NEoadjuvant Apalutamide (ARN-509) and Radical Prostatectomy in Treatment of Intermediate to High Risk Prostate Cancer (NEAR) Phase II Trial

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1 Background

- Prior approach to neoadjuvant androgen deprivation for prostate cancer (PCa) did not show benefits, but these older agents were limited by:
  - Incomplete suppression of serum testosterone
  - Partial agonist activity at androgen receptor (AR)
- Newer agents like apalutamide (ARN-509) exert **near total antagonists activity at AR**
- **Apalutamide as neoadjuvant treatment before radical prostatectomy (RP) has not been studied**

2 Objectives

- **To report on the oncological and pathological outcomes and safety profile of 12 weeks of neoadjuvant Apalutamide therapy and RP**

3 Materials & Methods

- **Phase II single arm study. Clinicaltrials.gov identifier: NCT03124433**
- **Eligibility criteria:**
  - ✓ Age 21-75 years old
  - ✓ Conventional adenocarcinoma on biopsy
  - ✓ Organ confined D'Amico intermediate to high risk Pca
  - ✓ Planned for RP as primary definitive therapy
  - ✓ No known hypersensitivity to drug
  - ✓ Able to swallow study drug as whole tablets
  - ✓ Adequate liver function
- **Exclusion criteria:**
  - × Small cell, neuroendocrine or ductal differentiation on biopsy
  - × Previous pelvic irradiation or ADT use
  - × Patients on anti-epileptics or anti-psychotics
  - × Renal impairment with serum creatinine twice upper limit of normal
  - × Other malignancy within 5 years
  - × ECOG performance status 2 or poorer
- **Primary outcomes:**
  - Serum total PSA response
  - Tumour response defined by residual cancer burden (RCB)
- **Secondary outcomes:**
  - Operative complications post RP
  - Adverse events (AE) by CTCAE grading
- **Trial design**

n= 30 enrolled and completed ARN-509 240mg daily for 12 weeks

→ **n=5 did not receive radical therapy within the protocol**

n=25
- **RP performed in 4-6 weeks**
- **Follow up in 4 weeks after RP**

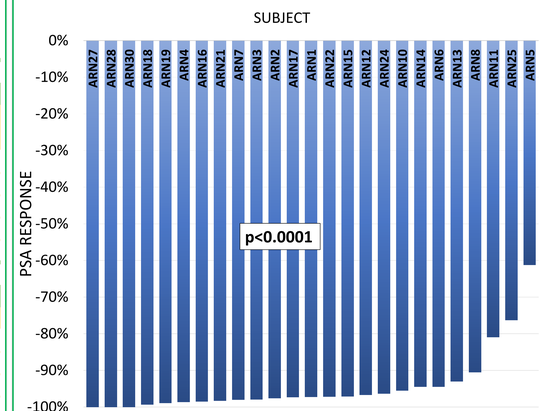
4 Results

Patient demographics	
Number of patients, n	25
Age median, years (range)	69 (55 – 75)
PSA baseline median, ng/mL (range)	11.6 (4.2 – 61.5)

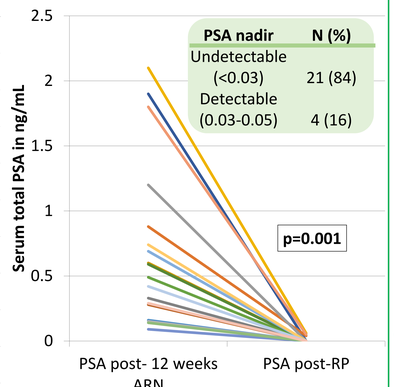
Histology ISUP Grade Group, n			
Pre-operative (biopsy)		Post-operative (wholemount)	
1	1	1	0
2	13	2	15
3	8	3	7
4	1	4	1
5	2	5	2

Clinical T-stage, n			
Pre-operative		Post-operative	
2b	19	2b	13
3a	*4*	*3a*	*10*
3b	*2*	*3b*	*2*

