Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Phase II trial of Pembrolizumab and Lenvatinib in Advanced Neuroendocrine Prostate Cancer (PLANE-PC)

**Ulka Vaishampayan**

vaishamu@med.umich.edu

University of Michigan

**Jeremy (M. G.) Taylor**

University of Michigan

**Deepak Kilari**

Medical College of Wisconsin

**Tanya Dorff**

City of Hope https://orcid.org/0000-0001-5990-298X

**Alexandra Sokolava**

Oregon Health Sciences University

**Yaxuan Huang**

University of Michigan

**Phillip Palmbos**

University of Michigan Health System https://orcid.org/0000-0002-3134-2965

**Jacqueline Brown**

Emory University

**Irene Tsung**

University of Michigan https://orcid.org/0000-0002-9105-8659

**Megan Caram**

University of Michigan

**Sarah Yentz**

University of Michigan

**Bassel Nazha**

Piedmont Cancer Institute

**Zachery Reichert**

University of Michigan https://orcid.org/0000-0003-0356-8796

**Joshi Alumkal**

University of Michigan Rogel Cancer Center https://orcid.org/0000-0003-1278-0166

**Article**

**Keywords:** immune checkpoint therapy, anti-vascular therapy, small cell prostate cancer

**Posted Date:** April 23rd, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-9471666/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:**
**Yes** there is potential Competing Interest. Conflicts of Interest: UV has consulting activity with Merck, BMS, Janssen, Bayer, Pfizer, Astra Zeneca and Exelixis ZR has consulted for Janssen and AstraZeneca

The study protocol and consent were reviewed and approved by University of Michigan IRB annually at the lead site and by the IRB of each participating site. A signed written informed consent was obtained from every patient enrolled on the study.

**Phase II trial of Pembrolizumab and Lenvatinib in Advanced Neuroendocrine Prostate Cancer (PLANE-PC)**

Ulka N. Vaishampayan[1], Jeremy M.G. Taylor[2], Deepak Kilari,[3] Tanya B. Dorff[4], Alexandra Sokolova[5], Yaxuan Huang[2], Phillip Lee Palmbos[1], Jacqueline T Brown[6], Irene Tsung[1], Megan EV Caram[1], Sarah Elizabeth Yentz[1], Bassel Nazha[6,7], Zachery R Reichert[1], and Joshi J. Alumkal[1].

1. Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI

2. Department of Biostatistics, University of Michigan, Ann Arbor, MI

3. Division of Hematology and Oncology, Froedtert and the Medical College of Wisconsin, Milwaukee, WI

4. City of Hope Comprehensive Cancer Center, Duarte, CA

5. OHSU Knight Cancer Institute, Portland, OR

6. Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA.

7. Piedmont Cancer Institute, Atlanta, GA

Running Title: Lenvatinib and pembrolizumab in Neuroendocrine Prostate Cancer

Keywords: immune checkpoint therapy, anti-vascular therapy, small cell prostate cancer,

Word count: 2934 Tables-3 Consort Diagram: 1 Figures: 4

**Corresponding Author:**

Ulka Vaishampayan M.D.

Professor of Medicine/Oncology

7219 Rogel Cancer Center SPC 5948, 1500 E Medical Center Drive, Ann Arbor MI 48109.

Tel 734-936-7813 Fax 734-647-9480 E mail: vaishamu@med.umich.edu

**Acknowledgments:**

University of Michigan Rogel Cancer Center, NIH grant CA-46592

*Funding*: Pembrolizumab and grant funding for the trial was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Eisai Inc provided lenvatinib.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data Sharing Plan:** Data requests can be sent to PI DR Ulka Vaishampayan at vaishamu@med.umich.edu. The request will be reviewed and data will be shared if approved by study team, HCRN and study sponsor Merck Inc.

**ABSTRACT**

**Background:** Effective therapies remain a currently unmet need for neuroendocrine prostate cancer (NEPC). Preclinical synergy in small cell cancer, and clinical tolerability led to the conduct of a multicenter phase II trial of lenvatinib and pembrolizumab combination.

**Patients and Methods:** Eligible patients had histologically proven prostate cancer with radiologic evidence of metastases and at least one of the following: A) Small-cell or NEPC morphology B) Positive staining for chromogranin and synaptophysin C) Presence of visceral metastases or high volume disease (> 4 sites of metastases) and a PSA< 5ng/ml.D) Serum chromogranin A level $\geq$ 5× upper limit of normal (ULN) and/or serum neuron specific enolase (NSE) $\geq$ 2× ULN. E) RB1 deletions or mutations F) Trans-differentiated carcinoma. Maximum of 2 prior chemotherapy regimens were allowed. Performance status of 0-1 and normal marrow, renal and liver function were required. Primary endpoint was 6-month progression free survival (PFS). Secondary objectives included radiologic PFS, safety, overall survival (OS), overall response rate (ORR) and duration of response (DOR). Treatment consisted of lenvatinib orally daily at a starting dose of 20 mg daily and intravenous pembrolizumab 200 mg every 21 days. Imaging was conducted every 9 weeks for the first 4 assessments and then every 12 weeks thereafter. PSA was monitored on day 1 of each cycle.

**Results:** 45 patients were enrolled; of which 4 (9%) were African American. Median age was 69 years (range- 37-88 years), 16 (36%) had Gleason $\geq$ 8, 30 (67%) had small cell/NEPC, 1 had transdifferentiated histology (2%). 18 (40%) patients had liver metastases and 39 (87%) had measurable disease. 6 (13%) patients were chemotherapy naïve and 28 (62%) had received prior platinum-based therapy. 5 patients had grade 3 or 4 immune related adverse events. No treatment related deaths were noted. Of 40 response evaluable patients 10 (25%) had a partial response and

18 (45%) demonstrated stable disease. 10 patients (25%) were progression free at 6 months. The median PFS and OS were 3.9 (2.9-6.0) and 8.0 (5.9-12.3) months respectively.

**Conclusion:** The combination of lenvatinib and pembrolizumab demonstrated promising efficacy in a patient population that currently has no therapeutic options.

Clinical trials.gov: NCT04848337

## Introduction

Neuroendocrine prostate cancer (NEPC) is a rare and aggressive subtype of prostate cancer with limited treatment options and a dismal prognosis. NEPC resembles small cell lung cancer in pathophysiology and clinical course and outcomes. Cis/carboplatin and etoposide combination therapy is considered the standard regimen, but response rate was 9% and median survival was 9.3 months [1]. The diagnosis of NEPC is multifactorial and can be associated with clinical picture of progressive visceral metastases with low PSA, elevated serum chromogranin A or NSE levels, synaptophysin or chromogranin staining on immunohistochemistry, and molecular signature of TP53 mutation and RB loss [2-4]. Lineage plasticity is noted with conversion from luminal epithelial cells to basal androgen independent cells. Sox 2 overexpression and Rb and p53 loss, have been reported to create this lineage plasticity [5]. N-Myc overexpression has also been attributed to neuroendocrine differentiation of prostate cancer [2-5]. In addition to small cell NEPC, rising incidence of a clinical presentation of an aggressive subtype of prostate cancer called treatment emergent neuroendocrine prostate cancer was reported in approximately 17% of advanced prostate cancers [6]. This subtype maintained androgen receptor amplification and had a distinct transcriptomic signature. This entity typically presented after prolonged duration of

androgen receptor axis therapies, (ARAT). The term "aggressive variant prostate cancer" (AVPC) was coined to encompass the forms of advanced prostate cancer with predominantly lytic bone metastases, bulky tumor masses, low prostate-specific antigen (PSA) levels relative to tumor burden, or short response to androgen deprivation therapy, and rapidly progressive course [7, 8].

Immune checkpoint therapy has demonstrated limited activity in NEPC and AVPC. A single agent trial of avelumab in NEPC and AVPC showed response rates of 6.7%, with median radiologic progression free survival (rPFS) of 1.8 months and median overall survival (OS) of 7.4 months [9, 10]. Effective therapies in NEPC and AVPC remain a currently unmet need. The results of second line therapies to date have demonstrated limited efficacy and minimal clinical impact. The addition of anti-angiogenic therapies targeting vascular endothelial growth factor (VEGF), such as cabozantinib and lenvatinib have been reported to sensitize the tumor microenvironment to immune therapy and to have the potential to enhance the efficacy of immune checkpoint therapy. Lenvatinib is a multitargeted tyrosine kinase inhibitor (TKI) with anti-VEGF, and FGFR inhibitory activity that demonstrated promising tumor regression effects in a small cell lung cancer tumor model; H 146. The tumor shrinkage was affected through stem cell factor (SCF) induced angiogenesis inhibition [10, 11]. In a murine immunocompetent model of anaplastic cancer, lenvatinib monotherapy increased tumor-infiltrating macrophages, CD8+ T-cells, regulatory T-cells, and most notably polymorphonuclear myeloid derived suppressor cells (PMN-MDSCs). Combination with other anti-vascular therapies led to increases in CD8+ T-cells, only the lenvatinib and anti-PD-1 combination decreased PMN-MDSCs [12]. Clinical trial of lenvatinib in intestinal and pancreas neuroendocrine cancers revealed promising efficacy [13]. Combination of lenvatinib and pembrolizumab has been investigated in metastatic castrate resistant prostate cancer with tolerability established, and preliminary efficacy of 36% measurable disease response rate

and median radiologic PFS of 7.9 months noted [14]. The combination demonstrated safety and robust efficacy in other malignancies and is currently FDA approved in advanced endometrial and renal clear cell cancer [15].

In summary preclinical studies suggested a potential synergistic effect when combining anti-VEGF and anti-PD-1/PD-L1 agents. Specifically, anti-VEGF therapy appeared to overcome resistance to immune checkpoint blockade by normalizing tumor vasculature, improving immune cell infiltration, and potentially modulating the immunosuppressive tumor microenvironment. Conversely, PD-1 inhibition may enhance the effects of anti-angiogenic therapies by promoting T-cell activity and suppression of PMN-MDSC. The rationale for combined targeting of angiogenesis and immune checkpoints led to initiation and conduct of current multicenter phase II clinical trial to investigate the safety and efficacy of lenvatinib combined with pembrolizumab in patients with NEPC and AVPC. The study aimed to evaluate the overall response rate and safety profile of this combination therapy, addressing the urgent need for improved treatment options in this challenging disease.

**Patients and Methods:**

This was a study conducted through the Hoosier Clinical Research Network (HCRN) and led by University of Michigan with 4 other centers participating: Emory University, Medical College of Wisconsin, City of Hope Cancer Center and University of Oregon. Eligible patients had histologically proven prostate cancer with evidence of metastases and at least one of the following:

1) Small-cell or NEPC morphology (determined by the enrolling center) based on tissue sample.

2) Prostate adenocarcinoma with IHC staining for neuroendocrine markers (e.g. Chromogranin and synaptophysin).
3) Presence of visceral metastases or high-volume disease (> 4 sites of metastases) with a PSA ≤ 5.
4) Serum chromogranin A level ≥ 5× upper limit of normal (ULN) and/or serum neuron specific enolase (NSE) ≥ 2× ULN.
5) RB1 deletions or mutations noted on genomic testing
6) Trans-differentiated carcinoma.

