**NEUROENDOCRINE PROSTATE TUMOURS: HISTOLOGIC FEATURES AND THERAPY**

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**Abstract**

Neuroendocrine tumors of the prostate are rare tumors, that can arise de novo but much more commonly occur after androgen deprivation therapy for prostate adenocarcinoma. Neuroendocrine tumors of the prostate are classified into: adenocarcinoma with neuroendocrine differentiation, well-differentiated neuroendocrine tumor/ carcinoid, small-cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, adenocarcinoma with Paneth cell neuroendocrine differentiation and mixed neuroendocrine carcinoma–acinar adenocarcinoma.

IHC plays a vital role and should be approached at 2 levels. For the issue of confirming NE

differentiation, markers for NE differentiation include synaptophysin, chromogranin, and

CD56. If there is any uncertainty about the histogenesis, that is, whether a tumor is primary to the

prostate, markers for prostatic lineage—PSA, PSAP, PSMA, prostein (p501s), NKX3.1,

ERG (by IHC or FISH)—may be used.

Actually, platinum-based chemotherapy is commonly administered to patients with pure small cell carcinoma based on SCLC data and the accumulating data for AVPC. This may consist of a combination of carboplatin (or sometimes cisplatin) plus either etoposide (based on SCLC) or a taxane (especially if mixed histology or AVPC features).

A combination regimen of cisplatin, etoposide, and doxorubicin has been also investigated but the benefit-risk ratio of the three-drug combination was considered unfavorable. Unfortunately, platinum-based chemotherapy oft presents high toxicity and a short OS. Results of currently ongoing preclinical and clinical studies are expected to enhance our understanding of these tumors’ underlying biology and guide our efforts toward the development of personalized medicine through targeted diagnostic and therapeutic approaches.

**Introduction**

Prostate cancer (PC) is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [1].

The actual prevalence of PC is at age < 30 years of 5% (95% confidence interval [CI]: 3-8%), increasing by an odds ratio (OR) of 1.7 (1.6-1.8) per decade, to a prevalence of 59% (48-71%) by age > 79 years [2].

The incidence of PC diagnosis varies widely between different geographical areas, being highest

in Australia/New Zealand and Northern America (age-standardized rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have shown a steady increase [1].

Based on the histological characteristics, PCs are mostly represented by acinar type adenocarcinoma, composed of tumor cells with luminal differentiation including the expression of prostate-specific antigen (PSA) and androgen receptor (AR) [3,4]. Differently, neuroendocrine (NE) tumors of the prostate are rare, and they usually occur after androgen deprivation therapy for prostate adenocarcinoma.

Neuroendocrine tumors of the prostate can arise de novo but much more commonly occur after androgen deprivation therapy for prostate adenocarcinoma.

The influence of androgens on the prostate gland represents an important risk factor for the development of PC in different ethnic/ racial groups and androgen deprivation therapy (ADT) combined with other therapies which target androgen receptor (AR) signaling such as abiraterone acetate or enzalutamide is a standard first-line approach for metastatic prostate cancer [5].

Most castration-resistant prostate cancers (CRPC) are still dependent on AR signaling through acquired AR gene mutation, amplification, or other means to re-activate the AR [5,6].

Approximately 15–20% of CRPC tumors will lose dependence on AR signaling at some point during their disease course but the identification of AR-independent disease in the clinic remains challenging. One apparent clinical manifestation is a histologic transformation from an AR-expressing prostate adenocarcinoma to an AR-negative, poorly differentiated small cell neuroendocrine carcinoma histology [7,8]. This cancer phenotype is often referred to as neuroendocrine prostate cancer (NEPC) to broadly encompass both pure small cell carcinomas and mixed adenocarcinoma neuroendocrine tumor morphologies. AR expression is typically

low but even when AR is expressed, NEPC tumors tend to be less dependent, or “indifferent,” to canonical AR signaling.

