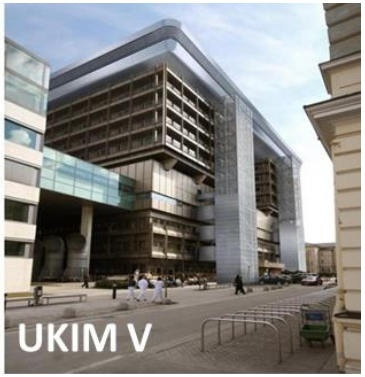
Nasopharynxkarzinome: Neue Therapiekonzepte



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DGHO/OEGHO/SGH/SMO
Hamburg 2023

Disclosures

Vortragstätigkeit: MSD, Merck, Sanofi

Beratertätigkeit: Roche, MSD, Merck, Sanofi, Janssen

Epidemiologie

DACH-Region

ASR: 0.3 pro 100.000

Europa

5000 Neudiagnosen

4% aller Fälle

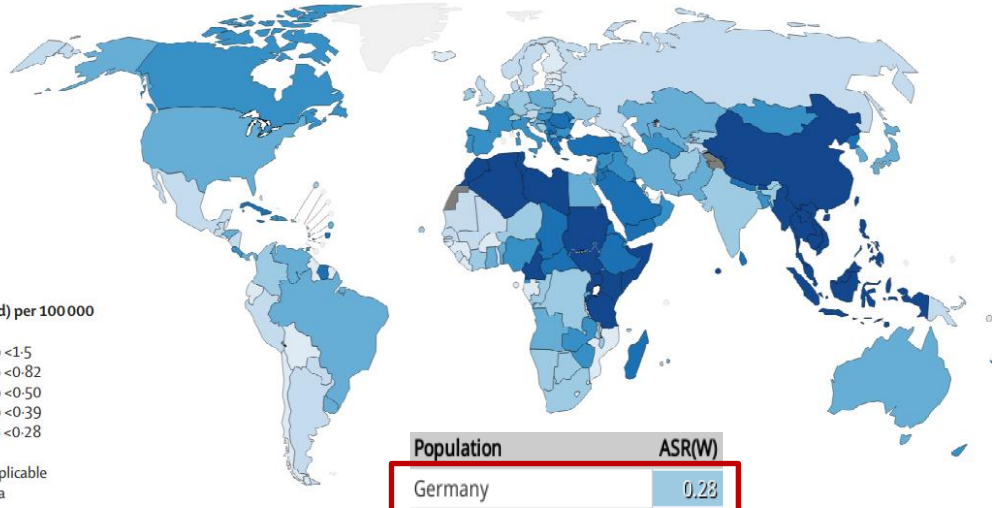
Global

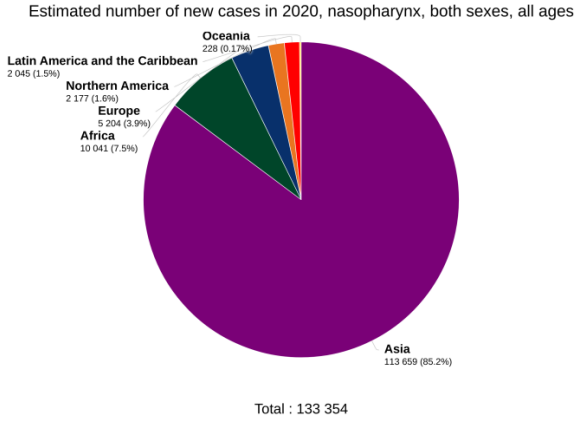
ca. 80% der Fälle in Asien

Hotspots Südostasien

133.000 Neudiagnosen

80.000 Todesfälle

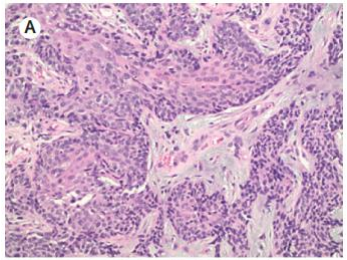




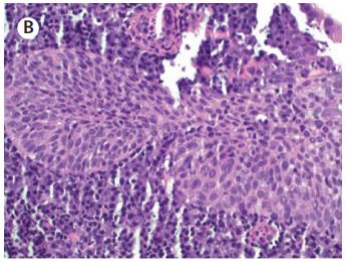
Population	ASR(W)
Germany	0.28
United Kingdom	0.28
Austria	0.28
Denmark	0.26
Lithuania	0.26
Slovenia	0.25
Belarus	0.24
Sweden	0.22
Luxembourg	0.21
Montenegro	0.16
Norway	0.16
Finland	0.14
Iceland	0
Switzerland	0.38
Croatia	0.37
Estonia	0.35
Latvia	0.34
Bosnia and Herzegovina	0.33
Ireland	0.33
Cyprus	0.32
The Netherlands	0.30
Czechia	0.29