PSA RESPONSE FOLLOWING 12 WEEKS APALUTAMIDE



PSA TREND WITH APALUTAMIDE AND SURGERY

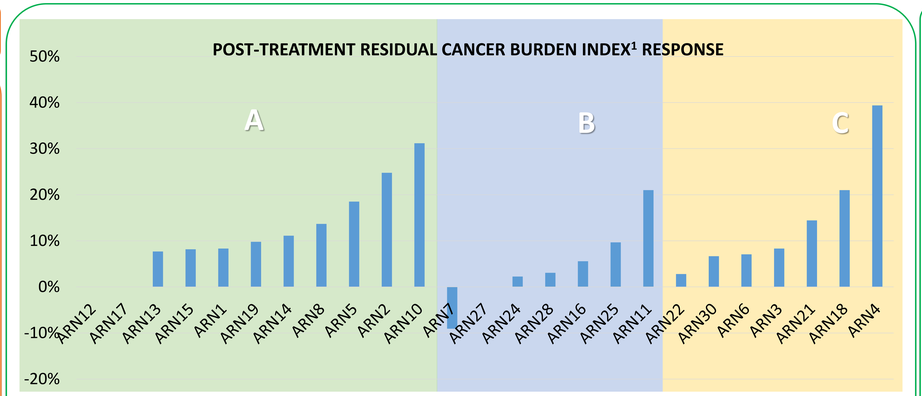


Surgical outcomes	
Estimated blood loss median, ml (range)	200 (50 – 400)
Length of stay median, days (range)	2 (1 – 6)
Catheter time median, days (range)	8 (3 – 14)
Positive surgical margin (PSM), n (%)	3 (12)

PSM locations:
- Right apex & right seminal vesicle
- Posterior right
- Posterior multiple foci
- each <1mm

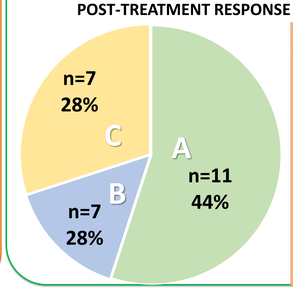
Surgical complications within 30-days		
Clavien – Dindo, n (%)		
I	3 (12)	3 fever, resolved without antibiotics
II	2 (8)	1 UTI, treated with IV antibiotics 1 left upper thigh paresthesia
III-V	0	No grade 3 & above complications

POST-TREATMENT RESIDUAL CANCER BURDEN INDEX[1] RESPONSE

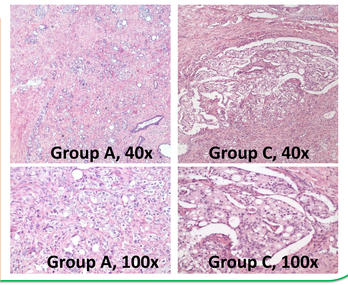


Residual cancer burden index (RCBI)[1] calculated from linear measurements of tumour, with surrogates of cancer burden as:
- **Pre-treatment**: maximum % of **biopsy core involved** by cancer
- **Post-treatment**: proportion % of cancer **within index lesion**

POST-TREATMENT RESPONSE GROUPING[2]



Post-treatment Response Grouping[2]		
Group	Dominant Architectural Pattern	Cribriform Pattern or Intraductal Spread
A	Cell clusters/cords, isolated cells	Absent
B	Small glands, fused glands	Absent
C	Any	Present



Adverse Events		
AE	N (%)	Causality
• **Skin disorders**	**20 (80)**	
- Dry skin	16 (64)	Probable
- Maculo-papular rash	12(48)	Possible
- Nipple area hyperalgesia	7 (28)	Definite
• **General disorders**	**17 (68)**	
- Fatigue	12 (48)	Definite
- Flu symptoms	7 (28)	Unlikely
• **Psychiatric disorders**	**9 (36)**	
- Decreased libido	5 (20)	Definite
- Insomnia	5 (20)	Definite
- Depression	1 (4)	Definite
• **Nervous system disorders**	**7 (28)**	
- Dizziness	3 (12)	Definite
- Memory impairment	1(4)	Definite

5 Discussion

- There was **good biochemical response** to 12 weeks of androgen deprivation by Apalutamide
- There was an **overall good oncological response**:
  - ❖ **Post-treatment response groups[2]** A & B in majority **72%**
    - reflects change in tumour **morphology**
  - ❖ **Majority positive RCBI response**:
    - RCB response represents an **estimate** of change in tumour viability post neoadjuvant treatment
    - Tumour proportion of needle biopsy core as **pre-treatment surrogate** tends to **underestimate** cancer burden, due to sampling of extralesional prostate tissue
    - However, using proportion of cancer *within* index lesion on wholemount **as post-treatment surrogate** tends to be **more accurate**
    - Overall RCBI response may be underestimated
    - Negative (*ARN7*) and non (*ARN12, ARN17 & ARN 27*) responders may represent measurement errors
- **Good safety profile:**
  - ❖ **AE** related to Apalutamide were **tolerable and of low severity grade**
  - ❖ **No increased surgical morbidities** observed

References:

1. Symmans WF, Peintinger F, Hatzis C et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007 Oct 1;25(28):4414-22.
2. Efstathiou E, Abrahams NA, Tibbs RF et al. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. Eur Urol. 2010 Jun;57(6):1030-8.