UNIVERSITY *of* MARYLAND MEDICAL CENTER

Phase 2 randomized high-risK metachroNous oligometastatIc prostate cancer with hiGh-risk mutations treated witH meTastasiS directed therapy and niraparib/abiraterone acetate plus prednisone (KNIGHTS) trial.

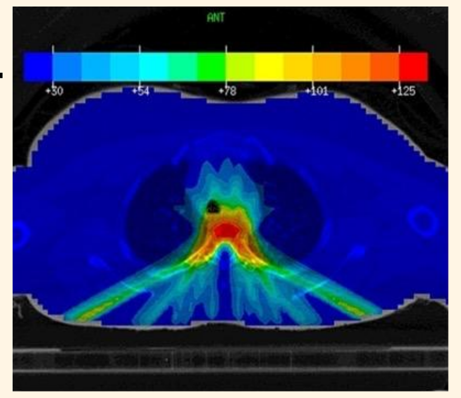
NCT Trial # 06212583

Noura Radwan[1] MD, Matthew Deek[3] MD, Xiaolei Shi[2] MD PhD, Caitlin Eggleston[1] MPH, Kaysee Baker[1] MS, Zaker Rana[1] MD, Matthew Ferris[1] MD, Young Kwok[1] MD, Soren Bentzen[1,4] PhD DMsc, Ronald Ennis[3] MD, Lara Hathout[3] MD, Biren Saraiya[3] MD, Tina Mayer[3] MD, Heather Mannuel[2] MD, Arif Hussain[2] MD, Matthew Abramowitz[5] MD, Alejandro Berlin[6] MD, Mark Mishra[1] MD, Phuoc Tran[1] MD PhD, Jason Molitoris[1] MD PhD

[1]Department of Radiation Oncology, University of Maryland School of Medicine, [2]University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, [3]Robert Wood Johnson Medical School, Rutgers University, [4]Department of Epidemiology & Public Health, University of Maryland School of Medicine, [5]University of Miami Miller School of Medicine, [6]Department of Radiation Oncology, Princess Margaret Hospital

BACKGROUND

- Metachronous or oligorecurrent castration-sensitive prostate cancer (CSPC) comprises a large number of men, potentially the majority of men following failed primary therapy. Assuming that these patients are possibly in a curable state before castration-resistance develops, additional treatment strategies are needed.
- There are recent encouraging randomized data supporting use of metastasis-directed therapy (MDT) using stereotactic ablative radiation (SABR) to delay progression in men with oligorecurrent prostate cancer[1]. We recently reported the long-term outcomes of pooled STOMP and ORIOLE trials demonstrating that the use of SABR MDT was associated with improvements in progression-free survival especially in patients with germline or somatic mutations in *TP53, BRCA1/2, ATM* and *RB1* also called high-risk (HiRi) mutations*[2,3].
- Thus, men with oligorecurrent CSPC and HiRi mutations likely need intensification of their therapy beyond androgen deprivation therapy (ADT) and SABR MDT.



* *TP53, BRCA1/2, PALB2, ATM, BRIP1, CHEK2, FANCA, RAD51B, RAD54L, MUTYH* by next-generation sequencing

PURPOSE

- NCT06212583 (KNIGHTS) trial is an investigator-initiated, multicenter, the first integral genomic biomarker driven randomized phase II trial of high-risk metachronous oligometastatic prostate cancer with high-risk mutations* treated with MDT and niraparib/abiraterone acetate and prednisone.
- The primary goal is to evaluate the efficacy of niraparib/abiraterone acetate and prednisone when added to ADT+SABR MDT.
- The primary hypothesis tested in the trial is that adding niraparib/abiraterone acetate and prednisone to ADT+SABR MDT will decrease the frequency of PSA failure.

