Neuroendocrine / Small Cell Carcinoma Prostate Cancer

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Outline

1. Background and general principles
2. First-line treatment
3. Second-line+ treatment
4. Future directions

Background

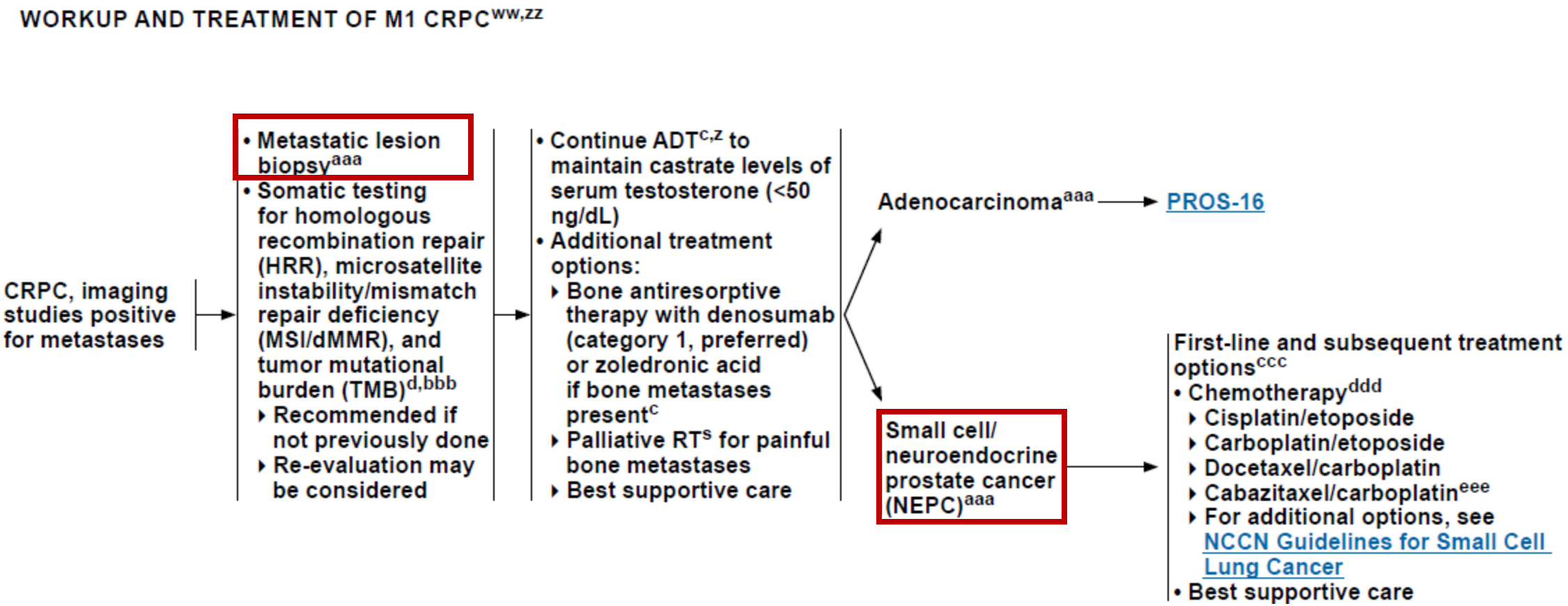
- *De novo* neuroendocrine prostate cancer (NEPC)[1,2]
  - Rare aggressive variant form (≤2% of cases)[3]
  - Poor prognosis
  - No standard treatment approach
- *Treatment-emergent* NEPC[2]
  - Histologic transformation from adenocarcinoma
  - May develop in 15-20% of pts with mCRPC

1. Wang HT et al. *J Clin Oncol*. 2014;32:3383-3390.
2. Aggarwal R et al. *J Clin Oncol*. 2018;36:2492-2503.
3. Beltran H et al. *Cancer Discov*. 2011;1(6):487.

Biopsy

General Principles

- Consider in all new mCRPC
- Particularly low PSA levels despite large met. burden + visceral disease
- Initial GG5 at especially high risk



National Comprehensive Cancer Network. Prostate Cancer (Version 1.2025).

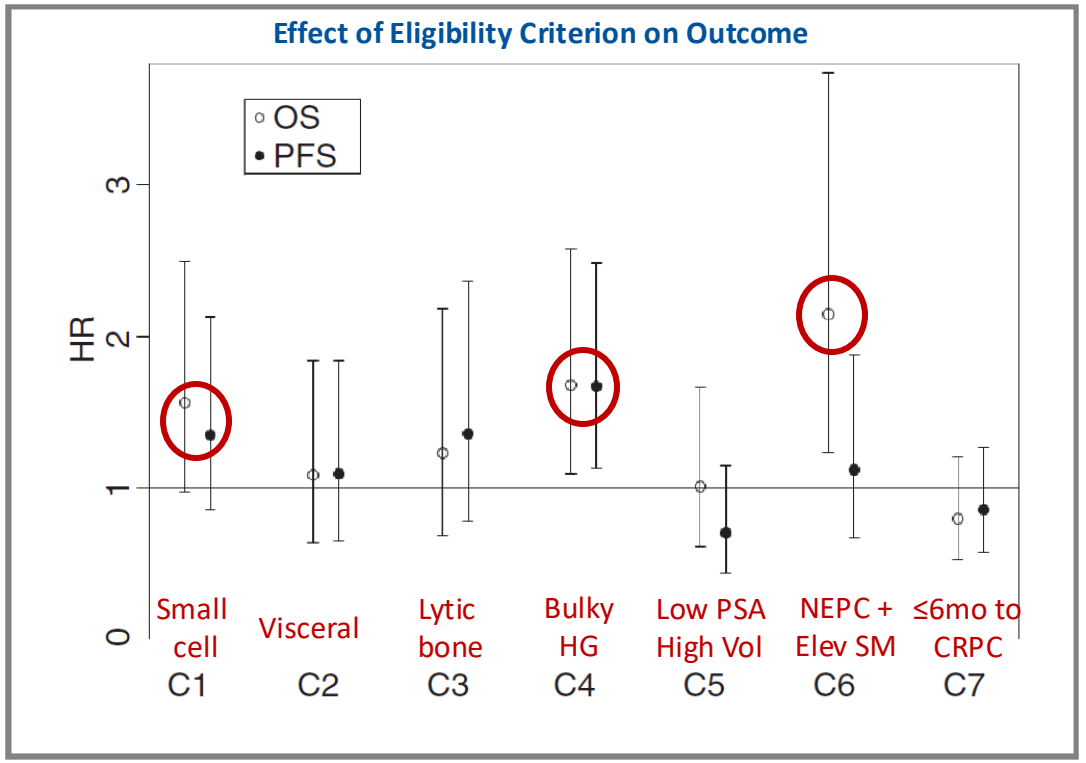
Platinum-Based Chemotherapy (N=120)

