Number Needed to Harm (NNH) in metastatic hormone-sensitive prostate cancer (mHSPC) – darolutamide (Daro), apalutamide (Apa) and enzalutamide (Enza) clinical trials

Daniel J. George, M.D[1]; Yen Yen Yip, MBA[2]; Shankar Srinivasan, PhD[3]; Alexander J. Upton, MSc[3]

1 – Duke Cancer Center - Durham, NC, USA; 2 – Bayer Healthcare Pharmaceuticals, Mississauga, Canada; 3 – Bayer Healthcare Pharmaceuticals, Whippany, NJ, USA

BACKGROUND

- Androgen receptor pathway inhibitors (ARPIs) in combination with androgen deprivation therapy (ADT) ± docetaxel have demonstrated benefit in non-metastatic castration-resistant prostate cancer (nmCRPC) and mHSPC.[1-6]
- Current evidence suggests that ARPIs have different adverse events (AE) risk profiles.[7]
- Number needed to harm (NNH) is a trial-based measure that estimates the number of patients needed to be treated before a harmful outcome occurs with the intervention, versus the control arm.
  - A higher NNH reflects a lower incremental likelihood of harm vs. the control arm. A NNH of 5 means for every 5 people exposed to a treatment, one additional adverse event is expected (compared to the control arm), over the time horizon of the study.
  - A negative NNH reflects a higher incremental risk of harm in the control arm, i.e. when the AE rate is higher with the control vs. intervention. Smaller negative NNH are generated when the control has a much higher AE rate than the intervention.
- Past NNH analyses in nmCRPC have shown a trend of higher (more favourable) NNH for daro (ARAMIS) versus apa (SPARTAN) and enza (PROSPER).[8,9]
- With the recent report of the Phase III ARANOTE trial, where daro + ADT significantly reduced the risk of radiological progression or death, a similar NNH analysis in mHSPC is possible.[1]
- Contextualizing AE risks through NNH analyses can help inform treatment choices.

OBJECTIVES

- To calculate NNH statistics for daro (ARANOTE), apa (TITAN) and enza (ARCHES) for patients with mHSPC .
- To extrapolate NNH results to a hypothetical mHSPC population of 50,000 patients.

METHODS

Study data

- MEDLINE and EMBASE were searched for relevant randomized controlled trials (RCTs).
- ARANOTE (daro), TITAN (apa), and ARCHES (enza) were Phase III RCTs which reported AEs of interest that could be compared between ARPIs and placebo.[1-3]
- Other Phase III ARPI trials in mHSPC were identified but not included in the analysis due to heterogeneity in comparators (ARASENS, PEACE-I, ENZAMET) or populations (LATITUDE, STAMPEDE).[10-14]
- AEs of interest in ARPIs or occurring in ≥5% of either trial arm were extracted from ARANOTE, TITAN and ARCHES primary analysis publications.[1-3] ARANOTE data on file were also referenced.
- NNH by AE (all grade and grade≥3) were calculated based on reported rates, using the inverse of the absolute risk increase.

$$NNH = \frac{1}{AE\ rate\ (experimental) - AE\ rate\ (control)}$$

Exploratory analysis

- NNH may be expressed as a population-based measure, assuming trial-based AE rates to be representative of the real world.
- NNH statistics were applied to a hypothetical population of 50,000 patients to estimate the number of additional all-grade AEs versus control for each treatment.
- Where NNH was negative (higher incremental risk of harm in the control arm), it was assumed conservatively that there was no additional risk of an event.

RESULTS

- Daro showed a trend of higher NNH than apa or enza for most all-grade AEs suggesting a lower risk of incremental harm for rash, hot flash, fatigue, arthralgia, cognitive impairment, hypertension, nausea, falls, hypertension, and dizziness. (Table 1)
- NNH for all-grade anemia, constipation and grade≥3 arthralgia, fractures, bone pain, and increased weight were lower for daro.
- Due to the lower incidence of Grade ≥3 AEs across the studies, NNH statistics may be informed by low events and should be interpreted with caution.
- For daro, apa and enza, more grade≥3 AEs compared to all-grade AEs were associated with negative or equal NNH statistics.
- Rash had the lowest NNH among all-grade (NNH = 5.4 in TITAN) and grade≥3 AEs (NNH = 17.5 in TITAN).

Extrapolating results to a mHSPC population

- Table 2 shows the application of all-grade NNH statistics reported in Table 1 to a population of 50,000 mHSPC patients. Results are shown for AEs where there were differences in NNH statistics.
- The results suggest that treatment with daro could translate to 8,950 and 2,200 fewer cases of all-grade rash and all-grade hot flash respectively than apa; and 650 and 350 fewer cases of all-grade cognitive impairment and all-grade falls respectively than enza.
- Total number of additional all-grade AEs was lower for daro than apa and enza.

Limitations

- Cross-trial comparisons of NHH should be interpreted with caution due to differences in study design and patient populations.[1-3]
  - ARANOTE had a smaller patient sample size than TITAN or ARCHES.
  - Patients in ARANOTE were randomized in a 2:1 ratio, while TITAN and ARCHES followed a 1:1 randomization.
  - Baseline characteristics varied: in ARANOTE, there were more patients with high volume disease and higher median baseline PSA.
  - TITAN and ARCHES included patients who received prior docetaxel. These patients were excluded from ARANOTE.
  - In TITAN and ARCHES, subjects with a history of seizure or any condition that may predispose to seizure were excluded, whereas ARANOTE did not have this exclusion criteria.
- This analysis was based on the primary reports of the studies, which had different median follow-up times (14-25 months). Time dependency in the occurrence of AEs may affect inference.
- Prospective comparative trials are needed to confirm these findings.

