Adding metformin to androgen deprivation therapy (ADT) for patients (pts) with metastatic hormone sensitive prostate cancer (mHSPC): Overall survival (OS) results from the multi-arm, multi-stage randomised platform trial STAMPEDE

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Background

Metformin is a widely used, well tolerated anti-diabetic agent. Several studies suggest metformin has anti-cancer activity in different malignancies, including prostate cancer. We hypothesised that metformin also reduces the development of ADT-induced metabolic adverse effects, possibly improving OS via these mechanisms.

Methods

Non-diabetic pts with mHSPC were randomly allocated 1:1 to standard of care (SOC) or SOC+metformin within STAMPEDE. SOC included ADT ± radiotherapy ± docetaxel ± androgen receptor pathway inhibitor (ARPI). The primary outcome was OS. Target hazard ratio (HR) 0.8 (92% power, 2.5% 1-sided significance). 7 subgroup analyses were pre-specified but not pre-powered.

Results

1874 pts with mHSPC were randomised Sep2016-Mar2023. Arms were well balanced: median age 69 years, IQR 63-73; median PSA 84ng/ml, IQR 24-352; de novo 1758 (94%) vs relapsed 116 (6%). Planned SOC included 82% Docetaxel and 3% ARPI. After a median follow-up of 60 months, the HR for OS between arms was 0.91 (p=0.148; 95% CI 0.80-1.03). The median (95%CI) OS was 63 (58-69) and 69 (63-73) months in the SOC and SOC+metformin arms respectively. In patients with high versus low volume disease (CHAARTED def), HR was 0.79 (p=0.006; 0.66-0.93) and 1.0 (p=0.992; 0.79-1.26) respectively. The interaction p-value = 0.086.

For progression-free survival: Overall HR was 0.92 (p=0.164; 0.81-1.04) with HRs of 0.76 (p=0.001; 0.64-0.89) and 1.10 (p=0.401; 0.88-1.37) in the high and low volume subgroups respectively, interaction p-value = 0.006.

Metabolic parameters that improved significantly with metformin included reduced weight gain, fasting glucose, HbA1c and total and LDL cholesterol. Fewer patients developed a metabolic syndrome.

Adverse events (AE) ≥grade 3 were reported in 52% and 57% in the SOC and SOC+metformin arms, respectively; Gastrointestinal AEs increased with metformin.

Conclusions
Metformin does not improve survival in unselected metastatic patients but may improve cancer outcomes and survival in high volume patients. Metabolic parameters were significantly improved overall.

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