II. Medizinische Klinik, UCCH, Universitätsklinikum Hamburg – Eppendorf

MARTINI-KLINIK

Das aggressive mCRPC- Was kann man tun?

Gunhild von Amsberg

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
ÖGHO SSMO SSOM SGMO SGHSSH

JAHRESTAGUNG
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie
www.jahrestagung-haematologie-onkologie.com

2023 13.–16. Okt. Hamburg

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition: nein

2. Beratungs- bzw. Gutachtertätigkeit: Advisory Boards: Roche, BMS, Astellas, Sanofi, Janssen, MSD, Ipsen, Pfizer, AstraZeneca, Merck, EISAI

3. Besitz von Geschäftsanteilen, Aktien oder Fonds: nein

4. Patent, Urheberrecht, Verkaufslizenz: nein

5. Honorare / Vorträge / Reisekosten/ Kongressunterstützung: Roche, BMS, Astellas, Sanofi, Ipsen, EISAI, Pierre Fabre, MSD, Astra Zeneca, Janssen, Pfizer

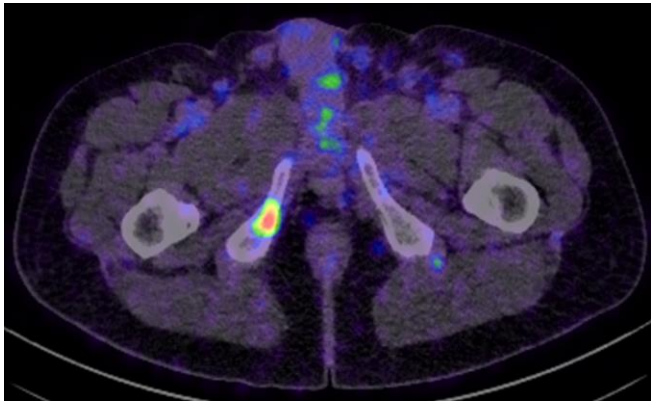
6. Finanzierung wissenschaftlicher Untersuchungen: im Rahmen Industrie-gesponserter Studien (Roche, BMS, MSD, Astra Zeneca, Sanofi, Pfizer, AvenCell, Lilly, Amgen)

7+8. Andere finanzielle Beziehungen und immaterielle Interessenkonflikte: nein

Fallbeispiel: aggressive Transdifferenzierung Prostatakarzinom

59-jähriger Patient mit primär ossär metastasiertem Prostatakarzinom, ED (09/19)
Gleason 9; iPSA 23µg/l
Risikoeinteilung: High Risk, Low Volume (nur Becken)

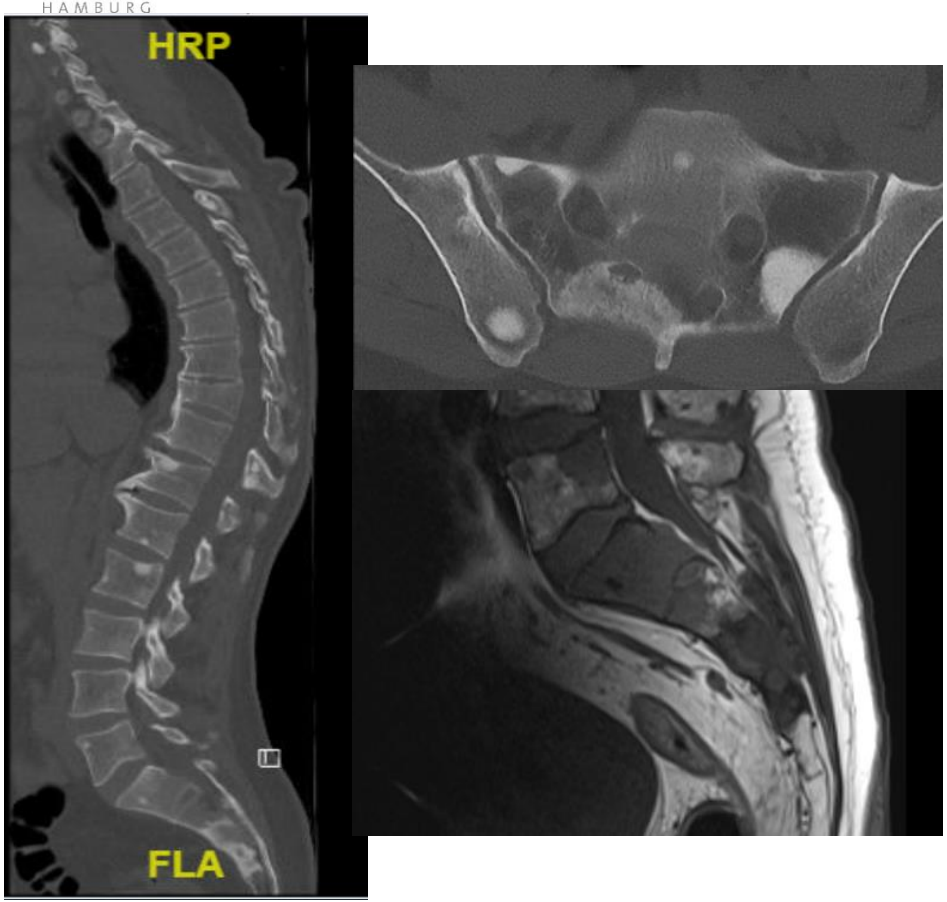
Start einer intensivierten Hormontherapie mit NHA 10/19



PSMA-PET-Scan (02/2020): Signifikante Verringerung der vorbestehenden lokalen Befunde. Knochenmetastasen mit rückläufiger PSMA-Expression und zunehmender Sklerose, als Hinweis auf Therapieansprechen

Hb, LDH, AP im Normbereich; PSA unter der Nachweisgrenze

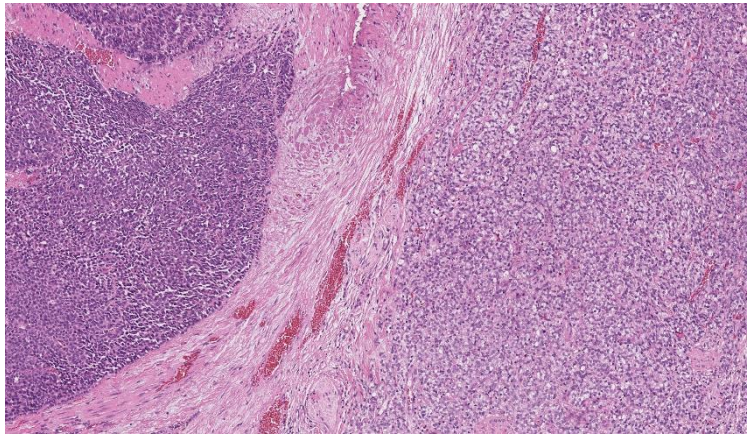
Fallbeispiel: aggressive Transdifferenzierung Prostatakarzinom

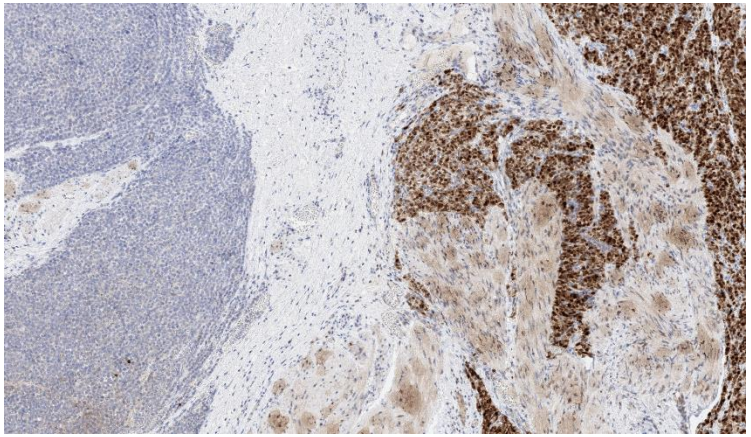


Neun Monate nach Therapiebeginn:

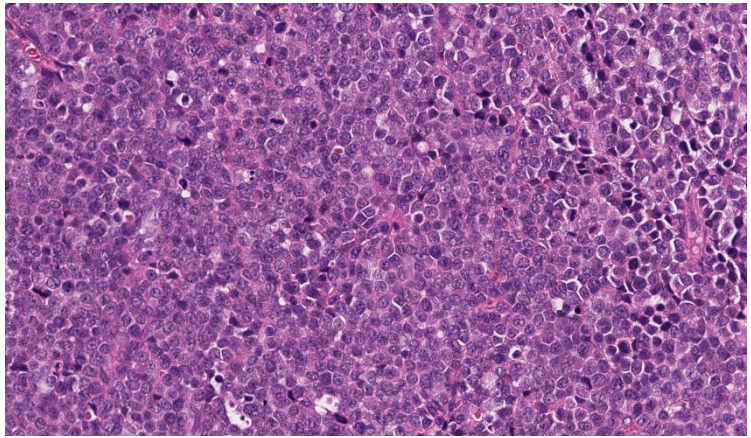
- Verschlechterung des Allgemeinzustandes
- Ausgeprägte Schmerzen, Taubheitsgefühl und Kraftverlust des rechten Beins
- Labor: **NSE 73 µg/l**
  CEA 34 µg/l
  LDH 438 U/l

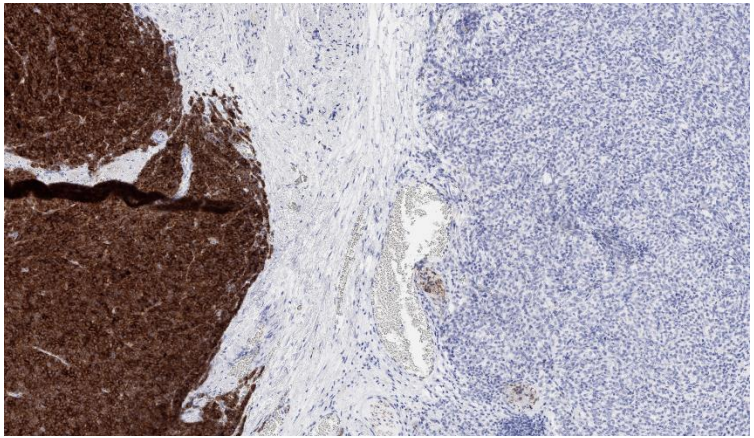
Transdifferenziertes neuroendokrines Prostatakarzinom