Histologische Subtypen

WHO Typ I:
Verhornendes Plattenepithelkarzinom

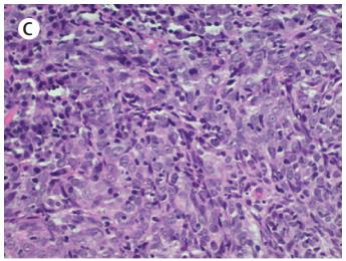


WHO Typ II:
Nicht-verhornendes Karzinom, differenzierter Subtyp

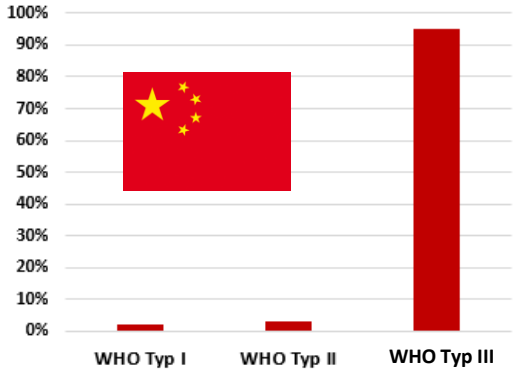


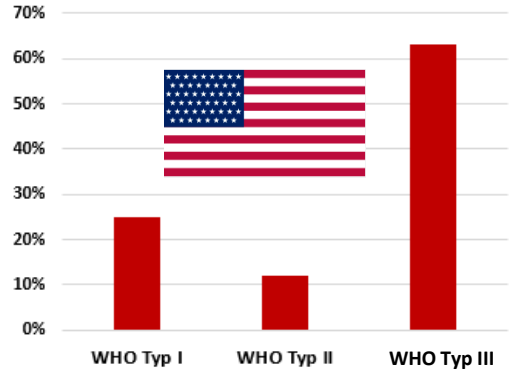
>95% EBV

WHO Typ III:
Nicht-verhornendes Karzinom, undifferenzierter Subtyp



>98% EBV





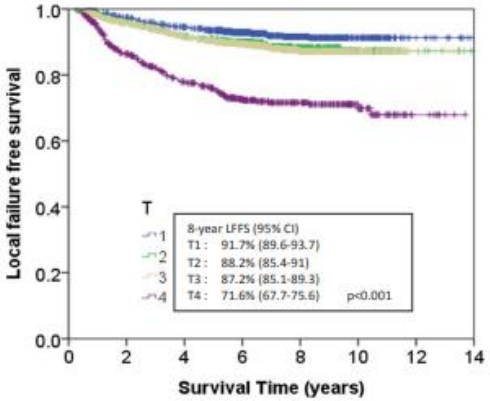
Chua Lancet 2016, Wei Lancet 2005

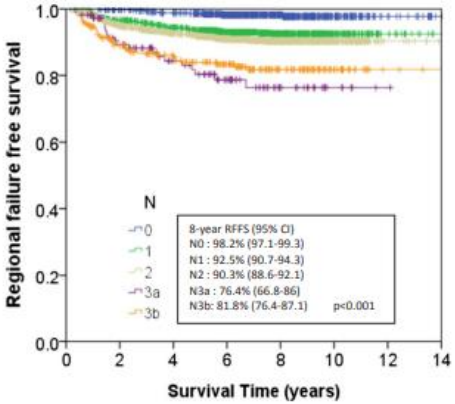
Early Stage NPC

Stadium I

alleinige IMRT

5-Jahres OS: 93%



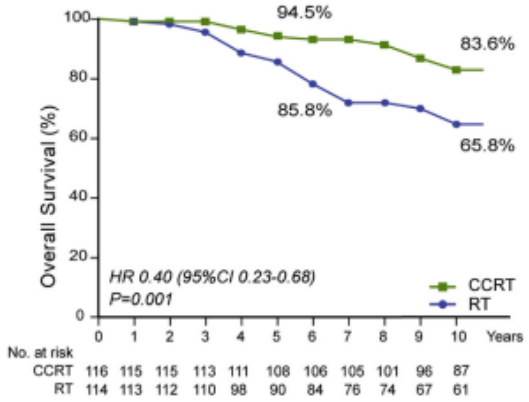


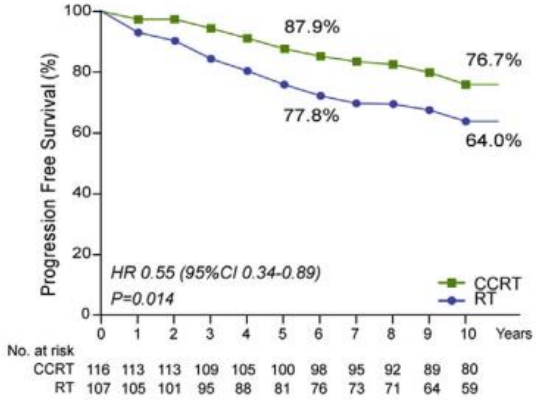
Stadium II + T3N0

Risiko-adaptierte Therapie

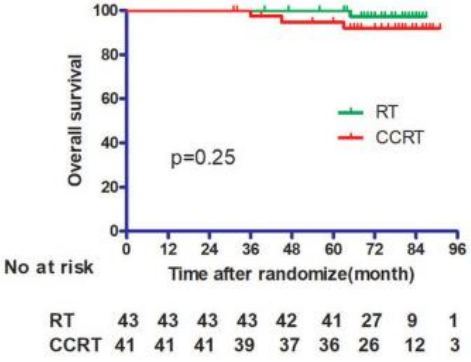
Stadium II NPC

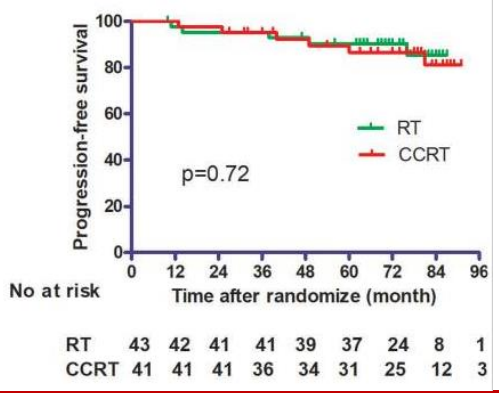
CCRT vs. RT
Phase III
2D-RT





IMRT vs. CCRT
Phase II





Chen JNCI 2011, Li Eur J Cancer 2019

Low-risk NPC Stadium II + T3N0M0

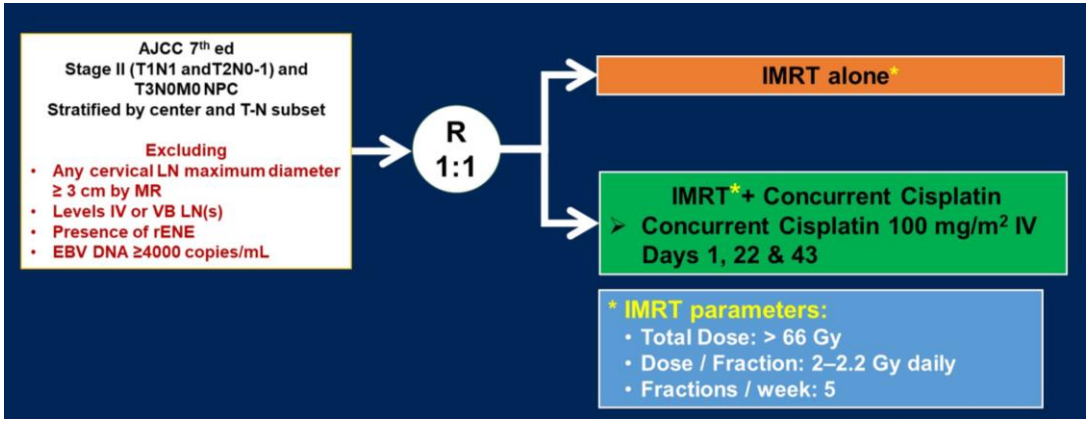
„Low-risk“ NPC Stadium II oder T3N0M0

Phase III

Ausschluss

- Max. Durchmesser cervikale LK ≥3 cm
- Positive LK Level IV oder VB
- EBV DNA ≥ 4.000 copies/ml

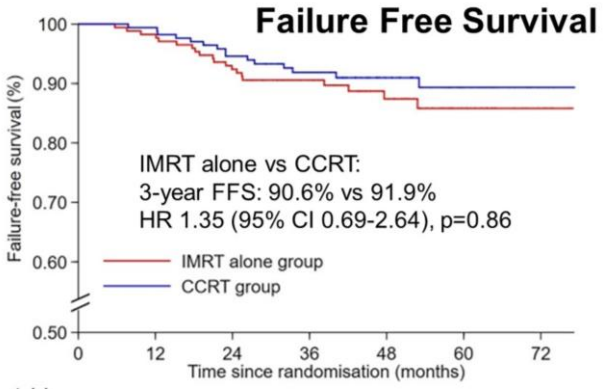
Non-inferiority: IMRT vs. CRRT

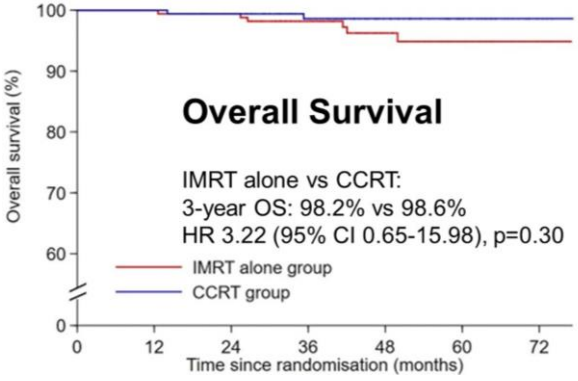


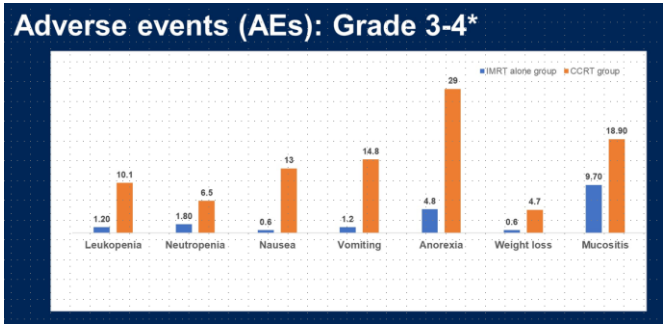
Low-risk NPC NPC Stadium II + T3N0M0

IMRT vs. CCRT

Phase III







EORTC QLQ-C30	ITEMS	Mean difference 95% CI	P-value
General quality of life (the higher the better)	**Global health status***	12.20 (10.64 to 13.76)	**<0.0001**
	Physical functioning	8.07 (6.98 to 9.17)	**<0.0001**
	Role functioning	5.03 (3.30 to 6.77)	**<0.0001**
	Emotional functioning	5.67 (4.28 to 7.06)	**<0.0001**
	Cognitive functioning	7.03 (5.69 to 8.38)	**<0.0001**
	Social functioning*	10.78 (8.72 to 12.83)	**<0.0001**
Symptom Burden (the lower the better)	**Fatigue***	-11.79 (-13.43 to -10.16)	**<0.0001**
	Nausea and vomiting*	-12.78 (-14.46 to -11.10)	**<0.0001**
	Pain*	-10.18 (-11.68 to -8.68)	**<0.0001**
	Dyspnoea	-6.82 (-8.29 to -5.36)	**<0.0001**
	Insomnia*	-10.35 (-12.48 to -8.23)	**<0.0001**
	Appetite loss*	-15.23. (-17.38 to -13.08)	**<0.0001**
	Constipation*	-17.83. (-19.76 to -15.89)	**<0.0001**
	Diarrhoea	-0.80 (-2.00 to 0.40)	0.19
	Financial difficulties	-1.89 (-4.18 to 0.41)	0.11

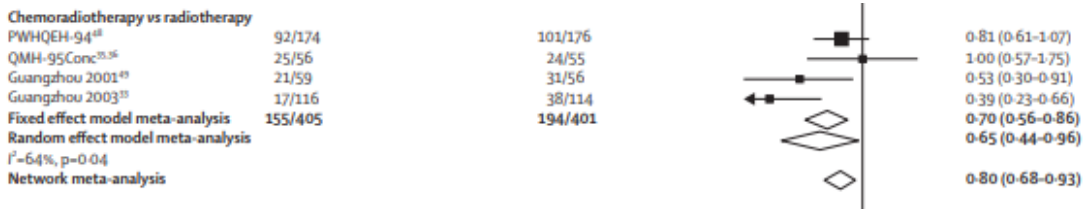
Lokal-fortgeschrittenes NPC

Stadium III-IV (T3-4 N+ bzw. N2-3)

Multimodale Therapiekonzepte

Kernelement der Therapie: **CCRT**
Studien: Cisplatin 100mg/m² q3
Kumulativdosis ≥ 200mg/m²