Table 1. Clinical features of "anaplastic" prostate carcinomas (eligibility criteria) — AVPC

Castrate-resistant[a] prostate carcinoma with at least 1 of the following:	*n* (%)
C1. Histologic evidence of small-cell prostate carcinoma (pure or mixed).	29 (25.4)
C2. Exclusively visceral metastases.	19 (16.7)
C3. Radiographically predominant lytic bone metastases by plain x-ray or CT scan.	16 (14.0)
C4. Bulky (≥5 cm) lymphadenopathy or bulky (≥5 cm) high-grade (Gleason ≥ 8) tumor mass in prostate/pelvis.	49 (43.0)
C5. Low PSA (≤10 ng/mL) at initial presentation (before ADT or at symptomatic progression in the castrate setting) plus high volume (≥20) bone metastases.	26 (22.8)
C6. Presence of neuroendocrine markers on histology (positive staining of chromogranin A or synaptophysin) or in serum (abnormal high serum levels for chromogranin A or GRP) at initial diagnosis or at progression. Plus any of the following in the absence of other causes: **A.** elevated serum LDH (≥2 × IULN); **B.** malignant hypercalcemia; **C.** elevated serum CEA (≥2 × IULN).	21 (18.4)
C7. Short interval (≤6 months) to androgen-independent progression following the initiation of hormonal therapy with or without the presence of neuroendocrine markers.	52 (45.6)

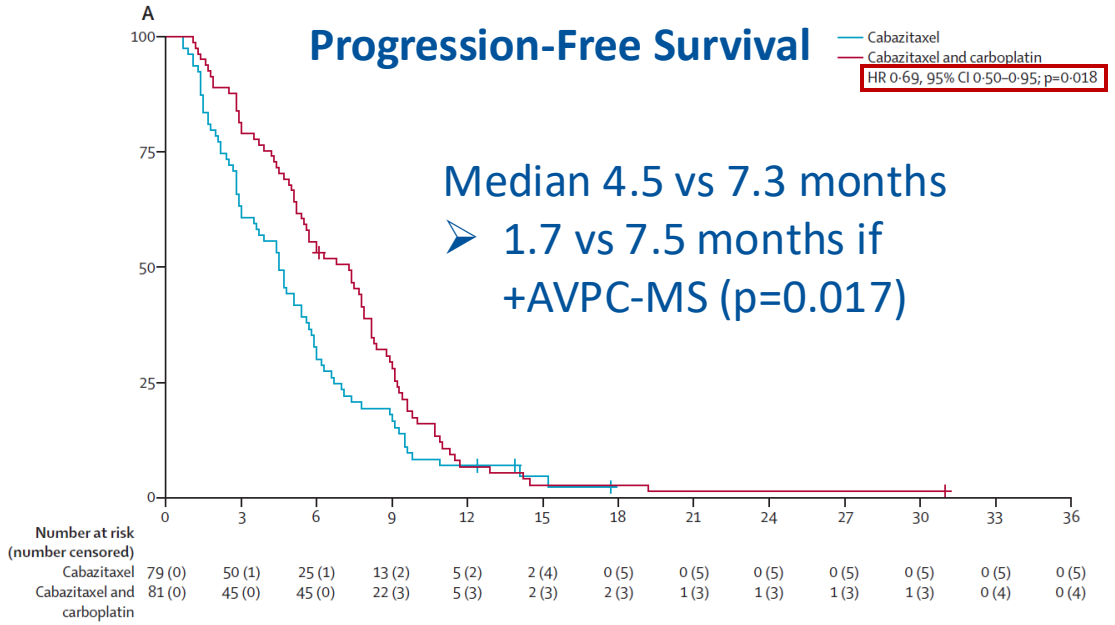
Abbreviation: GRP, gastrin-releasing peptide.
[a]Patients with small-cell prostate carcinoma on histologic evaluation were not required to have castrate-resistant disease.

- Carboplatin AUC 5 + docetaxel 75 mg/m2 D1
- Etoposide 120 mg/m2 + cisplatin 25 mg/m2 D1-3
- Median OS 16 months (95% CI, 13.6-19.0 months)
- After 4 cycles:
  - 65.4% progression-free (CD)
  - 33.8% progression-free (EP)



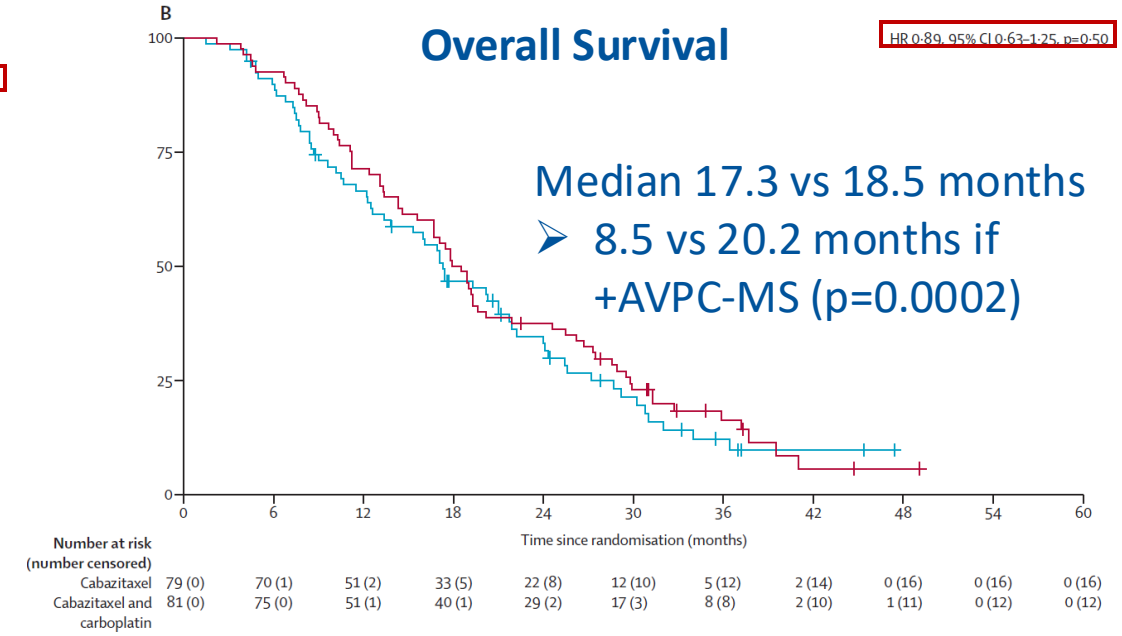
Aparicio AM et al. Clin Cancer Res. 2013;19(13):3621-3630.