**Treatment Plan and Monitoring:**

Lenvatinib was administered orally daily with starting dose of 20 mg daily and pembrolizumab was administered intravenously at a dose of 200 mg every 21 days. Toxicity monitoring was conducted at least every 21 days. Dose modification for lenvatinib was permitted. Holding pembrolizumab for severe immune related toxicities was advised. Tumor assessment by imaging was conducted every 9 weeks for the first 36 weeks and subsequently every 12 weeks.

**Statistical Methods**

***Study Design***

The primary objective of the study was to evaluate 6-month radiographic progression free survival (rPFS) with lenvatinib and pembrolizumab combination therapy in metastatic neuroendocrine prostate cancer (NEPC). In cases with measurable disease, radiological progression time was defined as the date of Cycle 1 Day 1 to date of progression per RECIST 1.1 criteria for measurable disease and for patients with bone only metastases per PCWG3 criteria for patients with non-

measurable disease [16, 17]. For the binary primary endpoint, a 2-stage Simon near optimal design was used [18], with these input parameters: p0 = 0.10; p1 = 0.25; alpha = 0.125; and power = 0.90. This resulted in the following design features: N1 = 27; R1 = 2; N = 40; R = 6; Probability of Early Termination = 0.485; and Expected Sample Size = 33.70. Hence, if there were at least 3 successes (patients who have had $\geqslant$ 6.00 months of rPFS) in the 27 patients in Stage 1 then the study would proceed to Stage 2, otherwise it would terminate early. If there were at least 7 patients progression free for 6 months or longer, in the 40 evaluable patients, then the treatment would be considered promising.

***Data Analysis Methods***

A consort diagram shows information on duration of treatment (<=21 days, 22-180 days, >180 days), best response (not assessed, PD, SD, PR), and overall survival (< 6months, > 6 months).

Patients who did not have radiological assessment of progression were considered non evaluable for response. The assessment of best response and duration of response was restricted to evaluable patients. For the outcomes of PFS, OS and toxicities, the data from all enrolled patients were analyzed. The time of the event for PFS was defined in the following way: (i) For patients who had radiologically assessed progressive disease (PD) or clinically determined progression, that time to progression determined the event time. (ii) For patients who had radiological assessment but did not show PD and did not have clinical progression, if they died within 9 weeks of the last scan they were considered to have progression at the time of death, whereas if they survived more than 9 weeks after the last scan they were censored for PFS at the time of the last scan. (iii)

Kaplan -Meier analysis depicting PFS and OS was conducted. Stratified Kaplan Meier plots were used to assess the association between patient characteristics and time-to-event endpoints.

Swimmer plots were used to display time to progression (as defined by either radiological or clinical assessment), time on treatment and overall survival. Patients were separated by best response based on scans. PSA response, e (PSA >=1.0), and change in lesion diameter, were displayed using waterfall plots and line trajectory plots. Long term survivors were defined as those alive 12 months after they received the first dose.

**Results:**

***Patient characteristics:***

Between July 2021 and November 2024, 45 patients were enrolled and 40 were evaluable for response and progression. Table 1 summarizes patient characteristics. 4 (9%) African American patients were enrolled. Median age was 69 years (range- 37-88 years), 16 (36%) had Gleason $\geq$ 8, 30 (67%) had small cell/NEPC, 1 (2%) had transdifferentiated histology. 18 (40%) patients had liver metastases, 8 (18%) had lung metastases, 13 (29%) had other soft tissue and 6 (13%) had bone only metastases. 39 (87%) cases had measurable disease. 6 (13%) patients were chemotherapy naïve and 28 (62%) had received prior platinum-based therapy. 11 cases had received prior taxane based chemotherapy. Pre-treatment PSA value was < 1.0 ng/ml in 21 (47%) patients. 42% of the patients had next generation sequencing available. RB deletion was noted in 6 patients with de novo small cell cancer.

***Toxicities***

Detailed list of clinically relevant toxicities are summarized in Table 2. Grade 4 toxicities of lipase elevation and acute kidney injury were noted in 1 patient each. Grade 3 toxicities of hypertension, diarrhea, fatigue and anorexia occurred in 9, 2, 8 and 3 patients respectively. 3 patients had grade 3 immune related adverse events; of adrenal insufficiency, colitis and transaminitis. No unexpected

toxicities or treatment related deaths were noted. Dose reductions or interruptions of lenvatinib occurred in 17 of the 45 patients in the first 3 weeks of therapy. 18 patients completed 3 cycles without modification or interuption.

***Response and Survival [Table 3 and Figures 1-4]***

40 of 45 enrolled patients were considered evaluable for radiological response, as shown in the Consort diagram. For the best response 10 (25%) had a partial response, (8 were confirmed PR and 2 were unconfirmed PR) and 18 (45%) demonstrated stable disease and 12 (30%) had progressive disease [Figure 2]. 10 patients were progression free at 6 months among which 9 patients remained on therapy over 6 months (PFS time: 6.0-14.2 months), and primary endpoint of the study was met. Amongst all 45 patients median PFS and OS were 3.9 (2.9-6.0) and 8.0 (5.9-12.3) months respectively [Figure 1A-B]. For OS and PFS no differences in outcomes were noted within the subgroups by age (35-65, 66-72, 73-88 years) and race. Analysis of endpoints by sites of metastases; liver, lung, bone only and lymph node suggested no differences in PFS outcomes however OS outcomes were shorter in the subgroup with liver metastases [Table 3, Fig 1C-D]. Patients with liver metastases had median PFS =2.0 months and median OS = 5.7 months. Duration of treatment, time to progression, and overall survival for each individual patient are noted in Fig 2A with swimmer plots. The median duration of response amongst the 10 patients with PR was 3.6 months (range 1.8 months to 13.3 months). 14 (31%) patients remained on therapy for 6 months or greater duration. 24 patients had a baseline PSA of 1.0 or greater. The waterfall plot depicts a decline in PSA noted in 19 (79%) out of 24 patients [Figure 2B].

Since patients with liver metastases had distinctly shorter OS than patients with no liver metastases, other parameters were analyzed such as PSA kinetics and lesion size trajectories [Fig 3 A-D], separated by liver or no liver metastases. PSA kinetics plots and lesion size trajectories

are shown separated by best response in figures 4A-F. The majority of those with PR show initial decreases in PSA, whereas only a minority of those with SD and PD show an initial decrease in PSA.

There were 11 patients who survived longer than 12 months. The treatment duration was greater than 6 months for 9 of these, and less than 6 months for the other two. Three patients had bone-only metastases and two had liver metastases. 6 had adenocarcinoma with neuroendocrine features, 4 had AVPC and 1 had small cell carcinoma.

**Discussion:**

NEPC continues to be an orphan disease with a rapidly progressive aggressive disease course and an abbreviated overall survival. De novo small cell cancer of the prostate is rare, however with the awareness of AVPC and treatment emergent NEPC, increasing incidence is noted, especially with current paradigm of prolonged duration of androgen receptor axis targeted therapies (ARAT). Regardless of the nomenclature, prostate cancer with neuroendocrine features is uniformly refractory to the standard therapies that have otherwise proven efficacy in metastatic castrate resistant prostate cancer. These diseases typically do not express prostate specific membrane antigen (PSMA) and due to the lack of PSMA avid disease are unlikely to derive benefit from PSMA-Lu177 therapy. Fluoro deoxy glucose positron emission tomography or standard computed tomography is typically required to stage this disease. The incidence of NEPC is increasing as oral androgen receptor based doublets are being used earlier in the treatment of metastatic prostate cancer. Development of effective therapies in NEPC will subsequently impact the outcomes in prostate adenocarcinoma, as NEPC can present from a refractory/undifferentiated clone arising after prolonged duration of ARAT therapy. Our study demonstrated a response rate of 25% with clinical benefit rate of 70%. 25% of the patients were progression free for at least 6 months. This

shows that the combination of lenvatinib and pembrolizumab has the potential to offer a durable therapeutic benefit in NEPC, especially since no therapy has yet shown benefit post chemotherapy in this disease.

The role of immunotherapy in advanced NEPC remains unclear. Although studies adding atezolizumab demonstrated improved response rates in extrapulmonary small cell lung cancer, it did not show a statistically significant impact on PFS and OS. Atezolizumab and durvalumab were evaluated in the IMPOWER-133 and CASPIAN trials respectively in extensive stage small cell lung cancer [19]. The median PFS was 5.2 and 5.1 months and median OS was 12.3 and 13 months with addition of atezolizumab and durvalumab respectively, to carboplatin and etoposide frontline in extensive stage small cell lung cancer [19]. In a trial conducted in extrapulmonary neuroendocrine cancers, the addition of atezolizumab revealed an improved response rate of 57.1% as compared to 23.8% with chemotherapy [20]. This study showed a median PFS of 4.5 months and median OS of 10.9 months in the atezolizumab cohort. There were very few NEPC cases included in this retrospective study. It is important to make a distinction that the above trials are demonstrating outcomes in frontline therapy of neuroendocrine cancers and the current study evaluated patients in a pretreated setting. This prospective multicenter trial helps establish a contemporary threshold response for future clinical trials evaluating novel agents in NEPC. Presence of liver metastases is an important stratification factor as the OS outcomes were distinct with 11.7 and 5.6 months respectively for patients with or without liver metastases. PSA response (if detectable PSA) and decrease in longest diameter were surrogates of OS outcome.

There are few prospective trials evaluating post platinum therapy in NEPC or AVPC. Aurora kinase inhibitor alisertib was evaluated in this setting [21]. The primary endpoint of six-month rPFS was 13.4%, and median overall survival was 9.5 months. A retrospective multicenter study

of patients with de novo NEPC or therapy emergent -NEPC who received second-line therapy, and were treated with wide variety of treatment regimens was reported [22]. The median OS was 7.4 months and in the 11 patients receiving immunotherapy the median OS was 2.4 months. On this background, the activity of lenvatinib and pembrolizumab with a six-month rPFS of 25%, clinical benefit rate of 70%, median PFS of 4 months and median OS of 8 months in a pretreated post platinum setting, appears favorable.

The current trial lays the foundation for future exploration of immune checkpoint therapy-based combinations specifically in NEPC/AVPC. It is also the first prospective trial evaluating immunotherapy in combination with a multi targeted TKI therapy such as lenvatinib in pretreated NEPC/AVPC. Southwest Oncology Group (SWOG) 2012 is an ongoing randomized phase II/III trial comparing the combination of first line platinum/etoposide with or without atezolizumab in patients with poorly differentiated extrapulmonary small cell neuroendocrine carcinomas [23]. SWOG 2312 is evaluating a chemotherapy-based regimen of cabazitaxel with or without carboplatin in metastatic castrate-resistant prostate cancer (mCRPC), with patient stratification by aggressive variant signature, enabling study of a distinct AVPC cohort.