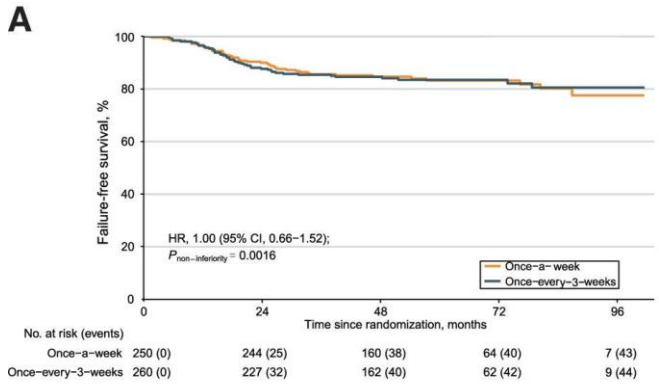
MAC-NPC Meta Analyse

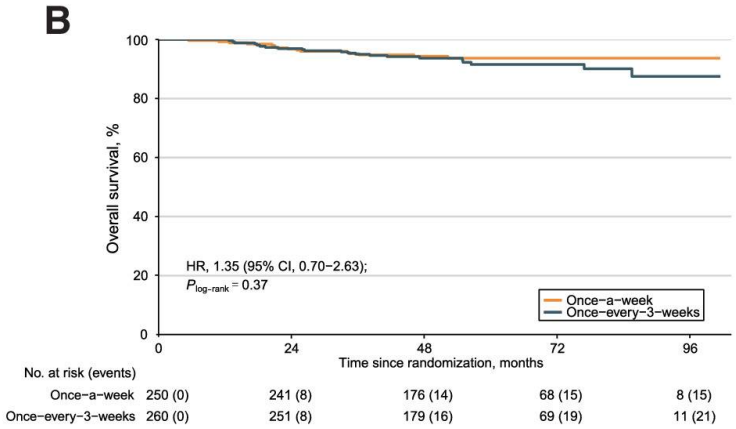


CCRT

Cisplatin 40 mg/m² weekly vs. Cisplatin 100mg/m² q3

Phase III





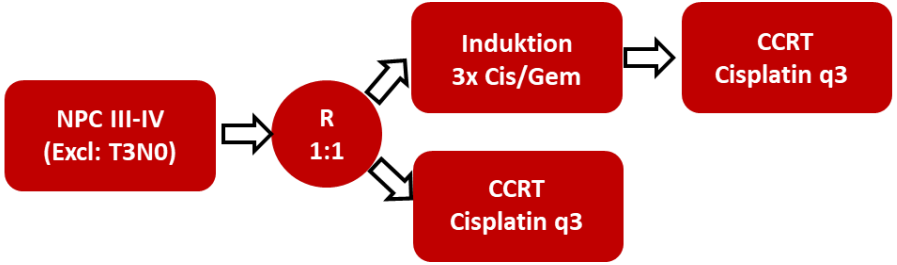
NW: Ototoxizität häufiger im weekly Arm

Induktionschemotherapie

Stadium III-IV

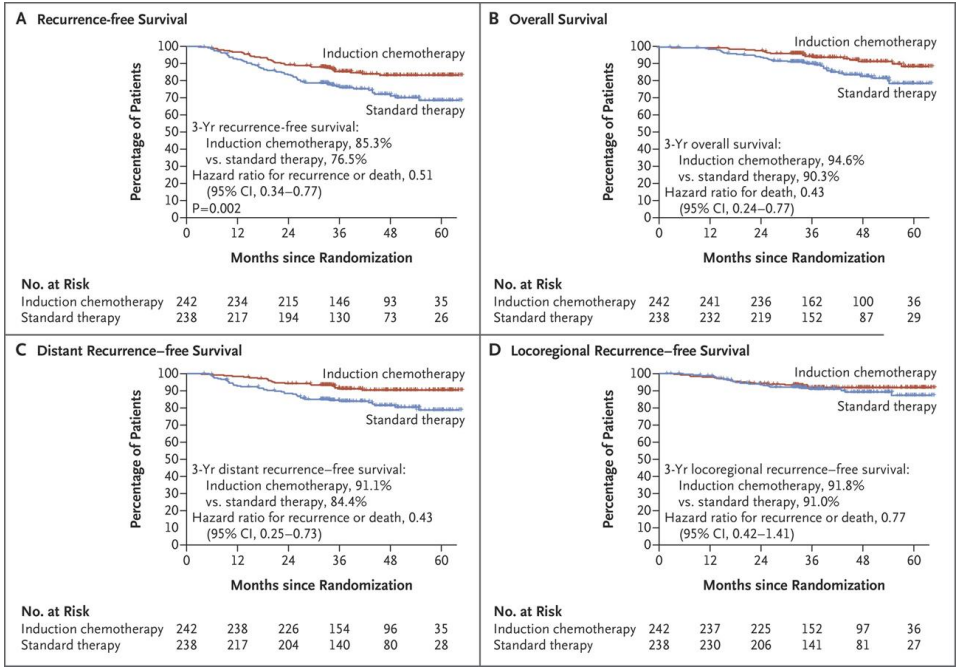
(ohne T3N0)

Phase III



3 Zyklen Induktion: 97%

ORR Induktion: 94%

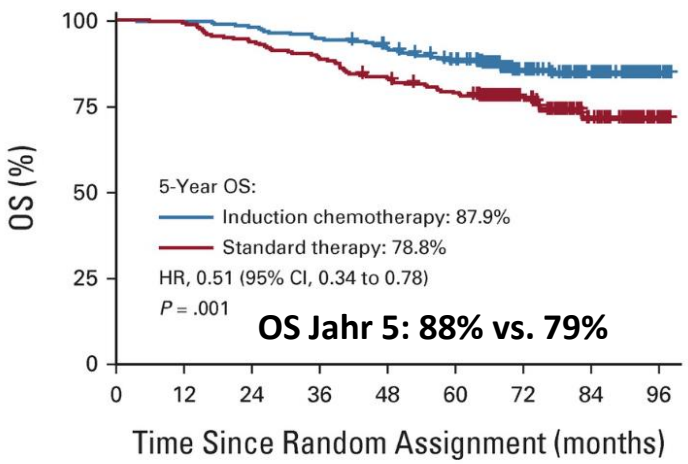


Induktionschemotherapie

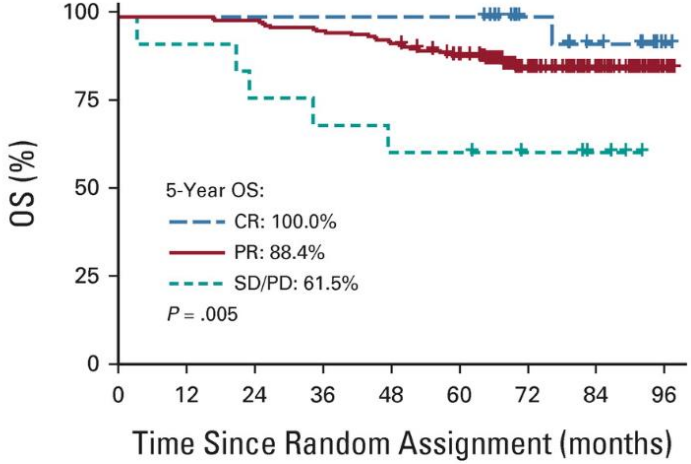
Stadium III-IV

(ohne T3N0)

Phase III



No. at risk:									
Induction chemotherapy	242	241	236	228	217	202	114	69	10
Standard therapy	238	234	221	209	195	183	105	53	10



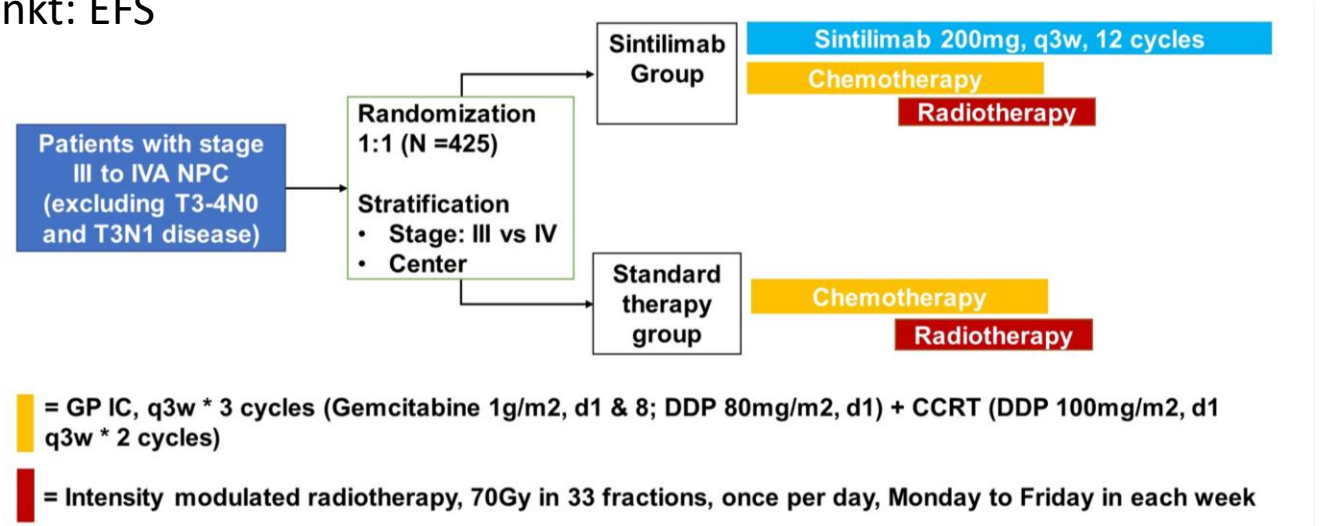
No. at risk:									
CR	24	24	24	24	24	2	13	9	2
PR	202	202	199	192	182	168	93	55	8
SD/PD	13	12	10	9	8	8	6	3	0

