Emerging Insights on the Association of Tumor Molecular Phenotype with Clinical Benefit in Metastatic Colorectal Cancer (mCRC) Subjects Treated with AB928 + Modified FOLFOX-6 (mFOLFOX-6)

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Abstract 338

Akshata R Udyavar[1], Michael Cecchini[2], Daniel DiRenzo[1], Sean Cho[1], Lisa Seitz[1], Kristen Zhang[1], Stephen W Young[1], Amy E Anderson[1], Kimberline Y Gerrick[1], Matthew J Walters[1], Houston N Gilbert[1], Cheng Quah[1], Juan Jaen[1] and William Grossman[1]

[1]Arcus Biosciences, Inc., 3928 Point Eden Way, Hayward, CA, USA ; [2]Yale University, New Haven, CT, USA

OVERVIEW

AB928 is an orally bioavailable and selective dual antagonist of adenosine $A_{2a}R$ and $A_{2b}R$ receptors, specifically designed to block the immunosuppressive effects associated with high adenosine concentration within the tumor microenvironment. It is the only adenosine receptor antagonist in active clinical trials that potently blocks $A_{2b}R$ to the same extent as $A_{2a}R$.

ARC-3 (NCT03720678) is an ongoing, Phase 1/1b, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, PK, and clinical activity of AB928 + mFOLFOX-6 in patients with metastatic colorectal cancer (mCRC). The dose escalation portion of the study enrolled patients with mCRC that had advanced on prior lines of therapy; these patients received either 75 mg or 150 mg AB928 daily in addition to standard of care (SOC) mFOLFOX-6. In the dose expansion portion of the study, subjects received 150 mg AB928 + mFOLFOX-6 either in front line (1L) or following progression to SOC chemotherapy. All patients were tumor mutation burden (TMB)-low/intermediate (<20 mutations/MB) and Microsatellite stable (MSS) by tumor biopsy exome sequencing. Of 30 sequenced patients, 15 were KRAS-mutant (11 G12*, 2 G13D, 1 A59G, 1 L19F). Preliminary results of this study were presented recently[1].

An extensive biomarker collection program (tumor IHC, RNA-seq, exome-seq and serum assays) was conducted, aimed at identifying molecular markers that correlate with clinical benefit in these various clinical settings. A preliminary analysis of some of these trends is presented here.

CLINICAL ACTIVITY

As of Data Cut-Off (DCO) October 16, 2020, the study had enrolled a total of 44 subjects: 15 subjects without prior therapy in the metastatic setting (1L), 6 subjects (2L) with 1 prior line of therapy (LoT), and 23 subjects (3L+) with ≥2 prior LoT. Seven (16%) subjects remained on treatment as of DCO. The safety profile was unchanged since our most recent update[1].

In the 1L setting, objective responses were seen in 8/15 subjects (53.3%; 1 CR, 7 PR), in addition to 6/15 SD. In the 3L+ setting, PR was seen in 2/23 subjects (Objective Response Rate, ORR: 8.7%) in addition to 17 subjects with SD as best overall response (BOR). This compares favorably to ORR for current SOC therapies (regorafenib: 1%[2]; Lonsurf: 1.6%[3]). Both PR's and 7/17 SD were in patients with ≥2 disease assessments, including those with MSS and KRAS/BRAF-mutant mCRC, previously treated with FOLFOX and/or FOLFIRI. Six subjects (5 in 1L, 1 in 3L+) experienced sufficient reduction in lesion size such that, at the investigator's discretion, they discontinued treatment to undergo surgery/radiotherapy with curative intent.

Median time on treatment (mToT) for 3L+ patients (n = 23) was 4.2 months (range: 0.4-11.1 months), which compares favorably with recent SOC therapy in 3L+ CRC, with median PFS of ~2 months[2,3]. Due to the significant number (5/15) of 1L subjects that discontinued treatment in order to undergo curative-intent surgery, the mToT for this group is not particularly informative.

For the purposes of biomarker analysis, we defined clinical response in 1L as either CR, PR or SD/curative surgery (10/15; 66.6%). For 3L+ patients, we segregated patients into those obtaining *better* clinical outcome (either PR or SD with ToT > 4 months, the mToT for this group) and those with *worse* clinical outcome (either PD or SD with ToT < 4 months).

