was 1.857. 10-m PFS was 49% in arm B vs 59.9% in arm A (HR = 1.51 [1.11-2.07]; p = 0.009). A subgroup of 189 RAS/BRAF wt evaluable pts had available tumor tissue for PRESSING analyses, with 46 (24%) PRESSING-pos tumors. Table 1 shows PFS according to PTL and PRESSING panel, overall and by treatment arm. In post-hoc combined analyses of PTL and PRESSING, right-sided and/or PRESSING-pos tumors were "predicted resistant (R)" (arm B/A: 31/32); left-sided + PRESSING-neg "predicted sensitive (S)" (arm B/A: 58/68). mPFS: 8.1 vs 13.2 mos for predicted R vs S (HR = 2.08 [1.47-2.93]; p < 0.0001); 7.7 vs 9.9 mos for arm B vs A in predicted R (HR = 2.12 [1.16-3.89]), 12.4 vs 14.2 mos for arm B vs A in predicted S (HR = 1.54 [0.98-2.40]) (interaction p = 0.126).

Conclusions: RAS/BRAFwt, right-sided and/or PRESSING-pos pts receiving maintenance with Pan alone had extremely poor PFS. The PFS benefit of 5FU/LV added to Pan was consistent in all subgroups.

Table: LBA22

	Number	Median PFS (95% CI), months	HR (95% CI)	log-rank test p	interaction test p
Right- vs left-sided	40 vs 189	7.4 (6.4-9.3) vs 11.2 (10.5-13.2)	1.83 (1.26-2.68)	0.002	-
Right-sided: arm B vs A	21 vs 19	7.0 (4.5-8.9) vs 8.7 (5.9-NE)	2.10 (1.96-4.16)	-	0.369
Left-sided: arm B vs A	91 vs 98	10.6 (9.4-12.6) vs 12.9 (10.6-15.3)	1.45 (1.03-2.05)	-	
PRESSING-positive vs -negative	46 vs 143	7.7 (6.9-10.3) vs 12.1 (10.8-14.2)	2.07 (1.43-2.99)	0.0001	-
PRESSING-positive: arm B vs A	22 vs 24	7.5 (5.5-8.8) vs 11.1 (6.9-14.6)	2.32 (1.12-4.81)	-	0.118
PRESSING-negative: arm B vs A	67 vs 76	11.1 (10.6-13.4) vs 13.4 (10.8-18.7)	1.61 (1.07-2.44)	-	