Cabazitaxel +/ Carboplatin (N=160)



Median 4.5 vs 7.3 months

- 1.7 vs 7.5 months if +AVPC-MS (p=0.017)



Median 17.3 vs 18.5 months

- 8.5 vs 20.2 months if +AVPC-MS (p=0.0002)

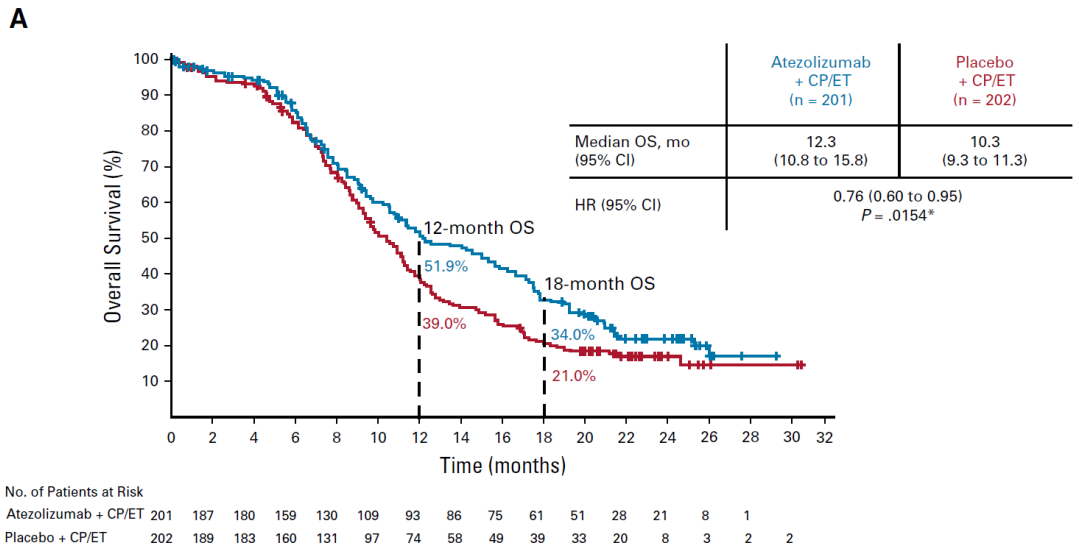
- Cabazitaxel 25 mg/m2 +/- carboplatin AUC4 (~29% prior docetaxel)
- Same clinico-pathologic AVPC criteria as Aparicio (54% had 1 criterion)
- AVPC-MS: loss of 2 of 3 tumor suppressors (TP53, PTEN, or RB1)

Corn PG et al. Lancet Oncol. 2019;20:1432-1443.

First-Line Extrapolation: Add a PD-(L)1 Inhibitor?

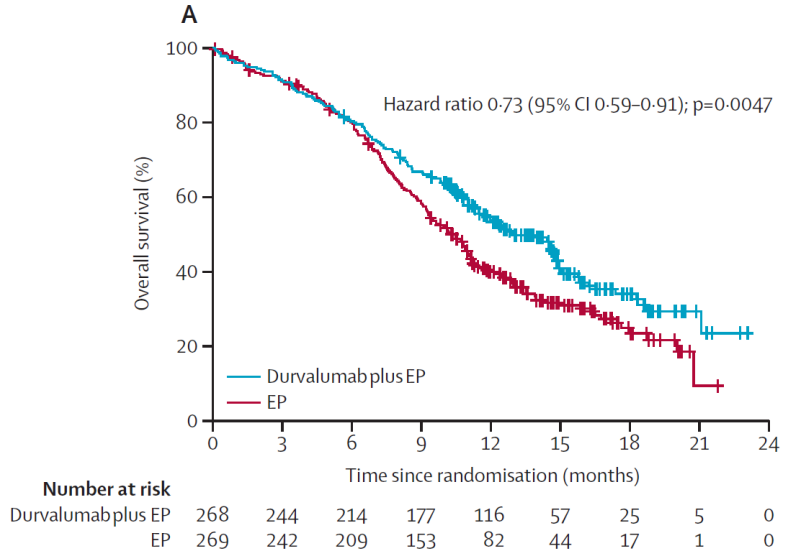
Untreated ES-SCLC

Atezolizumab + carboplatin-etoposide



Liu SV et al. J Clin Oncol. 2021 Feb 20;39(6):619-630.

Durvalumab + platinum-etoposide



- 13·0 (95% CI 11.5–14.8) vs 10.3 mo (9.3–11.2)
- 34% (26.9–41.0) vs 25% (18.4–31.6) alive at 18 months

Paz-Ares L et al. Lancet. 2019 Nov 23;394(10212):1929-1939.

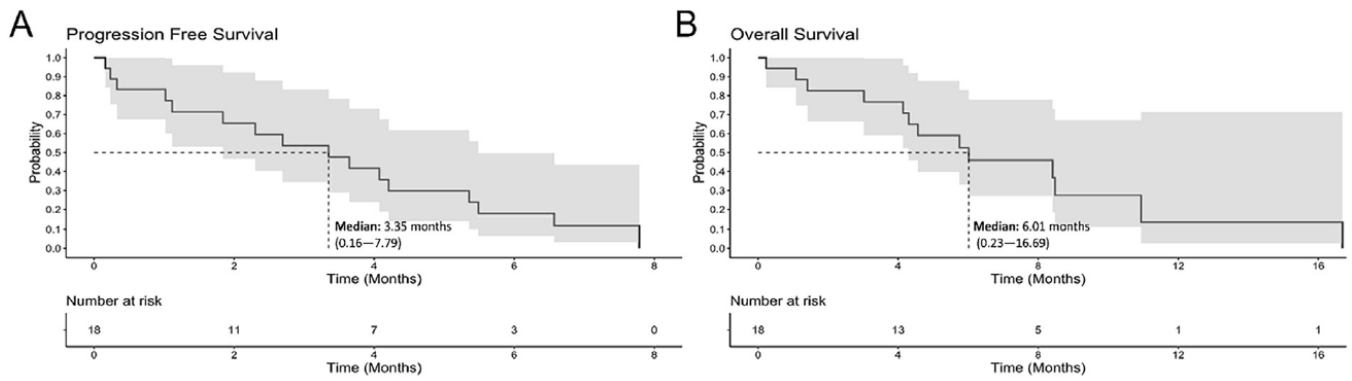
Second-Line Considerations

- What is the dominant histology?
- What are the key clinical features?
- Options:
  - Small cell lung cancer regimens (see NCCN guidelines)
    - Lurbinectidin
    - Topotecan
    - Tarlatamab
    - Ipi/nivo (limited data for IO: ORR 6.7% [N=1/15 response to avelumab in +MSH2/MSI-high][1])
  - mCRPC regimens
  - Molecularly-targeted therapy (i.e. PARP-inhibitors, pembrolizumab)
  - Clinical trials