Induktionschemotherapie + ICI

CONTINUUM Trial

Phase III

Primärer Endpunkt: EFS

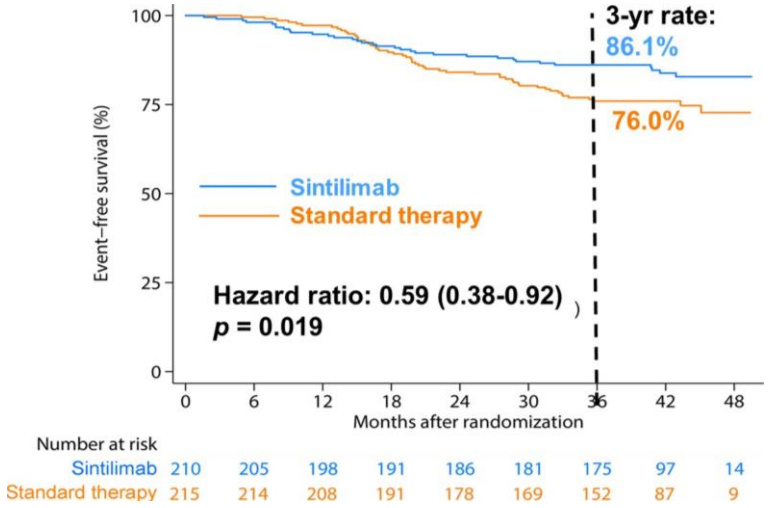


Induktionschemotherapie + IO

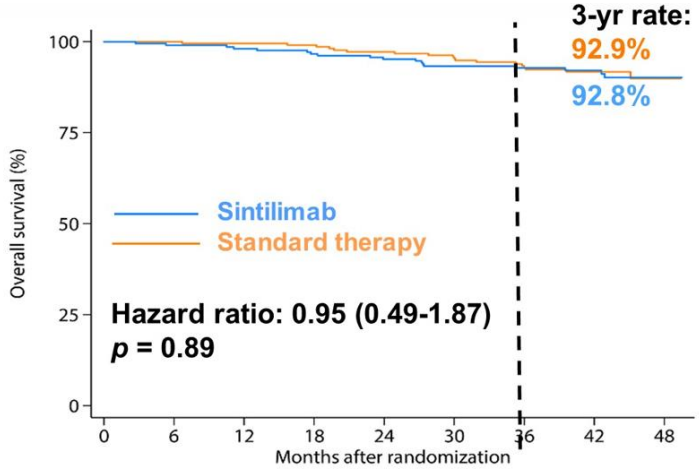
CONTINUUM Trial

Phase III

EFS



OS



Adjuvante Therapie nach CCRT

Capecitabine vs. Observation

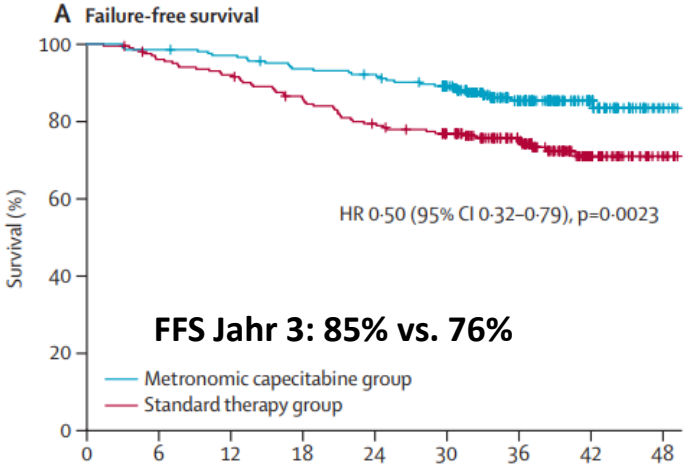
Phase III

Capecitabine metronomisch

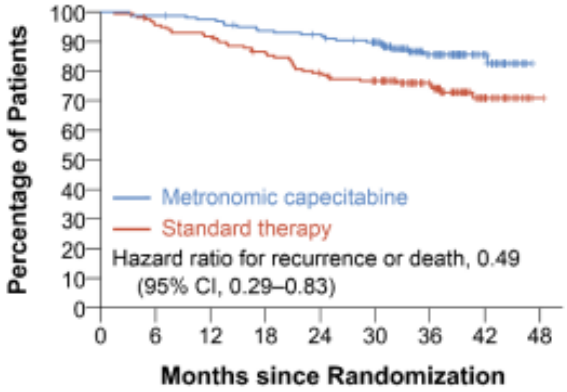
1 Jahr (650mg/m² BID)