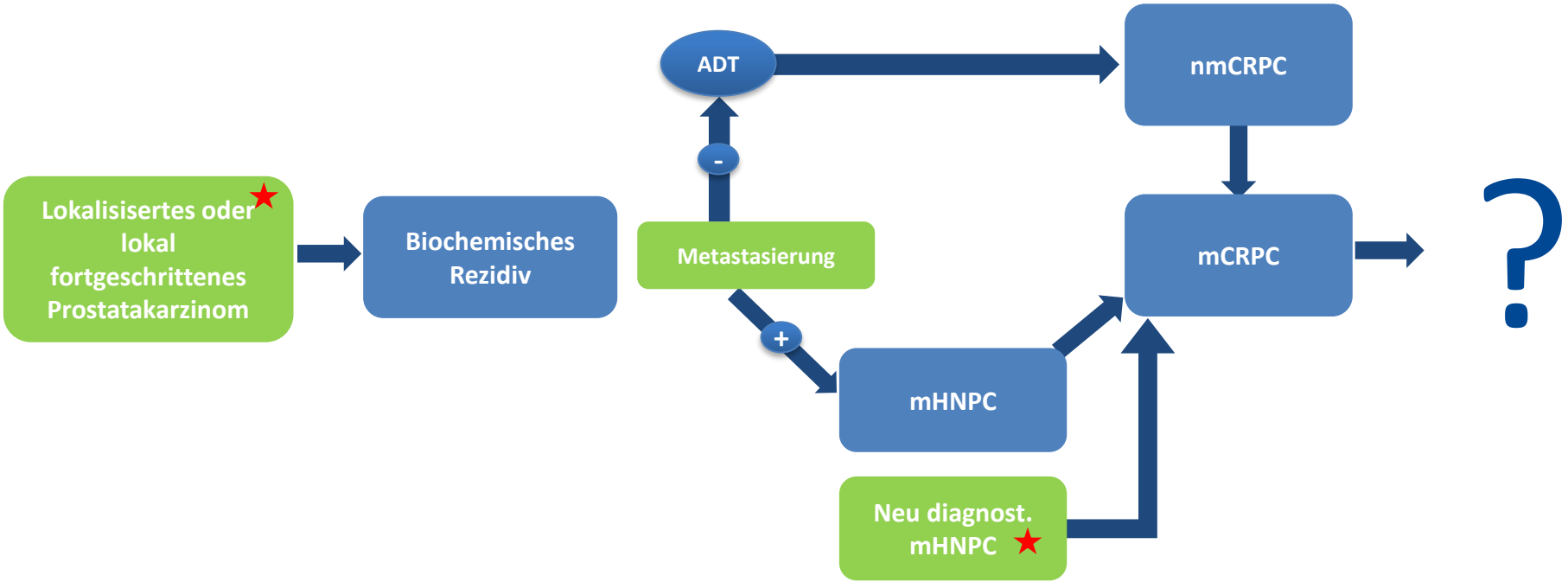
AR-Expression





Synaptophysin-Expression

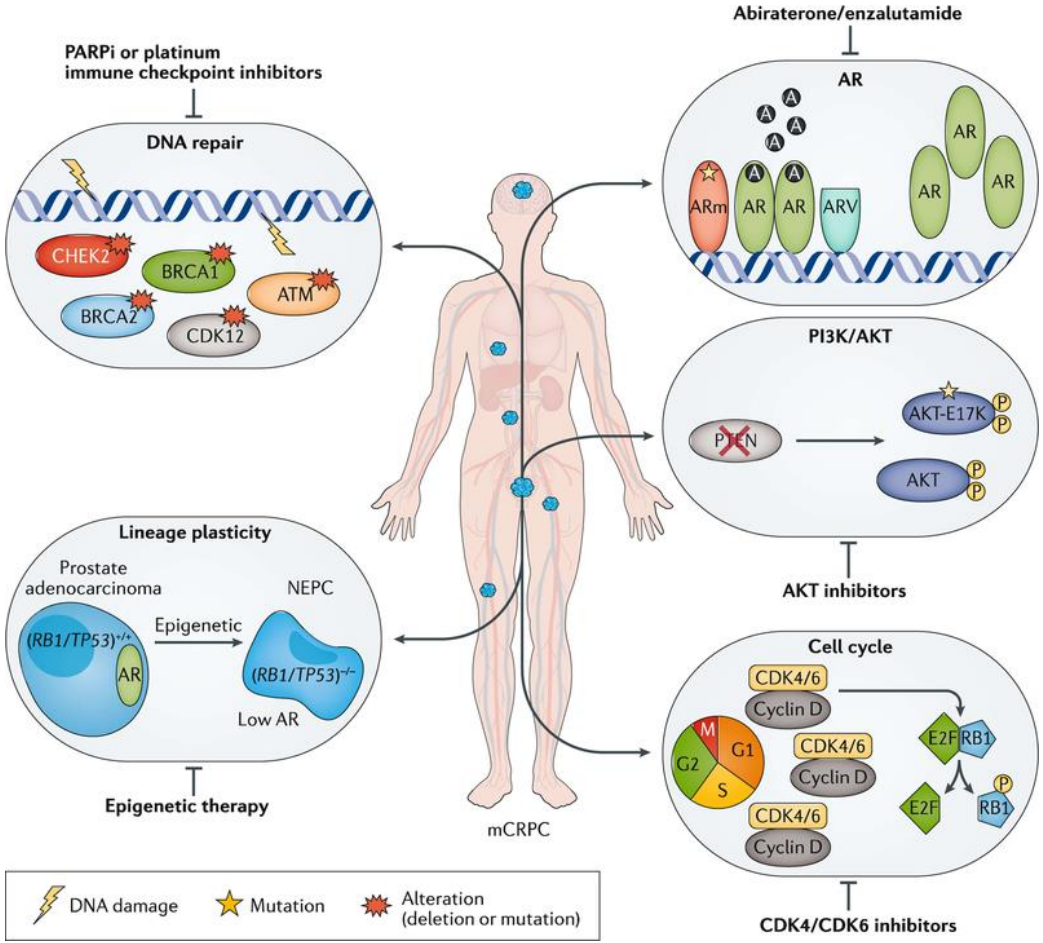
Entwicklung des mCRPC: Schematische Darstellung



★ First prostate cancer diagnosis

mCRPC, metastatic castration resistant prostate cancer; mHNPC, metastatic hormone-naïve prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer.

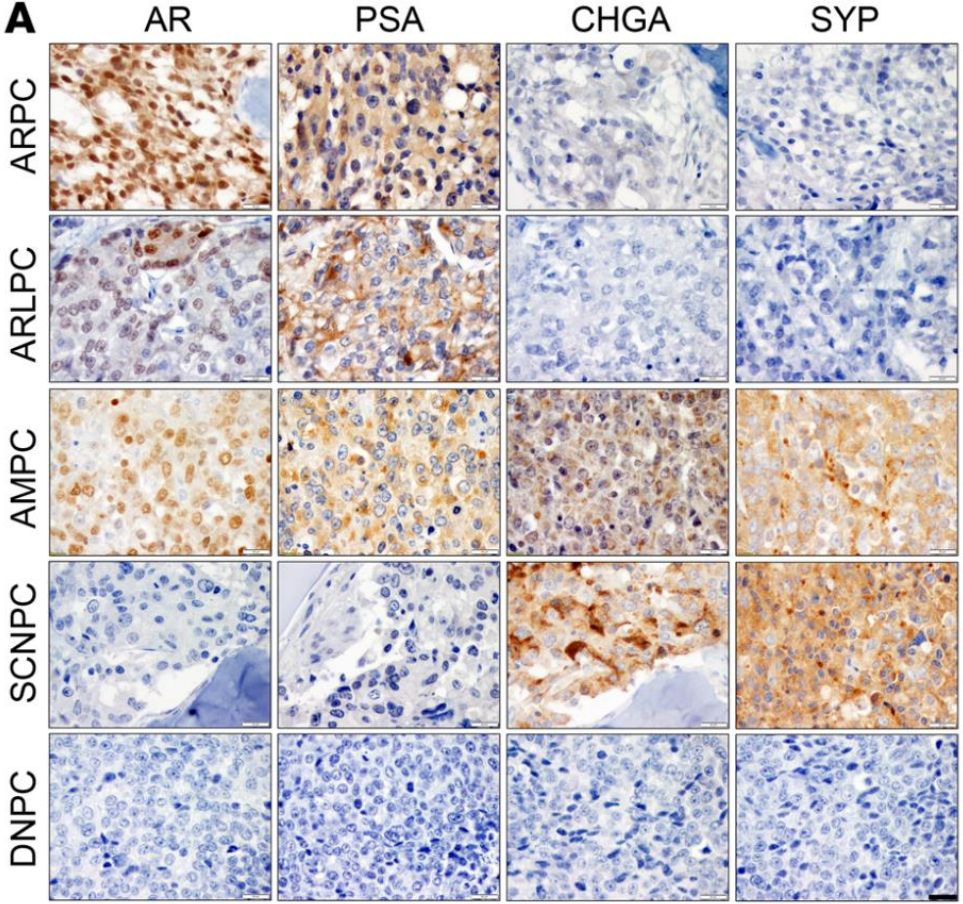
Unterschiedliche „Driver“ des mCRPCs: Die Heterogenität der Erkrankung



Ku et al. Nat Rev Urol 2019 Nov;16(11):645-654.

