Phase 2 Study of Acalabrutinib Window Prior to Frontline Therapy in Untreated Aggressive B-cell Lymphoma

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Background

- DLBCL is molecularly diverse; subsets are addicted to chronic active B-cell receptor (BCR) signaling
- Ibrutinib targets chronic active BCR signaling by inhibiting BTK and may improve outcomes in genetic subtypes of DLBCL, but has toxicity
- Acalabrutinib is a selective BTK inhibitor that can be safely added to R-chemotherapy but the profile of Acala-responsive tumors is unknown
- Circulating tumor DNA is a non-invasive method for genotyping tumors and determining early response to therapy, and can be quantified with extremely high sensitivity using PhasED-Seq technology.
- We are investigating the molecular correlates of acalabrutinib response with acalabrutinib as monotherapy in a 14 day window prior to R-chemo

Methods

Inclusion & Exclusion Criteria

- Untreated aggressive B-cell lymphomas: DLBCL and HGBL
- Age ≥18, stage II-IV
- All molecular subtypes of DLBCL allowed except PMBL
- All ages and any HIV status allowed
- Concomitant indolent lymphoma allowed
- CNS involvement excluded

Study Endpoints:

Accrual goal:
- 100 patients

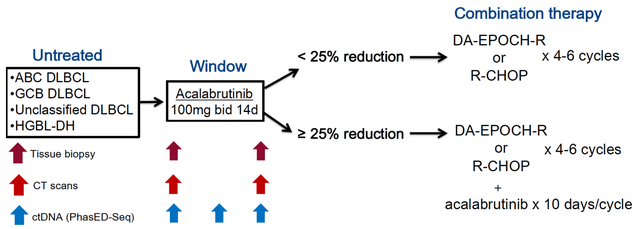
Primary:
- Response Rate to Acalabrutinib x 14 days in untreated DLBCL and HGBL

Secondary:
- Molecular profile of acalabrutinib-responsive tumors
- Safety of combination therapy
- EFS and OS

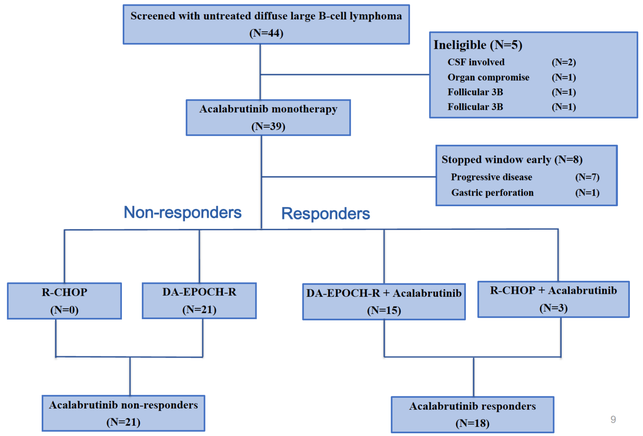
Exploratory:
- Identify a mutational signature associated with response to acalabrutinib
- Ability to genotype DLBCL from ctDNA*
- Explore prognostic role of early ctDNA dynamics*
- Rate of MRD negativity after combination*

*ctDNA levels were quantified using PhasED-Seq (Foresight Diagnostics Inc.) to track phased variants.