77% Induktions CTx

Prim. Endpunkt: FFS Jahr 3



Subgruppe Induktions CTx



1 Jahr Capecitabine: 74%
Dosisreduktion: 18%

Adjuvante Therapie nach CCRT

Capecitabine vs. Observation

Phase III

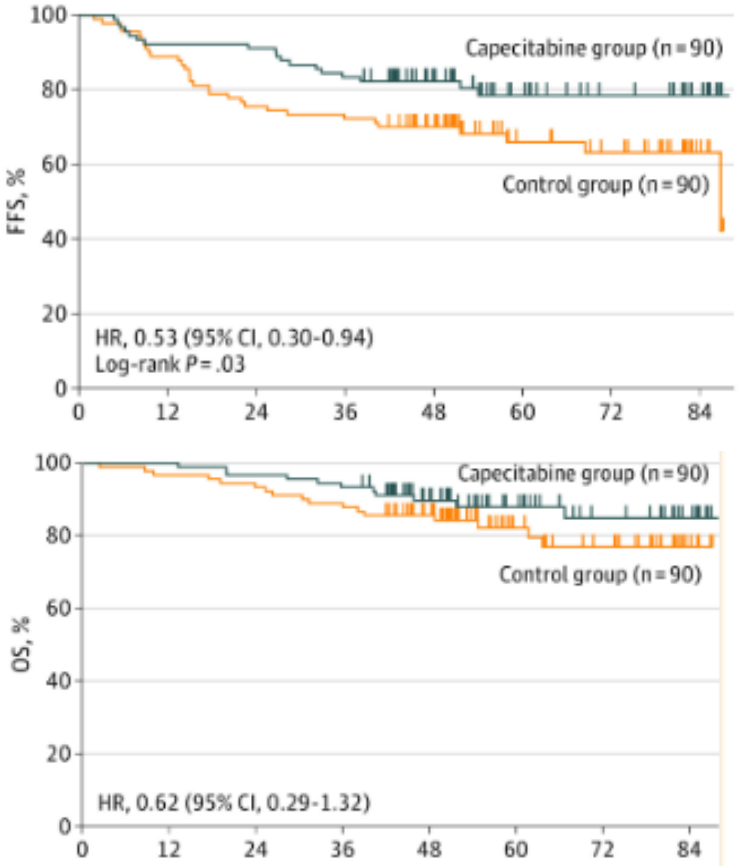
Capecitabine Standard

8 Zyklen (1000mg/m² BID, d1-14)

Ausschlusskriterium: Induktions CTx

Prim. Endpunkt: FFS Jahr 3

8 Zyklen Capecitabine: 78%
Dosisreduktion: 21%



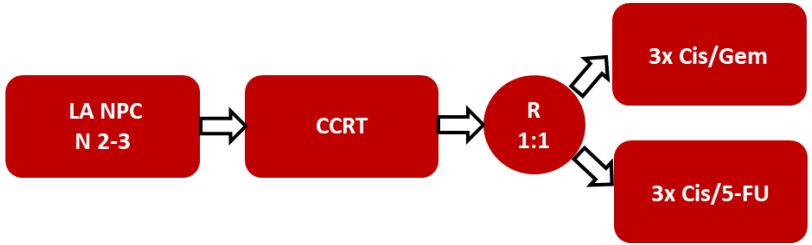
Adjuvante Therapie nach CCRT

Cis/Gem vs. Cis/5-FU

Phase III

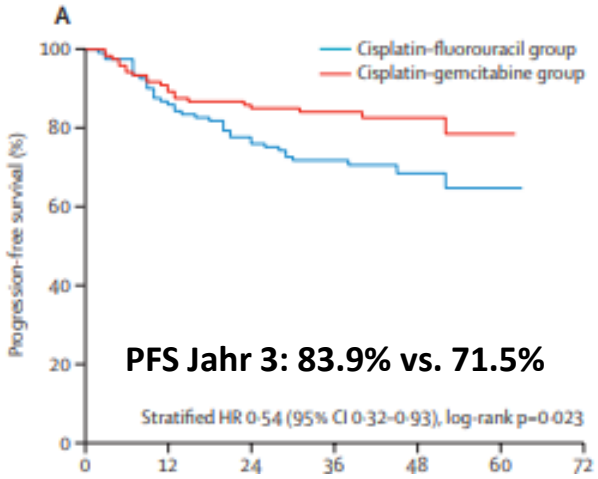
Ausschlusskriterium: Induktions CTx

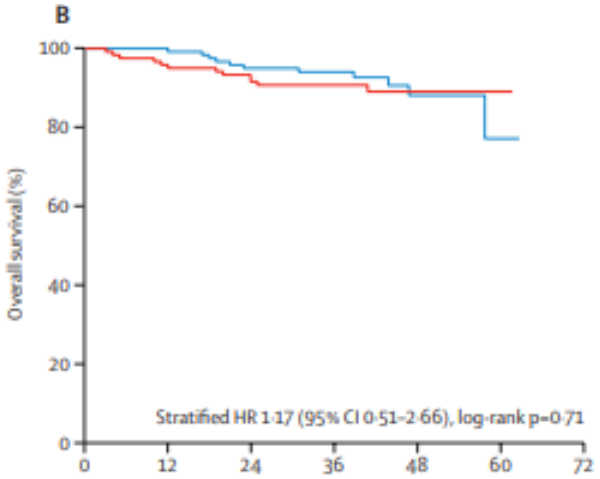
Primärer Endpunkt: 3 Jahres PFS



3 Zyklen Platin: 55% vs. 60%

Dosisreduktion: 53% vs. 40%

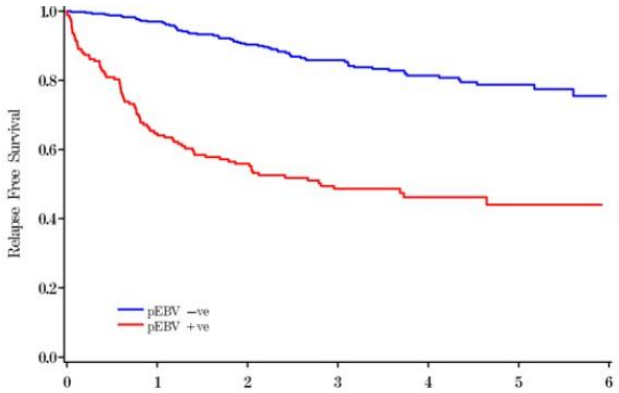




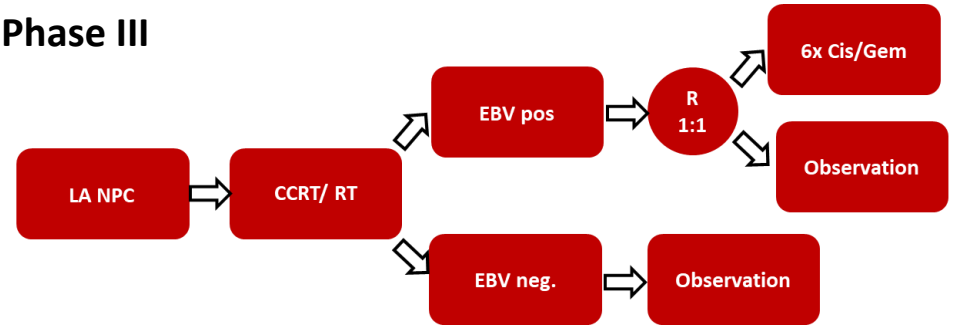
Adjuvante Therapie nach CCRT

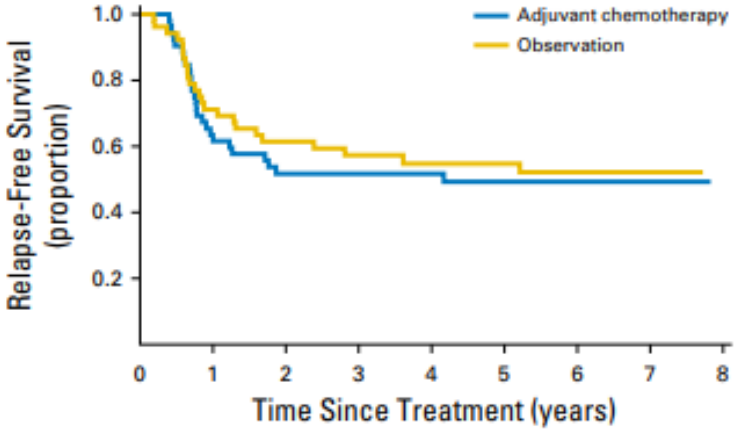
EBV als Stratifikationsmarker?

Plasma EBV DNA post RT → wichtigster prognostischer Faktor



Phase III





Hui Cancer 2015, Chan J Clin Oncol 2018

Zusammenfassung early/ locally-advanced NPC

Stadium II, T3N0

- Low-Risk → alleinige IMRT vermutlich ausreichend
- High Risk→ CCRT

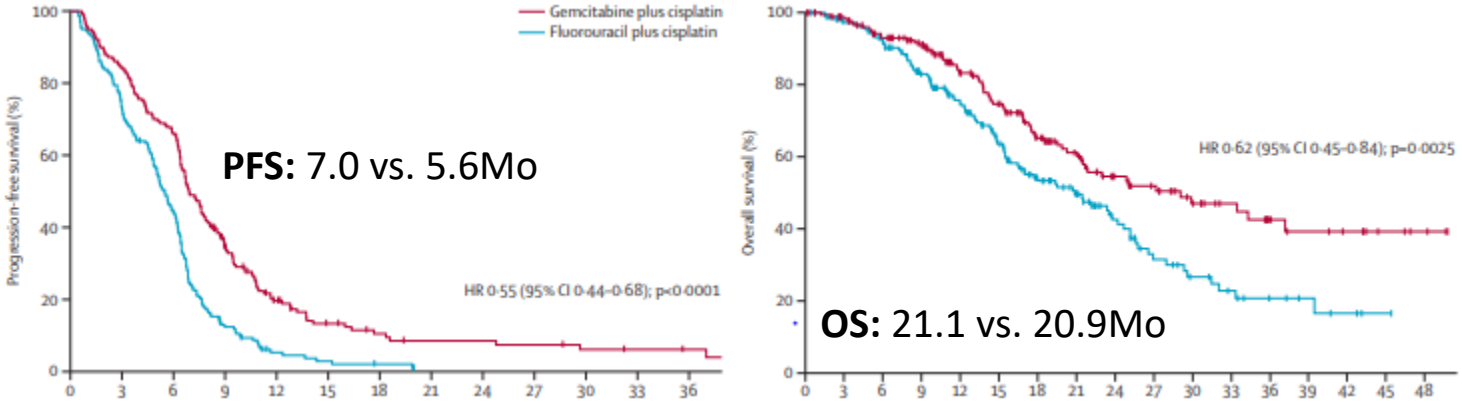
Stadium III-IV

- CCRT→ Kernelement der Therapie (Cis weekly gleich effektiv wie q3)
- Induktions CTX mit Cis/Gem → Standardvorgehen (hohe ORR, gute Therapieadhärenz, OS Verbesserung)
  → Sintilimab Zugabe verlängert FFS (OS noch unreif)
- Adjuvante Therapie → Stellenwert bei vorheriger Induktions CTx unklar
  → keine Induktions CTx: Cis/Gem 3x bzw. metronomisches Capecitabin 1 Jahr

Metastatic NPC First Line

Cis/Gem vs. Cis/5-FU

Phase III



ORR: 64% vs. 42%

Metastatic NPC First Line

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Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial

Prof Yunpeng Yang, MD * • Prof Song Qu, MD * • Prof Ji
Prof Mingjun Xu, MM * • Prof Weidong Li, MS * • et al.

Published: June 23, 2021 • DOI: https://doi.org/10.1016

ARTICLES
https://doi.org/10.1038/s41591-021-01444-0
nature medicine
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Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial

Hai-Qiang Mai[1,37], Qiu-Yan Chen[1,37], Dongping Chen[2], Chaosu
Jingao Li[6], Ying-Rui Shi[7], Feng Jin[8], Ruilian Xu[9], Jianji Pan[10], Sh
Yi-Chun Liu[14], Yi Jiang[15], Xia He[16], Hung-Ming Wang[17], Wan-Te
Xiaohui He[20], Xiaozhong Chen[21], Zhigang Liu[22], Xianglin Yua
Shanghua Jing[26], Yanju Chen[27], Yin Lu[28], Ching-Yun Hsieh[29], M
Jens Samol[32,33], Hui Feng[34,35], Sheng Yao[34,35], Patricia Keegan

Cancer Cell
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Article

Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309)

Yunpeng Yang,[1,24] Jianji Pan,[2,24] Hui Wang,[3,24] Yuanyuan Zhao,[1,24] Shenhong Qu,[4,24] Nianyong Chen,[5,24]
Xiaozhong Chen,[6] Yan Sun,[7] Xiaohui He,[8] Chaosu Hu,[9] Lizhu Lin,[10] Qitao Yu,[11] Siyang Wang,[12] Guihua Wang,[13]

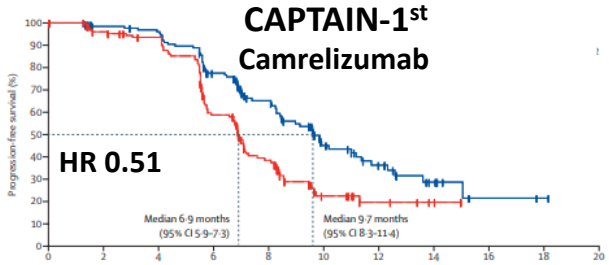
(Author list continued on next page)

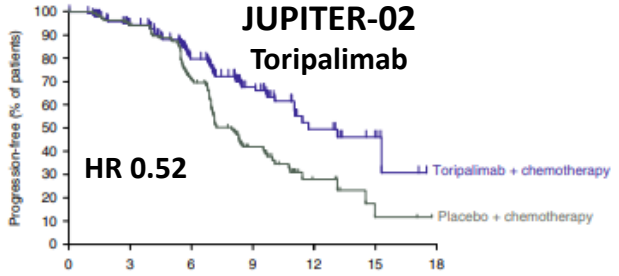
Mai Nat Med 2021, Yang Lancet Oncol 2021, Yang Cancer Cell 2023

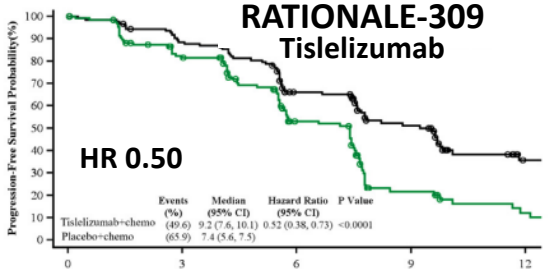
Metastatic NPC

CIS/GEM + ICI

Phase III







	Schema	N	ORR (%)	mDOR Monate	mPFS Monate		mOS, Monate	
GC Arm Phase III 2016	GC x 6, keine ET	181	64	-	7.0		21.1	
CAPTAIN-1st Phase III 2021	**Camrelizumab** + GC → Camrelizumab	134	87	8.5	10.8 (8.5-13.6)	HR 0.51 (0.37-.0.69)	NR	HR 0.67 (0.41-1.11)
	Placebo + GC → Placebo	129	81	5.6	6.9 (5.9-7.9)		22.6 (19.2-NR)	
JUPITER-02 Phase III 2021	**Toripalimab** + GC → Toripalimab	146	79	10	11.7 (11.0-NR)	HR 0.52 (0.36-0.74)	NR	HR 0.60 (0.36-0.99)
	Placebo + GC → Placebo	143	67	5.7	8.0 (7.0-9.5)		NR (22.8-NR)	
RATIONALE-309 Phase III 2022	**Tislelizumab** + GC → Tislelizumab	131	79	8.5	9.6 (7.6-11.7)	HR 0.50 (0.37-0.68)	NR	HR 0.60 (0.35-1.01)
	Placebo + GC → Placebo	132	55	6.1	7.4 (5.6-7.5)		23.0 (19.8-NR)	