**Neuroendocrine cells of the normal prostate**

Neuroendocrine (NE) cells of the prostate were originally described by Pretl in 1944 [9]. NE cells

with the dual properties of endocrine cells and neurons, i.e. acting in secretory and autocrine/paracrine fashions, are widely distributed in normal prostatic acini and ducts.

In 1999, Aumuller et al. suggested human prostate NE cells to be a cell lineage of their own, being of neurogenic origin and therefore distinct from the urogenital sinus-derived prostate secretory and basal cells [10].

There are two types: the open cells with extensions at their apex that connect with the lumen, and closed cells with dendritic processes that extend between adjacent cells, resting on the basal lamina and in close topographical relationship with nerves [11].

NEs are usually present in the transition zone and peripheral zone of the prostate than the central zone, suggesting their potential involvement in benign prostatic hyperplasia and PC, respectively. [4].

Neuroendocrine cells do not express luminal differentiation markers AR or PSA but they are positive for NE markers including chromogranin A (CgA), synaptophysin (SYN), and neural cell adhesion molecule 1 (CD56) [12].

Actually, we ignore the function of NE cells in the prostate. Nevertheless, these cells express serotonin, histamine, CgA, calcitonin, neuron-specific enolase, which play a role in the regulation of the prostate epithelium and sperm function [13].

**Pathologic Classification of Prostate Cancer with Neuroendocrine Differentiation**

In the last decade, the World Health Organization (WHO) and the Prostate Cancer Foundation (PCF) developed a histo-morphologic classification of prostate cancer with NE differentiation, in order to systematically describe this heterogeneous prostate cancer subtype [14,15] (**TABLE 1**)

Neuroendocrine differentiation (NED) is usually present in prostatic carcinomas than in other urogenital tumors because NED is a common feature of prostatic adenocarcinomas and is usually

determined by immunoreactivity for neuroendocrine markers, (CgA, NSE, or bioactive eutopic hormones such as somatostatin and 5-HT) [11,16].

As reported in the literature, NED is present in 30-100% of all prostate adenocarcinomas, even if there are other forms of NED associated with small cell carcinomas of the prostate [11,16]. According to the new WHO classification system, these are entitled small-cell neuroendocrine carcinoma. The malignant phenotype of NED is also found in certain carcinoid and carcinoid-like tumors. However, the most common histopathological pattern is focal NED in conventional adenocarcinomas of the prostate [11,16]

It has been suggested that NE tumor cells could be found at all stages of PC but they don’t express the androgen receptors (AR) [11, 16].

**USUAL PROSTATE ADENOCARCINOMA WITH NE DIFFERENTIATION**

An usual prostate adenocarcinoma with NE differentiation is referred to prostate adenocarcinoma with acinar or ductal type, in which focal NE cells are appreciable by IHC alone ( ie, synaptophysin, CD56, chromogranin).

The number of NE cells varies from case to case, but generally comprises no more than 1% of the entire tumor cell population. The detection of NE cells depends on the sensitivity and specification of the antibodies against NE markers such as CgA (the most sensitive and specific used marker) and SYN [4, 17]. Several studies have suggested that the number of NE cells is positively correlated with tumor grade and is particularly high in patients treated with hormonal therapy [4, 18].

However, the clinicopathologic significance of NE cells in prostate adenocarcinoma is still uncertain and the role of NED on prognosis could not be explained.

**WELL-DIFFERENTIATED NE TUMOR (CARCINOID TUMOR)**

A carcinoid tumor is a classic, well-differentiated NE tumor with a morphology similar to that of carcinoid tumors in other sites, including the lung, gastrointestinal tract, and bladder without arising from the urethra/bladder.

Carcinoid tumor arises from NE cells and they are positive for NE markers (SYN, CgA, or CD56), negative for PSA but in some cases, these tumors can be positive for prostate-specific acid phosphatase (PAP) [4, 19]

The diagnosis of carcinoid tumor in the prostate needs to meet the following criteria: (1) the tumor must originate from the prostate parenchyma rather than involvement of the prostate by a tumor arising from other organs, (2) the tumor should be distinct from coexisting adenocarcinoma,

and (3) the tumor must be positive for NE markers and negative for PSA [13].