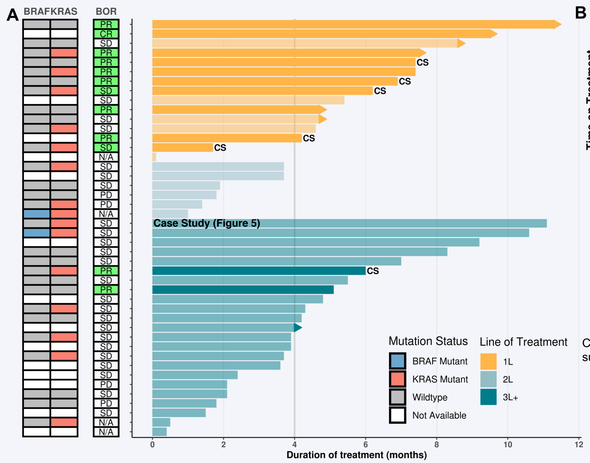

Figure 1. Time on AB928 + mFOLFOX-6 Treatment.
(A) Shows swimlane plot denoting time on AB928 + mFOLFOX-6 treatment. KRAS and BRAF mutation status and Best Overall Response (BOR) are indicated in the left panel. BOR cells highlighted in green are patients who achieved PR/CR and/or underwent curative-intent surgery/radiotherapy. (B) Clinical Outcome in the 3L+ setting defined as follows; *Better*: subjects with PR/CR, SD for greater than 4 months and/or still on study; *Worse*: subjects with less than 4 months on treatment.

BIOMARKER TRENDS

Tumor CD73 mRNA and protein levels are associated with better clinical outcome, while soluble CD73 in serum is associated with worse clinical outcome, in 3L+ mCRC (ARC-3)

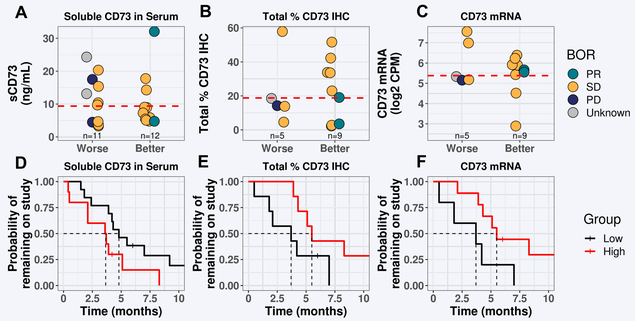

Figure 2. Baseline soluble CD73 (sCD73) in serum and tumor CD73 gene/protein measurements in 3L+ mCRC.
Top panel shows dot plots for clinical outcome on the x-axis (as defined in Fig. 1B) and on the y-axis for (A) sCD73 by ELISA, (B) total percent CD73 protein by tumor biopsy multi-plex IHC, and (C) CD73 mRNA by tumor biopsy RNA-seq. Red dashed lines denote cut-points that maximize sensitivity and specificity[4] for prediction of clinical outcome given each CD73 measurement. (D,E,F) Corresponding Kaplan-Meier (KM) curves denoting time in months on the x-axis and probability of remaining on study on the y-axis. The cut-points used for the KM curves are defined by the red dashed lines in panels A-C. Interestingly, our trend is in the opposite direction to prior studies that identified CD73 (protein and mRNA) as a strong negative prognostic/predictive (FOLFOX) biomarker in CRC[5,6], perhaps reflective of an AB928-mediated effect in the present study.

Arcus and Corvus adenosine signatures are associated with worse outcomes in 3L+ mCRC

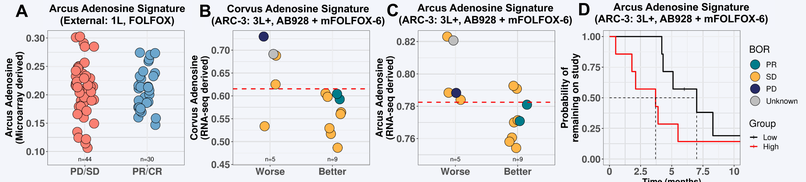

Figure 3. Adenosine gene signatures in 1L external cohort and 3L+ ARC-3 patients.
(A) Dot plots of Arcus adenosine signature on the y-axis in 1L FOLFOX-treated external mCRC cohorts[7-9]. (B) Corvus[10] and (C) Arcus adenosine signatures in the ARC-3 3L+ cohort with clinical outcomes on the x-axis. Red dashed lines denote cut-points that best distinguish clinical outcomes given each signature. (D) Kaplan-Meier plot showing probability of remaining on study, stratified by Arcus adenosine signature score split at cut-point specified in panel C. The trends towards better outcomes in "low-adenosine signature" subjects reflect the presence of higher levels of myeloid cells in "high-adenosine signature" mCRC. Opposite trends have been observed with competitor $A_{2a}R$i + anti-PD-L1 in other clinical settings[11,12].

