Healthcare

Consider Reading Vol.6: Nonredundant Adenosine Blocking & Implications for CRVS

See page 3 for previous volumes.

Yan Cui and colleagues recently demonstrated in a paper in Nature Communications titled “CD73 on cancer-associated fibroblasts enhanced by the A2AR-mediated feedforward circuit enforces an immune checkpoint” that cancer-associated fibroblasts (CAFs) are the prominent CD73-high cells in the TME of various colorectal tumors (Yu, et al. Nature Communications. 2020). CAFs are an activated subpopulation of fibroblasts; they have been shown to be a major source of CD73 activity and promote tumorigenesis. CAFs and mesenchymal stem cells preferentially express adenosine receptor A2b by up to 50x more than A2a. The authors provide a rationale for targeting non-redundant adenosine pathways to enhance existing immunotherapies. We draw parallels to put in perspective mCRPC data Corvus (CRVS-Buy) presented yesterday at the ASCO-GU.

In the poster presentation titled “Adenosine Receptor Blockade with Ciforadenant ± Atezolizumab in Advanced Metastatic Castration Resistant Prostate Cancer (mCRPC)” by Fong et al., Corvus showed that the combination of anti-PD-L1 mAb atezolizumab and adenosine A2a receptor (ADORA2a) antagonist ciforadenant achieved tumor regression in 9/24 (38%) patients. Though one patient achieved a partial response to date, the combination showed a clear benefit over ciforadenant monotherapy as 2/11 (18%) patients experienced tumor regression in the monotherapy cohort. The median follow-up was 3.2+ months. The median age of the combined population was 68 years, with a median of three prior therapies received. One obvious question is could responses possibly be higher? Given the known role of adenosine in downregulating immune cell functions in the tumor microenvironment (TME), it is conceivable that targeting non-redundant pathways to not only block adenosine production but also adenosine receptor activity may drive additional benefit for patients when used concurrently with immunotherapy (Noviskiy, et al. Blood, 2008; Raskovalova, et al. Immunol Res, 2006; Schnurr, et al. Blood, 2004; Visser, et al. Biochem Pharmacol. 2000; Scheibner et al. Cell Mol Biol 2009). Recall that, in a previous note, we referenced Goswami et al whose findings suggest that CD73 may be a good IO target given that CD73 is a major source of adenosine production in the TME; Corvus’ anti-CD73 mAb CPI-006 showed evidence of clinical benefit when used in combination with ciforadenant. The aforementioned paper by Yan Cui and colleagues provide additional evidence in support of the hypothesis that a combinatorial regimen directed at blocking the adenosine-CD73 axis through non-redundant pathways may be an answer (discussed below). Corvus is currently evaluating in a phase I trial the combination of ciforadenant, CPI-006 and anti-PD-1 mAb pembrolizumab to evaluate this hypothesis.

CAFs have a role in tumorigenesis. Fibroblasts, one of the vital components of the TME, contain an activated subpopulation of cells called cancer-associated fibroblasts (CAFs) that have been shown to dynamically regulate the TME and promote tumorigenesis. The TME has progressively been shown to play a vital role in tumor development and is a source of many signaling molecules that influence surrounding tissues including CD73, a nucleotidase whose high expression correlates to poor clinical outcomes. One role of CD73 in tumor progression has previously been described in its ability to hydrolyze AMP into immunosuppressive adenosine (ADO) molecules which consequently binds to the A2a receptor and suppresses immunogenic responses. The authors demonstrated that colorectal cancer-derived CAFs express high CD73 expression, which indicates that CAFs are a major source of CD73 activity. In order to validate the capacity of CD73 to promote tumorigenesis, this study used an EG7 murine model to compare

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ectopic tumor growth in CD73\textsuperscript{null} and WT mice. The results indicated that while WT mice injected with EG7 cells met the study end point within 15 days, the CD73\textsuperscript{null} mice showed tumor regression followed by complete clearance of the tumor.