1. Brown LC et al. Prostate Cancer and Prostatic Diseases (2022) 25:762–769

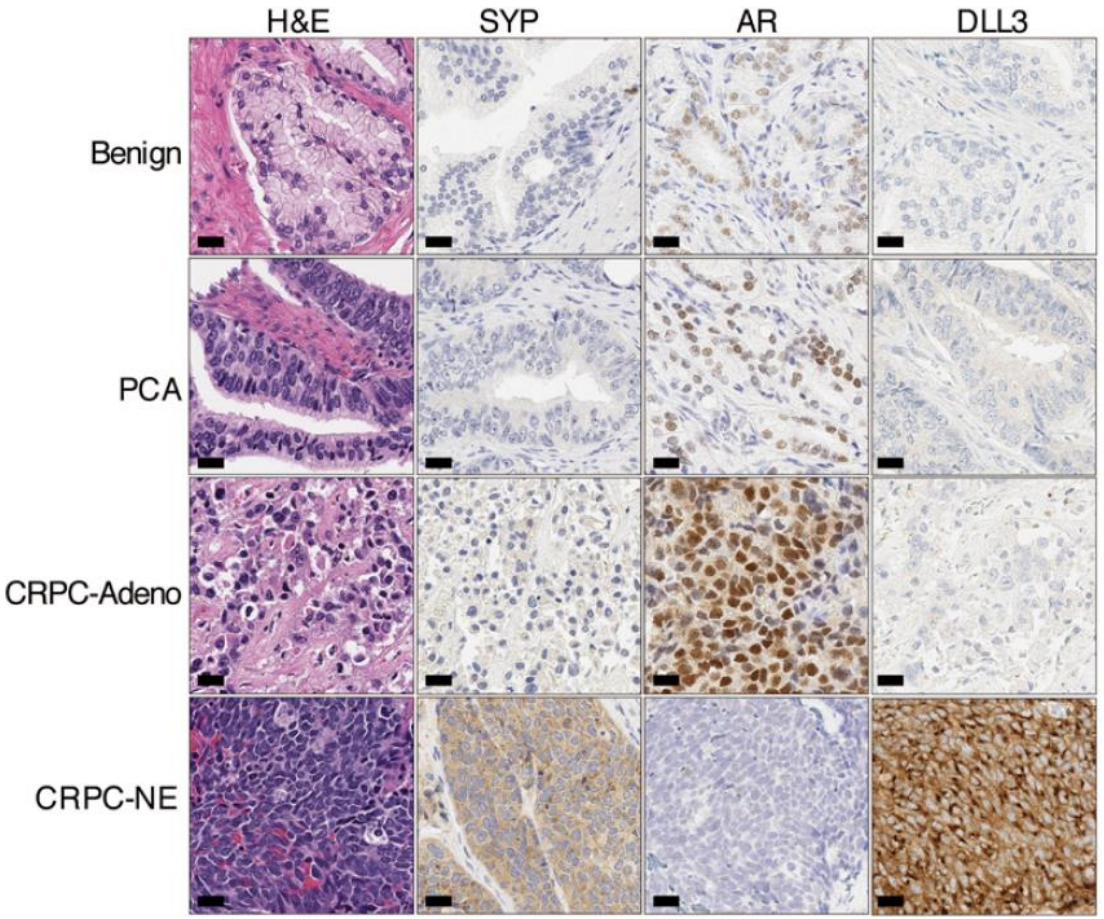
Lurbinectidin

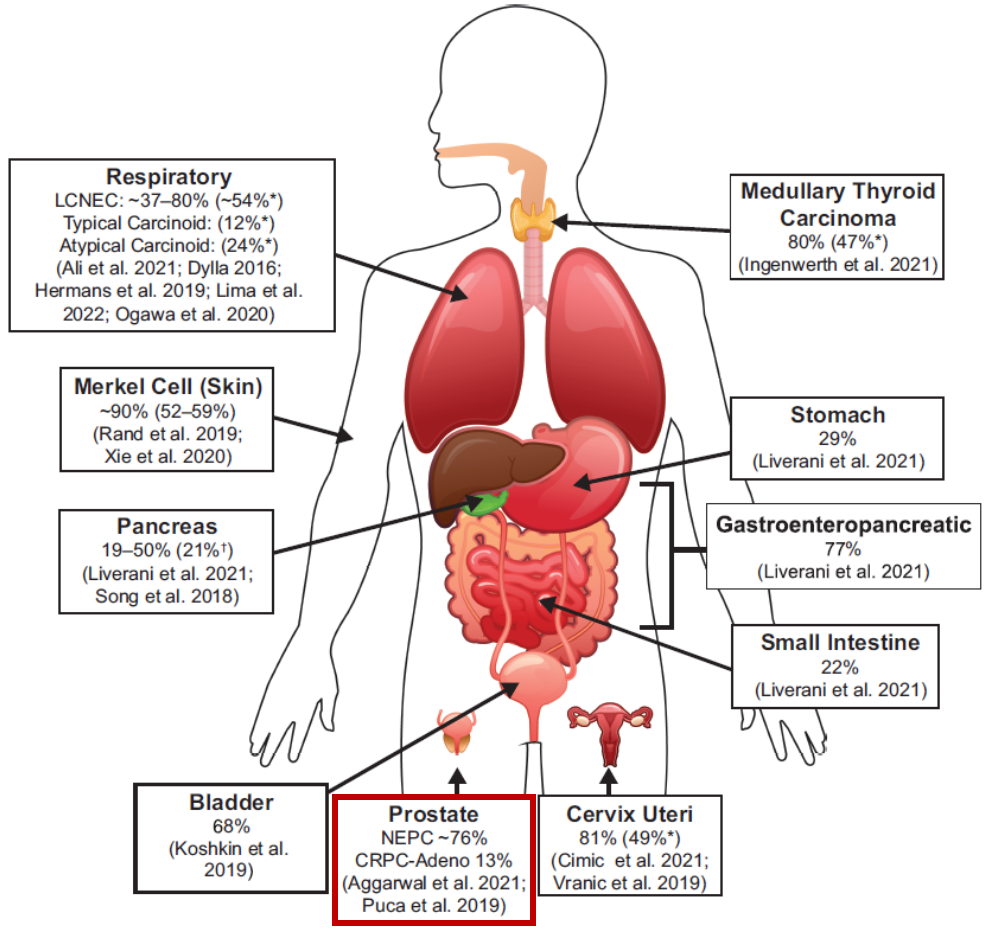
- Single-arm Phase II study in SCLC (N=105), one prior chemo[1]
  - ORR 35.2%, mDoR 5.1 months
  - PFS 3.5 months (95% CI: 2.6-4.3)
  - OS 9.3 months (95% CI: 6.3-11.8)
- Retrospective multi-center study (N=18), SC/NEPC, median 3 prior tx[2]
  - CBR 56% (9/16)
  - PFS 3.4 months
  - OS 6.0 months