True carcinoid tumor of prostate is very rare and we find in literature some cases which have carcinoid-like appearance but were positive for PSA stain so that they cannot be diagnosed as carcinoid tumor, and an alternative diagnosis of adenocarcinoma (with focal NE cells) should be considered [20,21].

**SMALL CELL NE CARCINOMA**

Small cell NE carcinoma (SCNC) is an aggressive, high-grade NE tumor with similar morphologic features to those of the lung and other organs. Small cell NE carcinoma is defined by characteristic nuclear features, including lack of prominent nucleoli, nuclear molding, fragility, and crush artifact and necrosis is oft frequent.

Approximately, 40% to 50% of small cell carcinomas have a history of usual prostatic adenocarcinoma, with a median interval of diagnosis between the 2 histological forms of small

25 months [13,22]. Furthermore, small cell NE carcinomas are generally negative for AR

and PSA.

Although most cases of SCNC arise in patients who have been treated with hormonal therapy for prostate adenocarcinoma, some patients can develop SCNC as a primary tumor in the prostate. Nevertheless, primary SCNC is rare and comprises less than 1% of prostate cancers [23].

The diagnosis of small cell carcinoma of the prostate is based on the evaluation of morphologic features which are similar to small cell carcinomas of the lung. However, SCNC presents some morphologic variations, such as intermediate cell type, which have slightly more open chromatin and visible small nucleoli in comparison to small cell carcinoma of the lung [22].

Using IHC techniques, the small cell component is positive for 1 or more NE markers (synaptophysin, chromogranin, CD56) in almost 90% of cases, whereas PSA is positive in about 17% to 25% of cases [13, 22].

In 24% and 35% of cases, positivity is noted for p63 and high–molecular weight cytokeratin, markers typically negative in prostatic carcinoma [24].

Considering the rarity of primary small cell carcinoma of the prostate, it is important to exclude the presence of metastasis or local extension from other sites such as the bladder. This differential diagnosis can be performed by applying the fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction of a gene fusion between members of the ETS family of genes, in particular ERG (ETS-related gene) and TMPRSS2, found in approximately one-half of the usual prostatic adenocarcinomas [25].

The median cancer-specific survival of patients with small cell carcinoma of the prostate in

191 men according to the SEER database from 1973 to 2004 was 19 months; 60.5% of men

presented with metastatic disease with a decreased survival related to the stage; 2- and 5-year

survival rates were 27.5% and 14.3%, respectively [26].

Clinically localized small cell prostate cancer is typically treated with multimodality therapy based

on chemotherapy and radiation similar to limited-stage small cell lung cancer. In presence of metastases, small cell carcinoma of the prostate is treated with platinum-based combination chemotherapy with regimens similar to those used to treat small cell lung carcinoma. Some experts treat pure small-cell carcinoma with chemotherapy alone, whereas others add ADT [27,28].

**LARGE CELL NE CARCINOMA**

Large cell NE carcinoma was newly included as a type of NE tumor of the prostate in the 2016 World Health Organization classification of prostate tumors [15].

The tumor cells of LCNC grow as solid sheets, ribbons, or nests with focal microscopic necrosis in the center and areas of peripheral palisading [29].

In contrast to SCNC, the tumor cells of LCNC tend to be large, with a polygonal shape and abundant cytoplasm.

Tumor cells of LCNC express one or more NE markers (SYN, CgA, or CD56), with variable expression of PSA, PAP, CK7, and CK20 but they are negative for AR. Ki-67 labeling index

often exceeds 50%. [30,31].

Pure LCNC is extremely rare and in 2006 Evans et al. presented the largest series of seven cases [29].

One patient had a primary prostate tumor, and the other 6 cases arose after hormonal treatment of adenocarcinoma of the prostate. The histologic features are identical to large cell neuroendocrine carcinomas diagnosed in other anatomic sites such as the lung. The outcome is poor, with a mean survival of 7 months after platinum-based chemotherapy.