The neuroendocrine pathway in prostate cancer has multiple key characteristics with disruption of N-myc complex, aurora kinase-A overactivity and EZH-2 overexpression. Previous studies addressing these potential targets have demonstrated disappointing efficacy [21, 22]. Emerging trials are evaluating targeting specific proteins or pathways involved in NEPC development and progression. Targeting specific proteins on NEPC cells, such as DLL3, which is found on the surface of some NEPC cells is another exciting target. Tarlatamab is a bispecific T-cell engager, that targets DLL3 (delta-like ligand 3) on tumor cells and the CD3 receptor on T-cells, triggering T-cell activation and the release of cytokines that lead to tumor cell destruction. It

is FDA approved in extensive stage small cell prostate cancer and a study in NEPC demonstrated an ORR of 10.7% with duration of response of 7.3 months [24]. The toxicities from the cytokine release syndrome are considerable. B7H3 overexpression was reported in advanced refractory prostate cancer especially on aggressive variants. B7H3 targeted antibody drug conjugates or immunotherapies are demonstrating early promising in phaseI/II clinical trial testing [25]. Numerous clinical trials are underway to evaluate the effectiveness of these emerging targeted therapies and combinations in mCRPC, however it is imperative to include specific cohorts of NEPC and AVPC.

In conclusion the combination of lenvatinib and pembrolizumab demonstrated tolerability, promising efficacy, and the potential for durable remission in both NEPC and AVPC. This prospective phase II multicenter trial will serve as the foundation for building future therapies to improve clinical outcomes in this lethal disease.

**References:**

1. Flechon A, Pouessel D, Ferlay C, Perol D, Beuzeboc P, Gravis G et al. Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: results of the French Genito-Urinary Tumor Group (GETUG) P01 trial. Ann Oncol. 2011;22(11):2476–81.

2. Apostolidis L, Nientiedt C, Winkler EC, et al. Clinical characteristics, treatment outcomes and potential novel therapeutic options for patients with neuroendocrine carcinoma of the prostate. Oncotarget. 2019 Jan 1;10(1):17-29.

3. Beltran H, Prandi D, Mosquera JM, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer Nat Med 2016 ; 22:298–305.

4. Ku SY, Rosario S, Mu P, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance Science 2017; 355 ( 6320): 78-83.

5. Beltran H, Hruszkewycz A, Scher HI, et al. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. Clin Cancer Res 2019 Dec 1;25(23):6916-6924

6. Aggarwal R, Huang J, Alumkal J, et al. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. J Clin Oncol 2018; 36: 2492-2503.

7. Aparicio AM, Shen L, Tapia EL, Lu JF, Chen HC, Zhang J, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 2016; 22:1520–30.

8. Himisha Beltran 1, Scott Tomlins 2, Ana Aparicio, et al. Aggressive variants of castration-resistant prostate cancer Clin Cancer Res 2014 Jun 1;20(11):2846-50.

9. Landon C Brown, Susan Halabi, Jason A Somarelli , et al. A phase 2 trial of avelumab in men with aggressive-variant or neuroendocrine prostate cancer. Prostate Cancer Prostatic Dis. 2022 Apr;25(4):762-769.

10. Calles A, Aguado G, Sandoval C, Álvarez R. The role of immunotherapy in small cell lung cancer. Clin Transl Oncol. 2019 Aug;21(8):961-976. 5.

11. Kato, Y. U., Tabata, K., Kimura, T., Yachie-Kinoshita, A., Ozawa, Y., Yamada, K. & Funahashi, Y. (2019). Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. PloS one, 14(2), e0212513.

12. Gunda V, Gigliotti B, Ashry T, et al. Anti-PD-1/PD-L1 therapy augments lenvatinib's efficacy by favorably altering the immune microenvironment of murine anaplastic thyroid cancer. Int J Cancer. 2019 May 1;144(9):2266-2278. 6.

13. Jaume Capdevila. Nicola Fazio 2, Carlos Lopez, et al. Lenvatinib in Patients With Advanced Grade 1/2 Pancreatic and Gastrointestinal Neuroendocrine Tumors: Results of the Phase II TALENT Trial (GETNE1509) J Clin Oncol 2021 Jul 10;39(20):2304-2312

14. Augustin M, Laguerre B, Baldini C, et al. Pembrolizumab (pembro) plus lenvatinib (lenva) in patients (pts) with docetaxel- pretreated, metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-365 cohort E. J Clin Oncol 42, 2024 (suppl 4; abstr 148)

15. https://www.lenvima.com/-/media/Project/EISAI/Lenvima/PDF/prescribing-information.pdf

16. Eisenhauer EA, Therasse P, Bogaerts, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).Eur J Cancer 45;2009:228-247.

17. Scher H, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016; 34(12): 1402–1418.

18. Two Stage Phase II Clinical Trials" program in the PASS (2019) software. PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville,Utah, USA, ncss.com/software/pass.

19. Luckson Mathieu 1, Sujay Shah 1, Lee Pai-Scherf , et al. FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer Oncologist; 2021 May;26(5):433-438.

20. Ho IW, Chiang NJ, Lai JI, et al. Efficacy of atezolizumab combined with platinum and etoposide in the treatment of extrapulmonary neuroendocrine carcinoma. Oncologist. 2025 Mar 10;30(3):oyae372

21. Beltran H, Oromendia C, Danila DC, et al. A Phase II Trial of the Aurora Kinase A Inhibitor Alisertib for Patients with Castration-resistant and Neuroendocrine Prostate Cancer: Efficacy and Biomarkers. Clin Cancer Res. 2019 Jan 1;25(1):43-51.

22. Corbin J Eule, Junxiao Hu, Sulaiman Al-Saad, et al. Outcomes of Second-Line Therapies in Patients With Metastatic de Novo and Treatment-Emergent Neuroendocrine Prostate Cancer: A Multi-Institutional Study. Clin Genitourin Cancer 2023 Aug;21(4):483-490.

23. https://www.swog.org/clinical-trials/s2312

24. Rahul Aggarwal, Rottey S, Bernard-Tessier A, et al. Safety and Efficacy of Tarlatamab in Patients with Neuroendocrine Prostate Cancer: Results from the Phase 1b DeLLpro-300 Study. Clin Cancer Res (2025) 31 (18): 3854–3863.

25. Christina Guo 1, Ines Figueiredo 2, Bora Gurel, et al. B7-H3 as a Therapeutic Target in Advanced Prostate Cancer Eur Urol 2023 Mar;83(3):224-238. Clin Genitourin Cancer. 2023 Apr 24;21(4):483–490.

**Conflicts of Interest:**

UV has consulting activity with Merck, BMS, Janssen, Bayer, Pfizer, Astra Zeneca and Exelixis

ZR has consulted for Janssen and AstraZeneca

**Table 1 Patient Characteristics**

| **Characteristic** | **Patients N=45 (%)** |
|---|---|
| **Age: Median, range** | 69 [37, 88] |
| **Race** | |
| White | 40 (88.9) |
| Black or African American | 4 (8.9) |

| | |
|---|---|
| Unknown | 1 (2.2) |
| **Sites of Disease** | |
| Bone only | 6 (13.3) |
| Liver + anything else | 18 (40.0) |
| Lung involved (no liver) | 8 (17.8) |
| Lymph node only | 0 (0.0) |
| Other soft tissue | 13 (28.9) |
| **Measurable disease** | |
| Yes | 39 (86.7) |
| No | 6 (13.3) |
| **Performance Status (ECOG)** | |
| 0 | 14 (31.1) |
| 1 | 31 (68.9) |
| **Prior Therapy** | |
| No prior chemotherapy | 6 (13.3) |
| Platinum based | 28 (62.2) |
| Taxane only based | 11 (24.4) |
| No prior ARPI | 15 (33.3) |
| Prior ARPI | 30 (66.7) |
| **Type of disease** | |
| Small cell | 7 (15.6) |
| Adenocarcinoma with Neuroendocrine Features | 23 (51.1) |
| Adenocarcinoma | 14 (31.1) |
| Transdifferentiated/Undifferentiated | 1 (2.2) |

| | |
|---|---|
| **RB deletion present** | |
| Yes | 6 (13.3) |
| No | 13 (28.9) |
| Unknown | 26 (57.8) |
| **Pre-therapy PSA** | |
| <0.1 | 8 (17.8) |
| 0.1 – 1 | 13 (28.9) |
| 1– 4 | 6 (13.3) |
| 4 – 10 | 8 (17.8) |
| >10 | 10 (22.2) |
| **Gleason Score** | |
| 6 or below | 5 (11.1) |
| 7 | 9 (20.0) |
| 8 | 3 (6.7) |
| 9 | 10 (22.2) |
| 10 | 3 (6.7) |
| Unknown | 15 (33.3) |

**Table 2 Treatment Emergent Toxicities ***

| **Toxicity (N=45)** | **Lenvatinib** | | **Pembrolizumab** | |
|---|---|---|---|---|
| | **Grade 1/2** | **Grade 3/4** | **Grade 1/2** | **Grade 3/4** |
| **Adrenal insufficiency** | 0 | 1 | 0 | 1 |
| Alanine aminotransferase increased | 6 | 0 | 4 | 0 |
| **Aspartate aminotransferase increased** | 7 | 1 | 3 | 1 |
| Arthralgia | 4 | 0 | 8 | 0 |

| | | | | |
|---|---|---|---|---|
| Anorexia | 17 | 3 | 10 | 2 |
| Creatinine increased | 3 | 1 | 3 | 0 |
| Dehydration | 2 | 0 | 2 | 0 |
| **Diarrhea** | 14 | 2 | 12 | 1 |
| Dizziness | 9 | 0 | 4 | 0 |
| Dysgeusia | 6 | 0 | 0 | 0 |
| Dyspnea | 4 | 1 | 7 | 0 |
| Erythema Multiforme | 1 | 0 | 1 | 0 |
| **Fatigue** | 22 | 8 | 19 | 5 |
| **Hypertension** | 9 | 9 | 2 | 1 |
| Hypothyroidism | 7 | 0 | 9 | 0 |
| Mucositis oral | 5 | 2 | 4 | 0 |
| Nausea | 19 | 0 | 9 | 0 |
| Proteinuria | 4 | 0 | 1 | 0 |
| Rash maculo-papular | 6 | 0 | 5 | 0 |
| Palmar-plantar erythrodysesthesia | 4 | 0 | 1 | 0 |

*Toxicities are included with worse grade noted per patient.