1. Trigo J et al. Lancet Oncol 2020; 21: 645–54.
2. Myer H et al. Clin Genitourin Cancer 2024; 22(5)1-9.

Delta-like protein 3 (DLL3) expression in NEPC

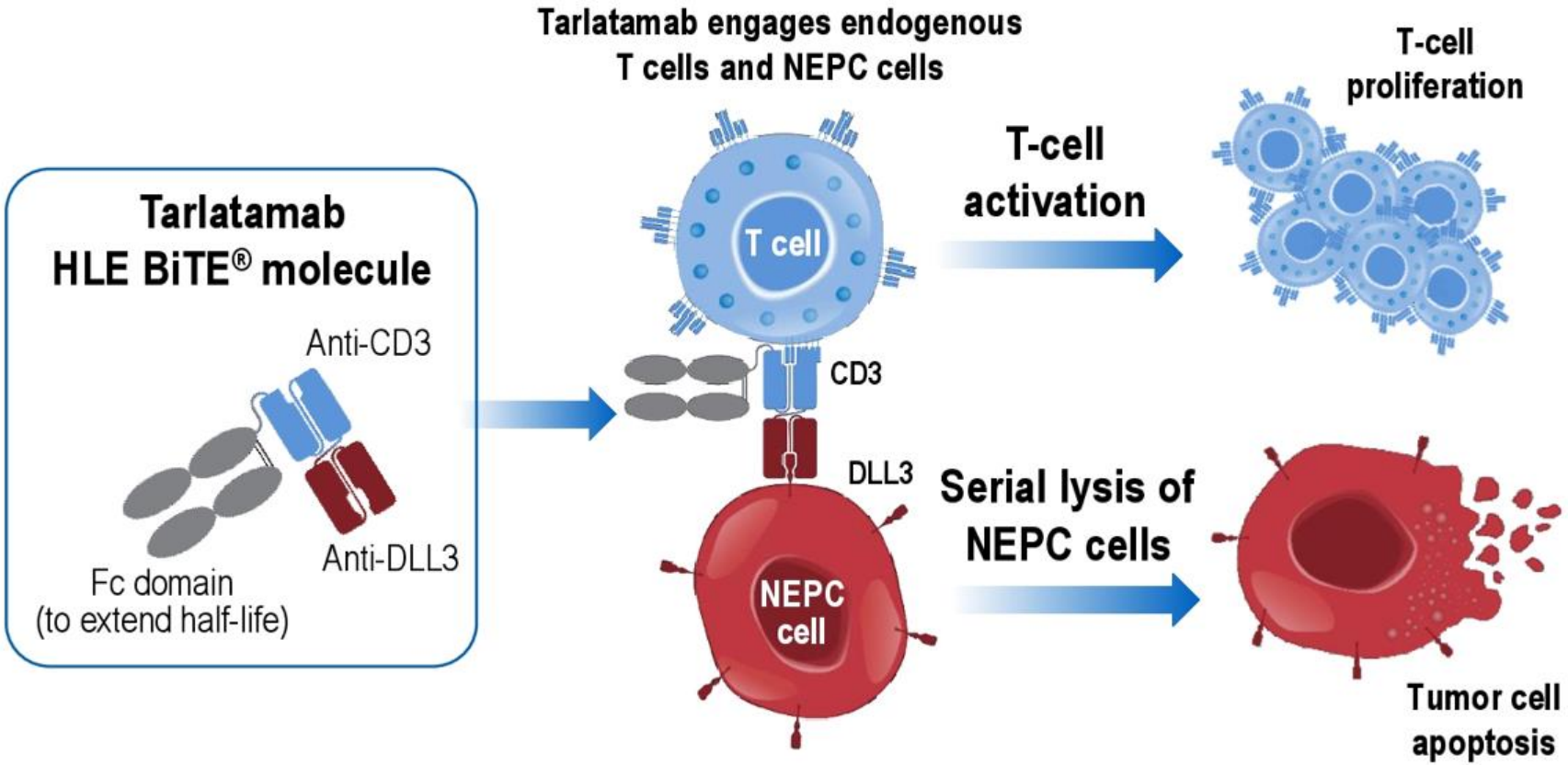




Puca L et al. Sci Transl Med 2019;11:1-12.