**ADENOCARCINOMA WITH PANETH CELL–LIKE NE DIFFERENTIATION**

Adenocarcinoma with Paneth cell–like NE differentiation is defined as typical adenocarcinoma of the prostate containing varying proportions of cells with prominent eosinophilic cytoplasmic granules on routine light microscopy (Paneth cell–like change).

Paneth cell– like NE differentiation in prostatic adenocarcinoma can be seen as

either patchy isolated cells or diffusely involving glands or nests [13, 32]. These

Paneth cell– like cells may be present in well-formed glands of Gleason pattern 3 but also

can be present in cords of cells with bland cytology, wherein strictly applying the Gleason

grading system one would assign a Gleason pattern 5.

Although Paneth cell–like NE differentiation could be found in pattern 5, their bland cytology, typically limited nature and frequent association with lower-grade prostate adenocarcinoma suggest not considering this unique histology as high-grade.

Epstein et al. reported 16 radical prostatectomy specimens with Paneth cell– like NE cells lacking glandular differentiation. An organ-confined cancer was found in 62.5% of cases, only 4 cases with seminal vesicle invasion and none with pelvic lymph node metastases. The postoperative course was also favorable with a > 90% actuarial PSA progression-free risk at 5 years and the prognosis was influenced by conventional parameters (i.e.the Gleason score, T stage, positive surgical margins) and not by independent of NE differentiation.

Paneth cell– like NE cells are diffusely positive for NE markers but they may not express prostate

markers.

**MIXED NE CARCINOMA—ACINAR ADENOCARCINOMA**

Mixed NE carcinoma – acinar adenocarcinoma is a carcinoma with distinct, recognizable, admixed components of NE (small cell or large cell) carcinoma and conventional acinar adenocarcinoma.

Usually, these tumors are represented by mixed small cell carcinoma and adenocarcinoma of the

prostate and each of both are readily identifiable as distinctive. As with other unusual subtypes of prostate cancer, a Gleason score is only assigned to the conventional adenocarcinoma component but not to the small cell carcinoma. In reported mixed cases, small cell carcinoma predominated (median: 80% of the tumor), and the Gleason score of the adenocarcinoma was ≥8 in 85% of these cases [22]. The presence of concomitant high-grade adenocarcinoma as opposed to lower-grade adenocarcinoma represents an independent predictor of worse cancer-specific mortality.

Most patients with mixed small cell carcinoma and adenocarcinoma present with metastatic castration-resistant disease and they are often treated with both ADT and chemotherapy (platinum + etoposide or platinum + taxane).

**IHC AND FISH IN THE DIAGNOSIS AND CLASSIFICATION OF NE DIFFERENTIATION IN PROSTATE CANCER**

IHC plays a vital role and should be approached at 2 levels. For the issue of confirming NE

differentiation, markers for NE differentiation include synaptophysin, chromogranin, and

CD56. Actually, CD57 (Leu7) and NSE are not more recommended.

If there is any uncertainty about the histogenesis, that is, whether a tumor is primary to the

prostate, markers for prostatic lineage—PSA, PSAP, PSMA, prostein (p501s), NKX3.1,

ERG (by IHC or FISH)—may be used.

Additional considerations for the role of IHC include diagnosis, prognosis, and predictive

purposes. The formal utility of Ki67/MIB-1 IHC is not established; however, generally

observed ranges are outlined in **Table 2**.

The IHC expression of AR across the proposed subtypes of NE carcinoma needs to be

systematically evaluated such that its role in the classification of these tumors may be

determined. Promising new molecular targets that may be amenable to future IHC-based or

FISH-based classification and predictive strategies include Aurora A kinase and N-Myc;

however, these markers are not yet validated for clinical use [13,33,34].

**Aggressive Variants of Castration-Resistant Prostate Cancer (AVPC)**

Primary small cell NE differentiation is rare with an incidence of less than 2%. Most NED develops in castration-resistant patients following androgen deprivation therapy [35].