Table 3 Response and Survival Outcomes for Lenvatinib + Pembrolizumab in NEPC and AVPC

| Patients (N) | ORR (%) | Median DOR* [min, max] | Median PFS (95% CI) | Median OS (95% CI) |
|---|---|---|---|---|
| Enrolled (45) | - | - | 3.9 (2.9, 6.0) | 8.0 (5.9, 12.3) |
| Evaluable (40) | 10/40 (25.0) | 3.6 [1.8, 13.3] | - | - |

| | | | | |
|---|---|---|---|---|
| Liver metastases (18) | 5/16 (31.3) | 2.2 [1.8, 4.7] | 2.0 (1.8, NA) | 5.7 (4.9, 9.9) |
| No liver metastases (27) | 5/24 (20.8) | 4.1 [2.1, 13.3] | 4.0 (3.4, 7.5) | 11.7 (7.4, 17.1) |
| Small cell (7) | 1/6 (16.7) | 3.2 | 2.0 (1.5, NA) | 8.0 (1.5, NA) |
| Adeno and Adeno w/ NEPC (37) | 9/33 (27.3) | 4.0 [1.8, 13.3] | 5.6 (2.9, 7.5) | 8.4 (5.6, 13.1) |
| Transdifferentiated/ Undifferentiated (1) | 0/1(0.0) | -- | 3.4 | 6.0 |
| Age > 69 years (22) | 6/18 (33.3) | 3.6 [1.9, 13.3] | 4.0 (2.0, 8.1) | 7.7 (5.9, 14.5) |
| Age < =69 years (23) | 4/22 (18.2) | 3.0 [1.8, 4.7] | 3.9 (2.9, 7.0) | 8.4 (5.4, NA) |

DOR: duration of response. The median DOR is calculated as the median of a set of individual response durations. For PFS and OS, the median is derived from the Kaplan-Meier (KM) curve.
ORR: overall response rate.

**Consort Diagram**

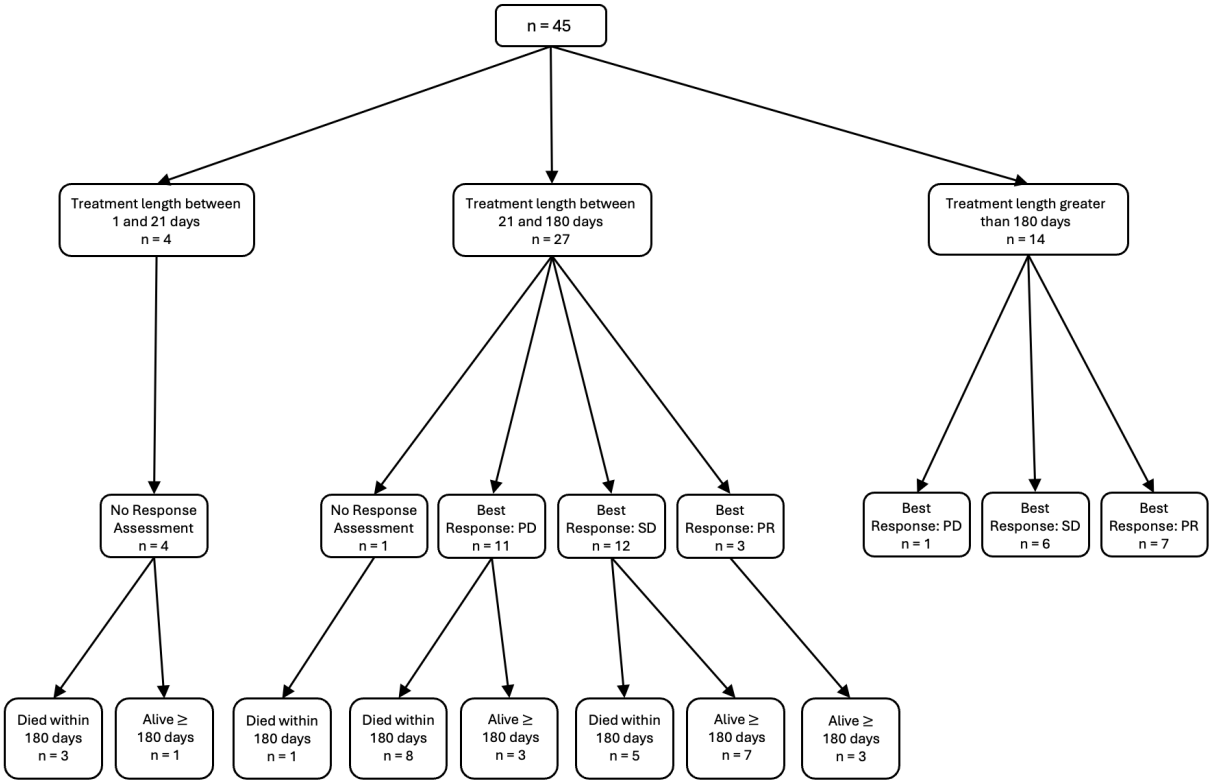

n = 45
Treatment length between 1 and 21 days n = 4
Treatment length between 21 and 180 days n = 27
Treatment length greater than 180 days n = 14
No Response Assessment n = 4
No Response Assessment n = 1
Best Response: PD n = 11
Best Response: SD n = 12
Best Response: PR n = 3
Best Response: PD n = 1
Best Response: SD n = 6
Best Response: PR n = 7
Died within 180 days n = 3
Alive ≥ 180 days n = 1
Died within 180 days n = 1
Died within 180 days n = 8
Alive ≥ 180 days n = 3
Died within 180 days n = 5
Alive ≥ 180 days n = 7
Alive ≥ 180 days n = 3

Fig 1A

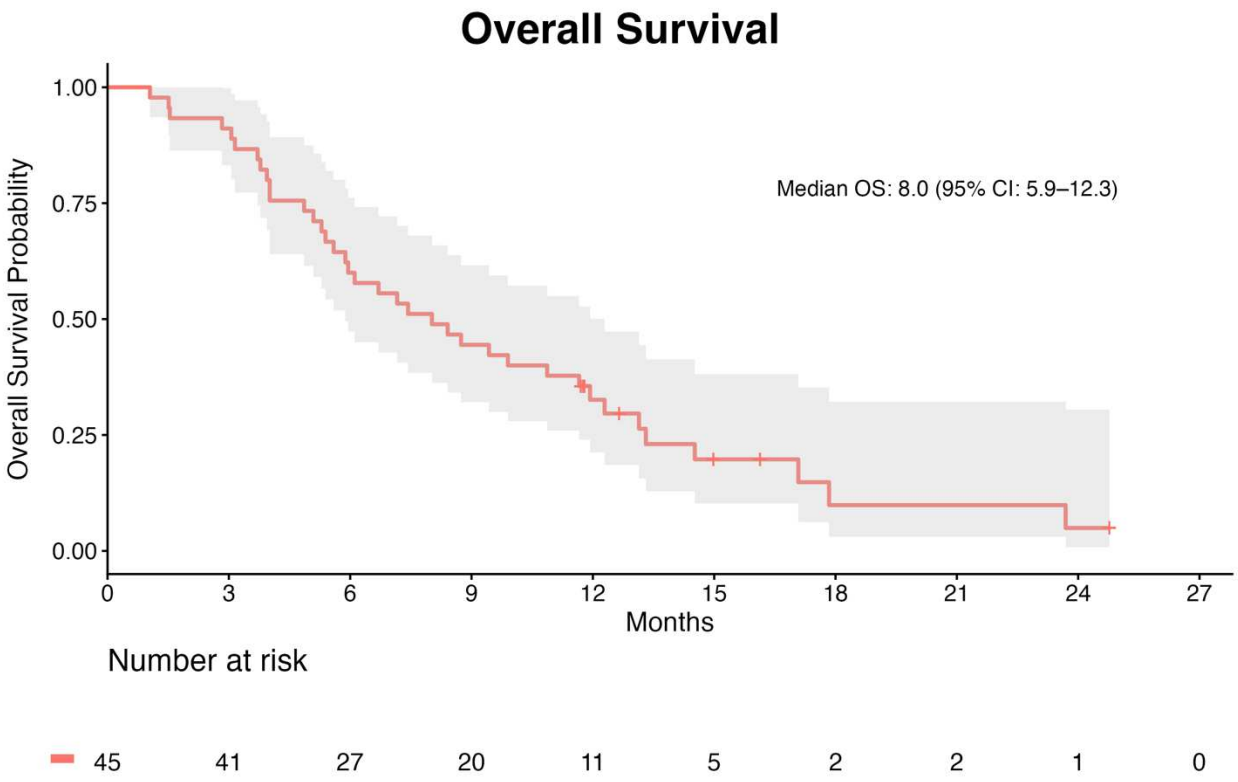

Overall Survival
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
Median OS: 8.0 (95% CI: 5.9–12.3)
0
3
6
9
12
15
18
21
24
27
Months
Number at risk
45
41
27
20
11
5
2
2
1
0

Fig 1B

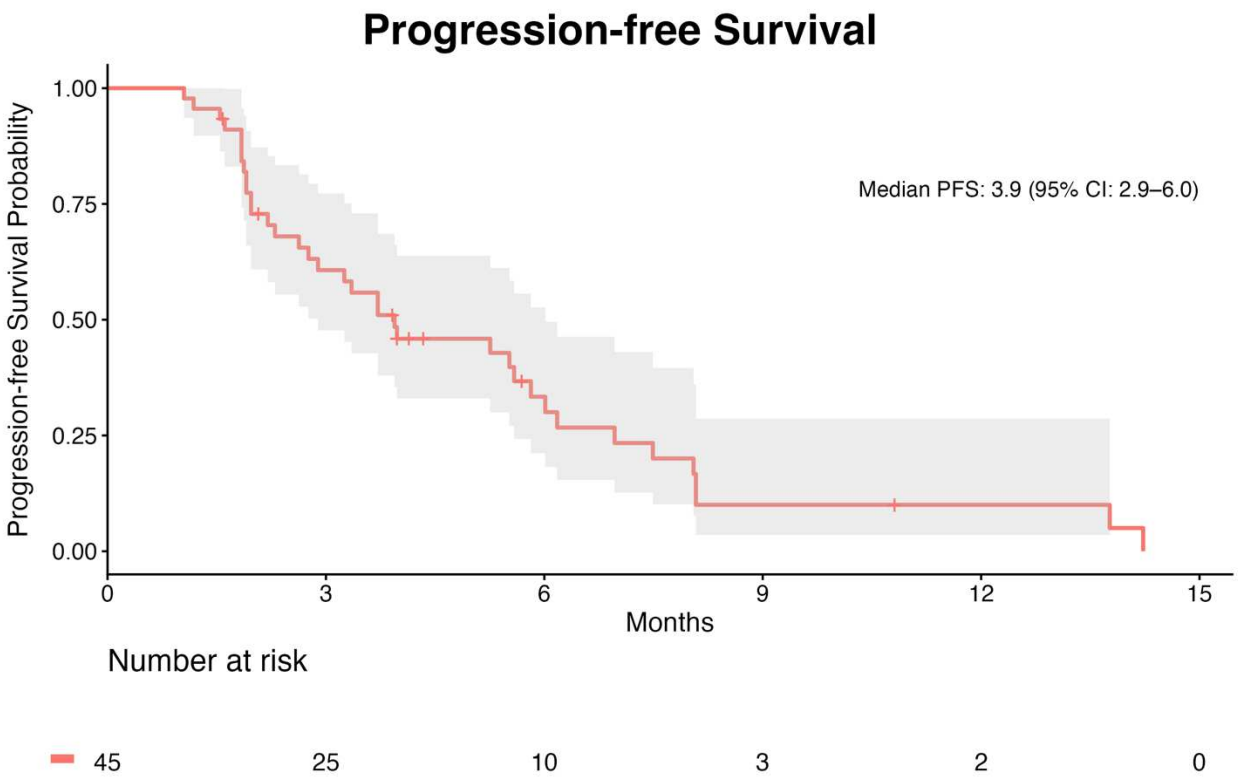

Progression-free Survival
Progression-free Survival Probability
1.00
0.75
0.50
0.25
0.00
Median PFS: 3.9 (95% CI: 2.9–6.0)
0
3
6
9
12
15
Months
Number at risk
45
25
10
3
2
0