Methods

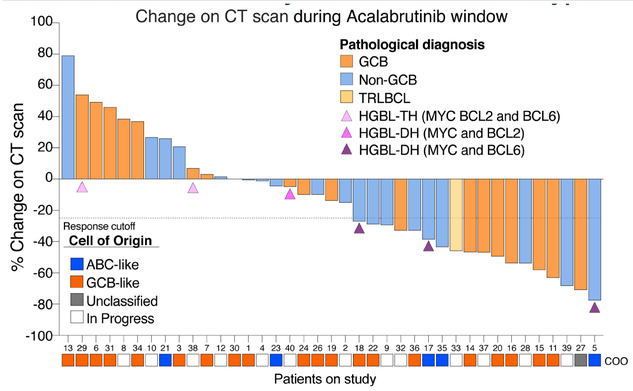


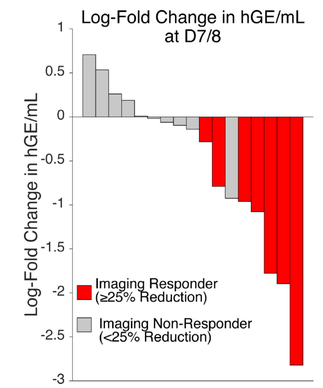
Results

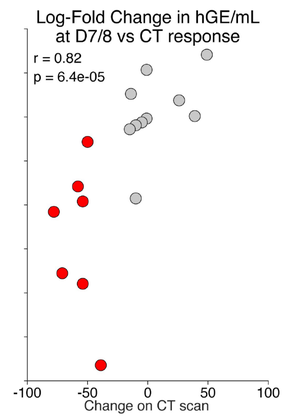


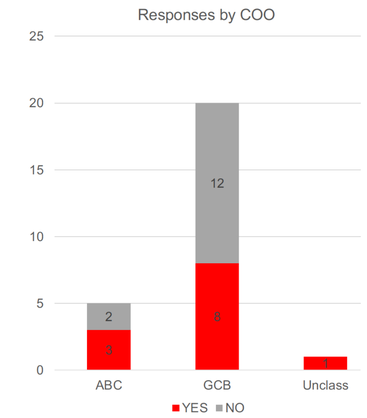
	N (%)
Number of patients enrolled	39
Male sex	23 (59%)
Age	
Median age (range) - yr	64 (28-85)
< 60 years	13 (33%)
60-69 years	17 (44%)
≥ 70 years	9 (23%)
HIV positive	3 (8%)
International Prognostic Index	
0-1 (low-risk)	10 (26%)
2 (low-intermediate risk)	9 (23%)
3 (high-intermediate risk)	13 (33%)
4-5 (high risk)	7 (18%)
Diagnosis to treatment – median (range), days	23 (4-53)
DLBCL subtype (Hans)	33 (85%)
Non-GCB	16 (48%)
GCB	16 (48%)
T-cell/histocyte rich	1 (2%)
HGBL with MYC and/or BCL2 or BCL6	6 (15%)
MYC and BCL6	3 (8%)
MYC and BCL2 and BCL6	2 (5%)
MYC and BCL2	1 (5%)
DLBCL subtype (RNA sequencing) – (N=26)	
GCB	20 (77%)
ABC	5 (19%)
Unclassified	1 (4%)

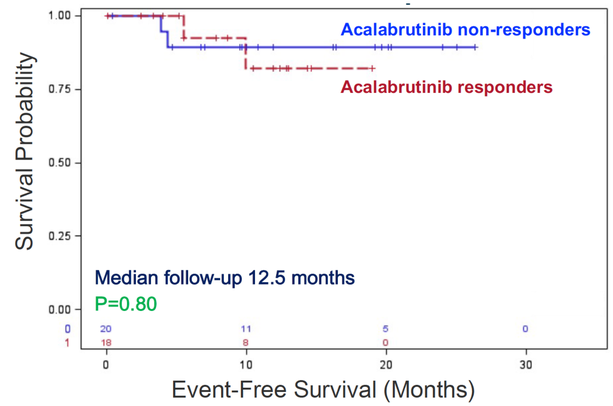
Results

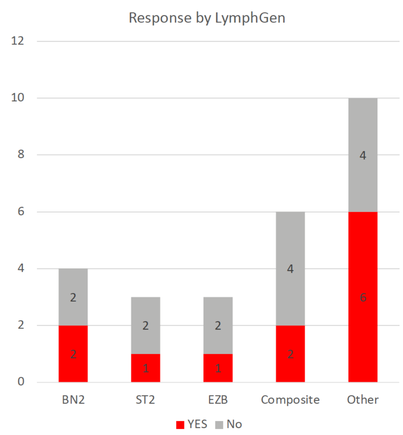












Conclusions

- Acalabrutinib has activity across genetic subtypes in the frontline setting
- 10 days of acalabrutinib is safe and effective with R-chemotherapy; accrual continues to this study
- Early ctDNA dynamics correlate with CT response,
- Genetic analysis of acalabrutinib-responsive tumors is ongoing and may reveal novel oncogenic mechanisms