Heterogenität des mCRPCs: immunhistochemische Phänotypen

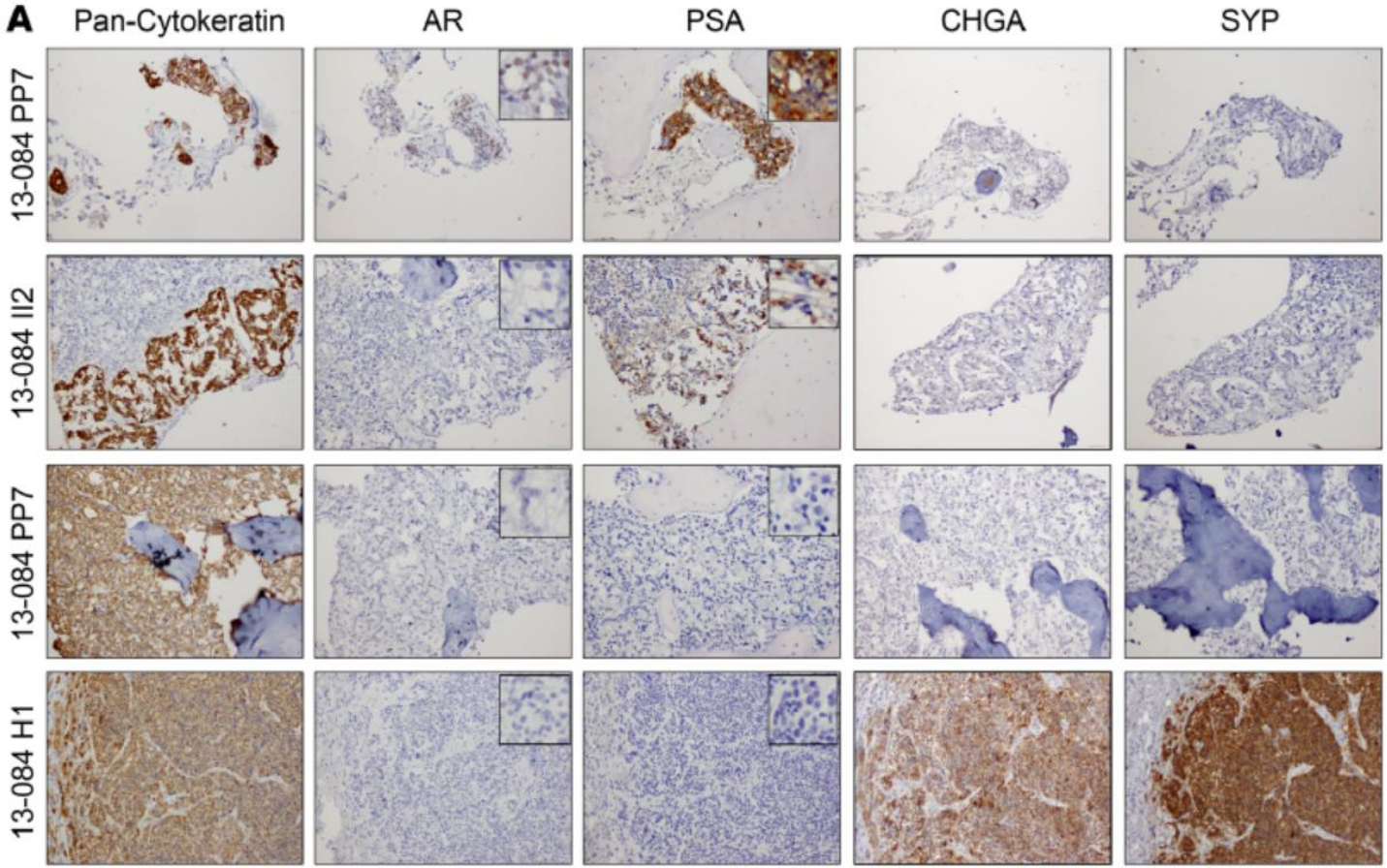
MARTINI-KLINIK



Sunbtyp mCRPC	AR-Marker-Profil	Neuroend. Marker-Profil
ARPC (AR high PCa)	+++ ubiquitär	-
ARLPC (AR low PCa)	+ heterogen	-
AMPC (amphicrine Pca)	+/++	+/++
SCNPC (neuroendocrine PCa)	-	++
DNPC (Double neg. PCa)	-	-

Labrecque MP, et al. J Clin Invest. 2019 Jul 30;129(10):4492-4505. doi: 10.1172/JCI128212. PMID: 31361600; PMCID: PMC6763249.

Intrapatient-Heterogenität des mCRPCs

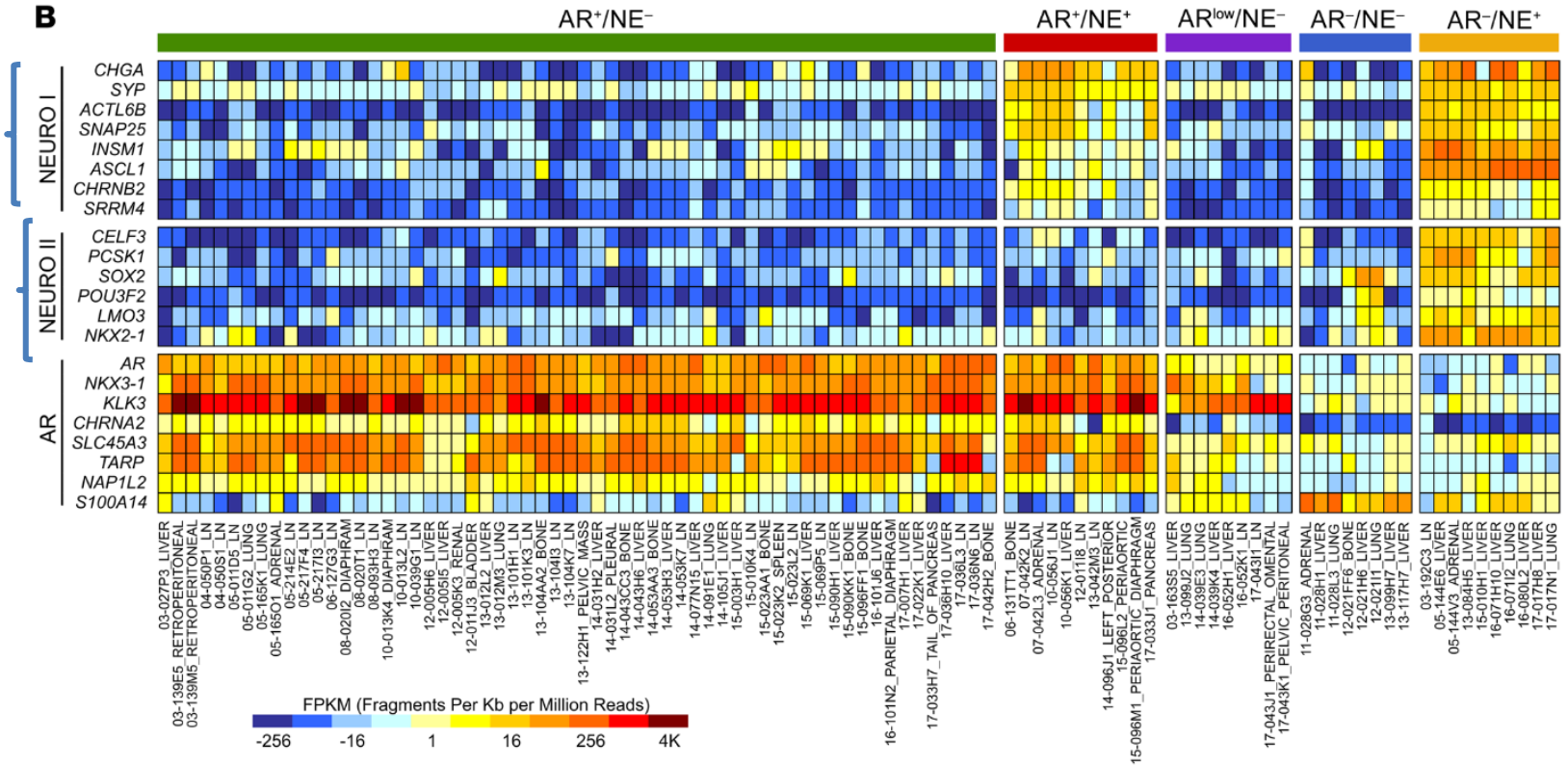


Labrecque MP, et al. J Clin Invest. 2019 Jul 30;129(10):4492-4505. doi: 10.1172/JCI128212. PMID: 31361600; PMCID: PMC6763249.

Heterogenität des mCRPCs: Subtypen im Transkriptom-Profiling

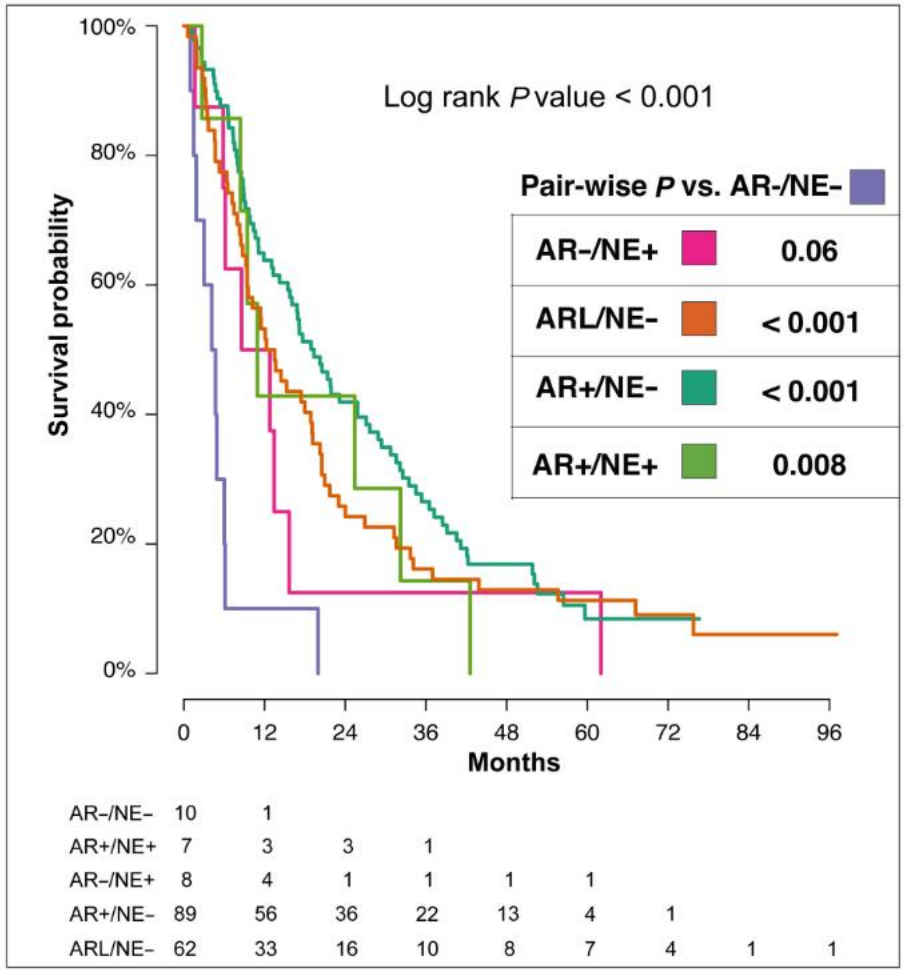
REST repressed genes

Transkriptions-faktoren



Labrecque MP, et al. J Clin Invest. 2019 Jul 30;129(10):4492-4505. doi: 10.1172/JCI128212. PMID: 31361600; PMCID: PMC6763249.