**Targeting non-redundant pathways can potentially enhance existing immunotherapies.** Adenosine, the end product of CD73 activity, can bind to four potential receptors (A1, A2a, A2b, A3), two (A2a and A2b) of which result in activation of pro-tumor signals. The authors find that in the fibroblastic stroma, A2a and A2b receptors are the major subtypes expressed. They also show with real-time (RT)-PCR that certain cell types express different levels of each receptor type, as T-cells mainly expressed A2a while CAFs and mesenchymal stem cells (MSCs) preferentially expressed A2b by up to 50-fold more. The difference in receptor subtype expression and adenosine’s differential affinity to each receptor type can be exploited for non-redundant pathway targeting that can potentially circumvent resistance to existing immunotherapy. The authors found that anti-CD73 with A2a and A2b antagonists cause suppression of EG7 tumor progression, increases in total TIL-CD8 cells, and IFN-gamma-producing CTLs in mice.

**A2b blockade-induced tumor regression is CAF-dependent, and multimodal adenosine pathway blockade may enhance antitumor effects of immunotherapy.** The authors found that while CAFs are scattered sparsely in the TME, the relative percentage of CD73-high CAFs elevated gradually during tumor progression. A2b antagonism suppressed adenosine-induced CD73 upregulation in CAFs. Moreover, CD73-neutralization contributes to suppression of CAF-assisted tumor progression. Neither A2b antagonism nor CD73-neutralization cause a marked alteration in CAF abundancy. While A2a and A2b antagonism without CD73-neutralization cause a reduction in CAFs, the combination does not affect the frequency of CD73-high CAFs. A reduction of CD73-high CAFs are seen only when CD73-neutralization is applied in addition with A2a and A2b antagonism. In metastatic prostate cancer, CAFs promote cancer metastasis (Cioni et al. Molecular Oncology. 2018; Ippolito et al. Oncogene. 2019). A combinatorial approach to target the adenosine-CD73 axis may aid in increasing the efficacy of immunotherapy in many cancers, including colorectal and prostate cancers.
Previously Published “Consider Reading”

Vol. 1: Could c-Jun Enhance CAR-T Therapeutics?
Vol. 2: CD73 Might Be A Good IO Target. Could CRVS Benefit?
Vol. 3: Cemiplimab and Oncolytic Virus Improves ORR in CSCC
Vol. 4: B-Cells May Aid In Checkpoint Inhibitor Therapy
Vol. 5: B-Cells May Aid IO Responses and Implications for CRVS
Valuation and Risks

Corvus Pharmaceuticals

Valuation
Our $6/share price target is derived from a risk-adjusted net present value (rNPV) analysis based on: (1) $3.10/share, driven by ciforadenant U.S. and EU sales in 4L RCC (2022 launch, 45% POS, $446M peak sales) and (2) $2.90/share, driven by ciforadenant U.S. and EU sales in 3L and 4L NSCLC (2023 launch, 35% POS, $804M peak sales). We take our model out to 2029 to account for currently known composition of matter patent expiry date in July 2029 and use a 15% discount rate.

Impediments to our price target include clinical failure of ciforadenant in either non-small cell lung cancer or renal cell carcinoma trials, difficulty for the company to raise additional funds to continue future operations, regulatory hurdles of approval, and ability to receive reimbursements for fourth-line RCC treatment.

Risks
Key risks to our valuation that could adversely impact the company shares include, but are not limited to:

- **Clinical risks:** We would like to see continuous durable response of ciforadenant (CPI-444) in RCC and NSCLC. As of April 2019 we have seen 5.8 months mPFS in RCC with 11.4% ORR in combination with Atezolizumab. If CRVS is unable to present updated efficacy data in Q419 similar to that of last year in RCC then the probability of approval in 4L RCC will be diminished.

- **Financial risks:** CRVS does not have any commercial-stage product right now, and is expected to incur operational losses in the near future primarily because of R&D expenses. If the company is unable to raise sufficient capital needed to complete phase 2 and, if needed, phase 3 trials then there will be materially adverse impact on the future of the company.

- **Regulatory risks:** All drug products are subject to high scrutiny from regulatory bodies in the U.S. and EU for efficacy and safety. Successful clinical development and commercialization will be heavily dependent on these two factors.

- **Reimbursement risks:** Many jurisdictions across the globe do not reimburse for treatment in 4L RCC. If CRVS is not able to secure reimbursement then our pricing assumption for ciforadenant may not be realized which may have a materially negative impact on our sales projections.
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For important disclosure information regarding the companies in this summary report, please contact: The Director of Research at (800) 678-9147 or write to: ROTH Capital Partners, LLC, Attention: Director of Research, 888 San Clemente Drive, Newport Beach, CA 92660

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Distribution of IB Services Firmwide

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Sell: A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

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