Effects of prior exposure to Tec kinase (BTK/ITK) inhibitors on KTE-X19 products

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Background

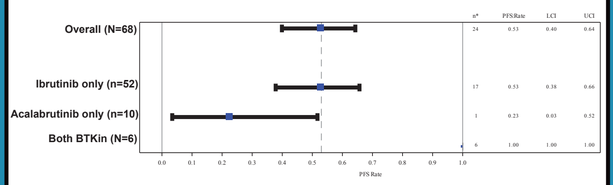
Frequent and durable responses were recently reported in the pivotal ZUMA-2 (NCT02601313) study for relapsed or refractory (R/R) mantle cell lymphoma (MCL) patients treated with KTE-X19, an autologous CD19-targeted chimeric antigen receptor-engineered T-cell (CAR-T) product (Wang et al. N Engl J Med. 2020). Most patients enrolled had received at least one line of Tec kinase inhibitor prior to KTE-X19 manufacturing, either in the form of ibrutinib, a Bruton's tyrosine kinase (BTK) and Inducible T cell kinase (ITK) inhibitor, or acalabrutinib, a more selective BTK inhibitor. Pharmacokinetic expansion of KTE-X19 was higher in ibrutinib-treated patients relative to acalabrutinib-treated patients. We previously showed that prolonged exposure to ibrutinib enhanced T cell effector function and proliferation in patients with CLL (Fraietta et al, Blood, 2016). To assess the impact of Tec kinase inhibitor on KTE-X19 products and downstream clinical outcomes, we examined the phenotype, transcriptional profile and cytokine production of KTE-X19 infusion products and post-infusion lymphocytes from patients with R/R MCL treated on the ZUMA-2 study.

Pre-treatment with Ibrutinib resulted in prolonged PFS among KTE-X19 treated MCL patients

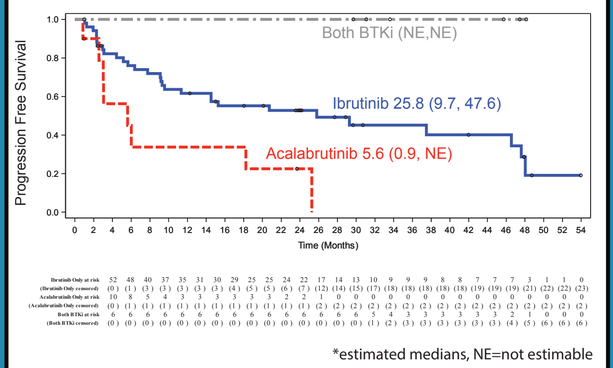
Baseline Characteristics of Ibrutinib and Acalabrutinib Treated Patients

Characteristic	Patients		
BTKi treatemnt	**Ibrutinib**	**Acalabrutinib**	**Both**
Previous BTK inhibitor therapy - no. (%)	52 (76)	10 (15)	6 (9)
Age (year) - no. (median)	52 (65.0)	10 (56.5)	6 (61.5)
Intermediate or high risk according to Simplified MIPI -no. (%)	30 (58)	5 (50)	3 (50)
Blastoid morphologic characteristics of MCL - no. (%)	12 (23)	3 (30)	2 (33)
Ki-67 proliferation index ≥30% - no. (%)	32 (62)	5 (50)	6 (100)
Ki-67 proliferation index ≥50% - no. (%)	27 (52)	4 (40)	6 (100)
TP53 mutation - no. (%)	4 (8)	1 (10)	1 (17)
TP53 non-mutation - no. (%)	24 (46)	1 (10)	5 (83)
Detected T(11;14) FISH - no. (%)	38 (73)	5 (50)	5 (83)
Positive CD19 IHC status - no. (%)	37 (71)	5 (50)	5(83)
Negative CD19 IHC status - no. (%)	3 (6)	1 (10)	1 (17)
Tumor burden (mm^2) - no. (median)	47 (2696.6)	10 (1144.2)	6 (515.6)
No. of previous therapies - median (range)	3 (1-5)	3 (1-5)	3 (1-5)
≥ 3 Previous lines of therapy - no. (%)	41 (78)	8 (80)	6 (100)
Prior autologous stem-cell transplantation - no. (%)	21 (40)	6 (60)	2 (33)
Relapsed or refractory disease - no. (%)			
Relapse after autologous stem-cell transplantation	21 (40)	6 (60)	2 (33)
Refractory to most recent previous therapy	22 (42)	2 (20)	3 (50)
Relapsed after most previous therapy	9 (17)	2 (20)	1 (17)
Disease that relapsed or was refractory to BTKi therapy - no. (%)			
Refractory to BTKi therapy	35 (67)	7 (70)	0 (0)
Relapse during BTKi therapy	11 (21)	3 (30)	4 (67)
Relapse after BTKi therapy	5 (10)	0 (0)	0 (0)
Intolerance	1 (2)	0 (0)	2 (33)

