HERCULES: a 3-arm noninferiority trial in advanced, HER2-positive cancers of the stomach and gastroesophageal junction

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- We had practical and ethical reservations regarding conducting a trial in a country with relatively low disease burden.
- Due to limited global access to trastuzumab treatment, we believed that HER-Vaxx held great potential from a global oncology perspective.

Where we were; where we are

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Where we are: our concerns led us to reformulate our trial as a non-inferiority trial comparing HER-Vaxx plus chemotherapy and trastuzumab plus chemotherapy.

- Dubious constancy assumption in the pivotal ToGA trial (2010) $\implies$ 3-arm non-inferiority design.
- Needed more participants and unethical to enroll a "chemotherapy only" arm in a U.S. trial $\implies$ relocated to China where disease burden is high and access to anti-HER2 therapy is limited.

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- Our mission: in order for HER-Vaxx plus chemotherapy to be non-inferior to trastuzumab plus chemotherapy it must (a) be superior to chemotherapy alone and (b) retain a clinically-relevant proportion of trastuzumab's effect.

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- Equivalent to testing $H_0^{NI} : H_0^{AS} \cup H_0^{RE}$ versus $H_a^{NI} : H_a^{AS} \cap H_a^{RE}$ $\implies$ testing sub-hypotheses at level α ensures global hypothesis is level α.

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- Trastuzumab treatment for confirmed HER2-positive breast cancer is 10-50% in China, likely lower for gastric cancers.
- Neighboring countries in East Asian countries – Mongolia, Bhutan – the highest gastric cancer ASRs in the world but virtually no centralized cancer care.

HER-Vaxx in resource-limited settings

- Cost
  - Inflation-adjusted cost of adding trastuzumab treatment to SoC in East Asia is $> \$23,000$ per patient (Shiroiwa 2011).
  - Cost of peptide vaccines are as low as $\$5 - \$10$/dose. 10-dose HER-Vaxx regimen could yield 10s-100s-fold savings.

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- Potentially enhanced mechanism of action
  - Multi-epitope formulation may offer more complete blockade of HER2 pathway, delaying progression/resistance/recurrence.
  - HER-Vaxx may extend survival *post*-progression.

Backup slides

Key trials we reference

- ToGA (2010): compared addition of trastuzumab to chemo for HER2-positive gastric/GEJ cancers. Participants not excluded on basis of HER2 expression level. Randomized 600 patients over 3 yrs. Addition of trastuzumab produced a 2.7 month improvement in OS, but benefit was restricted to the ICH3+/ICH2+ & FISH+ subgroup (4.2 month increase in OS, HR=0.65).
- JACOB (2018): compared addition of pertuzumab (another anti-HER2 mAb) to trastuzumab & chemo in advanced ICH3+/ICH2+ & FISH+ gastric/GEJ cancers. Randomized 800 participants over 2.5 year period between (2013-2016). Addition of pertuzumab led to non-significant 3.3 mo. increase in OS (p=0.057).
- EVIDENCE (2021): open-label registry trial to assess real-world treatment patterns, safety, and efficacy of trastuzumab for gastric cancer in China. Enrolled 1600 participants over 2.75-year span (2013-2016). Trastuzumab treatment was associated with better propensity-score matched survival outcomes & better tumor responses.

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2. Assay sensitivity is now testable.

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   - Interim testing and stopping procedures developed by Ochiai *et al.* 2017

