UPDATES IN PROSTATE CANCER
A REVIEW OF 2024 ASCO AND ESMO ANNUAL MEETINGS
MLS IRVINE

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF METFORMIN IN REDUCING PROGRESSION AMONG MEN ON EXPECTANT MANAGEMENT FOR LOW-RISK PROSTATE CANCER: THE MAST (METFORMIN ACTIVE SURVEILLANCE TRIAL) STUDY

Examine the effect of metformin on the rates of progression among men with low-risk localized PCa on AS

Biopsy-proven, low-risk, localized PCa diagnosed within the past 6 months, with a Gleason score of <6 observed in ≤1/3 of the total cores, less than 50% positivity in any one core, a PSA level of ≤10 ng/ml, and a clinical stage between T1c-T2a

Metformin 850 mg BID or placebo for 3 years

The earliest occurrence of primary PCa therapy (e.g., prostatectomy, radiation, hormonal therapy) or pathological progression (>1/3 of total cores involved, at least 50% of any one core involved, or Gleason pattern 4 or higher)

There was no statistically significant difference in progression-free survival (PFS) observed between patients treated with metformin and those receiving placebo (p=0.63).

Metformin does not prevent progression of low-risk prostate cancer on active surveillance

ASCO Annual meeting 2024

MANCAN2: A MULTICENTRE RANDOMISED CONTROLLED TRIAL OF SELF-HELP COGNITIVE BEHAVIOURAL THERAPY (CBT) TO MANAGE HOT FLUSH AND NIGHT SWEATS (HFNS) SYMPTOMS IN PATIENTS WITH PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION THERAPY (ADT)

MANCAN 1previously reported positive intervention for 6 weeks outcome

CBT was delivered by clinical psychologist in MANCAN1

Delivered by nurse in MANCAN2 and was designed to look into 6 month outcomes

Pt had 6 month planned ADT (+/- NHT)

Had issues with hot flashes

Group therapy session delivered by nurses who were trained by a clinical psychologist

Excercices-paced breathing, CBT strategies Spicy food, alcohol, caffeine and relaxation exercises

Pts were provided by a booklet and audio to continue work on managing hot flashes

CBT group session 2 was 4 weeks later– to review and help and reassure and continuing using these technic

ASCO 2024, Simon Crabb MD

MANCAN 2 CONT.

6 weeks data and 6 month data problem rating

Hot flashes and night sweats problem rating scale improved in 6 weeks in CBT arm but no difference in 6 month

Anxiety and depression better in 6 weeks but not 6 month

Non-Compliance- 14% in control arm vs 0% in intervention arm (P:0.006)

Can we make this more durable??

EMBARK POST HOC ANALYSIS OF IMPACT OF TREATMENT SUSPENSION (TXS) ON HEALTH-RELATED QUALITY OF LIFE (HRQOL)

EMBARK showed enzalutamide (ENZ) + leuprolide (L) and ENZ mono delayed metastasis-free survival vs placebo (P) + L while maintaining high global HRQoL in high-risk biochemically recurrent nonmetastatic hormone-sensitive prostate cancer

Treatment was suspended (TxS) at week 37 if PSA <0.2 ng/mL; reinstated if PSA rose to ≥2.0 ng/mL with radical prostatectomy (RP) or ≥5.0 ng/mL without RP

This analysis examined HRQoL after TxS

TxS, as expected, leads to clinically meaningful improvements in HRQoL

A numerical trend inHRQoL improvement after week 37 TxS was seen in all 3 arms

Post TxS, all arms reached clinically meaningful improvement in hormonal treatment side effects

No statistically significant differences were observed between arms in change from week 37 to week 205

EMBARK POST HOC ANALYSIS OF SEXUAL ACTIVITY (SA) PATIENT-REPORTED OUTCOME (PRO) MEASURES

Important for shared decision-making between physicians and patients

HRQoL was assessed at baseline and every 12 weeks until metastasis/death

Assessed effects on time to confirmed deterioration

Decline from baseline in sexual interest, activity, satisfaction, erectile function, and feeling like a man

using 5 different QOL questionnaires

Intent-to-treat principle was applied

EMBARK POST HOC ANALYSIS OF SEXUAL ACTIVITY (SA) PATIENT-REPORTED OUTCOME (PRO) MEASURES- CONT.