Mai Nat Med 2021, Yang Lancet Oncol 2021, Yang Cancer Cell 2023

Biomarker

PD-L1 Expression

CAPTAIN-1st: keine Information

JUPITER-02: keine Korrelation mit Outcome

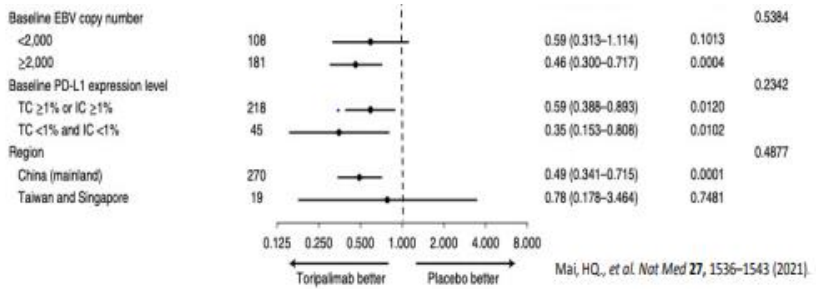
RATIONALE-309: keine Korrelation mit Outcome

Plasma EBV-DNA

Trend zu besserem Response bei niedrigeren EBV-Titern

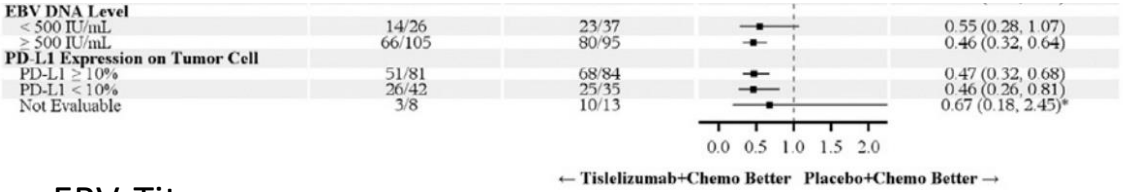
frühe EBV-Clearance korreliert mit Response

JUPITER-02



Mai, HQ., *et al. Nat Med* **27**, 1536–1543 (2021).

RATIONALE-309



NPC Guidelines

ESMO Guideline Update 2022

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Treatment of metastatic disease or locoregional recurrences not amenable to curative approaches

Recently, two randomised phase III trials showed an increase in progression-free survival (PFS) when immunotherapy (camrelizumab or toripalimab) was added to first-line treatment with cisplatin and gemcitabine followed by maintenance immunotherapy (camrelizumab or toripalimab) for recurrent and/or metastatic disease. The addition of immunotherapy should therefore be considered, pending long-term results of overall survival benefit and the assessment of the role of maintenance therapy (Figure 2).[4,5] This recommendation is based on data from two phase III trials of East-Asian populations.[4,5] At the time of publication, camrelizumab and toripalimab are neither European Medicines Agency (EMA)- nor US Food and Drug Administration (FDA)-approved for NPC and the applicability of the results to NPC patients in non-endemic areas warrants further investigation. Details on the ESMO-Magnitude of Clinical Benefit (MCBS) scores for these treatments are included in Table 1.

NCCN 2023

Recurrent, Unresectable, Oligometastatic, or Metastatic Disease (with no surgery or RT option)

Preferred Regimens

First-Line[d]
- Cisplatin/gemcitabine (category 1)[16,17]

Other Recommended Regimens

First-Line[d]
- Combination Therapy
  - Cisplatin/5-FU[18,19]
  - Cisplatin or carboplatin/docetaxel[20] or paclitaxel[18]
  - Carboplatin/cetuximab[21]
  - Gemcitabine/carboplatin[1]
  - Cisplatin/gemcitabine + PD-1 inhibitor (eg, pembrolizumab or nivolumab)[22,23]

Subsequent-Line
- Immunotherapy
  - Nivolumab if previously treated, recurrent or metastatic non-keratinizing disease (category 2B)[33,34]
  - Pembrolizumab if previously treated, PD-L1–positive, recurrent or metastatic disease (category 2B)[35]

ICI mono, Platin vorbehandelt

Single Arm Studien

	Phase	ICI	N	ORR (%)	mPFS Monate	mOS, Monate
KEYNOTE-028	Ib	**Pembrolizumab**	27	25.9%	6.5	16.5
NCI-9742	II	**Nivolumab**	44	20.5%	2.8	17.1
Fang et al.	II	**Camrelizumab**	91	32%	5.6	NR
POLARIS-02	II	**Toripalimab**	190	20.5%	1.9	17.4

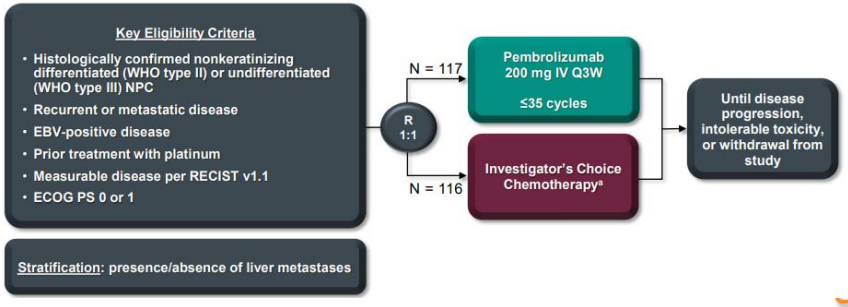
Hsu J Clin Oncol 2017, Ma J Clin Oncol 2018, Fang Lancet Oncol 2018, Wang J Clin Oncol 2021

ICI mono

ICI mono, Platin vorbehandelt

Phase III, KEYNOTE 122

Prim. Endpunkt: OS



Baseline Characteristics

	Pembro n = 117	Chemo n = 116
Age, median (range), years	51.0 (21-76)	53.0 (23-78)
Male, n (%)	98 (83.8)	95 (81.9)
Region, n (%)		
North America	22 (18.8)	11 (9.5)
Asia	95 (81.2)	105 (90.5)
ECOG PS 1, n (%)	81 (69.2)	77 (66.4)
PD-L1, n (%)		
CPS <10	54 (46.2)	62 (53.4)
CPS ≥10	55 (47.0)	46 (39.7)
Missing	8 (6.8)	8 (6.9)
Disease status, n (%)		
Recurrent	12 (10.3)	10 (8.6)
Metastatic	41 (35.0)	29 (25.0)
Recurrent and metastatic	64 (54.7)	77 (66.4)
Current or former smoker, n (%)	59 (50.4)	58 (50.0)

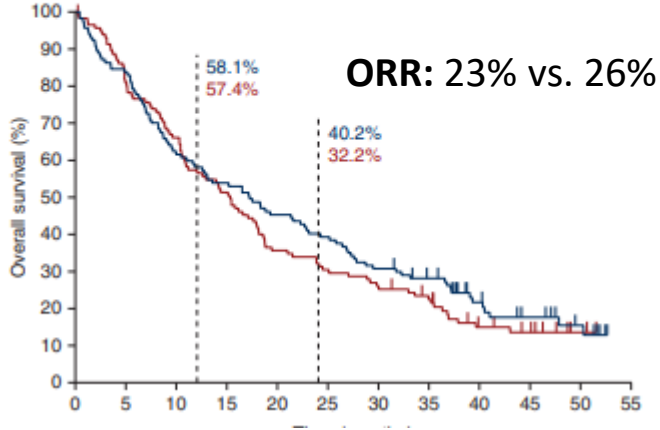
	Pembro n = 117	Chemo n = 116
Overall cancer stage,[a] n (%)		
IV	114 (97.4)	113 (97.4)
Metastasis stage, n (%)		
M0	12 (10.3)	10 (8.6)
M1	105 (89.7)	106 (91.4)
Presence of liver metastasis, n (%)	57 (48.7)	56 (48.3)
Prior radiation, n (%)	103 (88.0)	95 (81.9)
Prior therapy with curative intent,[b] n (%)	17 (14.5)	14 (12.1)
Prior lines of therapy, n (%)		
1	54 (46.2)	48 (41.4)
2	28 (23.9)	24 (20.7)
3	11 (9.4)	16 (13.8)
4	3 (2.6)	10 (8.6)
≥5	4 (3.4)	4 (3.4)

IO mono

KEYNOTE 122

Phase III, Platin vorbehandelt

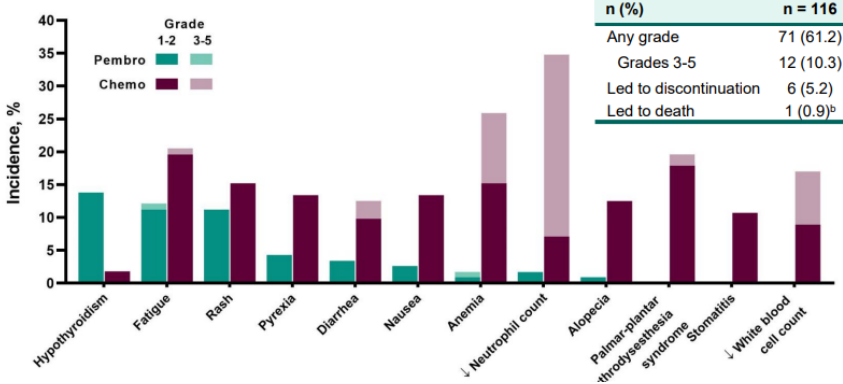
	Events, *n* (%)	Median OS, months (95% CI)	HR (95% CI)[a]	*P* value[b]
Pembrolizumab	95 (81.2)	17.2 (11.7-22.9)	0.90 (0.67-1.19)	0.2262
Chemotherapy	97 (83.6)	15.3 (10.9-18.1)		



ORR: 23% vs. 26%

Treatment-Related AEs[a] (≥10% in either arm)

n (%)	Pembro n = 116	Chemo n = 112
Any grade	71 (61.2)	98 (87.5)
Grades 3-5	12 (10.3)	49 (43.8)
Led to discontinuation	6 (5.2)	11 (9.8)
Led to death	1 (0.9)[b]	2 (1.8)[c]