Tumor Mutation Burden (TMB) is associated with better clinical outcome in 3L+ mCRC

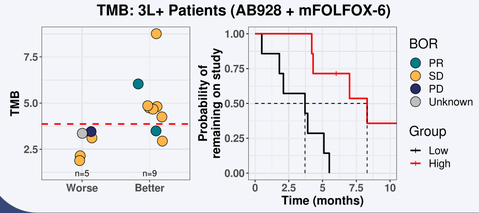

Figure 4. Tumor Mutation Burden (TMB) in 3L+ mCRC patients.
(A) Dot plot with TMB on the y-axis in 3L+ mCRC patients and clinical outcome on the x-axis. Red dashed line shows the cut-point[4] for TMB that best discriminates clinical outcome. (B) KM curves (probability of remaining on treatment) on the y-axis, stratified by cut-point defined in A. TMB is strongly associated with better clinical outcome and duration on treatment in 3L+ patients treated with AB928 + mFOLFOX-6. In contrast, TMB is not associated with outcome in 1L ARC-3 patients or 1L subjects in TCGA[13] treated with FOLFOX regimens (data not shown).

CASE STUDY OF 3L+ mCRC PATIENT

Immune activation is observed in 3L+ KRAS-mutant patient with longest ToT (>11 months)

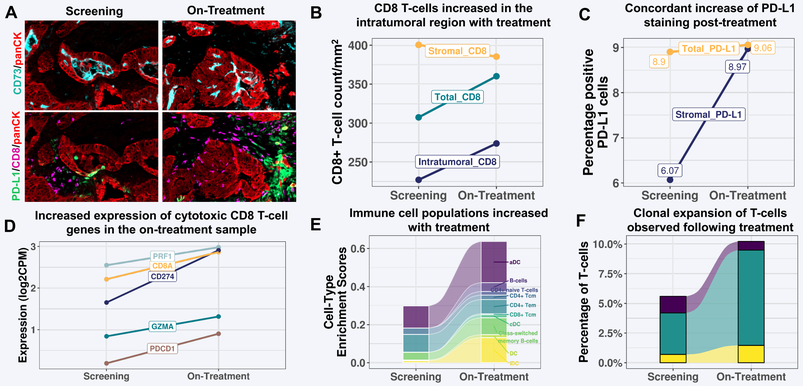

Figure 5. Evidence of CD73 expression, immune infiltration and activation in 3L+ patient with durable clinical benefit (SD).
Case study patient (annotated in Figure 1A with longest ToT > 11 months) was MSS, TMB-low and had TP53 loss-of-function, KRAS G13D, and SMAD4 D351G mutations. (A) Histologic images of tumor biopsy multi-plex IHC at screening and on-treatment (day 50). Quantification of (B) CD8 and (C) PD-L1 IHC showed increased CD8 T-cells after treatment in the intra-tumoral regions and increased stromal PDL1 expression. (D) Cytotoxic CD8 T-cell gene expression and (E) enrichment scores of various immune cells were increased upon treatment with AB928 + mFOLFOX-6. (F) Pre-existing T-cell clones (each color is a unique TCR clone) expanded upon treatment, from a total of 5.6% to 10.2% of all tumor infiltrating T-cells.

CONCLUSIONS

- **In the 1L setting, objective responses were seen in 8/15 subjects (53.3%; 1 CR, 7 PR), in addition to 6/15 SD.**
- **In the 3L+ mCRC setting, there were 2 PR and 7 SD in patients with ≥2 disease assessments, including those with MSS and KRAS/BRAF-mutated tumors, previously treated with FOLFOX and/or FOLFIRI.**
- **Six subjects (5 in 1L, 1 in 3L+) experienced sufficient reduction in lesion size such that, at the investigator's discretion, they discontinued treatment to undergo surgery/radiotherapy with curative intent.**
- **Tumor CD73 mRNA and protein levels are associated with better clinical outcome, while soluble CD73 in serum is associated with worse clinical outcome, in 3L+ mCRC subjects treated with AB928 + mFOLFOX-6, perhaps reflective of an AB928-mediated effect in the present study.**
  - Best outcomes in subjects treated with AB928 + mFOLFOX-6 were seen in high-CD73 subjects predicted (based on earlier published reports) to have poorer performance when treated with FOLFOX alone.
- **Tumor Mutation Burden (TMB) is strongly associated with better clinical outcome in 3L+ mCRC subjects treated with AB928 + mFOLFOX-6.**
  - No such association was seen in 1L patients (either in ARC-3 or external cohorts).
- **Arcus and Corvus adenosine gene signatures are associated with worse outcomes in 3L+ subjects treated with AB928 + mFOLFOX-6.**
  - In our 3L+ mCRC cohort, adenosine signatures appear to correlate with higher levels of myeloid cell infiltration, a negative prognostic factor.
- **Certain biomarkers, particularly TMB and CD73 expression, may offer the opportunity for patient selection in future studies of AB928 + mFOLFOX-6 in advanced mCRC.**

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