ENZ mono vs P + L: TTCD in interest, activity, satisfaction, and erectile function was delayed with ENZ mono

ENZ + L vs P + L: no significant differences in TTCD were observed in most categories

SA was better preserved with ENZ mono vs P + L in terms of interest, activity, satisfaction, and maintaining erection

Further, the SA PROs were similar between ENZ + L and P + L, implying there is no further SA burden when adding ENZ to androgen-deprivation therapy

EMBARK POST HOC ANALYSIS OF SEXUAL ACTIVITY (SA) PATIENT-REPORTED OUTCOMES (PROS) IN PATIENTS (PTS) WHO WERE SEXUALLY ACTIVE OR INTERESTED IN SEX AT BASELINE (BL)

To better understand effect on SA in relevant subgroups

Time to confirmed deterioration (TTCD) defined by one category change for sexual interest, activity, satisfaction, erectile function, and feeling like a man was examined

Intent-to-treat analysis was applied

Among pts interested in sex (n=694) or sexually active (n=437) at BL, TTCD in SA, interest, activity, satisfaction, and erectile function were significantly delayed with ENZ mono vs P + L.

In contrast, TTCD in erectile function was shorter with ENZ + L vs. P + L

ENZ mono better preserved SA vs P + L in terms of SA domain, interest, activity, satisfaction, and maintaining erection

Adding ENZ to L had no impact on interest, activity, or satisfaction but may adversely affect erectile function (a few days and clinically non-significant)

ESMO2024

LBA 69 PATCH + STAMPEDE

Lab 68 phase 3 ARANOTE

LBA70-phase 3 STAMPEDE ARM K mHSPC

PROSTATE CANCER EFFICACY RESULTS FROM A RANDOMISED PHASE III EVALUATION OF TRANSDERMAL OESTRADIOL **(TE2)** VERSUS LUTEINISING HORMONE RELEASING HORMONE AGONISTS (LHRHA) FOR ANDROGEN SUPPRESSION IN NON-METASTATIC (M0) PROSTATE CANCER

Open-label, randomised phase 3, **non-inferiority** (NI) comparison of LHRHa v tE2 patches.

Eligibility:

Newly diagnosed high-risk M0 [locally advanced or node positive (+)] prostate cancer

Relapsed disease with PSA≥4ng/ml and doubling in <6 months, PSA ≥20ng/ml or N+

Treatment:

standard LHRHa v tE2 100mcg/24h

Patches changed twice weekly for ≥2 years, (prostate radiotherapy and docetaxel permitted).

PROSTATE CANCER EFFICACY RESULTS FROM A RANDOMISED PHASE III EVALUATION OF TRANSDERMAL OESTRADIOL **(TE2)** VERSUS LUTEINISING HORMONE RELEASING HORMONE AGONISTS (LHRHA) FOR ANDROGEN SUPPRESSION IN NON-METASTATIC (M0) PROSTATE CANCER CONT

Primary outcome:

metastasis-free survival (MFS) (time from randomisation to metastatic disease or death from any cause)

Designed to rule out a >4% reduction in 3-year MFS (85% power, 1-sided 5% α)

Secondary outcomes:

overall survival (OS), castration rates and toxicity

PROSTATE CANCER EFFICACY RESULTS FROM A RANDOMISED PHASE III EVALUATION OF TRANSDERMAL OESTRADIOL **(TE2)** VERSUS LUTEINISING HORMONE RELEASING HORMONE AGONISTS (LHRHA) FOR ANDROGEN SUPPRESSION IN NON-METASTATIC (M0) PROSTATE CANCER CONT.