Clinically, treatment-emergent NE/small cell differentiation has been associated with distinct manifestations, including predominantly visceral or lytic bone metastases and bulky tumor masses,

frequently in the setting of low PSA levels with high-volume tumor burden [13].

These tumors are typically not responsive to hormonal therapy, while they are sensitive to cytotoxic chemotherapy [36]. However, responses are short-lived and overall survival is reduced.

CRPC characterized by one or more of the following was determined to be AVPC:

- histologic evidence of SCPC (pure or mixed), whose presence determines AVPC regardless of hormonal status

- the presence of only visceral metastases;

- predominantly lytic bone lesions;

- bulky (≥5 cm) lymphadenopathy or large (≥ 5 cm) high-grade (Gleason ≥ 8) tumor mass in

prostate/pelvis;

- low PSA at presentation with extensive bone metastatic disease;

- the presence of NE markers at histology (CgA and synaptophysin) or serum (CgA and gastrin-releasing peptide) combined with either elevated lactate dehydrogenase (LDH), malignant hypercalcemia or elevated serum carcinoembryonic antigen (CEA);

- progression to CRPC in six months or less after initiation of hormonal therapy.

Patients affected by CRPC should undergo biopsy of accessible metastatic lesions in order to

identify NED which can influence treatment decisions. Recently, Aggarwal et al. suggested that even patients without “atypical”/aggressive-variant clinical presentation may harbor

tumors with NED and hence diagnostic biopsy of metastatic lesions may be valuable in all mCRPC patients regardless of clinical manifestations [23].

**Systemic therapy**

In CRPC with small-cell histology, cytotoxic chemotherapy has been associated with improved outcomes and is generally considered the preferred treatment option [37]. Similarly, to small-cell lung cancer, platinum-based chemotherapy regimens are mainly being employed, with cisplatin/etoposide, carboplatin/etoposide, and docetaxel/carboplatin being the regimens recommended by the NCCN [38].

In patients with clinical AVPC (putting aside pure small-cell histology), there is no clear consensus on the optimal first-line therapy, with 58% of the Advanced Prostate Cancer Consensus Conference (APCCC) 2017 voting in favor of standard mCRPC treatment and 42% of platinum-based chemotherapy [39].

**Table 3** summarizes the actual chemotherapy trials in AVPC.

Since the combination of cisplatin with etoposide proved effective in the treatment of small cell

lung cancer, the same regimen was also suggested for poorly differentiated NE tumors.

Papandreou et al. investigated the efficacy of a combination of cisplatin/etoposide and doxorubicin in a phase II trial of 38 patients with histologically confirmed SCPC (67% pure, 33% mixed) [40]. The benefit-risk ratio of the three-drug combination was considered unfavorable in this study and thus the addition of doxorubicin to cisplatin/etoposide was not recommended for clinical practice.

Loriot et al investigated the combination of carboplatin with etoposide in a phase II trial of patients with mCRPC as a second-line therapy after docetaxel [41]. The combination was fairly well tolerated. The median number of cycles received was three and the median PFS in the overall study population was 2.1 months.

The phase II GETUG P01 examined the combination of carboplatin/etoposide in patients with anaplastic CRPC and visceral metastases or elevated serum CgA and/or NSE [42].

The objective response rate (ORR) was 9% with 3 patients presenting a partial response and one patient with a complete response. Nevertheless, the toxicity was high, with 4 patients (7%) presenting febrile neutropenia and one toxicity-related death. Even in this case, the benefit-risk ratio of this combination was considered to be not favorable.

Of note, the dosage and application mode of carboplatin and etoposide differed in both studies,

with GETUG P01 employing lower doses of carboplatin (AUC 4 vs. 5), but higher doses of etoposide (100 mg/m2/day i.v. for three days vs. 80 mg/m2/day i.v. on day 1 and p.o. on days 2 and 3)—a drug known for its myelotoxicity. Furthermore, the patients underwent 4 cycles in GETUG P01 in contrast with Loriot et al. where they underwent 3 cycles.