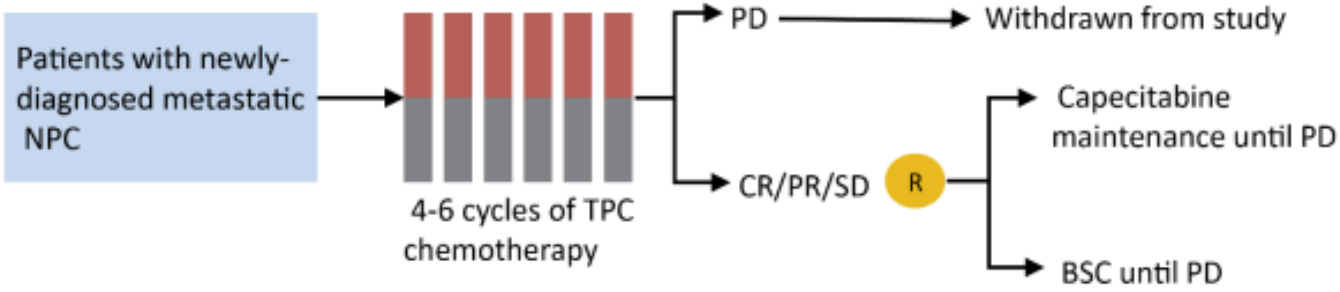
Erhaltungstherapie

Phase III, Single Center China

4-6 Zyklen Cis/Pacli/ Capecitabine

Capecitabine ET vs. BSC

Prim. Endpunkt: PFS



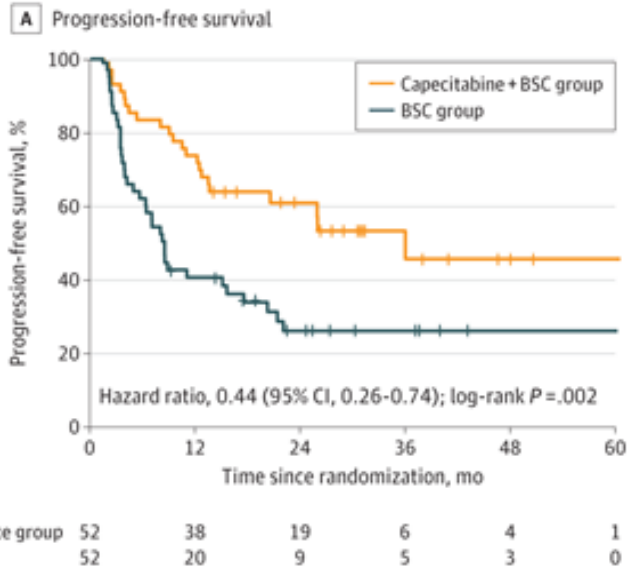
Erhaltungstherapie

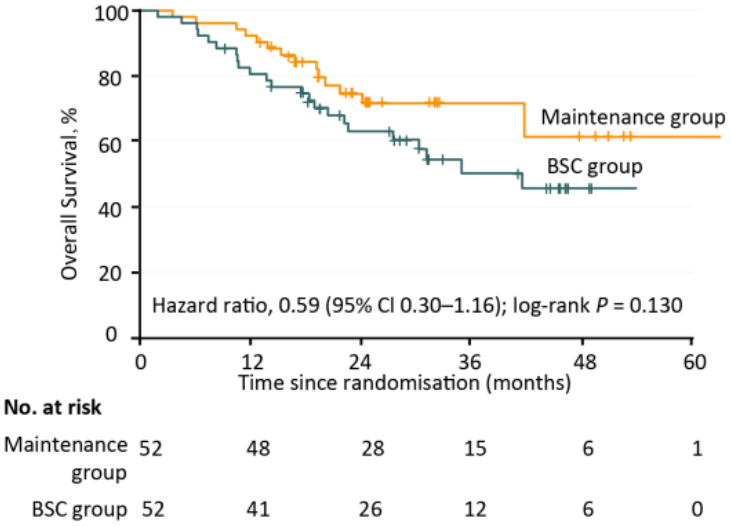
Phase III, Single Center China

4-6 Zyklen Cis/Pacli/Capecitabine

Capecitabine ET vs. BSC

Prim. Endpunkt: PFS

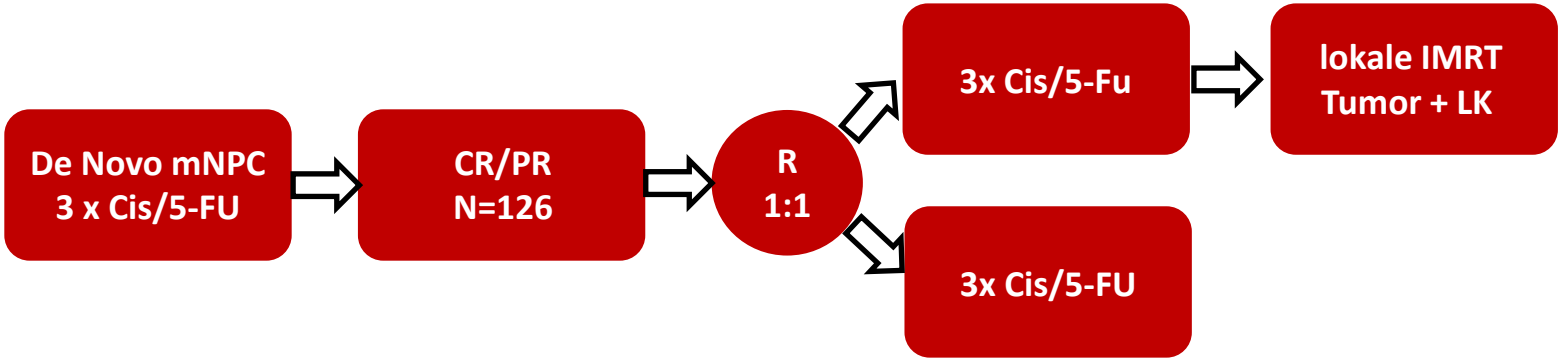




RT Konsolidierung

Phase III, China

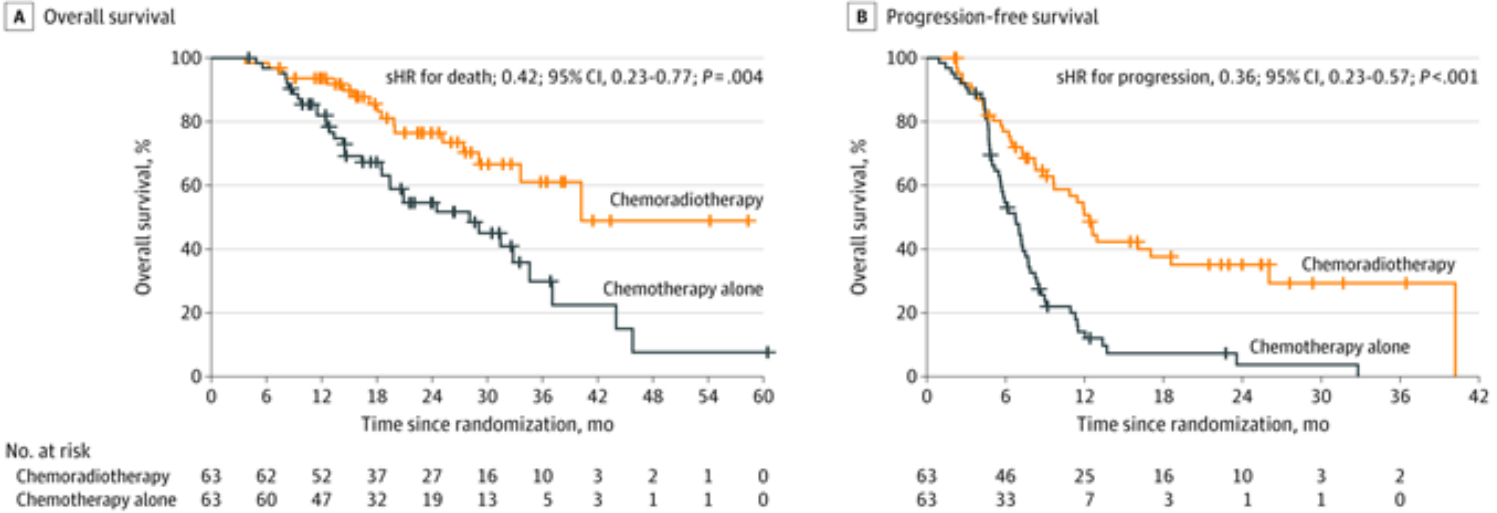
IMRT nach CTx



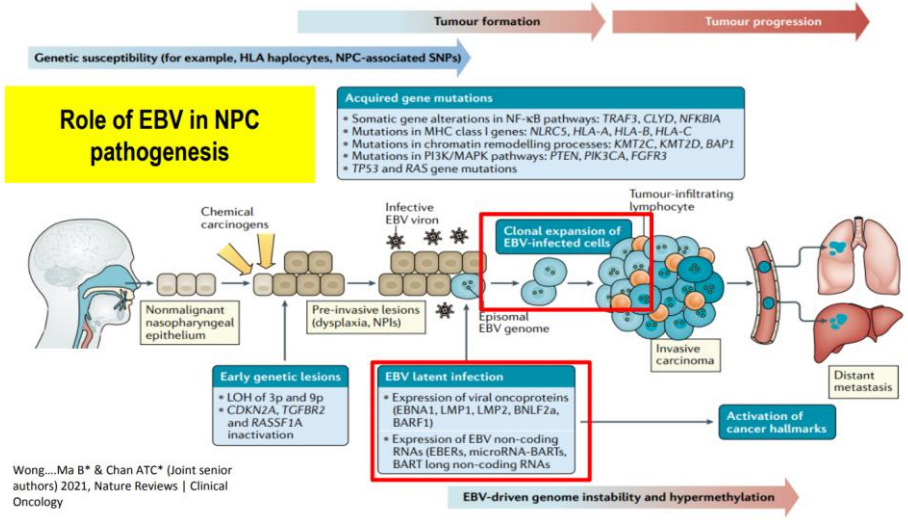
RT Konsolidierung

Phase III, China

IMRT nach CTx

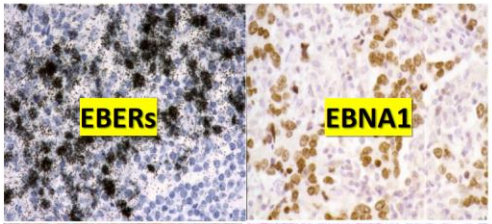


Targeting EBV



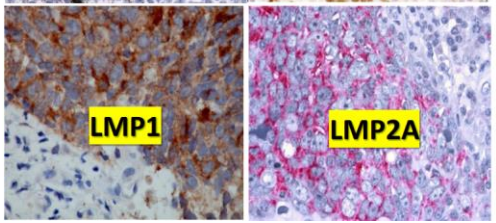
Wong....Ma B* & Chan ATC* (Joint senior authors) 2021, Nature Reviews | Clinical Oncology

highly abundant latent non-coding RNAs, innate immunity. Diagnostic utility



Ubiquitous in all EBV infected cells. Essential for Maintenance of the EBV episomal genome & latency. Druggable