Table 1. Number Needed to Harm statistics (in AEs of interest or occurring in ≥5% of patients in ARANOTE, TITAN or ARCHES)

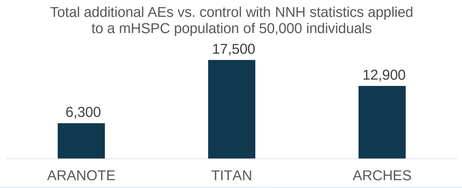
Type of AE	All grade AE			Grade≥3 AE		
	ARANOTE (Daro)	TITAN (Apa)	ARCHES (Enza)	ARANOTE (Daro)	TITAN (Apa)	ARCHES (Enza)
Rash	142.9	5.4	100.0	111.3	17.5	62.5
Hot flash	50.0	15.6	20.8	=	=	333.3
Fatigue	-40.0	33.3	23.3	-200.0	250.0	-1,000.0
Anemia	35.7	-23.3	NR	-166.7	-66.7	NR
Arthralgia	90.9	38.5	62.5	89.0	-200.0	-250.0
Cognitive impairment	90.9	NR	41.7	=	NR	142.9
Hypertension	-1,000.0	47.6	43.5	142.9	-142.9	62.5
Fractures	58.8	58.8	43.5	89.2	200.0	=
Bone pain	-20.8	-27.8	43.5	166.7	-166.7	=
Constipation	45.5	-55.6	-200.0	=	=	=
Dizziness	500.0	NR	62.5	-200.0	NR	=
Nausea	500.0	NR	71.4	=	NR	500.0
Asthenia	-142.9	-83.3	200.0	=	76.9	200.0
Falls	250.0	250.0	90.9	-200.0	=	1,000.0
Diarrhea	500.0	NR	500.0	-333.3	NR	-500.0
Seizure / convulsions	=	500	=	=	500	=
Weight increased	-333.3	-15.2	-62.5	250.0	-125.0	1,000.0
Back pain	-142.9	-50.0	-30.3	457.4	-250.0	250.0

NR: Data not reported, '=' :No Difference in rates (between experimental and control arms), Green cells denote highest NNH / higher AE risk in control / equal AE risk in control

Table 2. Estimated additional all-grade AEs vs. control with NNH statistics applied to a mHSPC population of 50,000 individuals

All-grade AE	ARANOTE (Daro)	TITAN (Apa)	ARCHES (Enza)	ARPI with lowest number of events
Rash	350	9,300	500	Daro
Hot flash	1,000	3,200	2,400	Daro
Fatigue	NEG	1,500	2,150	Daro
Anemia	1,400	NEG	NR	Apa
Arthralgia	550	1,300	800	Daro
Cognitive impairment	550	NR	1,200	Daro
Hypertension	NEG	1,050	1,150	Daro
Fractures	850	850	1,150	Daro or Apa
Bone pain	NEG	NEG	1,150	Daro or Apa
Constipation	1,100	NR	NEG	Enza
Dizziness	100	NR	800	Daro
Nausea	100	NR	700	Daro
Asthenia	NEG	NEG	250	Daro or Apa
Falls	200	200	550	Daro or Apa
Diarrhea	100	NR	100	Daro or Enza
Seizure /convulsion	=	100	=	Daro or Enza
Total additional AEs	6,300	17,500	12,900	Daro

NR: Not reported, NEG = negative, higher risk of AE in control arm; = risk of AE in experimental arm equal to control arm.



CONCLUSIONS

- **These findings support earlier NNH analyses in nmCRPC, suggesting a favorable safety profile of daro versus apa or enza.**
- **Daro was associated with higher number needed to harm for AEs such as hot flash, fatigue, and dizziness, which could affect patient quality of life, while higher number needed to harm for rash and falls may also result in lower cost burden on patients and health systems.**

REFERENCES

1. Saad F, Vjaters E, Shore N, et al. Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. J Clin Oncol. 2024:JCO2401798.
2. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-2986.
3. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.
4. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-1246.
5. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474.
6. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022;386(12):1132-1142.
7. Halabi S, Jiang S, Terasawa E, et al. Indirect Comparison of Darolutamide versus Apalutamide and Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer. J Urol. 2021;206(2):298-307.
8. George DJ, Waldeck AR, Guo H, Upton AJ. Number needed to harm (NNH) in patients with non-metastatic, castration-resistant prostate cancer (nmCRPC): A final analysis from the darolutamide (D), enzalutamide (E), and apalutamide (A) clinical trials. Journal of Clinical Oncology. 2022;40(28_suppl):326-326.
9. George DJ, Waldeck AR, Guo H, Upton AJ. Darolutamide (D), enzalutamide (E) and apalutamide (A), the risk of adverse events (AEs) in patients with non-metastatic castration-resistant prostate cancer (nmCRPC): Number needed to harm (NNH). Ann Oncol. 2020;31:S507-S549.
10. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet. 2022.
11. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022.
12. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-131.
13. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-360.
14. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017;377(4):338-351.

Disclosures

Study sponsored by Bayer Healthcare Pharmaceuticals. Daniel J. George received research funding from Bayer Healthcare Pharmaceuticals. Yen Yen Yip, Shankar Srinivasan and Alexander J. Upton are full-time employees of Bayer Healthcare Pharmaceuticals.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the authors.

Presented by Maxime Duflot. Corresponding author Alexander J. Upton (alexander.upton@bayer.com)