Überlebenswahrscheinlichkeit in Abhängigkeit des Subtyps



Lundberg A, et al. Cancer Res. 2023 Aug 15;83(16):2763-2774. doi: 10.1158/0008-5472.CAN-23-0593. PMID: 37289025; PMCID: PMC10425725.

Wann wir an eine aggressive Transdifferenzierung denken sollten… (die modifizierten “Hamburg Kriterien”)

- Viszerale Metastasen
- Dominierende oder neu aufgetretene lytische Knochenmetastasen mit und ohne Weichteilkomponente
- Großflächige Lymphadenopathie (≥ 5 cm) oder großflächige (progrediente) Tumormasse im Becken (≥ 8 cm)
- Niedriger PSA-Wert bei Erstvorstellung oder bei Progression im Vergleich zur Tumorlast
- Kurzes Intervall bis zur androgenunabhängigen Progression nach Beginn einer intensivierten Erstlinientherapie (ADT + ARSi; ADT + Docetaxel ± ARSi) (≤12 Monate) oder ADT allein (≤6 Monate)
- Verlust oder Fehlen der PSMA-Expression zum Zeitpunkt der Krankheitsprogression oder FDG-positive, PSMA-negative Läsionen im PSMA-PET-CT.
- Wenn keine anderen Ursachen vorliegen: (a) erhöhte Serum-LDH (≥ 2 x IULN); maligne Hyperkalzämie; (b) erhöhtes Serum-CEA (≥ 2 x IULN);

Modifiziert nach Aparicio A et al. Clin Cancer Res. 2016 Mar 15;22(6):1520-30. doi: 10.1158/1078-0432.CCR-15-1259

Was hilft bei der Diagnosestellung?

- Bestimmung der neuroendokrinen Serummarker
- Biopsie und (falls erforderlich) Re-Biopsie der auffälligsten/neu entstandenen Läsionen.
- Molekularpathologische Diagnostik (bei gesicherter Kostenübernahme)
- Bestimmung von zirkulierenden Tumorzellen (bisher nur im Rahmen von wissenschaftlichen Untersuchungen)

FOKUS: transdifferenziertes, neuroendorkines Prostatakarzinom (tNEPC)

Treatment-related neuroendocrine prostatic carcinoma- Neu in der WHO-Klassifikation

Tumours of the prostate

- Introduction
- **Epithelial tumours of the prostate**
  - Glandular neoplasms of the prostate
    - Prostatic cystadenoma
    - High-grade prostatic intraepithelial neoplasia
    - Intraductal carcinoma of the prostate
    - Prostatic acinar adenocarcinoma
    - Prostatic ductal adenocarcinoma
    - Treatment-related neuroendocrine prostatic carcinoma
  - Squamous neoplasms of the prostate
    - Adenosquamous carcinoma of the prostate
    - Squamous cell carcinoma of the prostate
    - Adenoid cystic (basal cell) carcinoma of the prostate
- Mesenchymal tumours unique to the prostate
  - Stromal tumours of the prostate
    - Prostatic stromal tumour of uncertain malignant potential
    - Prostatic stromal sarcoma

WHO 2022 Classification of Tumors of the Prostate (5th edition)

Pathologische Klassifikation

IHC of NE Differentiation in Prostate Tumors

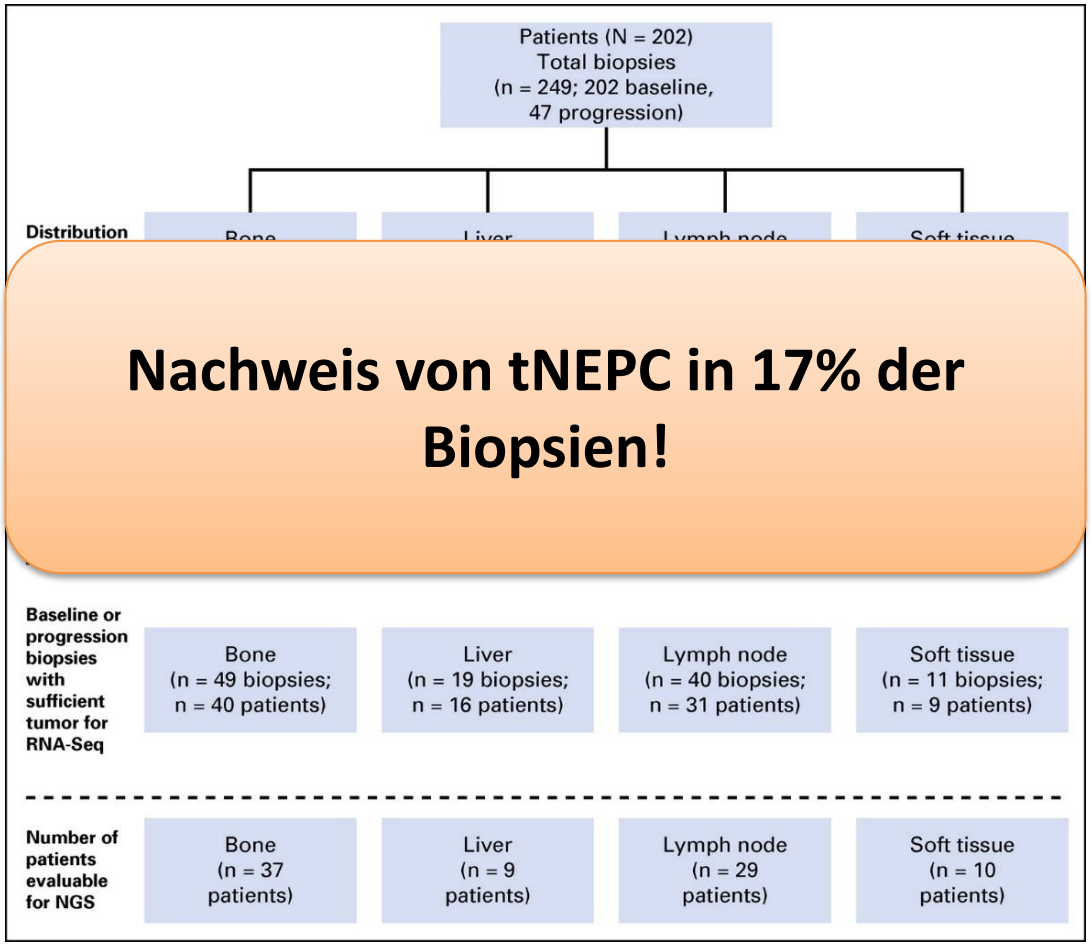
	PSA	NE Markers	Ki67
PCa.	Positive	Scattered + cells	Not increased in NE cells
PCa. with Paneth cell NE differentiation	Variably positive	Diffuse positive in Paneth cells	Few cases studied—not increased
Carcinoid-like tumor	Usually* positive	Positive	Not studied
Carcinoid tumor	Negative	Diffusely positive	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

*Results refer to carcinoid-like areas. Tumors usually associated with usual prostatic adenocarcinoma.

PCa. indicates adenocarcinoma; SC, small cell; LC, large cell.

Epstein Am J Surg Pathol. 2014 June ; 38(6): 756–767. doi:10.1097/PAS.0000000000000208

Rarität oder reale Bedrohung?

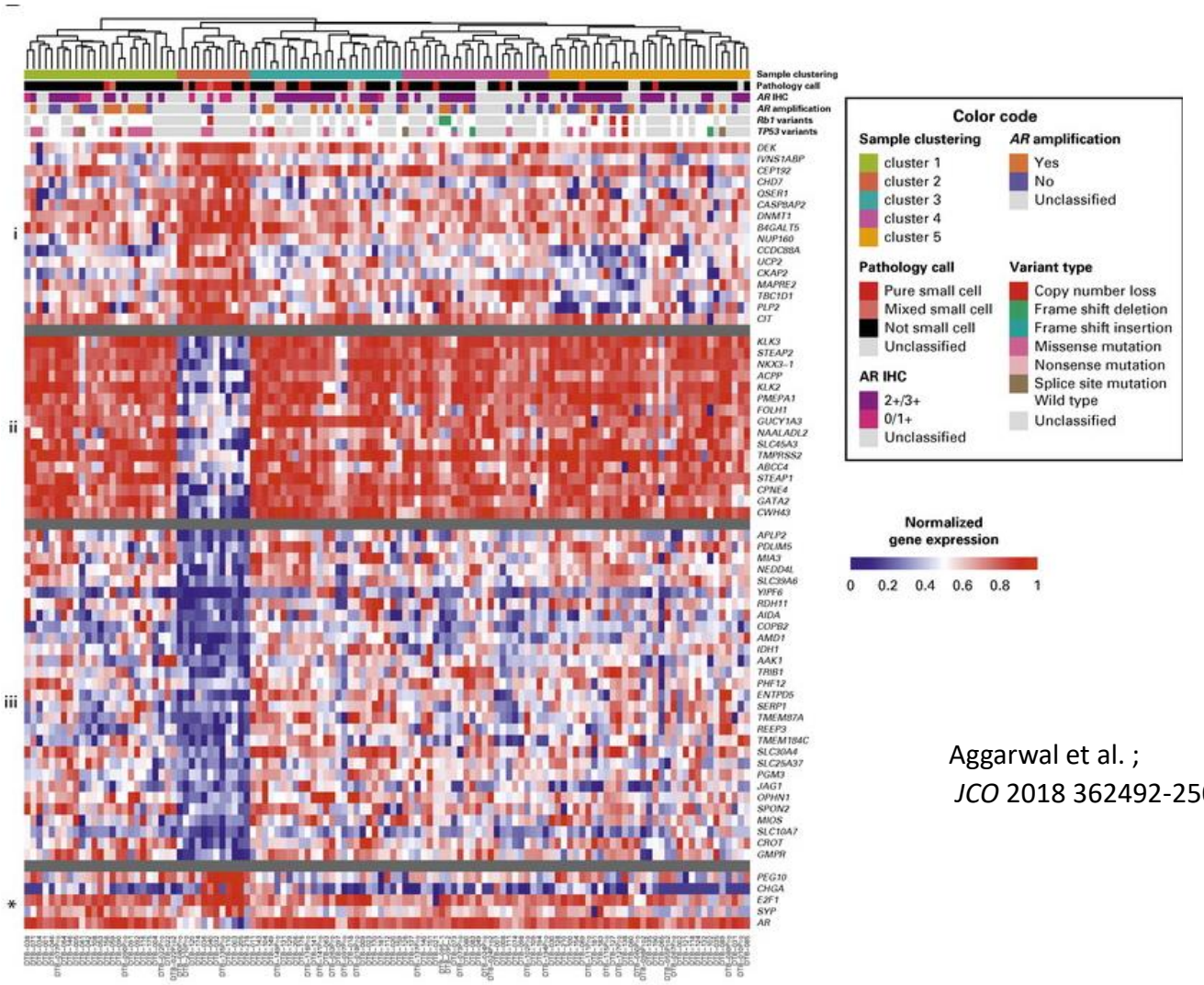


Nachweis von tNEPC in 17% der Biopsien!