Yao J et al. The Oncologist 2022;27:940–951

Tarlatamab: HLE BiTE Targeting DLL3

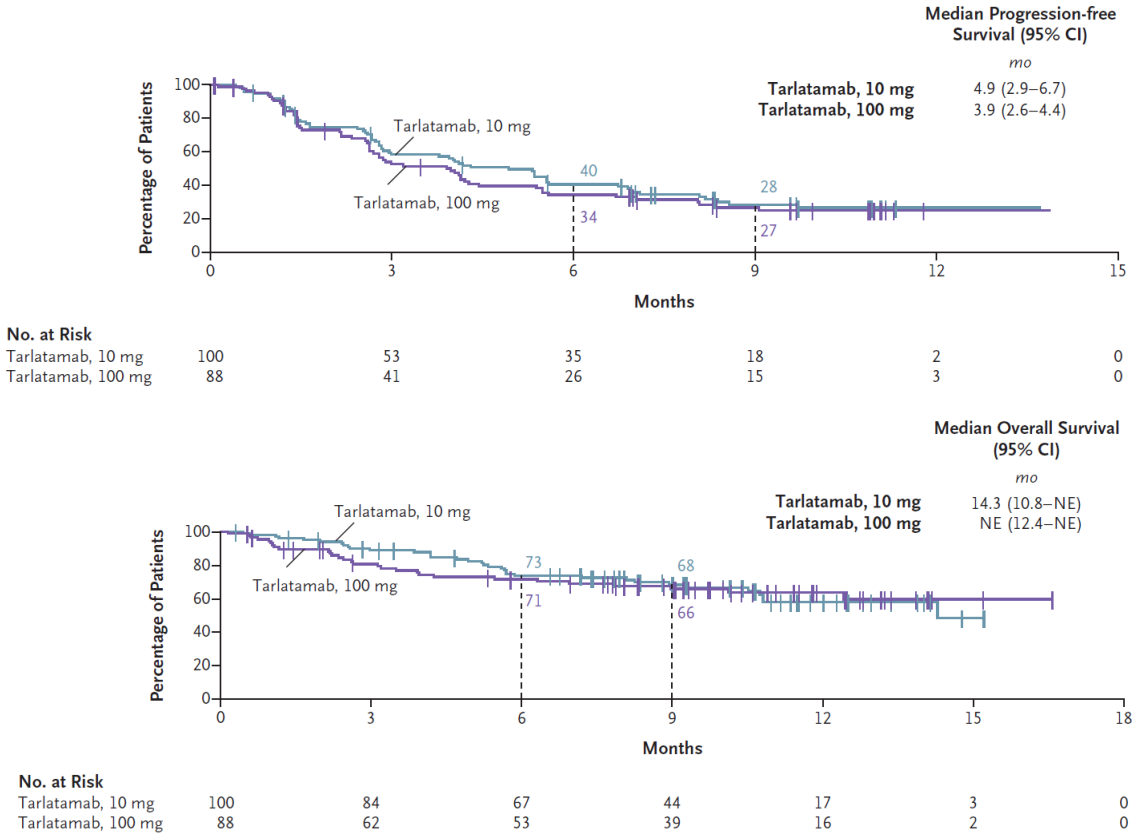


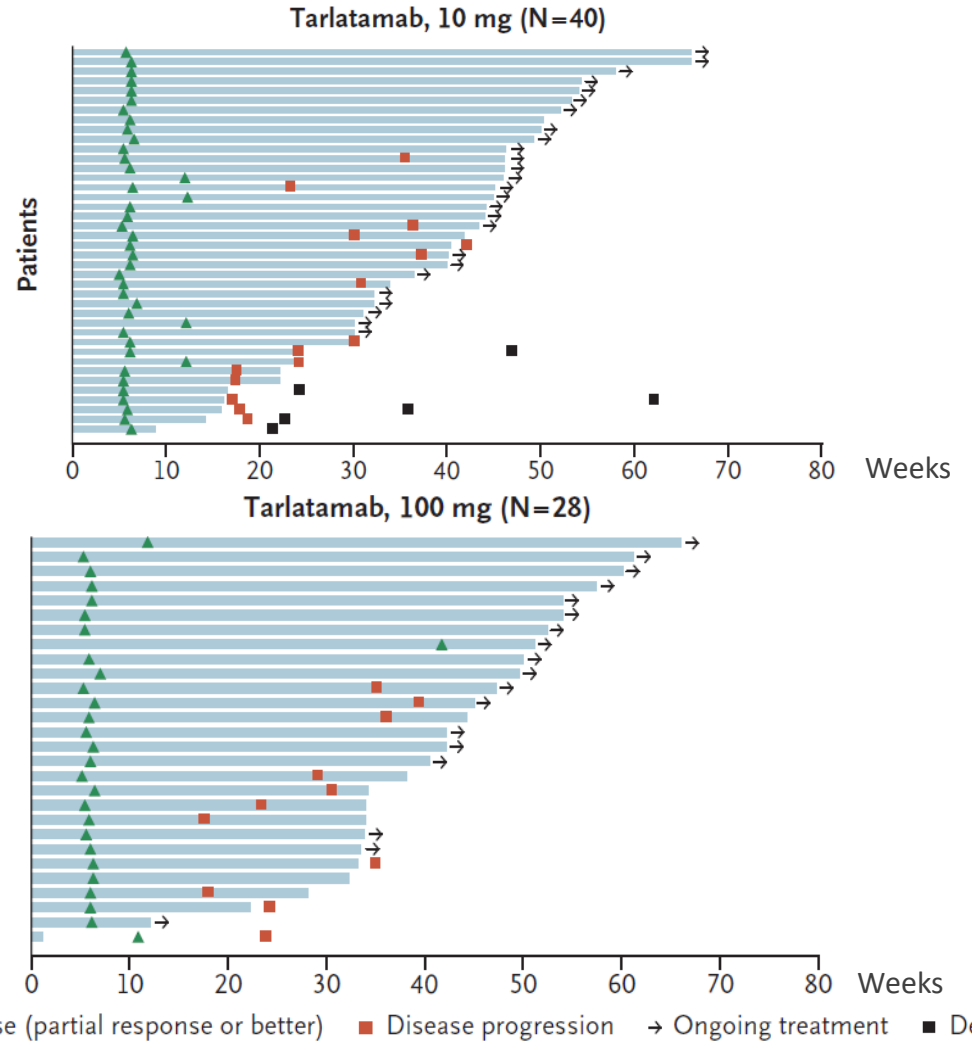
Aggarwal R et al. ASCO 2021. TPS5100

Second-Line

Ahn M-J et al. N Engl J Med 389;22:2063-2075

Tarlatamab in Previously Treated SCLC (N=188)





Granted accelerated approval by FDA May 16, 2024 for treatment of adult patients with ES-SCLC who have progressed on or after platinum-based chemotherapy.

5012 Rapid Oral Abstract Session

Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer (NEPC).

Rahul Raj Aggarwal, Sylvie Rottey, Alice Bernard-Tessier, Begoña Mellado-Gonzalez, Takeo Kosaka, Walter Michael Stadler, Shahneen Sandhu, Brian Yu, Crystal Shaw, Chia-Hsin Ju, Corbin Thompson, Ana Aparicio; University of California, San Francisco, San Francisco, CA; Gent University Hospital, Gent, Belgium; Gustave Roussy Cancer Campus, Villejuif, France; Hospital Clinic i Provincial de Barcelona, Barcelona, Spain; Keio University School of Medicine, Shinjuku-Ku, Japan; The University of Chicago Medicine, Chicago, IL; Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia; A
The University of Texas MD Anderson Cancer Center, Houston, TX

Exploratory analysis of DLL3 expression was assessed by IHC using the Ventana SP347 assay

Tarlatamab response per RECIST v1.1 (local assessment).

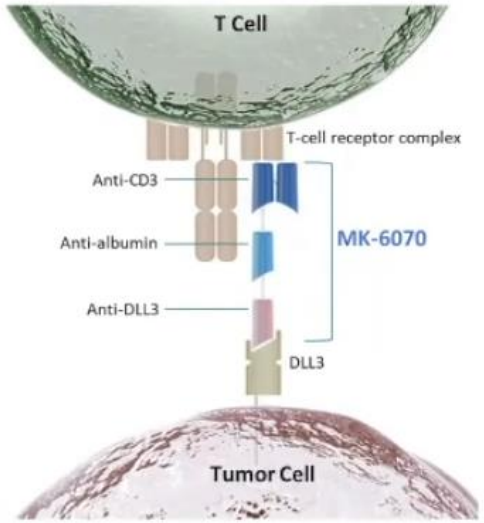
Variable, n (%)	Evaluable Patients (N=38)	DLL3+ (N=18)
Best overall response		
Complete response	0	0
Partial response	4 (10.5)	4 (22.2)
Disease control rate	12 (31.6)	10 (55.6)
Progressive disease	17 (44.7)	5 (27.8)
No post baseline scan	9 (23.7)	3 (16.7)

DLL3+ defined as ≥1% DLL3 tumor positivity.