Fig 1C

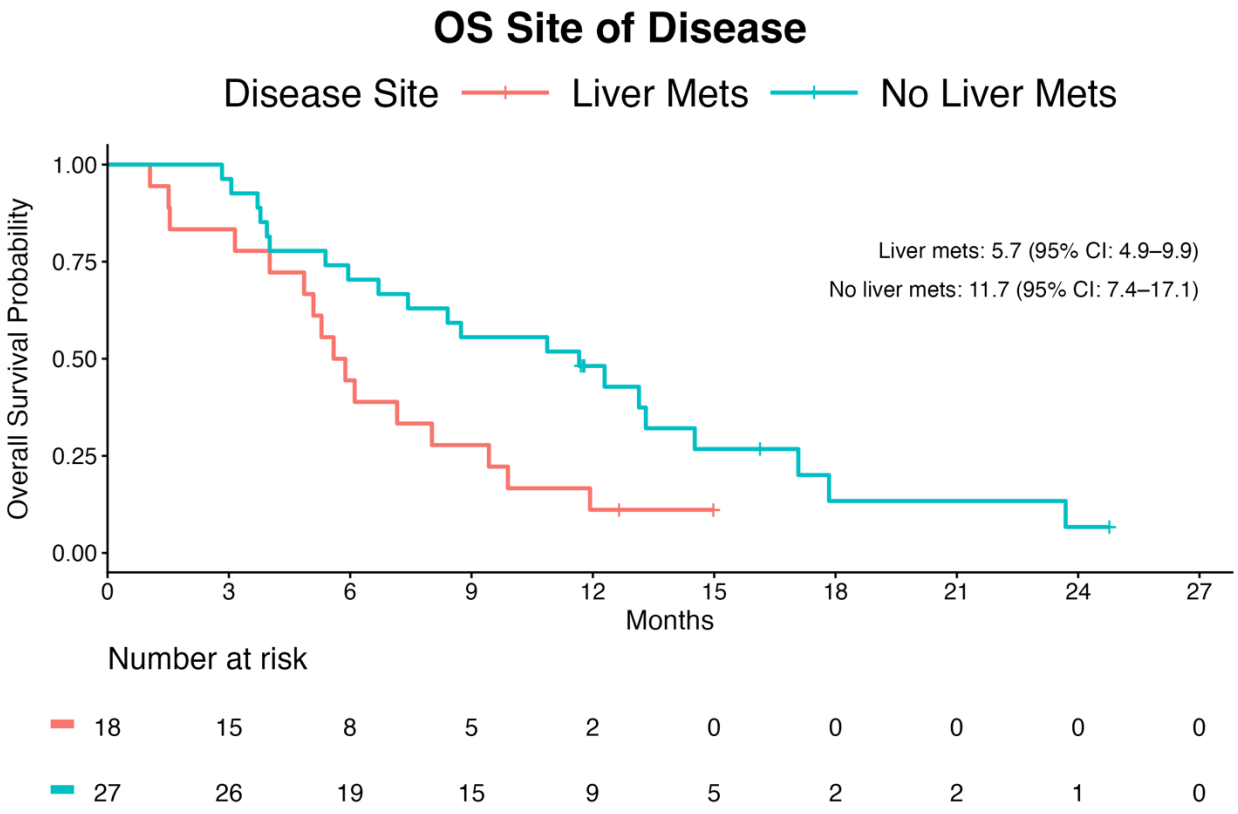

OS Site of Disease
Disease Site
Liver Mets
No Liver Mets
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
Liver mets: 5.7 (95% CI: 4.9–9.9)
No liver mets: 11.7 (95% CI: 7.4–17.1)
0
3
6
9
12
15
18
21
24
27
Months
Number at risk
18 15 8 5 2 0 0 0 0 0
27 26 19 15 9 5 2 2 1 0

Fig 1D

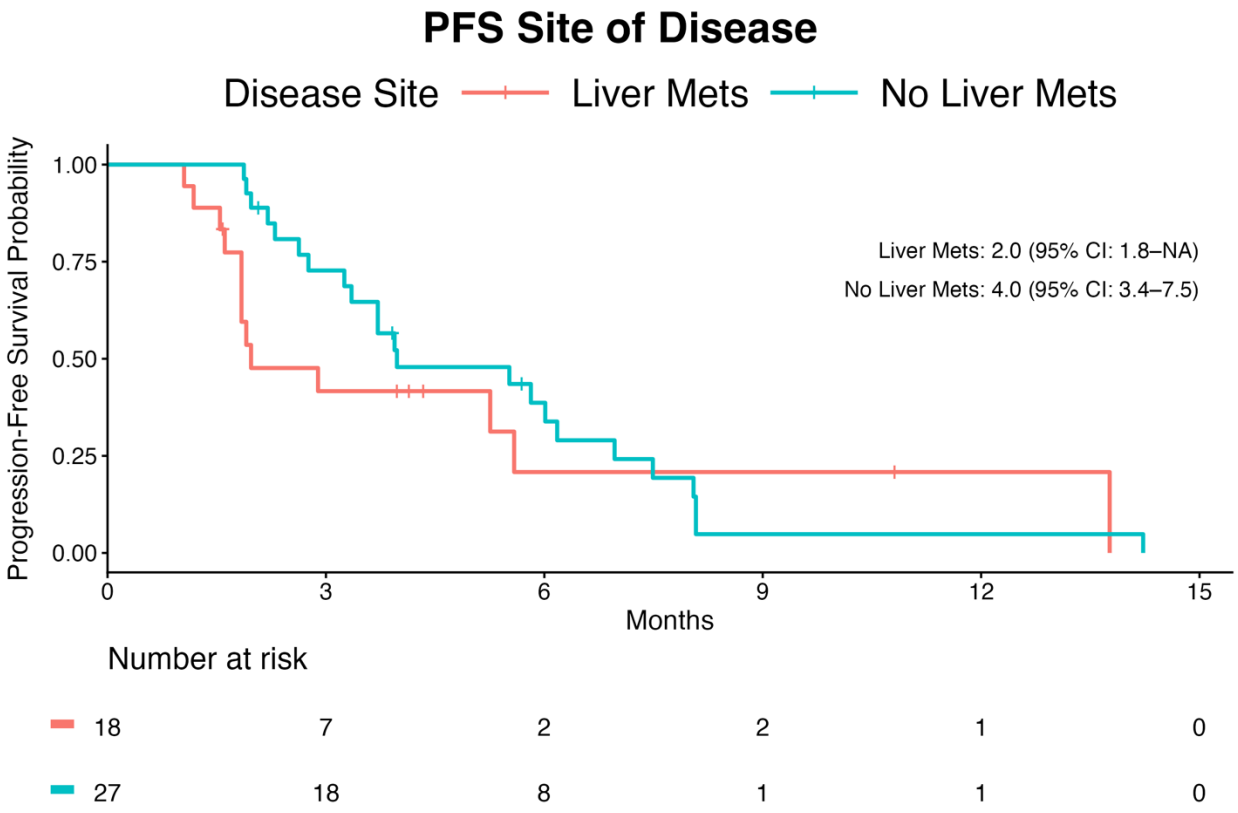

PFS Site of Disease
Disease Site
Liver Mets
No Liver Mets
Progression-Free Survival Probability
1.00
0.75
0.50
0.25
0.00
Liver Mets: 2.0 (95% CI: 1.8–NA)
No Liver Mets: 4.0 (95% CI: 3.4–7.5)
0
3
6
9
12
15
Months
Number at risk
18 7 2 2 1 0
27 18 8 1 1 0

Fig 2A Swimmer Plot (based on progression time in ‘Data Analysis Methods’ section)