ACKNOWLEDGEMENT

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ELIGIBILITY

Inclusions:

- Patient must have a histologically confirmed prostate adenocarcinoma (primary or metastatic tumor).
- Patient must have **metachronous oligometastatic disease**, defined as at least one and up to three asymptomatic metastatic tumor(s) on conventional imaging or up to five lesions on advanced functional imaging that develop within the past 6-mos.
- Patient must have a **HiRi pathogenic mutation***.
- EGOC ≤ 2 and life expectancy ≥ 12 months.
- Patient may have had prior systemic therapy and/or ADT so long as testosterone is > 100 ng/dL prior to enrollment.
- PSA > 0.5 but < 50 at enrollment.
- Patient must have a PSA doubling time < 15 months.
- Patient must have an adequate hematologic, renal, and hepatic function at screening.

Exclusions:

- Castration-resistant prostate cancer (CRPC).
- Prior radiation therapy to an overlapping site of a target lesion that would preclude further radiation therapy.
- No more than 3 years total of prior ADT is allowed (with the most recent ADT treatment having occurred within 2 months from the start of SABR).
- Spinal cord compression.
- Suspected intracranial and/or liver metastases. Radiographical evidence of cranial parenchymal metastasis.
- Active second primary malignancy; AML/MDS in medical history.
- Pathological finding of small cell or neuroendocrine carcinoma.
- Patient receiving any other investigational agents.
- Long-term use of systemically corticosteroids (> 5mg of prednisone or the equivalent) during the study is not allowed.

OBJECTIVES

Primary Objective:

To compare the **18-month PSA progression****, with testosterone >3-month who have oligometastatic CSPC with HiRi mutations** treated with ADT+SABR MDT (6-mos) versus ADT+SABR MDT+ niraparib/abiraterone acetate and prednisone (6-mos).

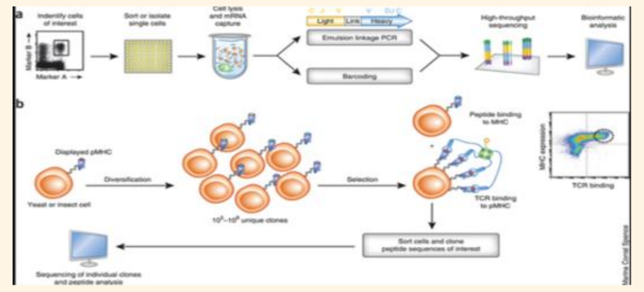
Secondary Objectives:

- To assess treatment-related adverse events.
- To assess local control at 18 months after ADT+ SABR MDT (6-mos) versus ADT+ SABR MDT+ niraparib/abiraterone acetate and prednisone (6-mos) in patients with metachronous oligometastatic CSPC disease.
- To assess time to locoregional progression, time to distant progression, time to new metastasis, radiographic progression-free survival and duration of response.
- To assess health-related quality-of-life (HRQoL) following completion of ADT+SABR MDT (6-mos) versus ADT+SABR MDT+ niraparib/abiraterone acetate and prednisone (6-mos).

** Defined as PSA > 0.2 ng/mL in patients initially treated with radical prostatectomy and greater than nadir +2ng/mL for patients initially treated with

CORRELATIVES

- To enumerate circulating tumor cells (CTC), store plasma and quantitatively sequence T-cell receptor (TCR) repertoires at baseline, 3month follow-up and 6 month follow-up[4].



- To determine frequency of germline and somatic DNA repair mutations in the oligometastatic state.