Results:

1360 men, [639 LHRHa, 721 tE2 (randomisation ratio 1:2 then 1:1)]

Subjects recruited from PATCH (NCT00303784, n=1082) and STAMPEDE (NCT00268476, n=278) trial sites between 2007-2022

Baseline characteristics were well-balanced between randomised groups

LHRHa 3-year MFS 86% (giving a target NI hazard ratio (HR) of 1.31)

tE2 3-year MFS 87% HR 0.96 (95% CI 0.81-1.14) in favour of tE2, excluding a 2% reduction in MFS

OS HR 0.89 (CI 0.74-1.07) in favour of tE2

PROSTATE CANCER EFFICACY RESULTS FROM A RANDOMISED PHASE III EVALUATION OF TRANSDERMAL OESTRADIOL **(TE2)** VERSUS LUTEINISING HORMONE RELEASING HORMONE AGONISTS (LHRHA) FOR ANDROGEN SUPPRESSION IN NON-METASTATIC (M0) PROSTATE CANCER CONT.

Prostate cancer, CVS and 2nd malignancy deaths similar between randomized groups

overall Quality of Life scores Mean difference in 6-month overall score +4.2 (1.2, 7.1) in favour of tE2 (p=0.006)

Improved Bone Mineral density over 2 years

Sustained castration rates (testosterone ≤1.7nmol/L over 1 year (n=1066), with tE2 use confirmed as oestradiol ≥250 pmol/L, 85% both groups

LHRHa v tE2 any grade:

Gynaecomastia 42% v 85%

Hot flushes 89% v 44%

PROSTATE CANCER EFFICACY RESULTS FROM A RANDOMISED PHASE III EVALUATION OF TRANSDERMAL OESTRADIOL **(TE2)** VERSUS LUTEINISING HORMONE RELEASING HORMONE AGONISTS (LHRHA) FOR ANDROGEN SUPPRESSION IN NON-METASTATIC (M0) PROSTATE CANCER CONT.

Conclusion:

Prostate cancer outcomes and overall survival are non-inferior when tE2 is used to commence androgen suppression

tE2 provides men with choices about the expected side-effect profile and route of administration

These data complement those showing improved metabolic parameters and overall QL scores with tE2 v LHRHa

This approach should be considered a standard of care

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

Several studies suggest metformin has anti-cancer activity in different malignancies, including prostate cancer.

? If Metformin could also reduce 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

LBA70 - **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

Results

1874 pts with mHSPC were randomised Sep2016-Mar2023

Arms were well balanced: median age 69 years, median PSA 84ng/ml, de novo 1758 (94%) vs relapsed 116 (6%)

Planned SOC included 82% Docetaxel and 3% ARPI

After a median follow-up of 60 months

HR for OS between arms was 0.91 (p=0.148; 95% CI 0.80-1.03).

The median OS was 63 and 69 months in the SOC and SOC+metformin arms

In patients with **high** versus low volume disease **HR was 0.79** (p=0.006; 0.66-0.93) and 1.0 (p=0.992; 0.79-1.26)

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 CONT.

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.

ESMO 2024

LBA68 - EFFICACY AND SAFETY OF DAROLUTAMIDE PLUS ANDROGEN-DEPRIVATION THERAPY (ADT) IN PATIENTS WITH METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC) FROM THE PHASE III ARANOTE TRIAL-

The phase 3 global ARANOTE trial compared DARO + ADT vs ADT in pts with mHSPC

Methods

Eligible pts had mHSPC by conventional imaging

ECOG performance status of 0–2

Started ADT ≤12 weeks

Randomized 2:1 to DARO 600 mg twice daily or placebo (PBO), each with ADT

Primary endpoint: Radiological progression-free survival (rPFS)

Secondary endpoints: OS, time to initiation of subsequent anticancer therapy, time to castration-resistant prostate cancer (CRPC), time to prostate-specific antigen (PSA) progression, time to pain progression, and safety.

ARANOTE CONT.

Results

A total of 669 patients were randomized (DARO, N=446; PBO, N=223)

Median age was 70 y

31% were Asian, 9.7% were Black

Median PSA at baseline was 21.3 ng/mL

71% had high-volume mHSPC

DARO + ADT significantly improved rPFS vs PBO + ADT (HR 0.54; 95% CI 0.41–0.71; P<0.0001) with consistent benefits observed across prespecified subgroups, including patients with high- and low-volume mHSPC

DARO was associated with a positive trend for OS (HR 0.81; 95% CI,0.59–1.12) and clinical benefits across all secondary efficacy endpoints

Improved time to CRPC (HR 0.40; 95% CI, 0.32–0.51), time to PSA progression (HR 0.31; 95% CI 0.23–0.41), time to subsequent therapy (HR 0.40; 95% CI, 0.29–0.56), and time to pain progression (HR 0.72; 95% CI, 0.54–0.96).