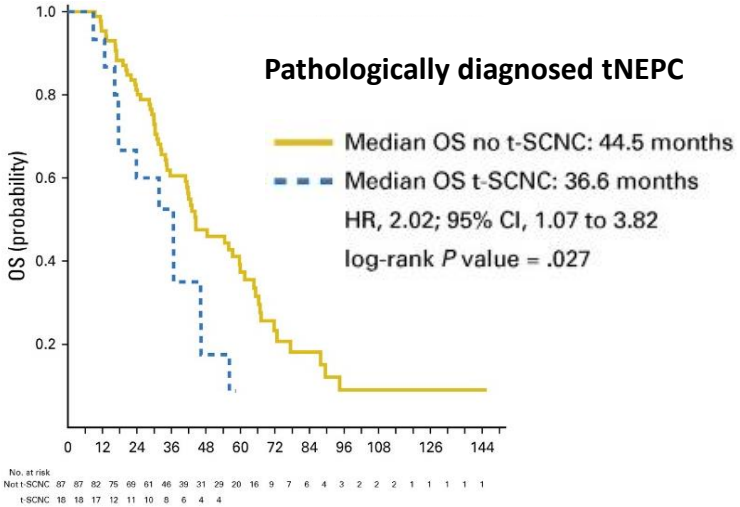
Aggarwal et al. ;
JCO 2018 362492-2503.

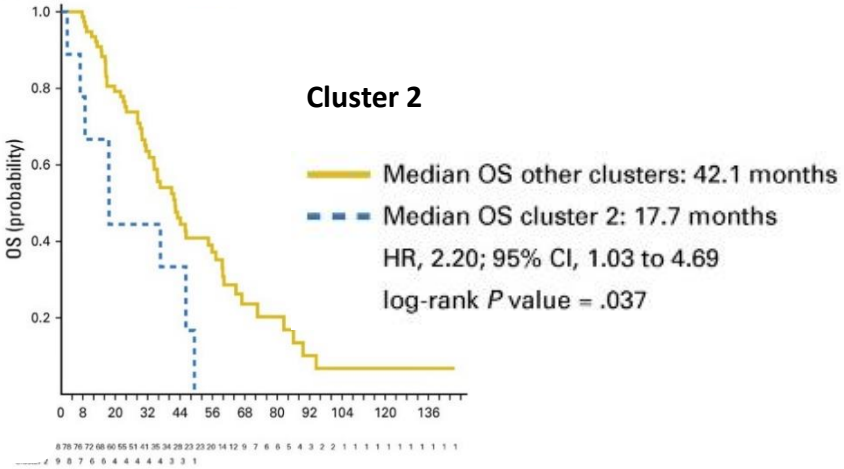
UKE
HAMBURG

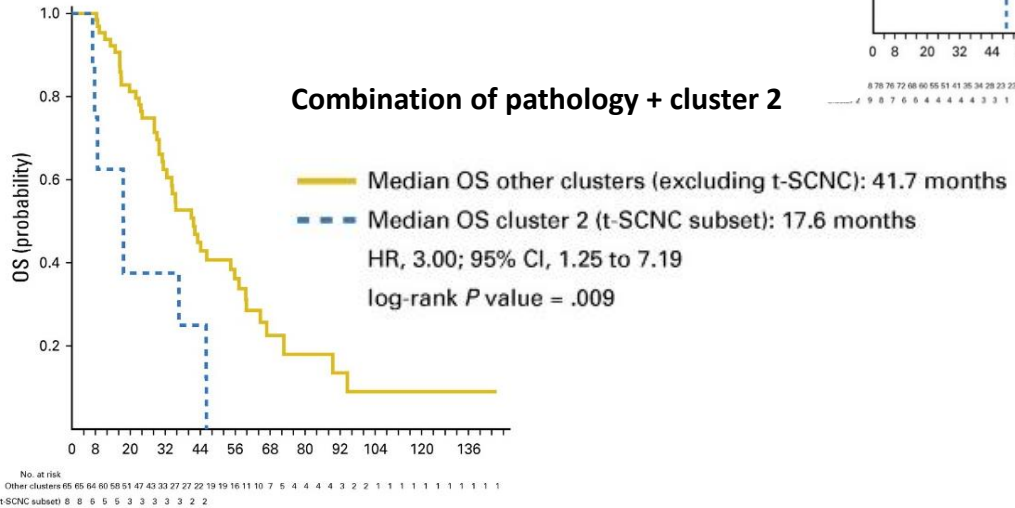
Transkriptomprofil der t-NEPC



Aggarwal et al. ;
JCO 2018 362492-2503.

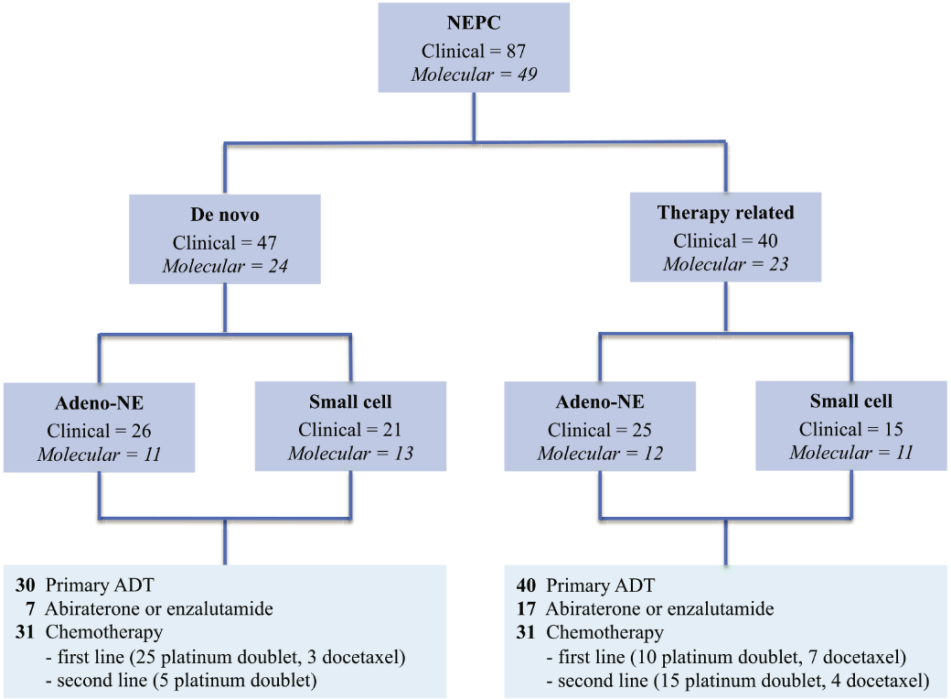


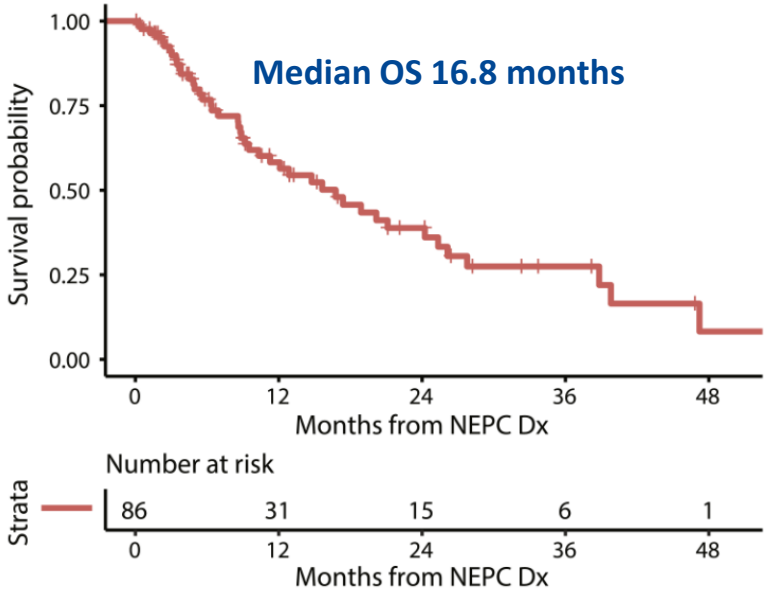




Aggarwal et al. ;
JCO 2018 362492-2503.

