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POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

JAK2/mTOR Inhibition Fails to Prevent Acute Gvhd Despite Reduced Th1/Th17 Cells: Final Phase II Trial Results

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Introduction: Our phase I graft-versus-host disease (GVHD) prevention trial of pacritinib (recommended phase II dose: 100mg po BID day 0 to +70, dose level 2) plus sirolimus (8-14ng/ml) and tacrolimus (3-7ng/ml) (PAC/SIR/TAC) demonstrated the regimen was safe and free of pan-JAK myelosuppression after allogeneic hematopoietic cell transplantation (alloHCT). PAC inhibits JAK2 with no activity against JAK1, avoiding off-target suppression of IL-2 required by Tregs. JAK2/STAT3 activity mediates IL-6, IL-12, and IL-23 receptor signaling and subsequent pathogenic Th1 and Th17 differentiation. JAK2/mTOR blockade supports Treg potency, providing further rationale for the PAC/SIR/TAC combination. Herein we report on our completed phase II trial of PAC/SIR/TAC after 8/8-HLA matched alloHCT.
Methods: This single-arm phase II trial (NCT02891603) was powered to determine if PAC/SIR/TAC suppressed %pSTAT3 $^{+}$ CD4 $^{+}$ T cells at day +21 (primary endpoint: %pSTAT3 $^{+}$ CD4 $^{+}$ T cells $\leq$ 35%) and determine the cumulative incidence of grade II-IV acute GVHD by day +100. We also evaluated the impact of PAC/SIR/TAC on CD4 T cell differentiation (Treg, Th1, Th17) and related CD28 (pS6 and pH3ser10) and IL-2 receptor (pSTAT5) signal transduction after alloHCT. Eligible patients (n=28) received alloHCT for AML, MDS, ALL, and MF. Reduced (n=21) or myeloablative (n=7) intensity conditioning was permitted. HLA-A, -B, -C, and -DRB1 matched-related (n=7) or unrelated donors (n=21) were allowed. Adequate vital organ function and Karnofsky performance status (KPS $\geq$ 80%) were required.
Results: PAC/SIR/TAC (PAC 100mg BID) met the primary endpoint of the phase II study, reducing %pSTAT3 $^{+}$ CD4 $^{+}$ T cells to 9.62% at day +21 (**Figure 1A**). PAC/SIR/TAC significantly improved CD4 $^{+}$ T cell STAT5 phosphorylation at day +21, increasing the ratio of pSTAT5 $^{+}$ to pSTAT3 $^{+}$ CD4 $^{+}$ T cells (ratio 80.7 v 1.71 P<0.0001) compared to dose level 1 PAC/SIR/TAC of the phase I trial that lacked effective JAK2 blockade (PAC 100mg daily, day +21 %pSTAT3 $^{+}$ CD4 $^{+}$ T cells 59.5%). Partial CD28 signaling blockade was achieved by PAC/SIR/TAC compared to dose level 1, with suppression of mTOR (%pS6 $^{+}$ CD4 $^{+}$ T cells 7.67 v 22.5% P=0.0009) but only modest inhibition of Aurora kinase A activity (%pH3ser10 $^{+}$ CD4 $^{+}$ T cells 71.3 v 98.6% P<0.0001), a pathway for escape alloreactivity. Th1 (0.01 v 0.03 k/µl P=0.026) and Th17 (0.016 v 0.032 P=0.031) cells were reduced at day +21, increasing the ratio of Tregs to Th1 and Th17 cells (0.84 v 0.21 P=0.043) with PAC/SIR/TAC compared to dose level 1. Like JAK2 KO murine T cells, Th2 cells at day +21 were increased with PAC/SIR/TAC (0.056 v 0.001 k/µl P=0.036), compared to dose level 1. T, B, and NK cell engraftment at day +21 was comparable to dose level 1. Despite suppression of Th1 and Th17 cells, the cumulative incidence of grade II-IV acute GVHD by day +100 with PAC/SIR/TAC was similar to historic SIR/TAC values (46.4 v 43%) (**Figure 1B**). Acute GVHD onset did not correlate with duration of PAC therapy, depth of pSTAT3 inhibition, or burden of circulating Th1, Th17, or Th2 cells.