Incidences of TEAEs were low and similar between groups

Treatment discontinuations due to TEAEs were lower in patients receiving DARO vs PBO (6.1% vs 9.0%).

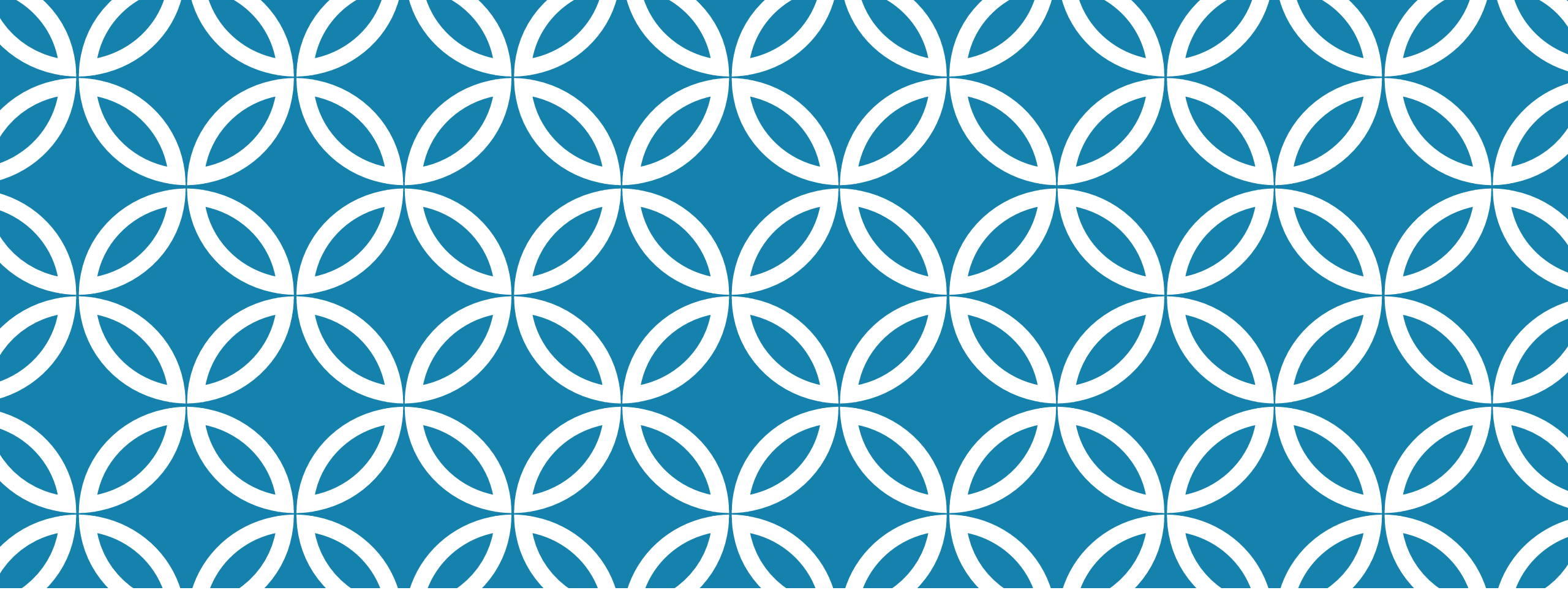
ESMO 2024 -Presenter Fred Saad MD

ARANOTE CONCLUSION

ARANOTE confirms the strong efficacy and favorable tolerability of DARO in mHSPC.

ARASENS and ARANOTE demonstrate the benefit of DARO with and without chemotherapy

Providing the option to tailor treatment, and allowing patients to live longer without progression and with minimal treatment burden



THANK YOU!

Questions?