Gesamtüberleben von NEPC Patienten in einer retrospektiven Analyse (N=87)

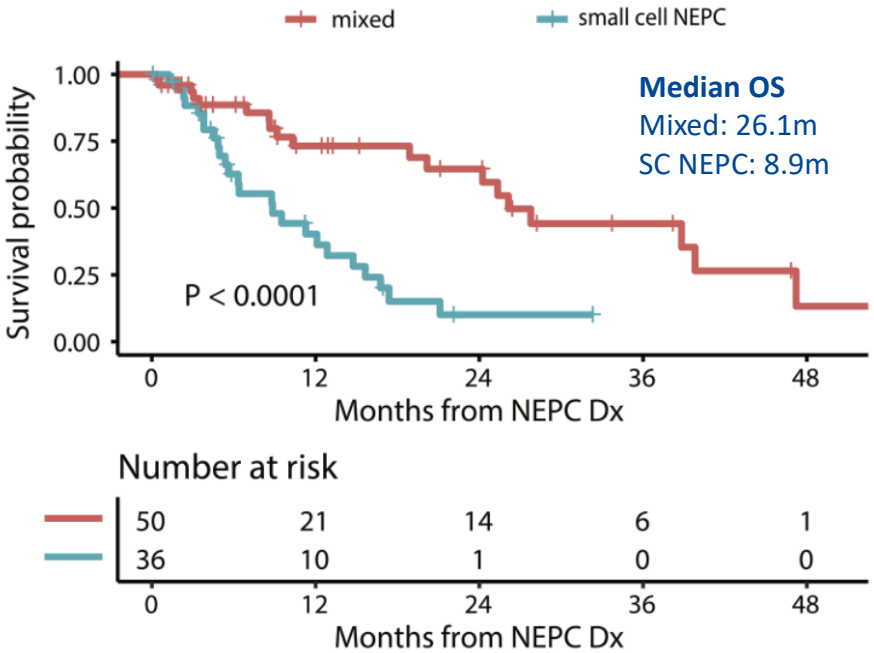




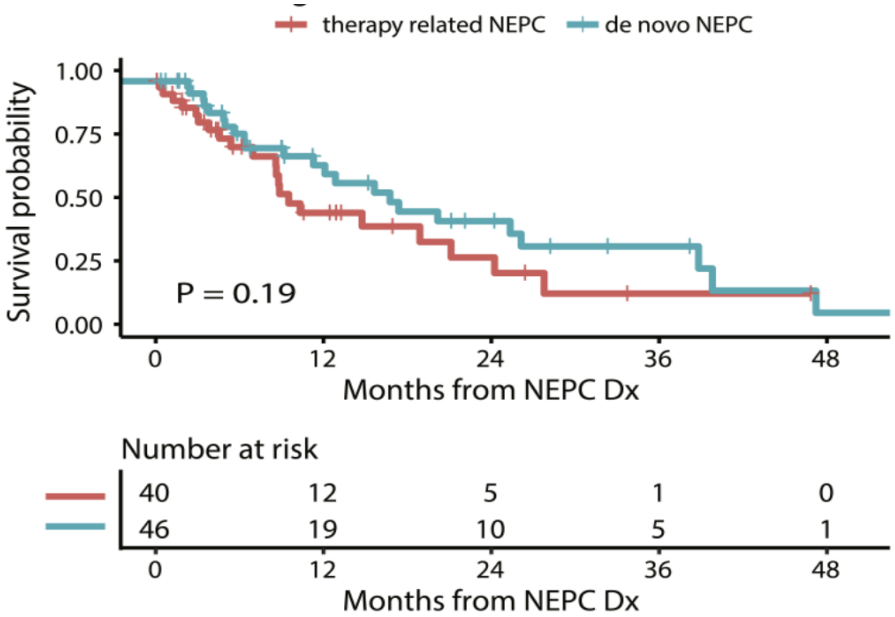
Conteduca et al. Eur J Cancer. 2019; 121: 7–18. doi:10.1016/j.ejca.2019.08.011

Gesamtüberleben von NEPC Patienten in einer retrospektiven Analyse (N=87)

Mixed versus small cell NEPC



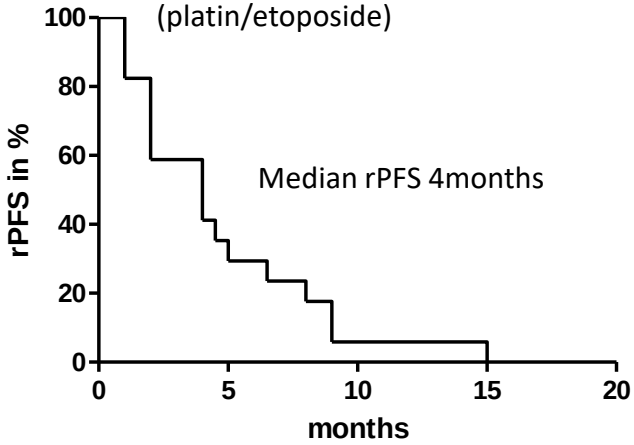
De Novo NEPC versus tNEPC



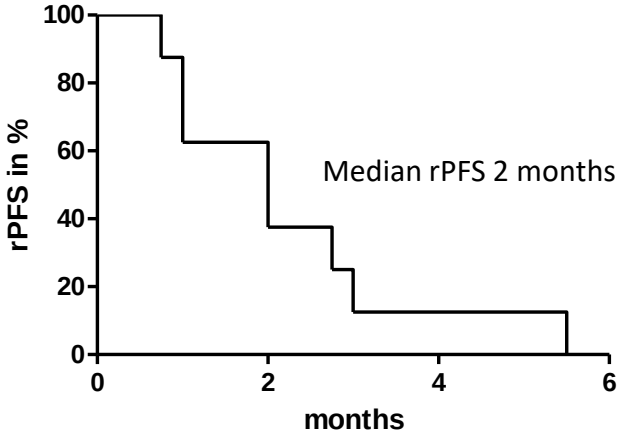
Conteduca et al. Eur J Cancer. 2019; 121: 7–18. doi:10.1016/j.ejca.2019.08.011

Erste Daten aus Hamburg

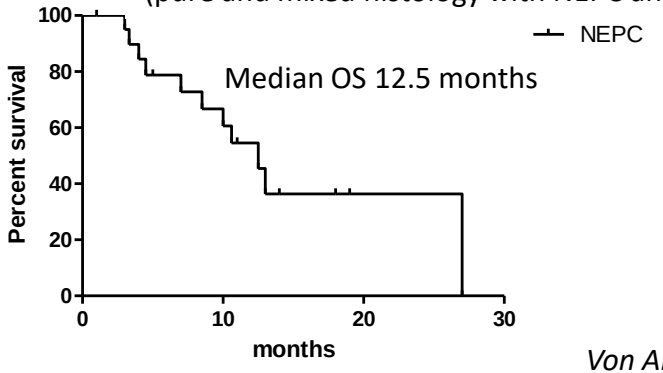
rPFS on 1st line therapy
(platin/etoposide)



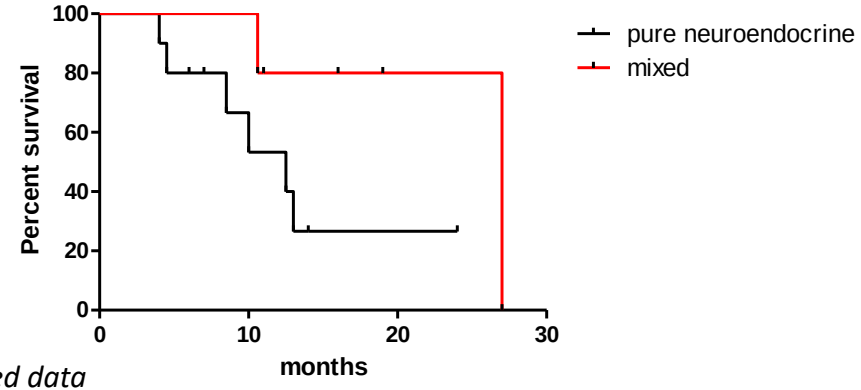
rPFS on second-line therapy



Median OS of newly diagnosed NEPC patients
(pure and mixed histology with NEPC and AC)



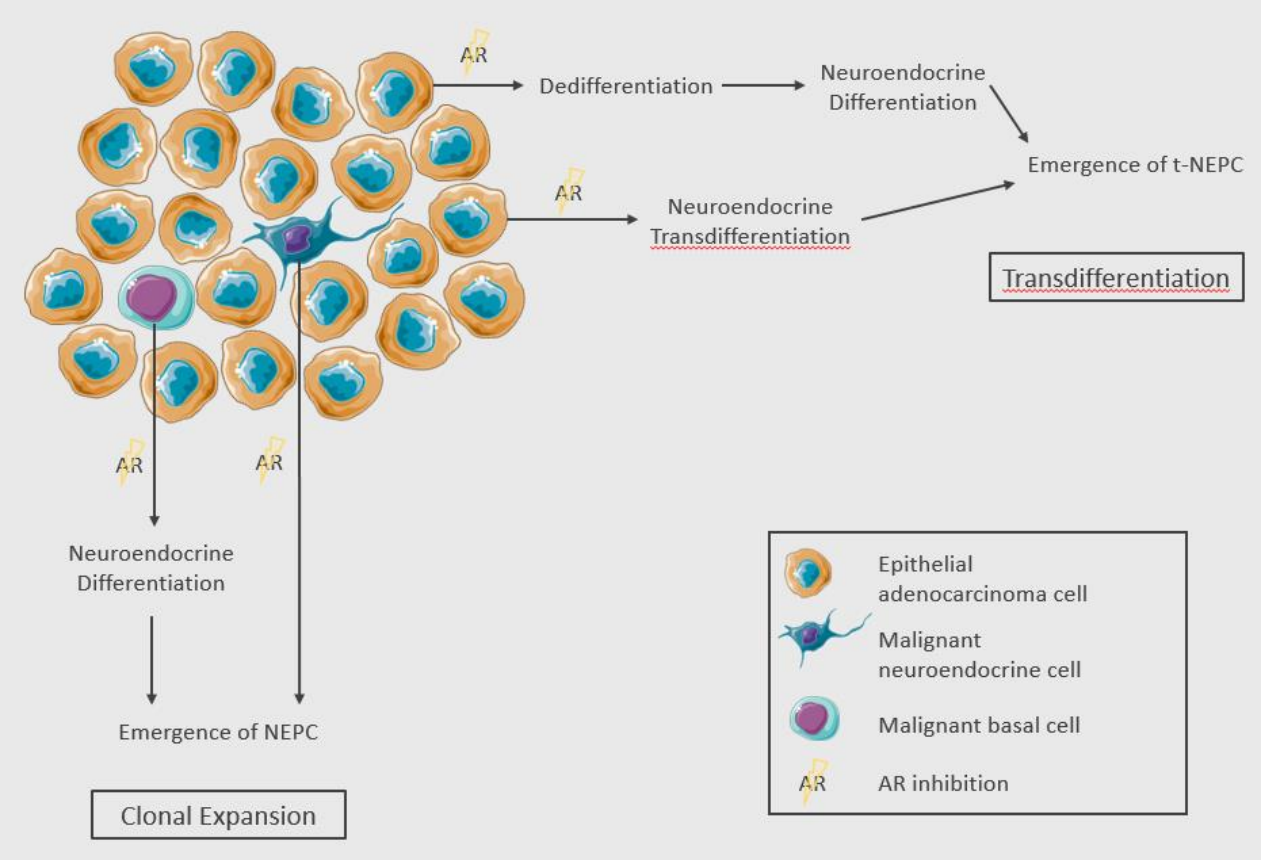
Median OS of pure versus mixed NEPC histology