Conclusions: While PAC/SIR/TAC successfully reduced pSTAT3, increased pSTAT5, and suppressed Th1 and Th17 cells, the regimen did not reduce acute GVHD risk. Completed phase II and III trials testing tocilizumab (anti-IL-6 monoclonal antibody, ACTRN12612000726853, ACTRN12614000266662) and now PAC reveal a biologic disconnect between effective IL-6/JAK2/pSTAT3 axis blockade and a disappointing lack of clinical improvement in acute GVHD prevention. We surmise uncontrolled T cell Aurora kinase A activity contributed to acute GVHD via CD28 costimulation in this trial. As PAC polarizes the pSTAT5:pSTAT3 CD4 $^{+}$ T cell ratio and targets IRAK1 and CSFR1, it may have activity in refractory chronic GVHD. This concept is now being tested by others (NCT05531786).

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OffLabel Disclosure: Pacritinib is a JAK2 inhibitor FDA-approved for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet count below 50 Ã- 109/L. Off-label use of pacritinib will be discussed in the context of GVHD prevention.

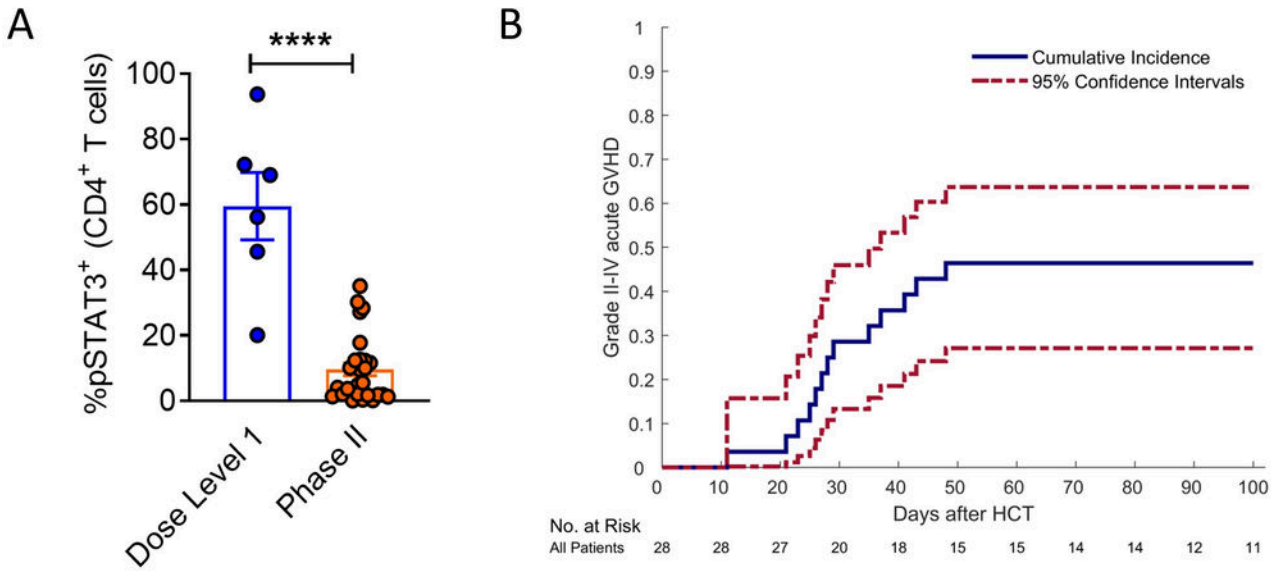

Figure 1: PAC/SIR/TAC reduces the frequency of pSTAT3$^+$ CD4$^+$ T cells but does not improve acute GVHD prevention. Recipients of HLA-matched alloHCT received PAC/SIR/TAC according to a single-arm phase II trial. Peripheral blood samples were collected at day +21. (A) Graph shows the %pSTAT3$^+$ CD4$^+$ T cells at day +21 among patients with SIR/TAC and a biologically inactive dose of PAC (100mg po daily) from the phase I trial versus those treated with the recommended phase II dose (100mg po BID). The primary endpoint was % pSTAT3+ CD4+ T cells at day +21, with success met if the mean was ≤35%. (B) The cumulative incidence of grade II-IV acute GVHD by day +100 with PAC/SIR/TAC (shown) was a secondary endpoint of this trial. The historic rate of grade II-IV acute GVHD by day +100 with SIR/TAC alone was 43% per a randomized phase II trial of SIR/TAC versus TAC/MTX.

Figure 1

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