Future Directions

Updated results from a phase 1/2 study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T-cell engager in patients (pts) with small cell lung cancer (SCLC) and other neuroendocrine cancers (NEC)

- MK-6070, also known as HPN328, is a DLL3-targeting T-cell engager developed using the TriTAC® platform[2]
  - Redirects T cells to kill DLL3-expressing cancer cells
  - Small protein of ~50 kDa designed to minimize non-specific T-cell activation and Fc receptor engagement



Phase 1/2 HPN328-4001 study of MK-6070

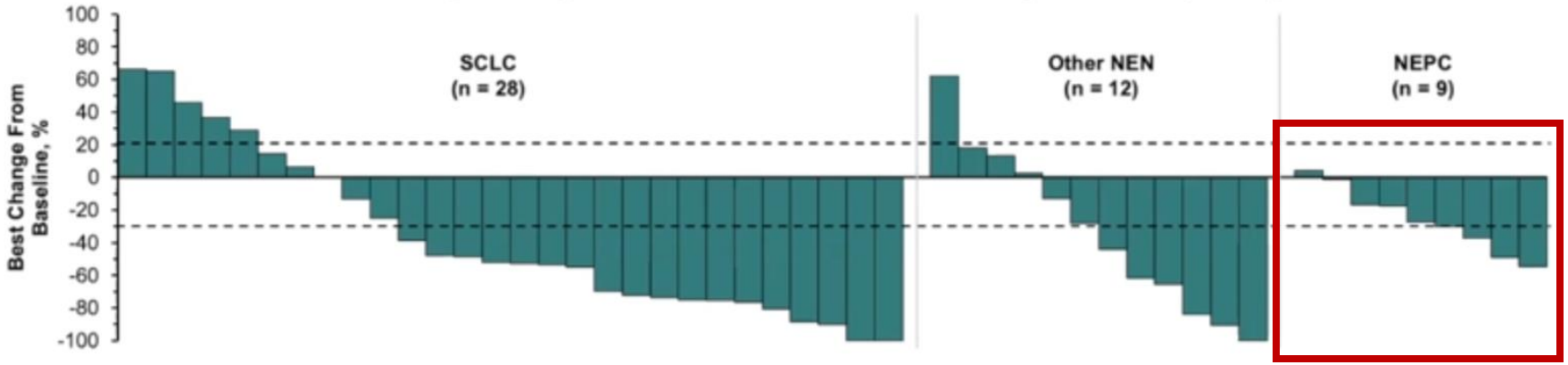
- Design: 3+3 dose escalation
- Dose optimization cohorts: 1-mg priming dose with target doses of 12 mg Q1W or Q2W and 24 mg Q1W or Q2W
- **Target population**
  - **SCLC relapsed/refractory after platinum-based chemotherapy**
  - **NEPC relapsed/refractory to SOC**
  - **Other high-grade NEN with DLL3 expression relapsed/refractory to SOC or no SOC available**
- Objectives
  - Assess safety and tolerability
  - Determine RP2D or MTD
  - Characterize PK and PD
  - Evaluate preliminary antitumor activity
- Current enrollment in monotherapy cohorts
  - All cohorts: N = 97
  - Dose optimization cohorts: n = 57

Beltran H et al. J Clin Oncol 42, 2024 (suppl 16; abstr 8090)

Anti-tumor Activity

Cohorts With a 1-mg Priming Dose and a 12- or 24-mg Target Dose

Best Percentage Change from Baseline in the Sum of Target Lesions (n = 49)[a]



Confirmed Response per RECIST v1.1

n (%)	SCLC (n = 28)	Other NEN[b] (n = 13)
ORR	11 (39%)	6 (46%)
DCR	20 (71%)	6 (46%)

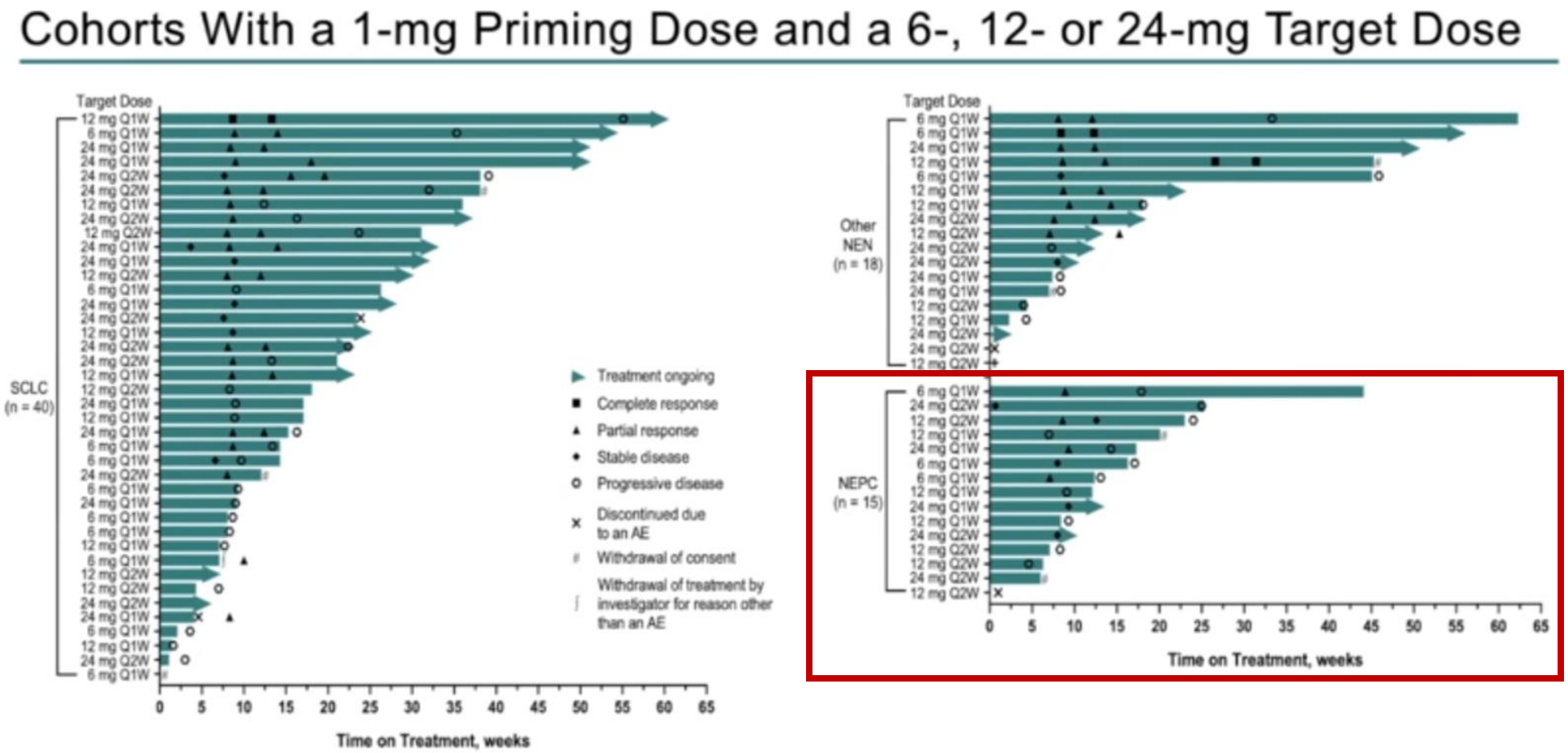
Confirmed Extracranial Response per RECIST v1.1[c]

n (%)	SCLC (n = 28)	Other NEN[b] (n = 13)
ORR	14 (50%)	6 (46%)
DCR	21 (75%)	6 (46%)

