The risk of recurrence/death in the experimental group minus ANA.

Results

Method

The key requirements to perform an NNT analysis are:

- Comparable inclusion and exclusion criteria between the trials.
- Similar follow-up duration between the trials (for measuring OS).
- The efficacy data must be presented in absolute terms (as NNT cannot be calculated directly from hazard ratios).

Study Population

- Trial populations were similar:
  - BIG-1/8 included HR+ only (99.9% were HR+).
  - ATAC included both HR+ and HR- unknown patients.
  - Median age and the number of women with tumors >2 cm, node positive disease, and prior chemotherapy use was similar across the studies.
  - Overall survival data for ANA from ATAC (median follow-up: 68 months) and for LET from BIG-1/8 (median follow-up: 36 months, censored analysis) was used in this analysis.1 This allowed for similar follow-up duration times between the two trials (OS data for ANA from ATAC was similar at a median follow-up of 48 and 100 months).1,1
  - At the 26 month reporting of BIG-1/8, the improvement in disease free survival (DFS) led to unblinding of the monotherapy arms; patients on TAM could crossover to LET.
  - The intent to treat (ITT) analysis reported a relative improvement in OS despite the crossover of 23% of women in the TAM arm to LET; with a 13% reduction in risk of death (HR=0.87, 95% CI 0.75-1.02).

The censored analysis was used for comparison. This includes those patients who remained on the assigned treatment and did not crossover to LET from TAM once the TAM arm was unblinded. The censored analysis reported an improvement in OS with a 9% reduction in risk of death (HR=0.91, 95% CI 0.88-0.96).

The crossover trial was blinded. A 3% risk reduction in death was reported in patients treated with ANA in ATAC at 68 and 100 months follow-up, respectively (HR=0.97, 95% CI 0.93-1.01).1

Discussion

- The ATAC and BIG-1/8 trials were similar enough to allow an NNT analysis of the early distant recurrence and OS data for ANA and LET, respectively.
- The NNT required to avoid an early distant recurrence was substantially lower with LET compared to ANA.
- Fewer patients needed to be treated with LET in place of TAM to avoid one early distant recurrence, 100 versus 303, representing a 3 fold difference.
- The NNT required to avoid one death was lower with LET compared to ANA.
- Fewer patients needed to be treated with LET than ANA in place of TAM to avoid one death, 43 vs. 161, respectively, representing a 2.5 fold difference.
- This could be due to the significant reduction in early distant recurrence observed with LET in BIG-1/8, which then may translate into improved OS.

The analysis compares data across two trials, ATAC and BIG-1/8. Differences in trial populations and the time points for measuring early distant recurrences and OS between ANA and LET may impact these findings.

- Use of the censored analysis for BIG-1/8 may also bias the results used for the NNT calculation due to the number of patients crossing over from TAM to LET.
- However, the net absolute difference for each trial was relative to a common comparator (i.e., TAM), which should minimize bias.
- In the absence of direct comparison trials of ANA and LET, this data needs to be interpreted with caution as the differences observed could be due to differences in the trial population, extent of disease, and/or true differences in efficacy.

Conclusions

- The current analysis suggests, given different trial populations and study designs that letrozole may more effectively improve survival than anastrozole.
- The early significant reductions in distant metastases observed with letrozole could be responsible for larger improvement in overall survival with a NNT of 43 to save one additional life when compared to tamoxifen in contrast to the NNT of 161 with anastrozole.
- Ongoing trials (i.e. FACE, MA.27) comparing aromatase inhibitors directly will help us to better understand these potential differences.

References