Finally, the GETUG P01-population had an overall lower ECOG performance status in comparison to Loriot’s study (ECOG PS 2 at baseline: 22% vs 5%), which can explain the poorer safety profile of this regimen in GETUG P01 and underlines the importance of a good performance status prior to chemotherapy initiation.

Culine et al. investigated the combination of cisplatin with docetaxel which represents a standard-of-care option in patients affected by mCRPC [43]. The authors presented a phase 2 study including 41 mCRPC patients with elevated serum NSE and/or CGA. Almost half of the patients

experienced a PSA response (i.e., PSA decline ≥ 50%), and 12 patients (41%) had an objective partial response. The median OS was 12 months. Unfortunately, 91% of the patients experienced Grade 3–4 neutropenia, and one patient died from sepsis.

Another phase 2 trial studied the combination of carboplatin/docetaxel in 120 mCRPC patients with clinical AVPC followed by second-line etoposide/cisplatin as salvage therapy [28].

A median of four cycles of carboplatin/docetaxel was administered. A PSA decline ≥50% at course 2 was achieved in 47% of the patients, while objective response of measurable disease in 34%. The median PFS on carboplatin/docetaxel was 5.1 months. The median OS was 16 months. Toxicity was fairly manageable overall; most common Grade 3 events were represented by infection

(n = 8) and febrile neutropenia (n=3). Grade 4 events included thrombosis (n=2) and thrombocytopenia (n = 1) and toxicity-related death was also registered.

Corn et al. conducted a phase 2 randomized trial of cabazitaxel vs.cabazitaxel plus carboplatin in patients with mCRPC stratified for the presence of AVPC (ca. 55% per arm) [44]. The platinum-based combination demonstrated improved efficacy, especially in the AVPC subgroup. More specifically, median PFS was improved in the combination arm vs. cabazitaxel alone (7.3 vs. 4.5 months), with prespecified subgroup analysis demonstrating that the platinum-combination

favored only those with clinical AVPC (HR 0.58; 95% CI 0.37–0.89).

Median OS was similar between the two arms (HR 0.89, 95% CI 0.63–1.25, p = 0.50) but the combination regimen was tolerated fairly well with a median of six cycles received.

**Conclusions**

Neuroendocrine prostate cancer is an increasingly recognized histologic subtype of prostate cancer that most commonly arises in the later stages of the disease as a mechanism of treatment resistance.

These tumors are typically refractory to hormonal therapies and, although they usually respond well to platinum-based chemotherapy regimens, the overall survival of the patients is generally short, with a dismal prognosis overall.

Immune checkpoint inhibition with monoclonal antibodies against cancer immune evasion (PD-L1/2, PD-1, CTLA-4) is currently being studied in combinations or alone in several phase 1/ 2 interventional trials for neuroendocrine prostate cancer.

Results of currently ongoing preclinical and clinical studies are expected to enhance our understanding of these tumors’ underlying biology and guide our efforts towards the development of personalized medicine through targeted diagnostic and therapeutic approaches.

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**TABLE 1:** **Histomorphologic classifications of prostate cancer with neuroendocrine (NE) differentiation**

|  |  |  |
| --- | --- | --- |
| **Histomorphologic classifications** | **2016 WHO Classification** | **PCF Classification** |
| Adenocarcinoma with neuroendocrine differentiation | YES | YES |
| Well-differentiated neuroendocrine tumor/ carcinoid | YES | YES |
| Small-cell neuroendocrine carcinoma | YES | YES |
| Large cell neuroendocrine carcinoma | YES | YES |
| Adenocarcinoma with Paneth cell neuroendocrine differentiation | NO | YES |
| Mixed neuroendocrine carcinoma–acinar adenocarcinoma | NO | YES |