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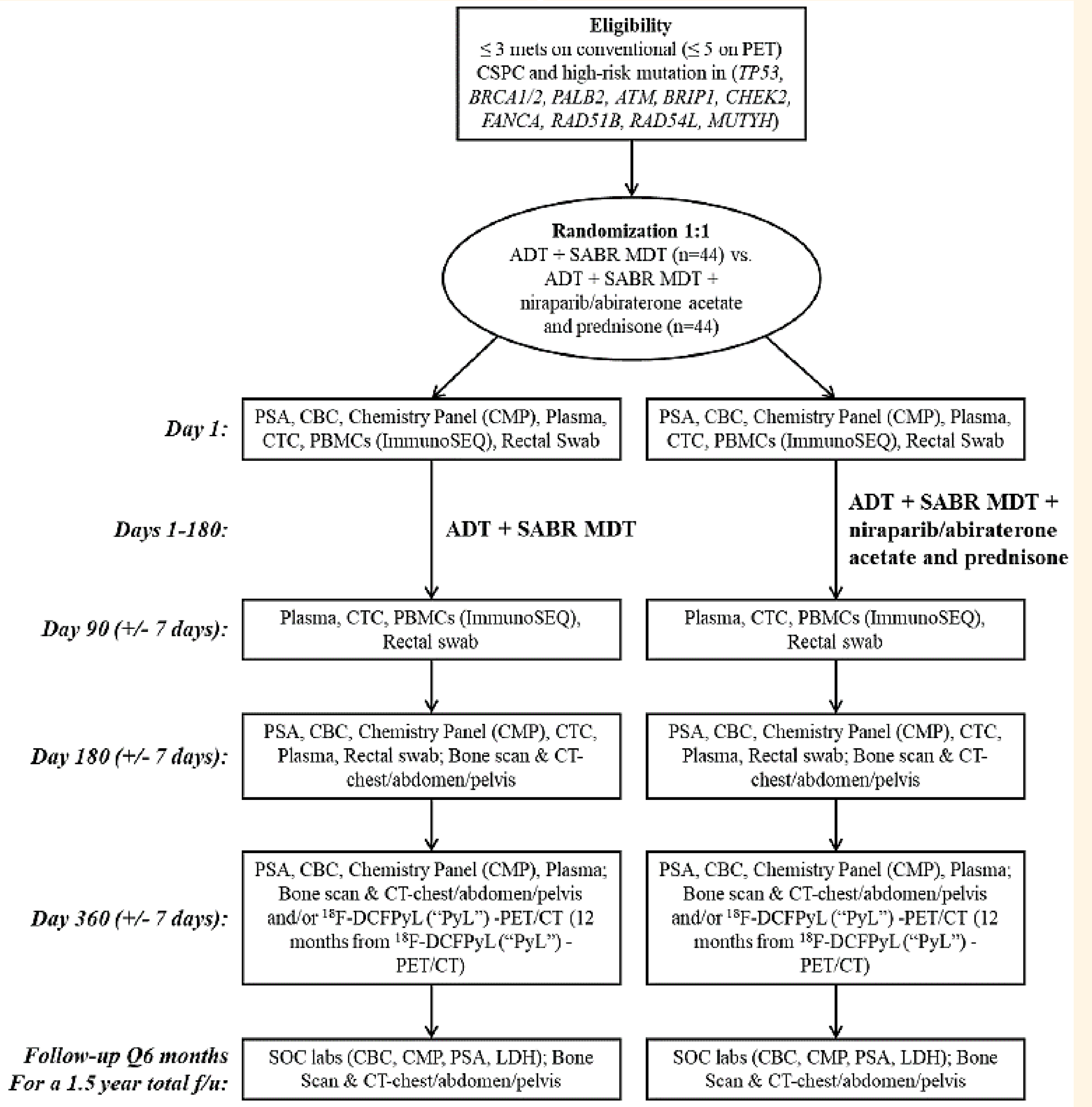
TREATMENT SCHEMA



TRIAL & STATISTICAL DESIGN

- Phase II trial randomizing to ADT+SABR MDT without or with niraparib/abiraterone acetate and prednisone.
  - Target accrual – 88 patients (44 patients in each arm)
  - Accrue for 24 months with 18 months of follow up
  - Date of recruitment began: Apr 17, 2024
  - Approximate date of recruitment completion: Dec 31, 2028
- Power and Statistical Assumptions: 80% power to find success of the experimental arm relative of the control arm based on a one-sided test at alpha 0.20.