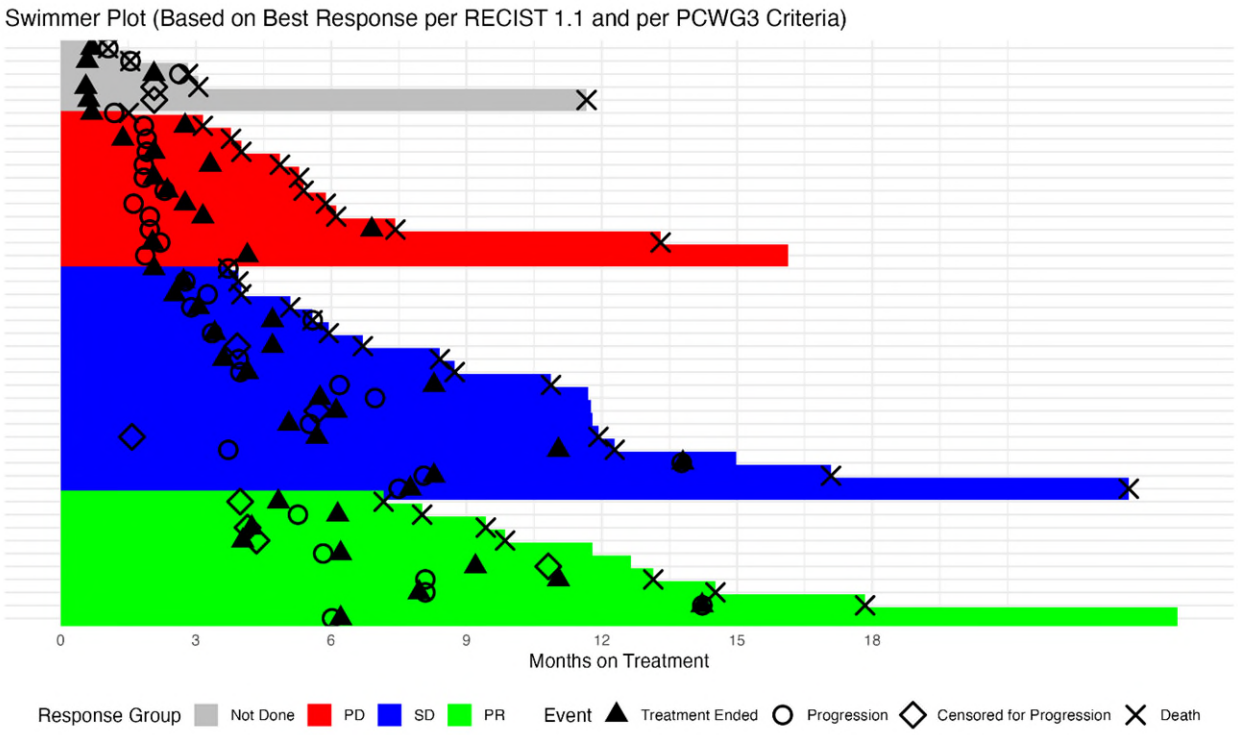
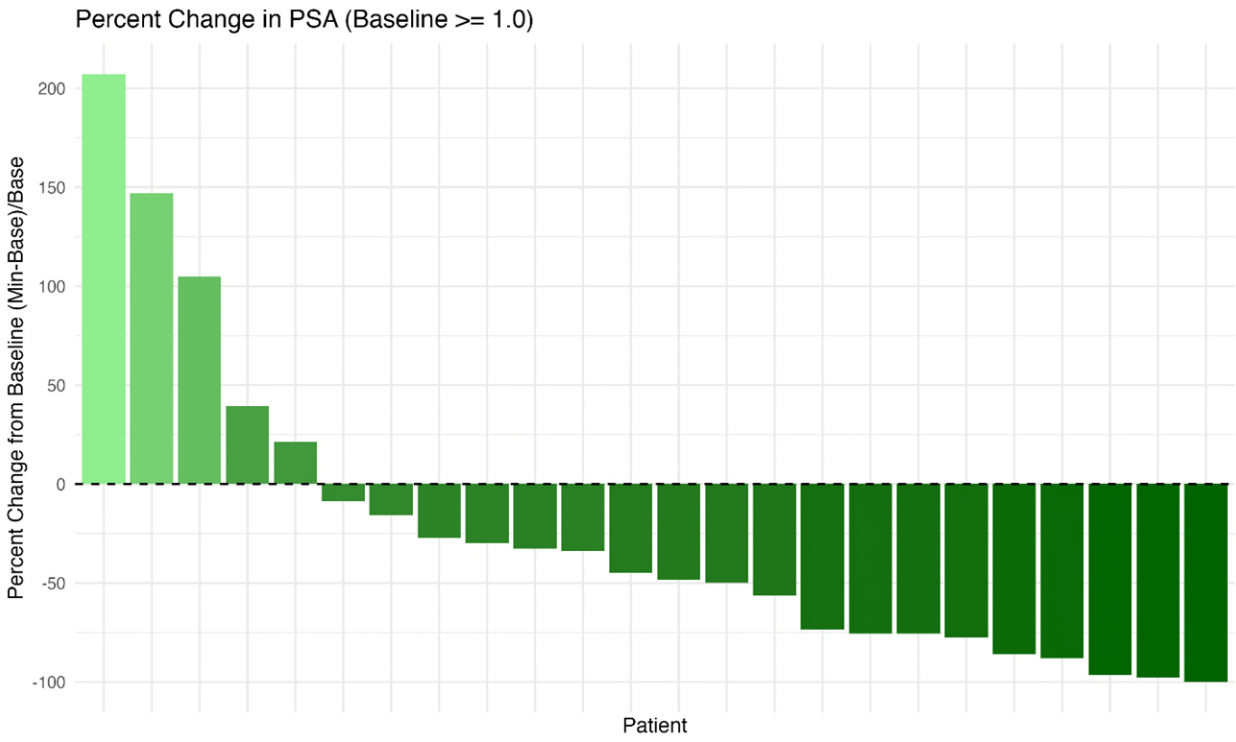


Fig 2B Waterfall Plot of maximal PSA change



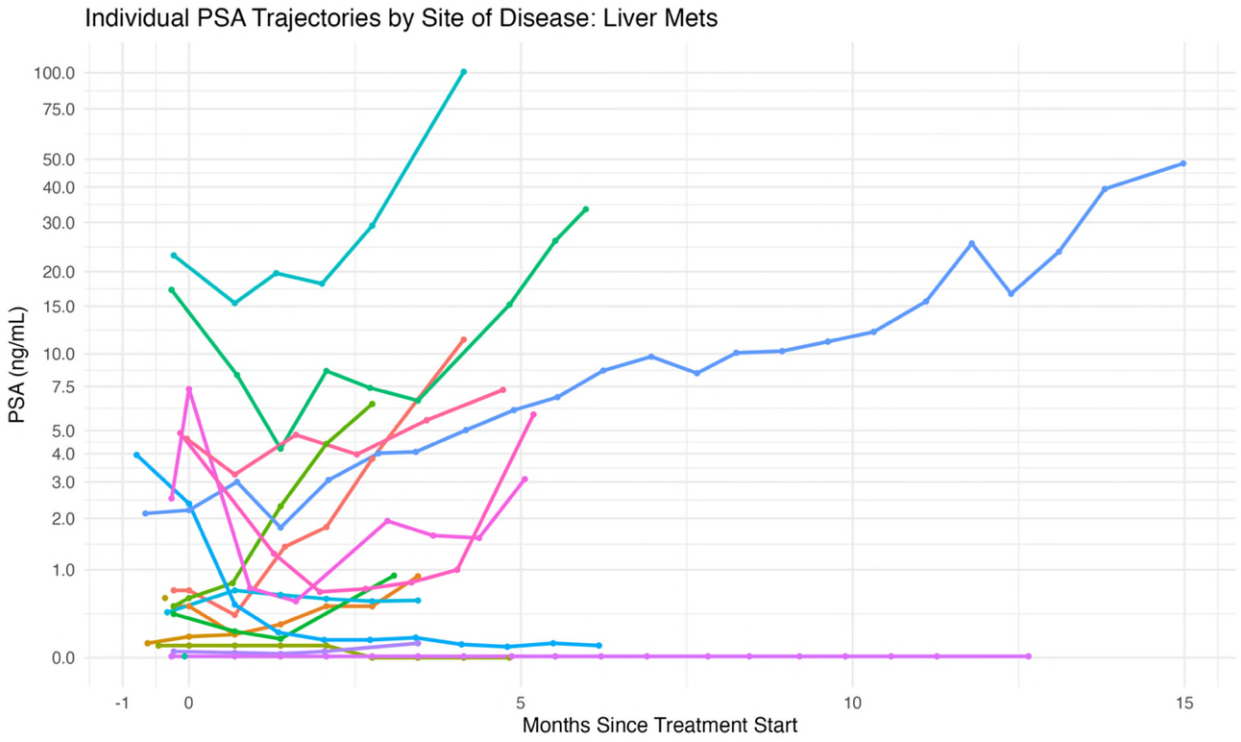
Figures 3 A-D

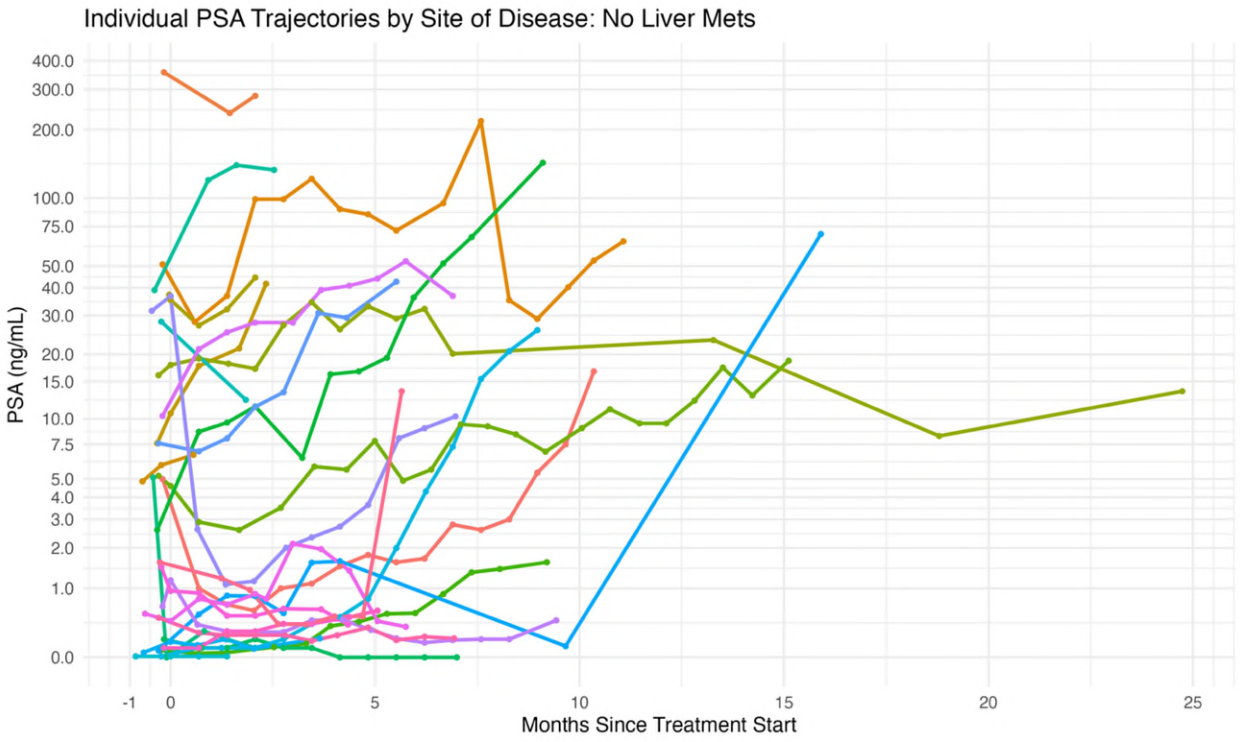
3A PSA change in patients with liver metastases

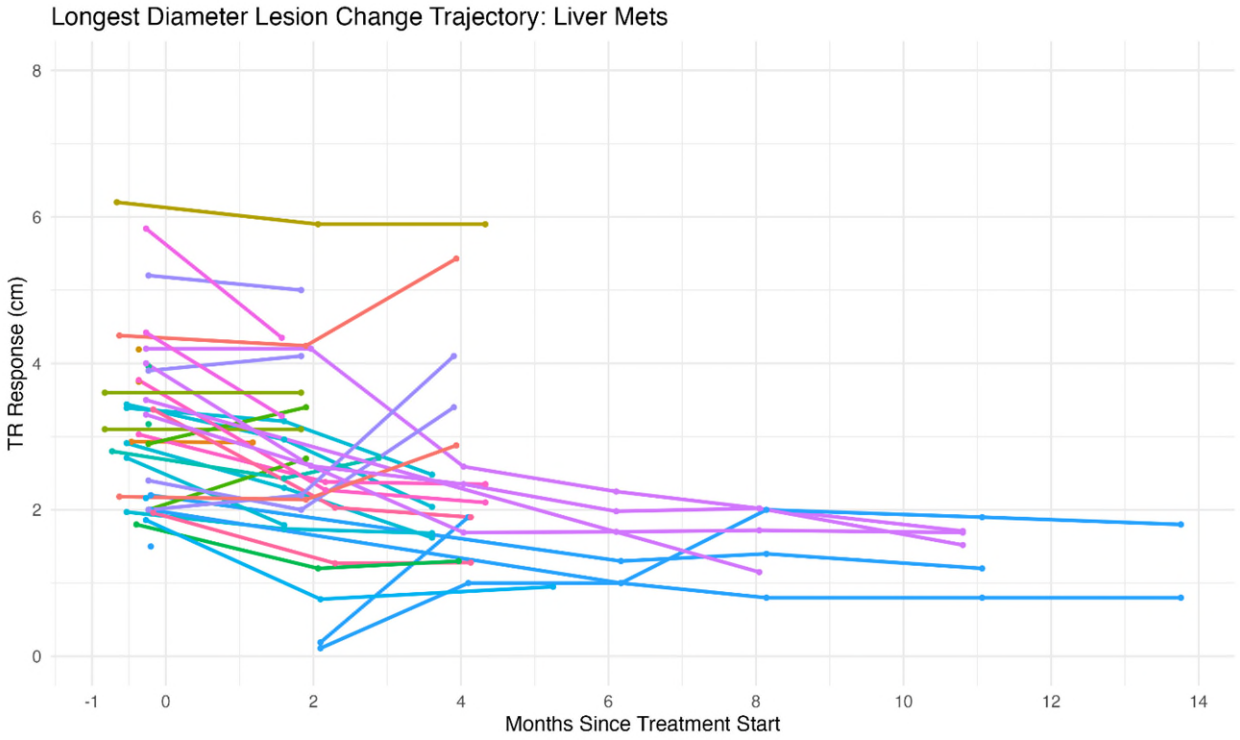
3B- PSA change in patients with no liver metastases