Von Amsberg unpublished data

Pathogenese des neuroendorkinen Prostatakarzinoms

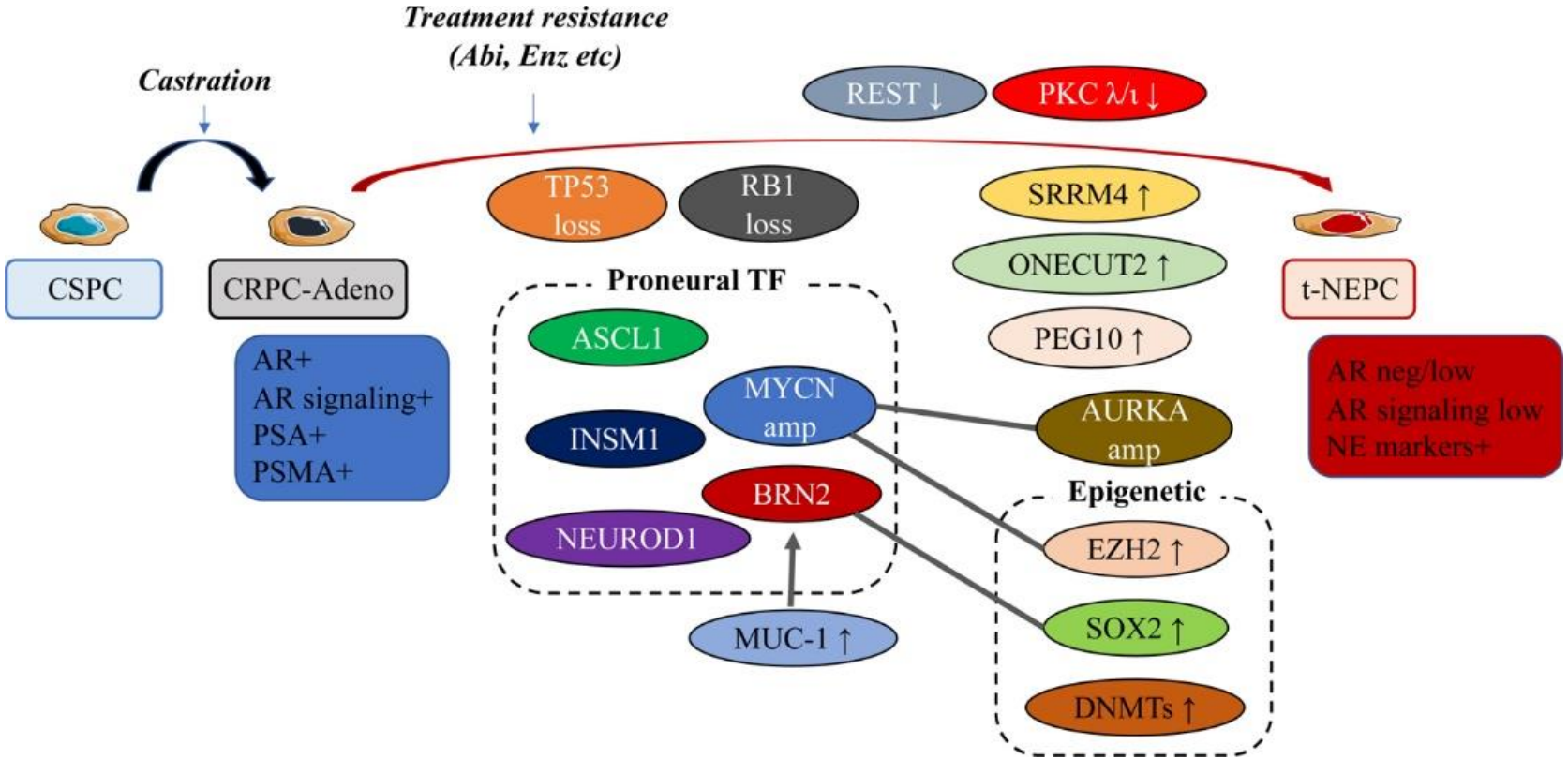
Wie entstehen neuroendokrine Prostatakarzinome



Dedifferenzierung:
AC verlieren zunächst die AR-spezifische Genexpression und akquirieren basale oder Stammzell-ähnliche Eigenschaften, bevor sie sich in einem zweiten Schritt in NE-Zellen differenzieren
Transdifferenzierung: Die Transdifferenzierung geht direkt vom Adenokarzinom aus und überspringt dieses vermeintlich entdifferenzierte Zwischenstadium

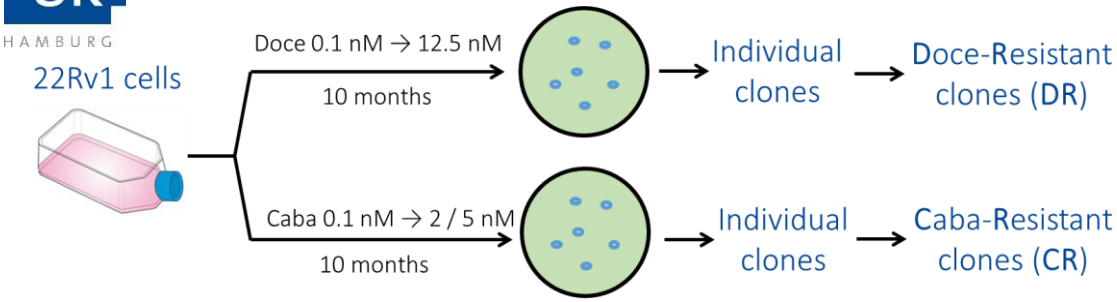
Merkens… von Amsberg. J. Exp. Clin. Cancer Res. 2022

Was passiert im Rahmen der aggressiven Transdifferenzierung? Molekularpathologische Schlüsselereignisse



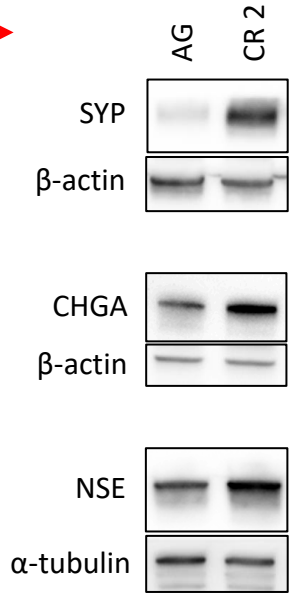
Yamada & Beltran *Curr Oncol Rep* **23**, 15 (2021). https://doi.org/10.1007/s11912-020-01003-9

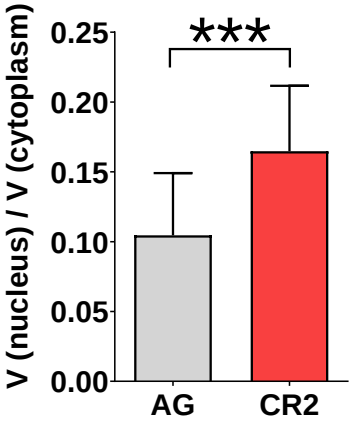
Resistenzentwicklung unter Taxanexposition

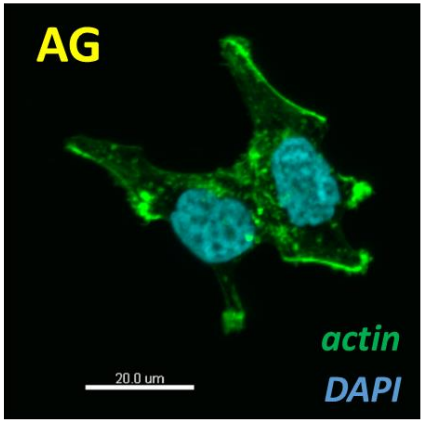


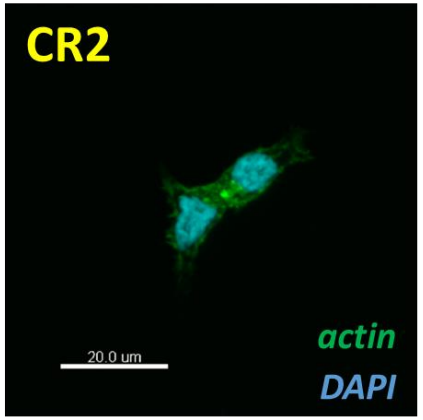
Clone	p-value, DisGeNET „Neuroendocrine tumors“
CR2	1.25e-08
CR9	1.74e-05
CR11	1.24e-05
DR7	1.09e-03
DR8	0.908e-03
DR11	5.66e-03

