FACT SHEET

THE ASPEN TRIAL (NCT03053440) – A PIVOTAL PHASE 3 HEAD-TO-HEAD TRIAL OF THE BTK INHIBITORS ZANUBRUTINIB AND IBRUTINIB IN WALDENSTRÖM'S MACROGLOBULINEMIA (WM)

ABOUT THE TRIAL[i,ii]

The ASPEN trial is a pivotal Phase 3 randomized, open-label, multicenter study evaluating zanubrutinib compared to ibrutinib in patients with relapsed/refractory or treatment-naïve patients with Waldenström's macroglobulinemia (WM). It was the first randomized Phase 3 study comparing two Bruton's tyrosine kinase (BTK) inhibitors in any indication and is the largest prospective randomized Phase 3 study in WM.

TRIAL DESIGN[ii]

<table>
<tr><th colspan="4">COHORT 1
201 PATIENTS WITH MYD88 MUTATION</th><th>COHORT 2
28 PATIENTS WITH MYD88 WILD-TYPE OR MUTATION UNKNOWN</th></tr>
<tr><td colspan="2">ARM A:
102 patients, randomized to receive zanubrutinib 160 mg twice daily</td><td colspan="2">ARM B:
99 patients, randomized to receive ibrutinib 420 mg once daily</td><td rowspan="2">ARM C:
non-randomized, all patients to receive zanubrutinib 160 mg twice daily; previous trials showed poor responses to ibrutinib therapy for patients with these mutations</td></tr>
<tr><td>83
relapsed/ refractory patients</td><td>19
treatment naïve patients</td><td>81
relapsed/ refractory patients</td><td>18
treatment naïve patients</td></tr>
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- Randomized, open-label, Phase 3 trial comparing the highly selective next generation BTK inhibitor zanubrutinib and first-generation BTK inhibitor ibrutinib in patients with WM who required treatment according to consensus criteria.[i]
- 1:1 assignment of patients with $MYD88^{L265P}$ disease to receive either ibrutinib at the approved dose of 420 mg once daily or zanubrutinib 160 mg twice daily in 28-day cycles until progression or intolerance (cohort 1).[i]
- Stratified randomization by $CXCR4^{WHIM}$ (CXCR = chemokine receptor type 4; WHIM = Warts, Hypogammaglobulinemia, Immunodeficiency and Myelokathexis syndrome) mutation status and number of prior lines of therapy.[i]
- Exploratory cohort 2 included patients with MYD88 wild-type (MYD88WT) or with undetermined MYD88 mutation status. They received zanubrutinib in a third non-randomized arm.[i]
- Allowed treatment interruption for ≤ 2 consecutive cycles and ≤ 2 dose reductions to treat recurrent grade 3/4 treatment-related toxicities.[i]
- No crossover was allowed for progression or due to intolerance in cohort 1.[i]

- A total of 211 patients were enrolled from research sites in Australia, Europe and the United States.[i]

Primary Efficacy Endpoint: Proportion of participants achieving either a complete response (CR) or a very good partial response (VGPR) in Cohort 1 per response criteria updated at the 6th International Workshop on WM (IWWM-6) as assessed by an independent review committee.[i]
Key secondary endpoints: major response rate (MRR), progression-free survival (PFS), duration of response (DOR), disease burden and safety, overall survival (OS) and quality of life (QoL).[i]

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[i] Tam CS, et al. ASPEN: Results of a Phase 3 Randomized Trial of Zanubrutinib versus Ibrutinib for Patients with Waldenström Macroglobulinemia (WM). Presented at the American Society of Clinical Oncology, May 2020.
[ii] Tam CS, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. October 2020. 136(18): 2038-2050.