A Phase 2 clinical trial of Pembrolizumab in combination with Carboplatin and Cabazitaxel in Aggressive Variant Metastatic Prostate Cancer: PEAPOD trial

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BACKGROUND

- Metastatic **prostate cancer (mPC)** is usually dependent on the **androgen receptor (AR) pathway**. Around 20% of metastatic prostate cancers are **AR independent** with an aggressive behavior[1].
- **Aggressive Variant PC (AVPC)** is considered a distinct entity and it has been defined by seven **clinical-pathological criteria (AVPC-C)[1].**
- AVPC has been also molecularly defined by **loss of key tumor supressors** as **TP53**, **PTEN** and **RB1**. **Neuroendocrine** features have also been found in this subgroup[2].
- These tumors have **poor response rates** to conventional treatments and increased sensitivity to platinum-based combinations.
- **Carboplatin (CBDCA)** and **cabazitaxel** is a recommended regime in this scenario, with a **6-m progression-free survival (PFS) of 35%**[3].
- These tumors are excluded from many mPC clinical trials and treatment options remain an **unmet medical need**.

AIMS

- To assess **efficacy** and **safety** of **pembrolizumab** in combination with **CBDCA** and **cabazitaxel in patients with metastatic PC**
- To explore potential **molecular biomarkers** associated with efficacy and safety in **tissue** and **circulating cells**.

KEY ELEGIBILITY CRITERIA

Metastatic PC (de novo, relapsed or castration resistant) patients with at least one of the **AVPC-C**:

- Histologically proven **small cell** or **neuroendocrine** differentiation.
- Exclusive **visceral** metastases.
- Predominantly **lytic bone** metastases (by investigator criteria).
- **Bulky lymph nodes** (≥ 5 cm in longest dimension) or high grade **pelvic/prostatic** masses
- **Low PSA** (≤10 ng/ml) at initial presentation in the presence of **extensive disease** (≥20 metastases)
- **Elevated** serum **LDH** (≥2 x ULN) or **CEA** (≥2 x ULN)
- **Short** time to **castration resistance** (≤6 months).

ECOG 0-1

Previoulsy **untreated** patients or prior therapy with **docetaxel** and/or **novel hormonal agents** are allowed.

Prior therapy with **anti-PD1/anti-PDL1**, **CBDCA** or **cabazitaxel** is not allowed.

STUDY DESIGN

TREATMENT SCHEDULE

Induction

Pembrolizumab 200mg + **CBDCA** AUC 4 + **Cabazitaxel** 25mg/m^2 Q3W for **6 cycles** or PD. Mandatory G-CSF support.

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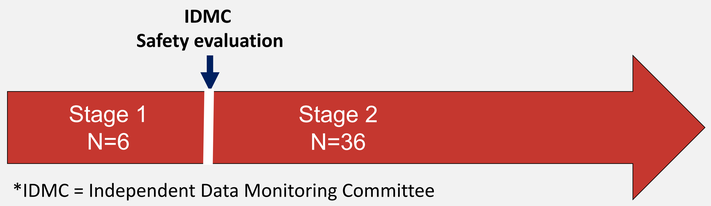
Maintenance

Pembrolizumab 400mg Q6W for **15 cycles** or PD

STUDY DIAGRAM



*IDMC = Independent Data Monitoring Committee

CT and **Bone scan** will be repeated **every 6 weeks** the **first 6 months** and every **12 weeks** thereafter.

PCWG3 and **RECISt 1.0** will be used for tumor response **evaluation.**

STATISTICAL CONSIDERATIONS

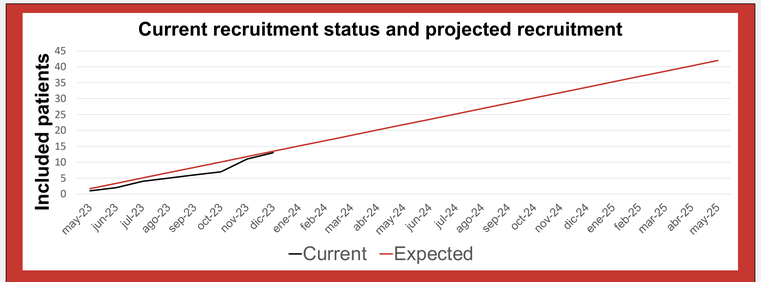
Sample Size calculation: To accept the treatment efficacy, we assume that the 6-m rPFS in patients treated with CBDCA + cabazitaxel + pembrolizumab will improve from a reference PFS rate of 35%[3] to 55%. 42 patients are required to to accept a 6-months PFS of at least 55% with an 80% power and a two-sided alpha error of 0.05.

Representative **FFPE tumor** and serial **blood samples** are being collected for future **translational studies.**

ENDPOINTS

- **Primary endpoints:**
  - 6-month progression-free survival.
- **Secondary endpoints:**
  - 12-month progression-free survival.
  - Response rate by PCWG3.
  - PSA progression-free survival.
  - Progression free survival.
  - Overall survival.
- **Safety endpoints:**
  - Abnormalities in vital signs, laboratory test values and ECG data.
  - Treatment modifications.
  - Patients' withdrawals for safety reasons.
- **Exploratory endpoints:**
  - Correlative efficacy for the AVPC-molecular classified.
  - Neuroendocrine signature by DNA methylation.

RECRUITMENT STATUS at Dec 13th 2023



13 patients have been included in the study and 2 patients are on screening

Stage 1 has been completed and the IDMC has considered safe to continue Stage 2 with the same dose.

References

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