BTKi Subgroup Analysis of Progression-Free Survival Rate at Month 24



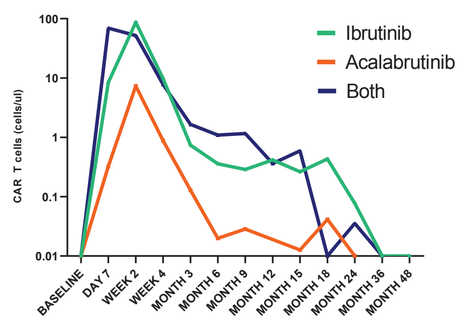
Progression-Free Survival for ZUMA-2 patients stratified by BTKi



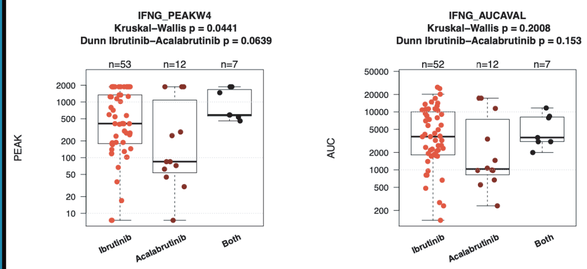
*estimated medians, NE=not estimable

Pre-treatment with Ibrutinib results in elevated CAR T cell peak expansion, toxicity, and serum inflammatory cytokines relative to acalabrutinib

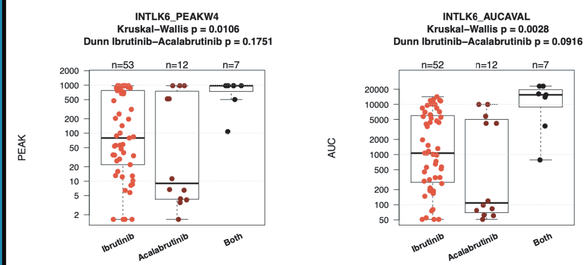
CAR-T cells in blood over time



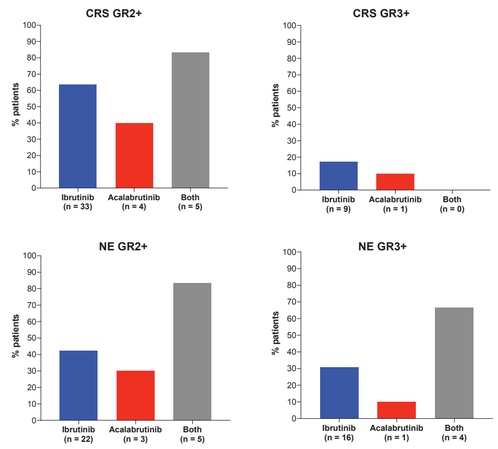
Serum peak and AUC IFNg levels stratified by BTKi use



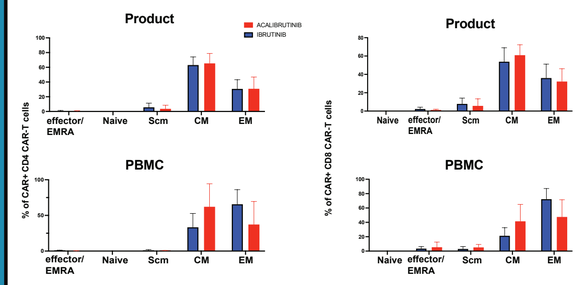
Serum peak and AUC IL6 levels stratified by BTKi use