3C Longest diameter lesion change trajectory with liver metastases

3D Longest diameter lesion change trajectory with no liver metastases




Individual PSA Trajectories by Site of Disease: No Liver Mets
PSA (ng/mL)
400.0
300.0
200.0
100.0
75.0
50.0
40.0
30.0
20.0
15.0
10.0
7.5
5.0
4.0
3.0
2.0
1.0
0.0
-1
0
5
10
15
20
25
Months Since Treatment Start


Longest Diameter Lesion Change Trajectory: Liver Mets
TR Response (cm)
8
6
4
2
0
-1
0
2
4
6
8
10
12
14
Months Since Treatment Start

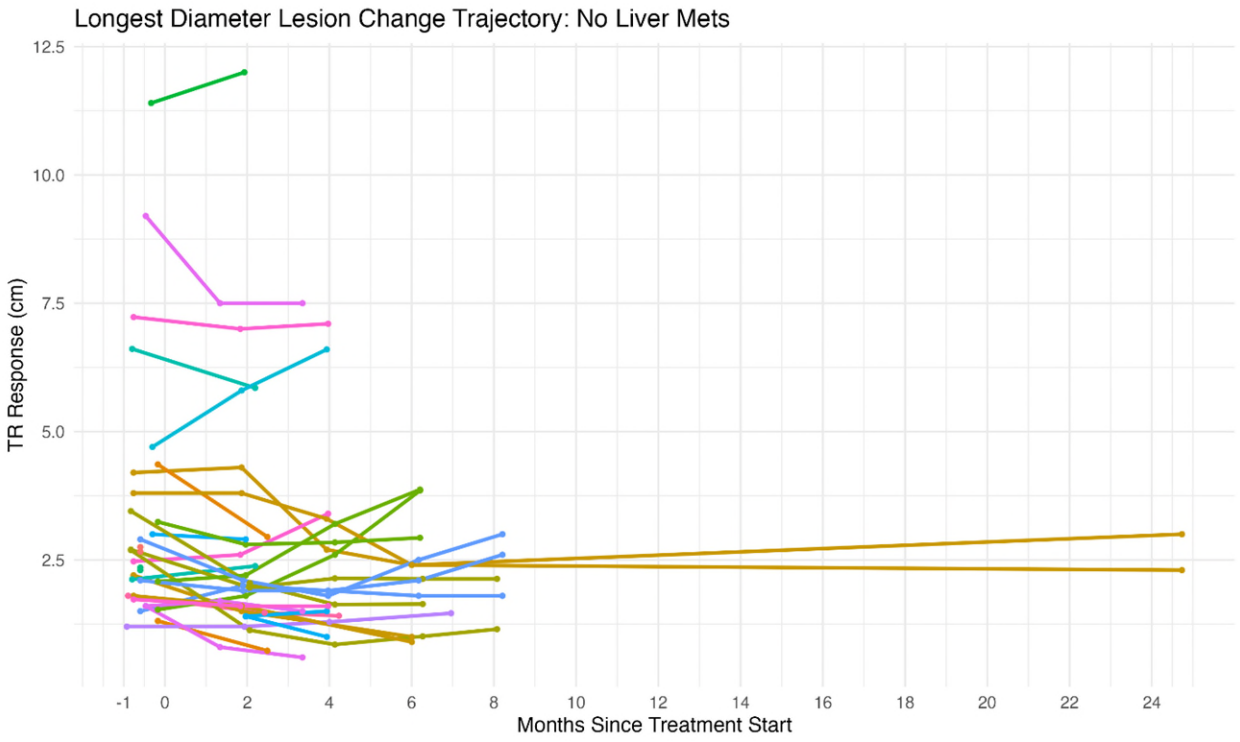



**Figure 4 PSA trajectories Stratified by Best Response**

**Fig 4 A-F**

**4A: PSA trajectories in Partial Response cases**

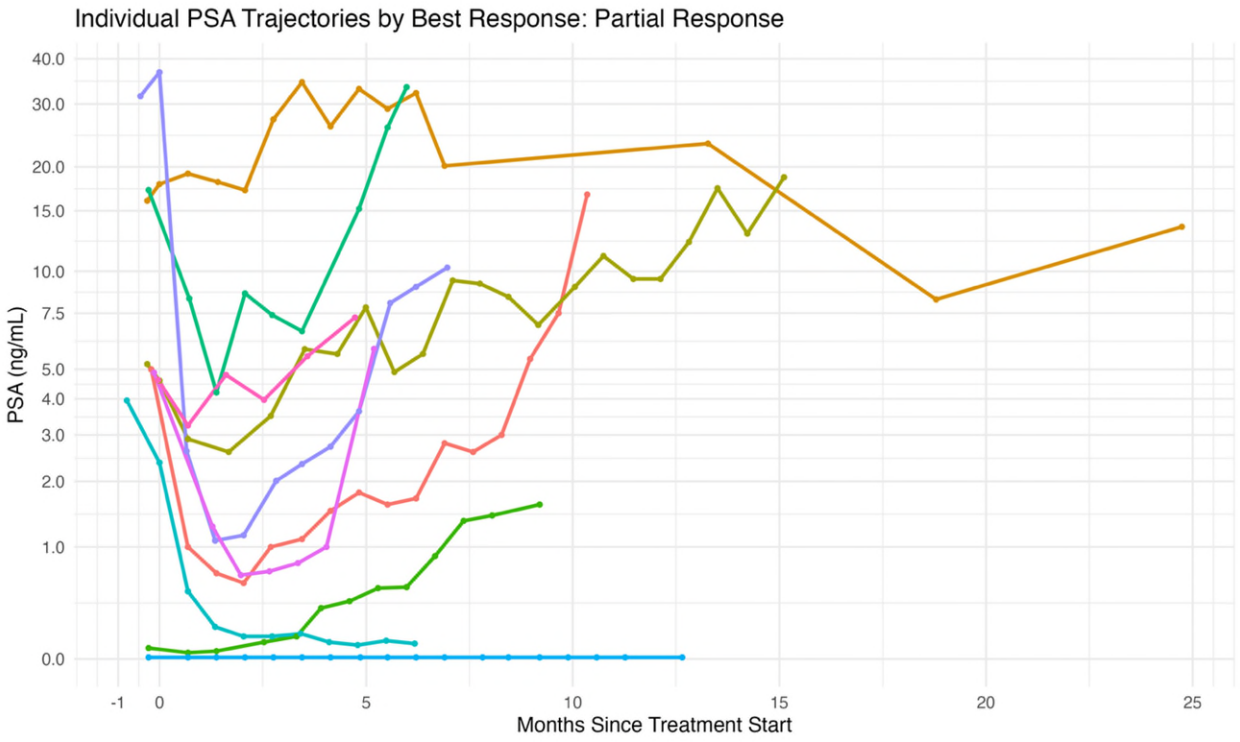
**4B: PSA trajectories in Stable Disease cases**

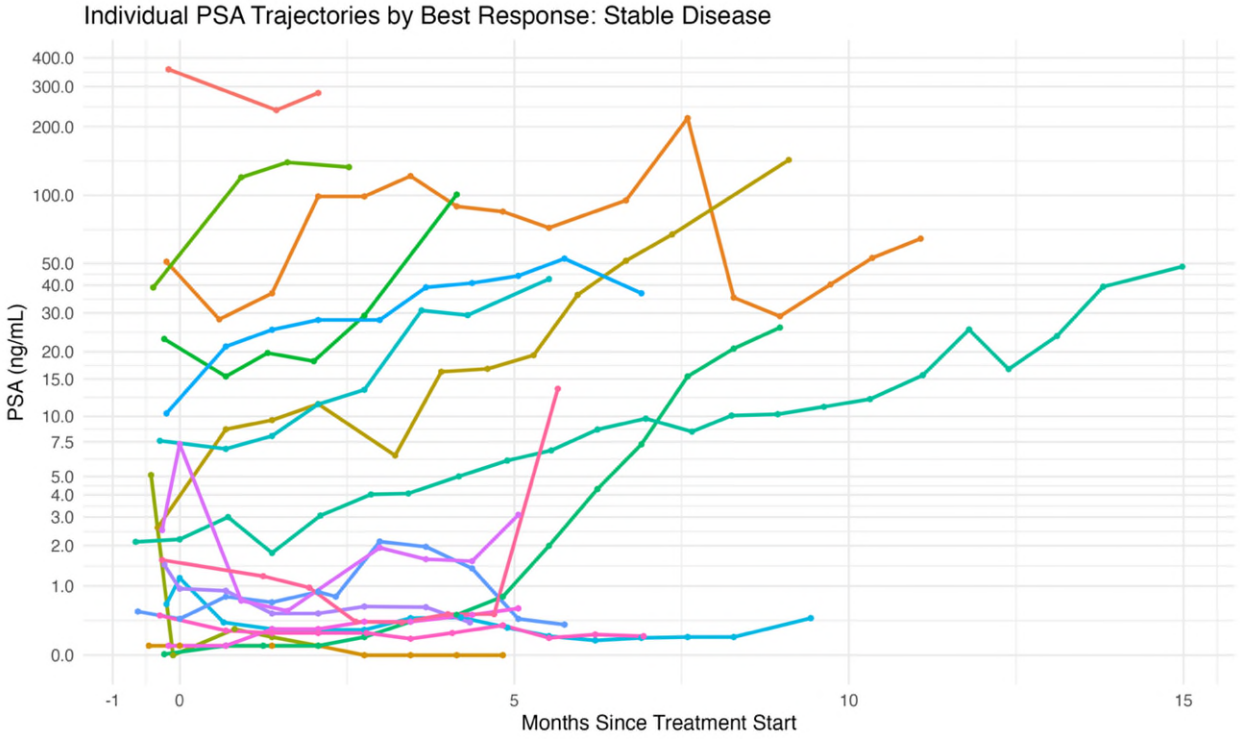
**4C: PSA trajectories in Progressive Disease cases**