PCF = Prostate Cancer Foundation, WHO = World Health Organization

**TABLE 2: IHC of NE Differentiation in Prostate Tumors**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PSA** | **NE Markers** | **Ki67** |
| **PCa** | Positive | Scattered + cells | Not increased in NE cells |
| **PCa. with Paneth cell NE**  **Differentiation** | Variably positive | Diffuse positive in Paneth cells | Few cases studied—not increased |
| **Carcinoid-like tumor** | Usually positive | Positive | Not studied |
| **Carcinoid tumor** | Negative | Diffusely positive | Usually low  Rarely increased (typically <5%–  20%) |
| **SC carcinoma** | Usually negative or scattered  positive cells | Positive in ~90% of cases | > 50%, typically >80% |
| **LC NE carcinoma** | Usually negative but may be  Positive | Diffusely positive | Usually >50% |
| **Mixed NE (SC/LC) usual PCa** | Same as above for each  component | Same as above for each  Component | Same as above for each component |

**TABLE 3: Chemotherapy trials in aggressive-variant prostate cancer (AVPC)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Papandreou et al. [40]** | **Loriot et al. [41]** | **GETUG P01 [42]** | **Culine et al. [43]** | **Aparicio et al. [28]** | **Corn et al. [44]** |
| **Study design** | Phase 2,  single-arm | Phase 2,  single-arm | Phase 2,  single-arm | Phase 2,  single-arm | Phase 2,  single-arm | Phase 2,  randomized |
| **Drug combination** | Cisplatin/etoposide  + doxorubicin | Cisplatin/etoposide | Cisplatin/etoposide | Cisplatin/docetaxel | Carboplatin/docetaxel  (then second-line cisplatin/etoposide) | Carboplatin/cabacitaxel  vs. cabacitaxel |
| **Patient population** | Histologically confirmed  SCPC (pure or mixed) | CRPC after docetaxel with or  without elevated NSE/CgA | mCRPC with visceral  metastasis or  elevated NSE/CgA | mCRPC with  elevated NSE/CgA | AVPC (per  clinical criteria) | mCRPC stratified by  presence of AVPC (per  clinical criteria) |
| **n** | 38 | 40 | 60 | 41 | 121 | 160 |
| **Efficacy** | 36% PSA response  61% OR of  measurable disease  84% pain improvement  Median PFS 5.8mo  Median OS 10.5mo | 23% PSA response  2 out of 5 OR of  measurable disease  54% pain improvement  Median PFS 2.1 mo  Median OS 19mo  Note \*: No association of  outcome with NSE/CGA levels | 8% PSA response  9% OR of  measurable disease  No pain evaluation  Median PFS 2.9 mo  Median OS 9.6 mo | 48% PSA response  41% OR of  measurable disease  45% pain improvement  Median OS 12 mo | 47% PSA response (at  course 2)  34% OR of  measurable disease  Median PFS 5.1 mo  Median OS 16 mo | 62 vs. 41% PSA response  57 vs. 21% OR  Median PFS 7.3 vs. 4.5 mo  Median OS 18.5 vs. 17.3 mo  Note \*: PFS and OS  improvement with  combination greater in  AVPC subgroup (clinical  and/or molecular) |
| **Safety-Grade 3-4 AEs > 15%** | 100% neutropenia  68% infection  66% thrombocytopenia  34% nausea  26% anemia  21% vomiting | 38% neutropenia (2%  neutropenic fever)  25% anemia | 66% neutropenia (7% neutropenic fever)  33% thrombocytopenia  27% anemia | 91% neutropenia (17%  neutropenic fever)  34% anemia  17% thrombocytopenia  15% fatigue | None | 23% anemia  20% fatigue |
| **Safety—Toxicity-related**  **deaths** | 3 (sepsis) | None | 1 (febrile neutropenia) | 1 (sepsis) | 1 (sepsis during  second-line  etoposide/cisplatin) | 1 (thromboembolic event in  cabazitaxel arm) |

AVPC = aggressive variant prostate cancer, CgA = chromogranin A, mCRPC = metastatic castration resistant prostate cancer, NSE = neuron-specific enolase, OR = objective response,

OS = overall survival, PSA = prostate specific antigen, PFS = progression-free survival, SCPC = small-cell prostate cancer. \* Results refer to the overall study population (including patients with and without AVPC)