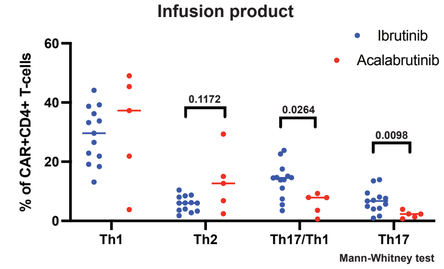
CRS and neurologic events stratified by BTKi use



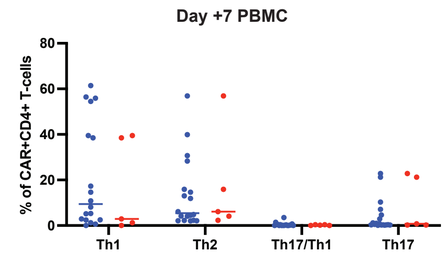
Ibrutinib exposure promotes an effector memory (EM) shift and a more pronounced inflammatory phenotype in pre- and post-infusion CAR T cells relative to Acalbrutinib



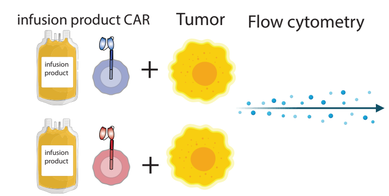
Infusion product



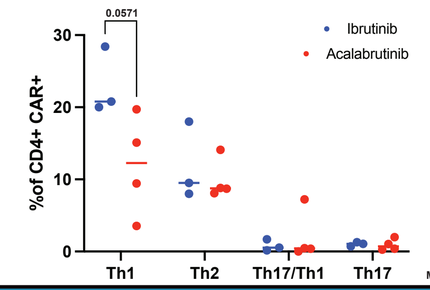
Day +7 PBMC



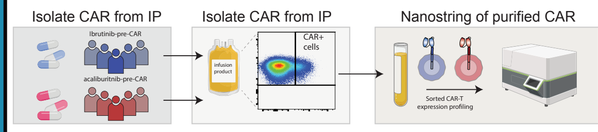
IP stimulation with CD19+tumor x 7 days



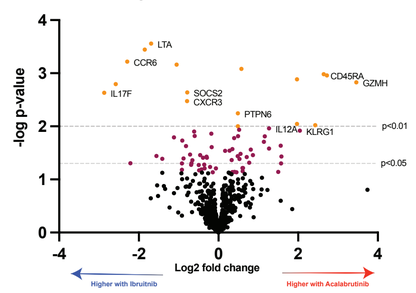
CAR T product at day 7 post stim

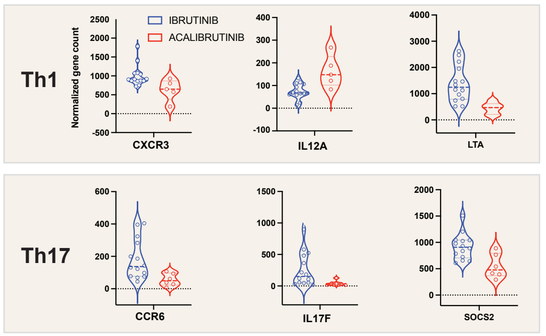


Infusion product CAR-T cells express higher levels of Th17-related genes after ibrutinib pretreatment relative to acalabrutinib.

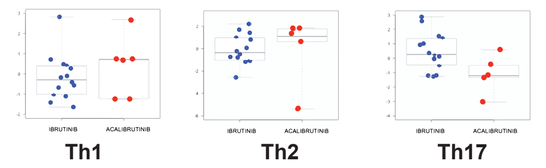


Differential expression Acalibrutinib vs Ibrutinib





Pathway Score



Conclusions

In summary, relative to patients pretreated with acalabrutinib, MCL patients treated on ZUMA-2 who were pre-treated with ibrutinib prior to CAR-T cell therapy have:

1) Prolonged PFS
2) Increased peak CAR T cell expansion and peripheral Th-1-type cytokines
3) Trends towards increased rates of CRS and neurotoxicity
4) A predominant inflammatory phenotype in baseline and activated infusion product
5) CAR T cells with a Th17-enriched gene expression profile

This work is exploratory and further highlights the importance of the modulatory effects of pharmacologic therapy proximal to apheresis amd suggests upfront exposure to ibrutinib may increase CAR T cell effector function.

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