Classic Oncogene: activates NF-kB, PI3K/AKT signaling, induce cancer stem cells. 25-30% of NPC



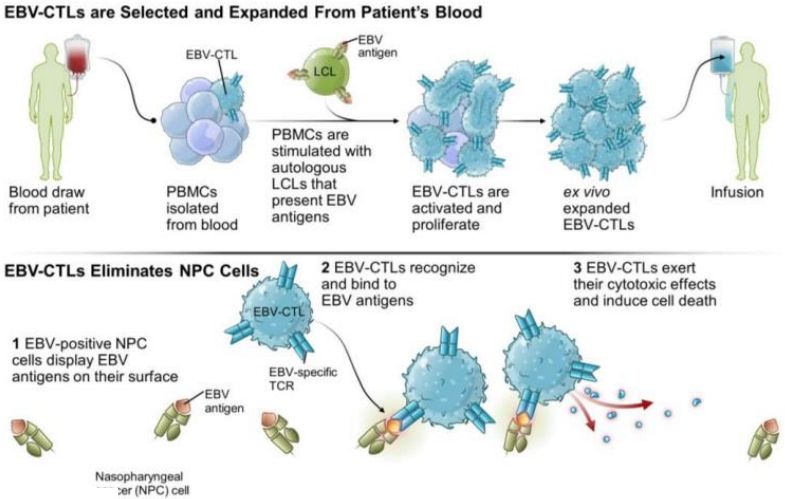
Promote proliferation, angiogenesis, cell invasion, metastasis, anti-apoptotic Heterogeneous expression

Autologe EBV-spezifische CTLs

VANCE Trial

Phase III, First Line

Cis/Gem +/- EBV CTLs



Multicenter, randomized, open-label, Phase III clinical trial

Study Population

Patients with EBV+ NPC:

- ≥18 years old
- Metastatic or locally recurrent, not amenable to further curative chemoradiation or surgery.
- ECOG performance status ≤2
- >6 months since last chemotherapy/adjuvant immunotherapy

Study Treatment (Arm A: n = 165, Arm B: n = 165)

Arm A

- Gemcitabine and carboplatin (4 cycles)
- EBV-CTL (6 cycles; 1×10^8 cells/m^2)*

Arm B

- Gemcitabine and carboplatin (6 cycles)

Gemcitabine = 1000 mg/m^2; carboplatin = AUC2

Endpoints

Primary

- Overall Survival

Secondary

- 2, 3 and 5-year OS
- PFS
- ORR, CBR, QoL
- Safety

Autologe EBV-spezifische CTLs

VANCE Trial

Phase III, First Line

Cis/Gem +/- EBV CTLs

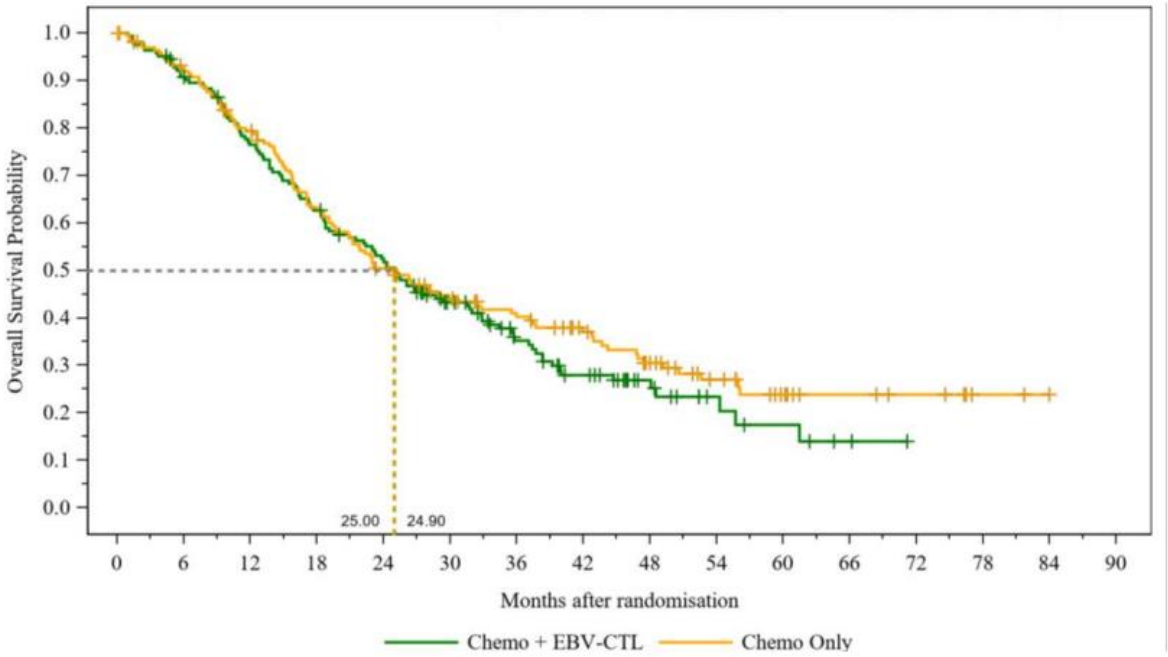
Median OS (months; 95% CI)

Chemo + EBV-CTL: 25.0 (19.7, 31.8)

Chemo Only: 24.9 (19.7, 32.8)

Hazard ratio (95% CI): 1.19 (0.91, 1.56)

p = 0.1942



Zielgerichtete Therapien

NPC

Niedrige Mutationslast (<1/MB)

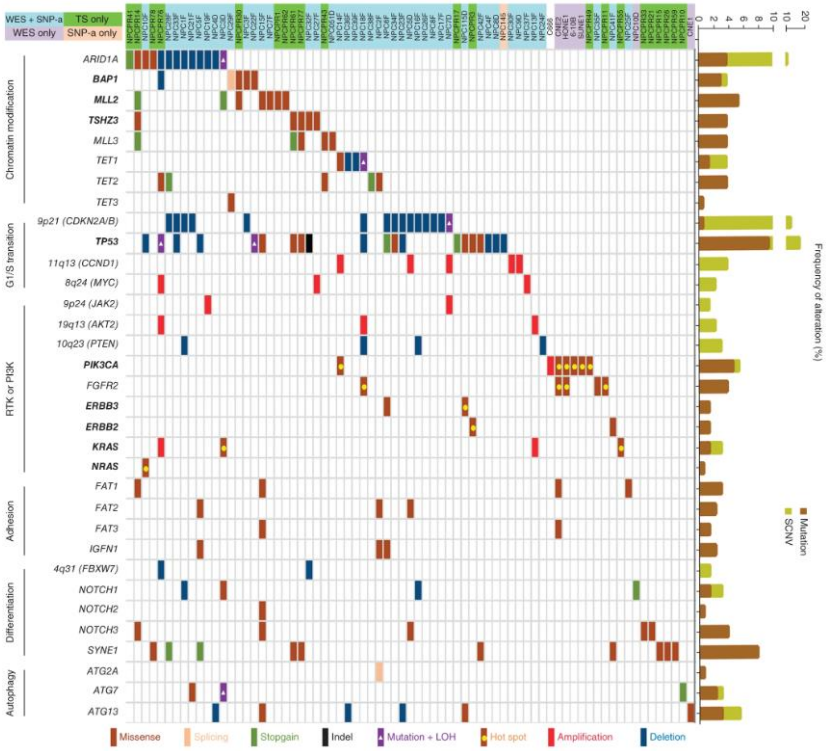
PI3K Alterationen→ vorwiegend Passenger Mutationen

Häufig Mutationen Chromatin Regulatoren/HR-Genen

- ARID1A, BAP1, KMT2D3, TSHZ3

POINT-Study

Olaparib + Pembrolizumab, Phase II (NCT04825990)



Zusammenfassung metastatic NPC

First Line

- Cisplatin/Gemcitabine→ Standardvorgehen
- Cis/Gem + ICI → verlängert PFS, OS noch unklar
- Capecitabine Erhaltungstherapie → Verlängert PFS, nach TPC
  → Effekt nach Cis/Gem nicht geprüft
- Konsolidierende RT→ bei de novo mNPC sinnvoll
  → verlängert OS

Second Line

Pembrolizumab→ weniger NW als mono CTx

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CCCI comprehensive cancer center innsbruck

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UNIVERSITÄTSKLINIKEN
INNERE MEDIZIN
Hämatologie und Onkologie

Vielen Dank für Ihre Aufmerksamkeit!