Beltran H et al. J Clin Oncol 42, 2024 (suppl 16; abstr 8090)

Future Directions

Duration of Treatment and Response (RECIST v1.1)



Beltran H et al. J Clin Oncol 42, 2024 (suppl 16; abstr 8090).

Future Directions

Selected summary of clinical studies in NEPC

APCCC ADVANCED PROSTATE CANCER

Agent	Target	Class	Phase	Result
Alisertib	Aurora kinase A	Small molecule	II	Futile: 6 mo PFS 13%, PFS 2 mo
Rovalpituzumab tesirine	DLL3	ADC	I/II	Terminated ORR 4.8%, PFS 4.5 mo
Avelumab	PD-1	Checkpoint inhibitor	II	Terminated, ORR 7%, PFS 1.8 mo
Carboplatin/cabazitaxel/ipi/nivo	CTLA-4/PD-1	Chemotherapy + checkpoint inhibition	II	Ongoing, successful stage 1!
Pembrolizumab + talabostat (BXCL701)	Checkpoint inhibitor + DPP 8/9	Checkpoint inhibitor + small molecule	II	Ongoing
Carbo/cabazi/cetrelimab followed by cetrelimab + niraparib	PARP	Checkpoint + PARP inhibitor	II	Ongoing
Pembrolizumab + lenvatinib	VEGF/MET/AXL/other	Checkpoint + TKI	II	Ongoing
Tarlatamab (AMG 757)	DLL3/CD3	Bi-specific T cell engager	I/II	Ongoing
HPN328	DLL3/CD3/albumin	TriTAC	I	Ongoing
JBI-802	LSD1/HDAC6	Small molecule	I	Ongoing
ORIC-944	EED/PRC2	Small molecule	I	Ongoing
ZEN-3694 + pembrolizumab + ENZ	BET bromodomain	CPI + small molecule	II	Ongoing
FOR46	CD46 epitope	ADC	I/II	Ongoing

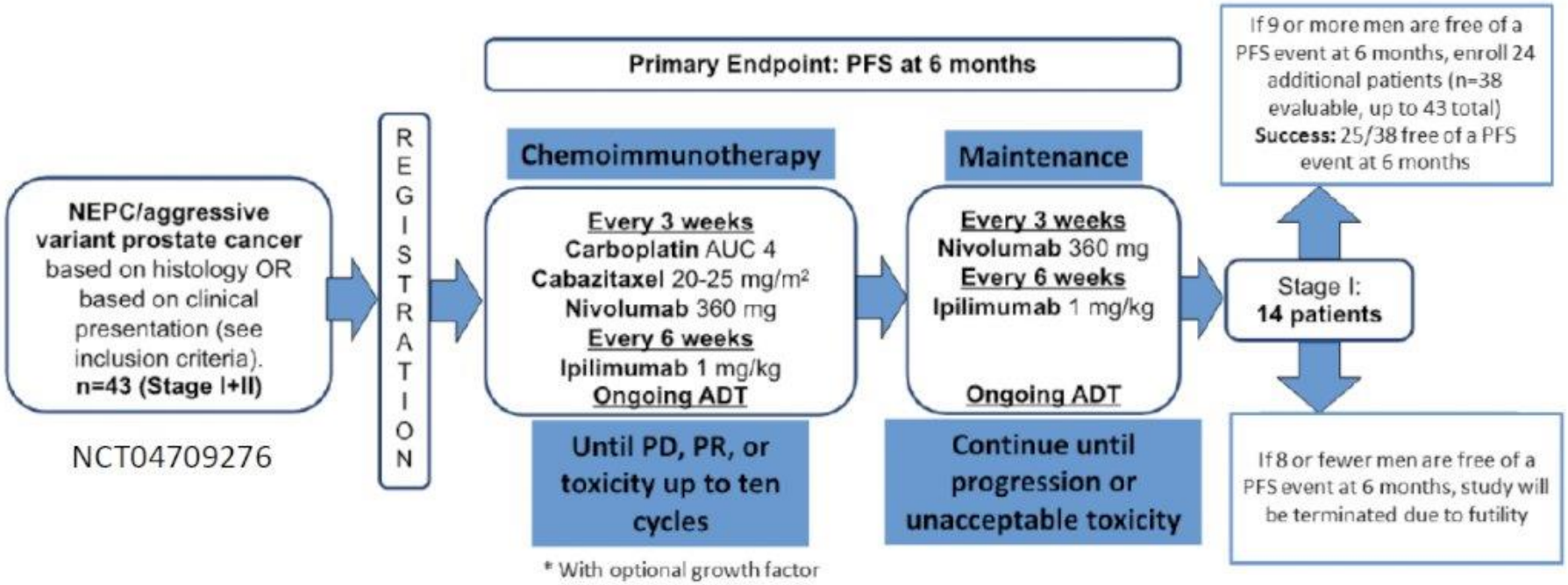
Slide Credit: Andrew J. Armstrong, MD, APCCC 2024

Future Directions

Duke Cancer Institute
Center For Prostate & Urologic Cancers

The CHAMP Trial

pcdtc The Prostate Cancer Clinical Trials Consortium



Stage 1 completed successfully: 64% free of progression/death at 6 mo
Stage 2 is now open (Duke, coming soon at MD Anderson and Cornell)

NCT04709276 (PI: Andrew J. Armstrong, MD)

Conclusions

- Repeat tumor or liquid biopsy in mCRPC setting when AVPC suspected
- Molecular profiling recommended
- Front-line platinum chemotherapy has become standard of care
  - Treatment generally follows SCLC per guidelines
- DLL3 is an attractive target
  - BiTE approved for eSCLC (tarlatamab) and TriTAC in development (MK-6070)
- Combination approaches may be needed given challenges of heterogeneity and disease plasticity
- Clinical trial enrollment necessary to define novel therapies

Thank you!

Grand Tetons National Park, August 2024