Drug resistance





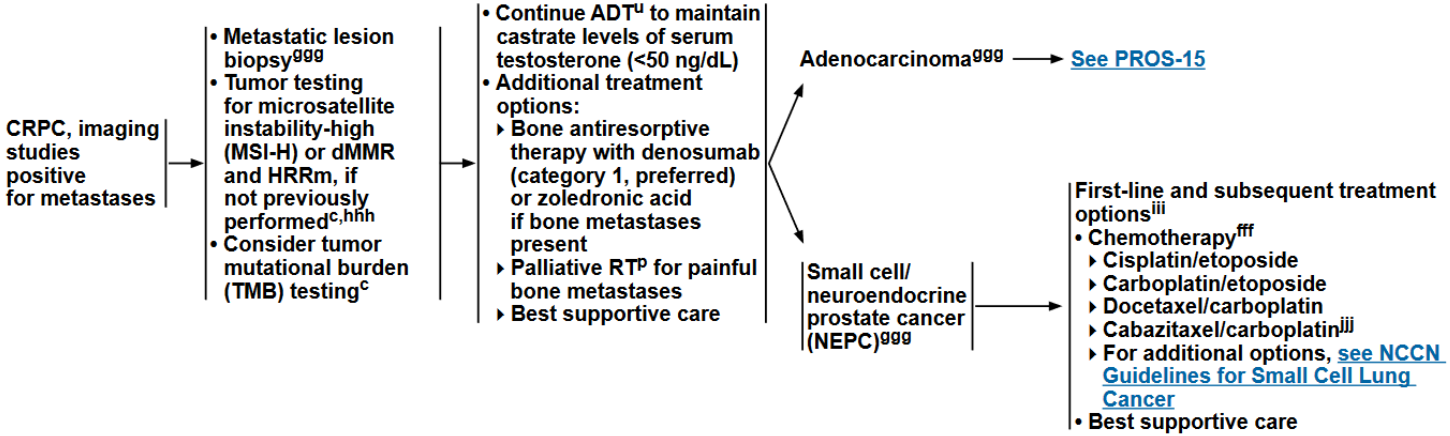




Dyshlovoy …. Von Amsberg ASCO GU 2023

Therapie des NEPCs/ AVPCs

Empfehlungen der NCCN Guidelines



[c] See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[p] See Principles of Radiation Therapy (PROS-G).
[u] See Principles of Androgen Deprivation Therapy (PROS-I).
[eee] CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, et al. J Clin Oncol 2008;26:1148-1159.
[fff] See Principles of Non-Hormonal Systemic Therapy (PROS-J).
[ggg] Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed.
[hhh] Germline testing for HRRm is recommended if not performed previously. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[iii] Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. See Principles of Imaging (PROS-E) and Discussion.
[jjj] Cabazitaxel 20 mg/m² plus carboplatin area under the curve [AUC] 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high lactate dehydrogenase [LDH], high carcinoembryonic antigen [CEA], lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53*, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

… keine Empfehlungen zum NEPC und AVPC

Last update 2022

Last update 2020

6.5.11 ***Platinum chemotherapy***

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1276]. More recently, the combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95, p = 0.018) and the combination was well tolerated [1277]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including *TP53*, *RB1*, and *PTEN* [1278].

Leitlinienprogramm Onkologie

S3-Leitlinie Prostatakarzinom

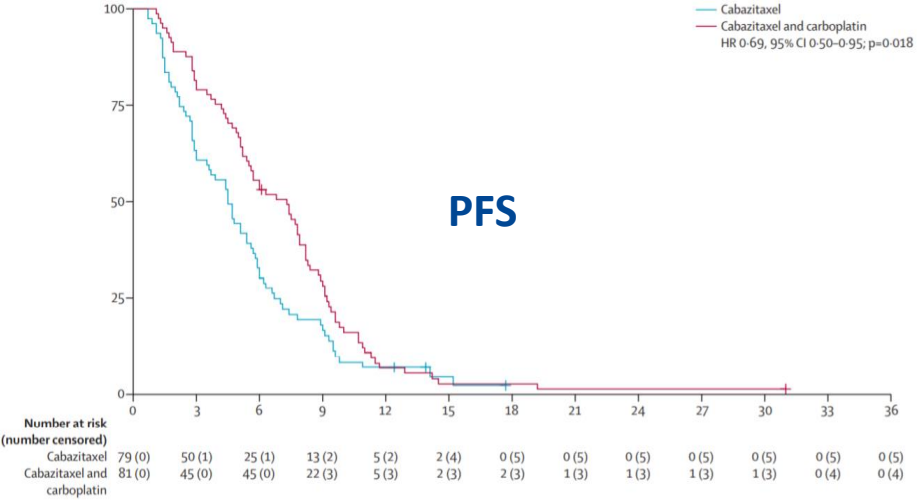
Version 6.2 – Oktober 2021
AWMF-Registernummer: 043/022OL

Frühere Studien mit NEPC/ AVPC

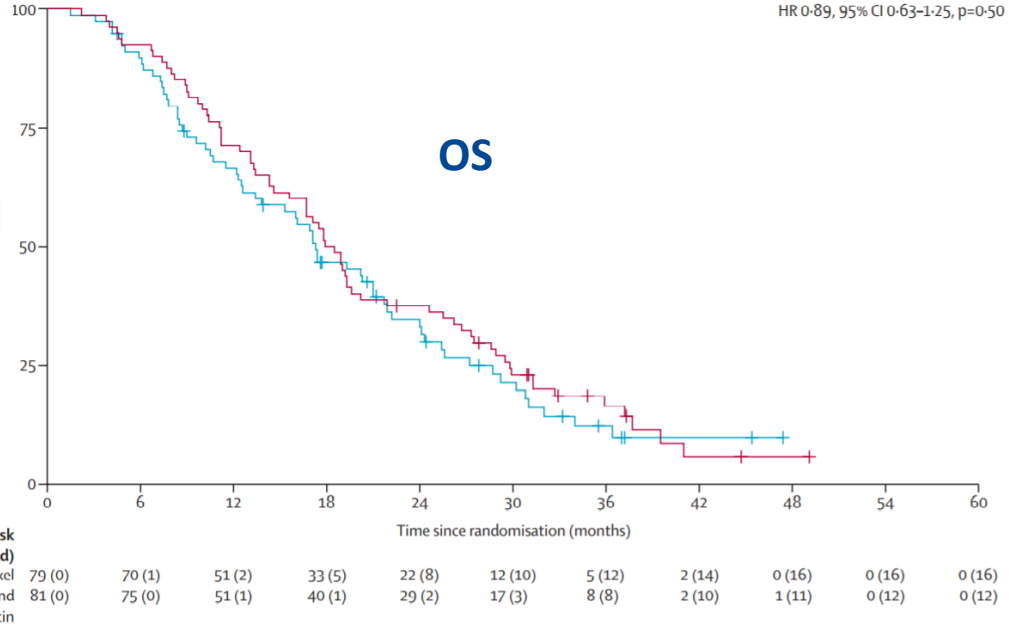
Author/year	Study design	Patient n	Patient population	Regiment	Treatment result
Papandreou et al. 2002	prospective	36	67% NEPC 33% mixed	Cis/ Eto/ Dox	RR 61%; TTP 5,8m OS 10,5m
Steineck et al. 2002	retrospective	30	30% NEPC, 43% anaplastic, 13% mixed	Cis *oder* Carbo/ Eto/ Est	RR 50%; OS 8-941 d
Culine et al. 2007	Prospective Single arm	41	CRPC and sNE marker	Cis/ Doc	RR 41%; OS 12m
Flechon et al. 2011	Prospektive Single arm	55	CRPC + M (visz) *And/or* sNE Marker	Carbo/ Eto	RR 8,9%; PFS 2,9m, OS 9,6m
Aparicio et al. 2013	Prospective, single arm	113; 74	mCRPC , stratified for AVPC	1st line: Carbo/ Doc 2nd line: Cis/ Eto	TTP1: 5,1m, TTP2: 3,0m OS 16m
Beltran et al. 2018	Prospective, Single arm	60	NEPC, AdenoCa + NE markers, liver Mx without PSA, sNE	Aurorakinase A Inhibitor Alisertib	13,4% without progression at 6 months; PFS 2,2m, OS 9,5m
Corn et al. 2019	prospective randomised	160	CRPC, stratified for AVPC	Carbo/ Caba vs. Caba	AVPC: PFS: 6,0 m vs. 2,2 m OS: 17,4m vs. 9,9m
Apostolidis et al. 2019	retrospektive	46	45,7% NEPC 43,5% mixed	Carbo/Cis + Eto	RR 48,1%; OS 15,5m
Brown et al. 2022	Prospective Single arm	15	AVPC/ NEPC	Avelumab	RR 6.7%; rPFS 1.8m; OS 7.4 m

Modified according to Tsaur et al. Cancer Treatment Reviews 2019: 20-26

Phase I/II: Cabazitaxel +/- Carboplatin (ITT-Population)



PFS



OS

Corn et al. Lancet Oncol. 2019; 20:1432-43

Phase I/II: Cabazitaxel +/- Carboplatin with/without AVPC-MS (PostHoc Analysis)

	Cabazitaxel (months)	Carbo/ Caba (months)	P-value
ITT			
PFS	4.5	7.3	P = 0.018
OS	17.3	18.5	p = 0.5
AVPC-MS (cDNA or immunohistochemistry)			
PFS	2.2	9.9	p = 0.00033
OS	6.0	17.4	p = 0.0024
AVPC-MS neg.			
PFS	5.9	6.0	p = 0.74
OS	22.2	18.9	p = 0.29

Corn et al. Lancet Oncol. 2019; 20:1432-43

Aktuell rekrutierende Studien: Phase 2

NCT number	design	Number of pts	intervention	Primary endpoint(s)	status
NCT02834013	Phase 2, non-randomized	818[1]	Ipilimumab +Nivolumab or Nivolumab alone	ORR	recruiting
NCT04926181	Phase 2	24	Apalutamid + Cetrelimab	Composite Response Rate[2]	recruiting
NCT04709276	Phase 2	43[3]	Nivolumab + Ipilimumab + Carboplatin + Cabazitaxel	PFS at 6 months	recruiting
NCT02861573	Phase 2	1000[4]	Pembrolizumab + lenvatinib (cohort F); Pembrolizumab+Vibostolimab (cohort H), Pembrolizumab+Carboplatin+Etoposide (Cohort I)	PSA response, ORR, safety and tolerability	recruiting

[1]Rare malignancies including NEPC; [2]determined by PSA decline of >= 50% AND/OR CR or PR determined RECIST 1.1 criteria; [3] AVPC and NEPC; [4]Including cohorts A-I

Aktuell rekrutierende Studien: Phase 1

NCT number	design	Number of pts	intervention	Primary endpoint	status
NCT04702737	Phase 1b	60	Tarlatamab (AMG757) (BiTE against DLL3 + CD3)	safety	recruiting
NCT05652686	Phase 1 dose escalation	58[4]	PT217 (bsAb against DLL3 and CD47	Safety (DLT, MTD, RP2D)	Not yet recruiting
NCT05413421	Phase 1/1b dose escalation	42[5]	ORIC-944 (small molecule inhibitor of PRC2)	Safety (MTD; RP2D)	recruiting
NCT02709889	Phase 1/2	200[6]	Rovalpituzumab tesirine + Dexamethasone	TEAEs by Dose and NEC or Non-NEC Disease	Terminated (Strategic considerations)

[4]includes SCLC, LCNEC, NEPC, GEP-NET; [5]metastatic PC and NEPC; [6] solid tumors including NEPC

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MARTINI-KLINIK

Herzlichen Dank für Ihre Aufmerksamkeit

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