Justifying NI margin

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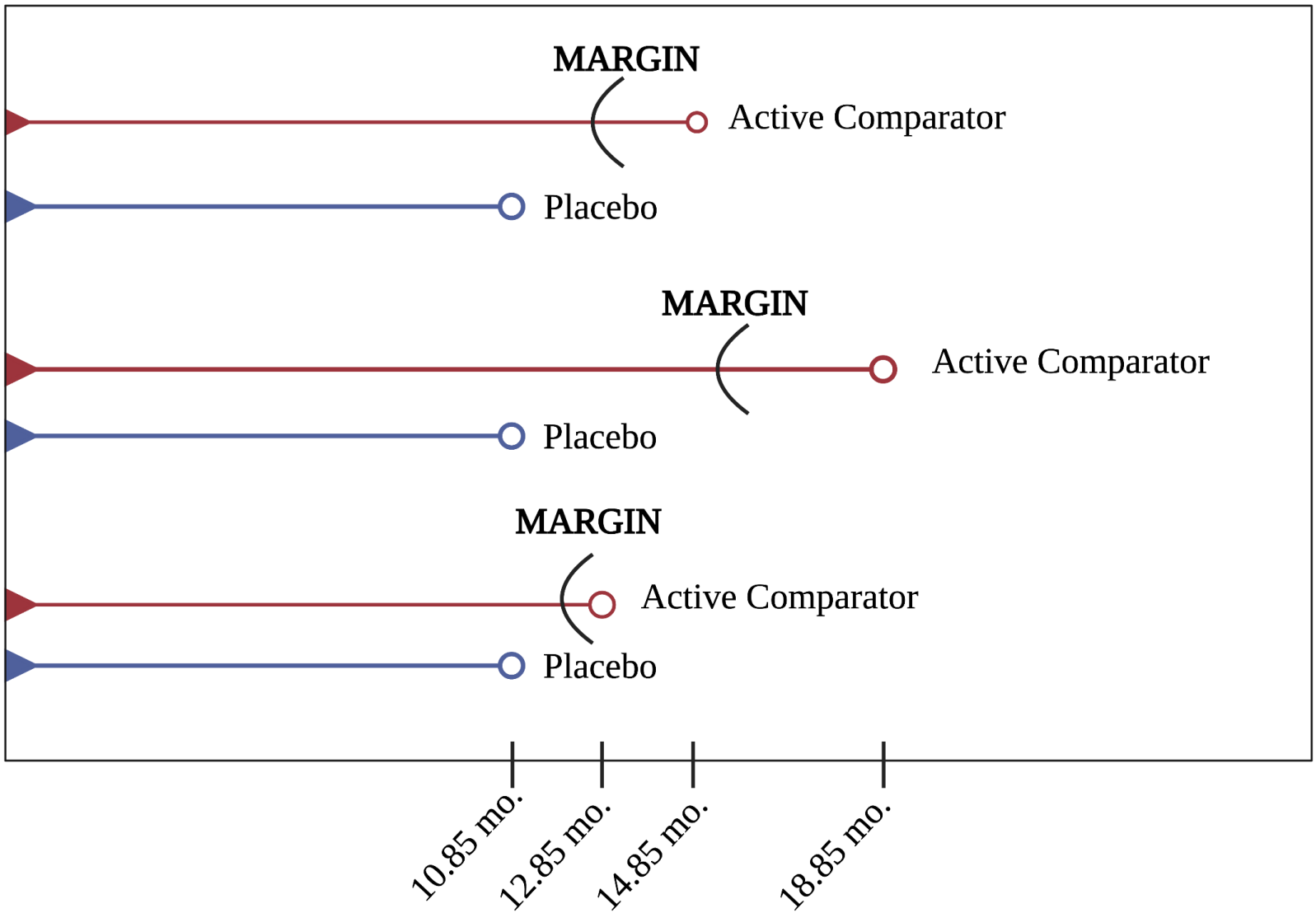
2. If HER-Vaxx was to *replace trastuzumab* in clinical care, one would need to demonstrate that HER-Vaxx is non-inferior in *months survived* (fixed margin). As a first step, we hope HER-Vaxx will *replace chemotherapy alone* and retain a substantial fraction of trastuzumab's effect (fraction margin).
   - 2.1 If HER-Vaxx is shown non-inferior in this trial, we may conduct a second non-inferiority trial with a fixed margin for non-inferiority.

Justifying NI margin



Interim Monitoring

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We propose using the DF-A stopping rule (Ochiai *et al.* 2017) for interim testing of $H_0 : H_0^{a.s.} \cup H_0^{r.e.}$. Assay sensitivity hypothesis $H_0^{a.s.}$ tested first, then tests retention of effect $H_0^{r.e.}$ once assay sensitivity is demonstrated. Multiplicity adjustment using O'Brien-Fleming boundary.

AMENDMENT: we propose a single sample size recalculation at 50% information using conditional power calculation based on CHW statistics as described by Ochiai *et al.* (2017).