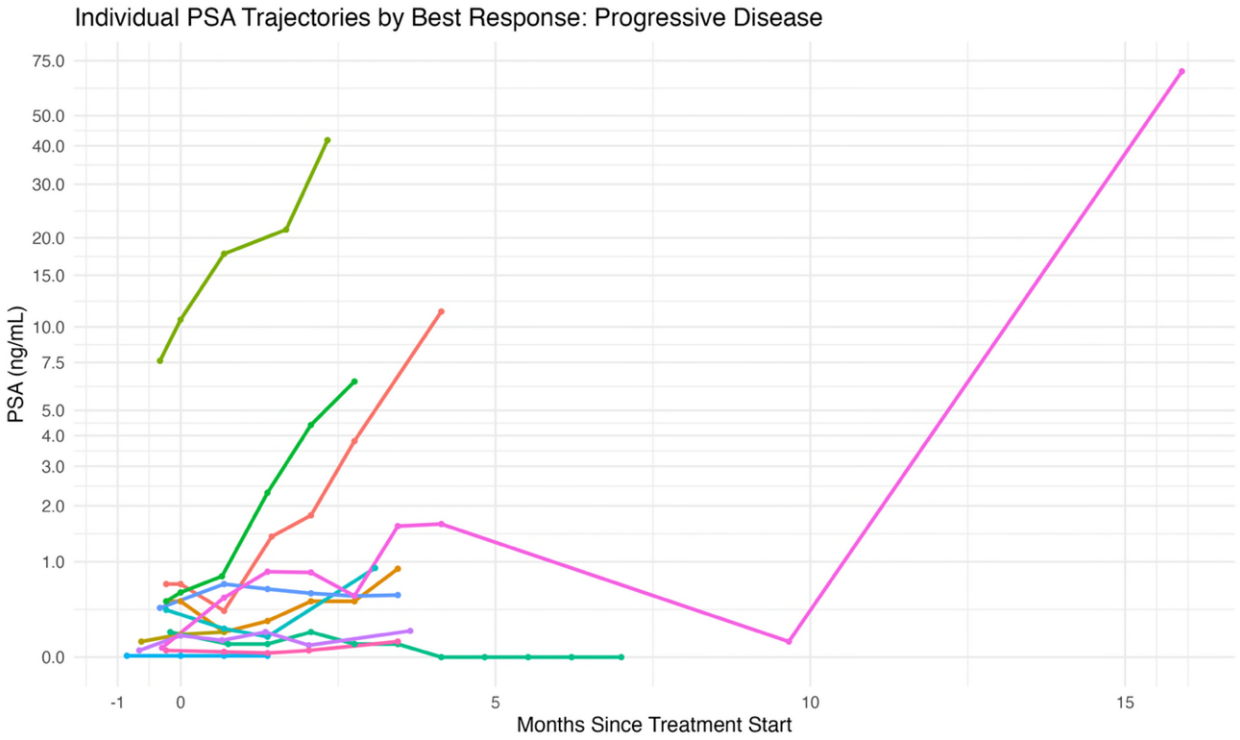
**4D: Longest diameter lesion change trajectory in Partial Response cases**

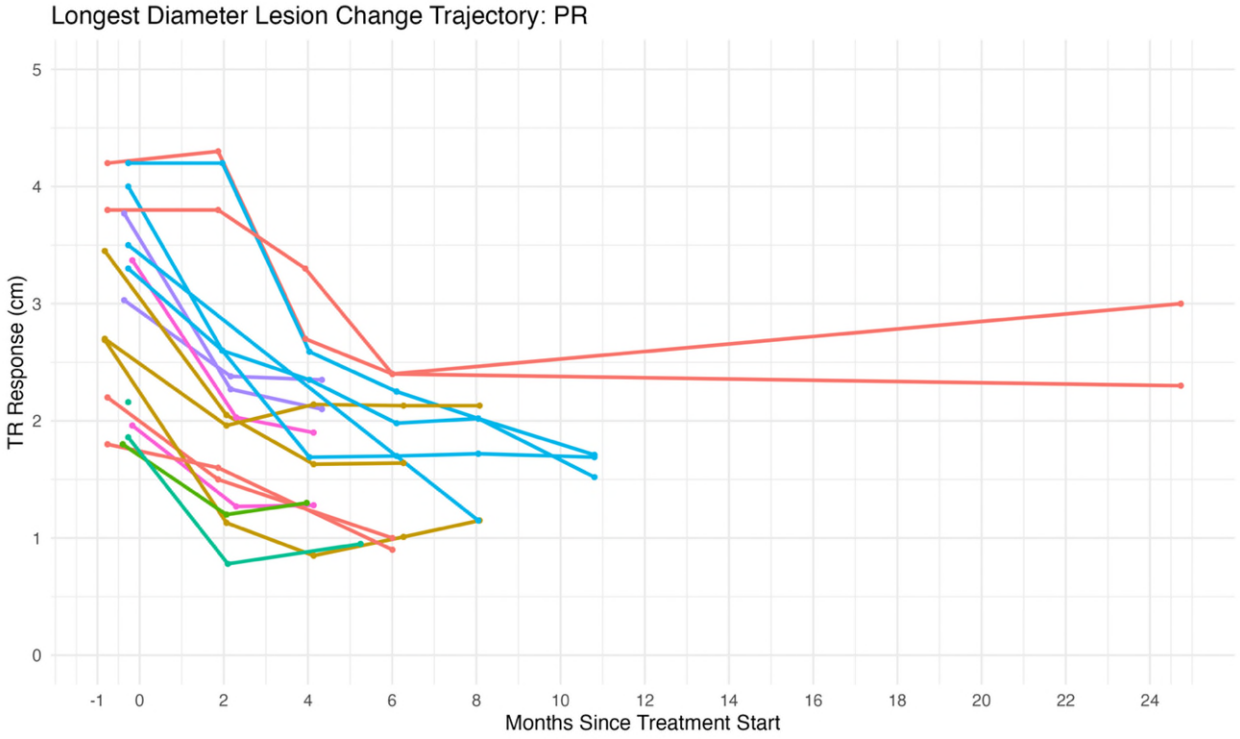
**4E: Longest diameter lesion change trajectory in Stable Disease cases**

**4F: Longest diameter lesion change trajectory in Progressive Disease cases**

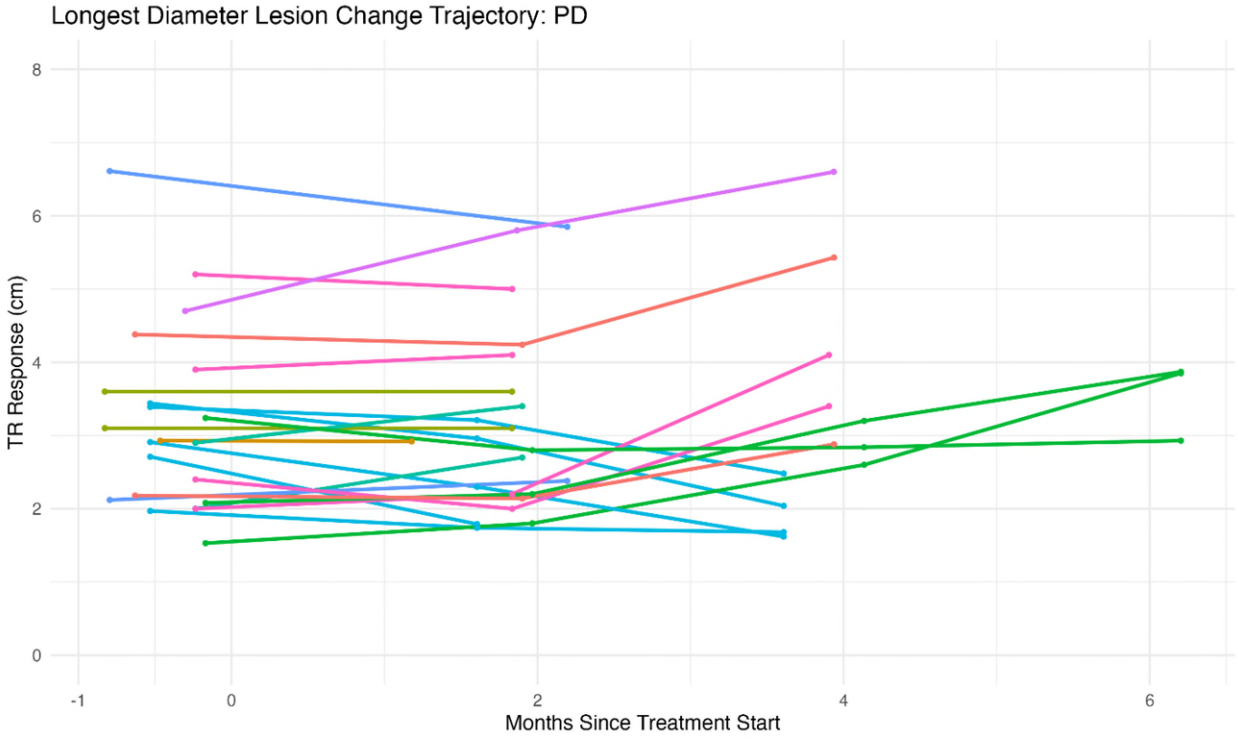

Individual PSA Trajectories by Best Response: Partial Response
PSA (ng/mL)
40.0
30.0
20.0
15.0
10.0
7.5
5.0
4.0
3.0
2.0
1.0
0.0
-1
0
5
10
15
20
25
Months Since Treatment Start


Individual PSA Trajectories by Best Response: Stable Disease
PSA (ng/mL)
400.0
300.0
200.0
100.0
50.0
40.0
30.0
20.0
15.0
10.0
7.5
5.0
4.0
3.0
2.0
1.0
0.0
-1
0
5
10
15
Months Since Treatment Start


Individual PSA Trajectories by Best Response: Progressive Disease
PSA (ng/mL)
75.0
50.0
40.0
30.0
20.0
15.0
10.0
7.5
5.0
4.0
3.0
2.0
1.0
0.0
-1
0
5
10
15
Months Since Treatment Start


Longest Diameter Lesion Change Trajectory: PR
TR Response (cm)
5
4
3
2
1
0
-1
0
2
4
6
8
10
12
14
16
18
20
22
24
Months Since Treatment Start


Longest Diameter Lesion Change Trajectory: SD
TR Response (cm)
12.5
10.0
7.5
5.0
2.5
0.0
-1
0
2
4
6
8
10
12
14
Months Since Treatment Start


Longest Diameter Lesion Change Trajectory: PD
TR Response (cm)
8
6
4
2
0
-1
0
2
4
6
Months Since Treatment Start

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- StatisticalAnalysisPlan.docx