Standardized Definitions for Efficacy End Points (STEEP, STEEP2) in the CCTG MA.32 randomized breast cancer trial of metformin versus placebo: Implications of the type of recurrence and new non-breast cancer primary on outcome assessment

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INTRODUCTION

- STEEP criteria were developed to standardize interpretation of adjuvant breast cancer (BC) clinical trial outcomes.
- Invasive disease–free survival (IDFS), defined as time from randomization to the earliest occurrence of invasive local, regional, or distant recurrence, new primary invasive cancers (breast or non-breast), and death due to any cause, was initially recommended as a preferred optimal outcome in STEEP [1].
- Non-breast primary cancers were excluded in Invasive BC-Free Survival (IBCFS) in STEEP 2 [2].

OBJECTIVE

To examine these STEEP outcomes, as well as Distant Recurrence-Free Survival (DRFS), BC Specific Survival (BCSS) and Overall Survival (OS) in CCTG MA.32.

METHODS

- MA.32 (NCT01101438) evaluated the efficacy of metformin versus placebo among 3,649 non-diabetic women with high-risk early BC enrolled between 2010 and 2013.
- The previously reported analysis of the primary outcome measure (IDFS) and OS showed no metformin benefit on hormone receptor positive or negative BC (any HER2) but suggested a beneficial effect in HER2+ BC [3]
- We summarized individual components of IDFS across BC subtypes– luminal (ER/PR+, HER2-), triple negative (TN; ER/PR/HER2-), HER2+ (any ER/PR) and analyzed treatment effect (metformin versus placebo) on IDFS, IBCFS, DRFS, BCSS and OS to determine whether conclusions regarding treatment efficacy differed by endpoint selection.
- Statistical methods included Cox regression models and log rank tests.
- All analyses were two-sided and statistical significance was defined at the p=0.05 level.

RESULTS

- In the overall population, 710 patients experienced an invasive cancer event:
  - - 127 (17.9%) patients experienced local/regional events
  - **- The majority of recurrences were distant:** Luminal 55.8%, TN 47.5%, HER2+ 54.5%
  - - The minority of recurrences were new non-breast primary cancers: Luminal 20.4%, TN 15.2%, HER2+ 20.2%
- Within each BC subtype, there was little variation in the hazard ratios (HRs) comparing metformin to placebo and no difference in statistical significance across outcomes (IDFS, IBCFS, DRFS, BSCC, OS).
- The types of events and HRs for efficacy endpoints of interest are summarized by subtype in Table 1.

Table 1. Metformin efficacy by outcome measure

Subtype	Median follow-up, months	IDFS	IBCFS	DRFS	BCSS	OS
		HR (95% CI), p-value				
Luminal n=2104	96.2	1.05 (0.87-1.28), p=0.61	1.03 (0.84-1.25), p=0.81	1.05 (0.84-1.31), p=0.69	1.09 (0.81-1.48), p=0.57	1.13 (0.87-1.47), p=0.37
TN n=925	94.5	1.18 (0.90-1.56), p=0.24	1.09 (0.81-1.47), p=0.58	1.07 (0.78-1.48), p=0.67	0.99 (0.68-1.44), p=0.95	1.08 (0.76-1.52), p=0.68
HER2+ n=620	95.2	0.64 (0.43-0.95), p=0.03	0.56 (0.36-0.80), p=0.013	0.55 (0.34-0.88), p=0.01	0.57 (0.29-1.07), p=0.08	0.54 (0.30-0.99), p=0.04

Legend: IDFS= Invasive Disease-Free Survival; IBCFS= Invasive Breast Cancer-Free Survival; DRFS= Distant Recurrence-Free Survival; BCSS= Breast Cancer Specific Survival; OS= Overall Survival.

CONCLUSIONS

- MA.32 enrolled patients with high-risk breast cancer, resulting in a predominance of distant breast cancer recurrences.
- All endpoints provided similar information regarding metformin efficacy across BC subtypes.
- This was regardless of whether metformin was ineffective (luminal, TN) or showed potential efficacy (HER2+).

REFERENCES

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