Qualitätskonferenz des Bayerischen Krebsregisters
Online-Veranstaltung in Kooperation mit dem Bayerischen Zentrum für Krebsforschung (BZKF) und dem Comprehensive Cancer Center (CCC) Erlangen-EMN

Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit

Tumortherapie im Kopf-Hals-Bereich

A. Gostian

Hals-Nasen-Ohren-Klinik, Kopf- und Halschirurgie

Universitätsklinikum Erlangen

Direktor: Prof. Dr. med. Dr. h. c. Heinrich Iro

FAU Friedrich-Alexander Universität Erlangen-Nürnberg Medizinische Fakultät

DZI Deutsches Zentrum Immuntherapie

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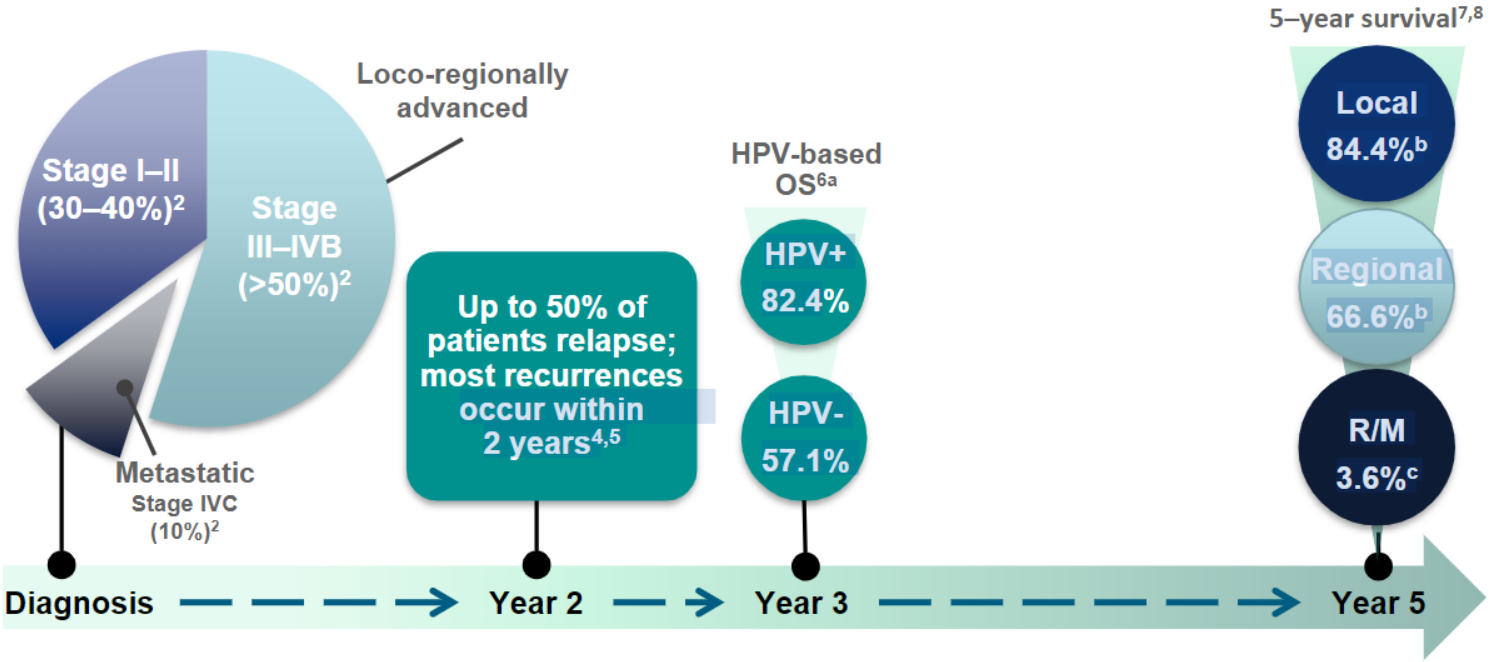
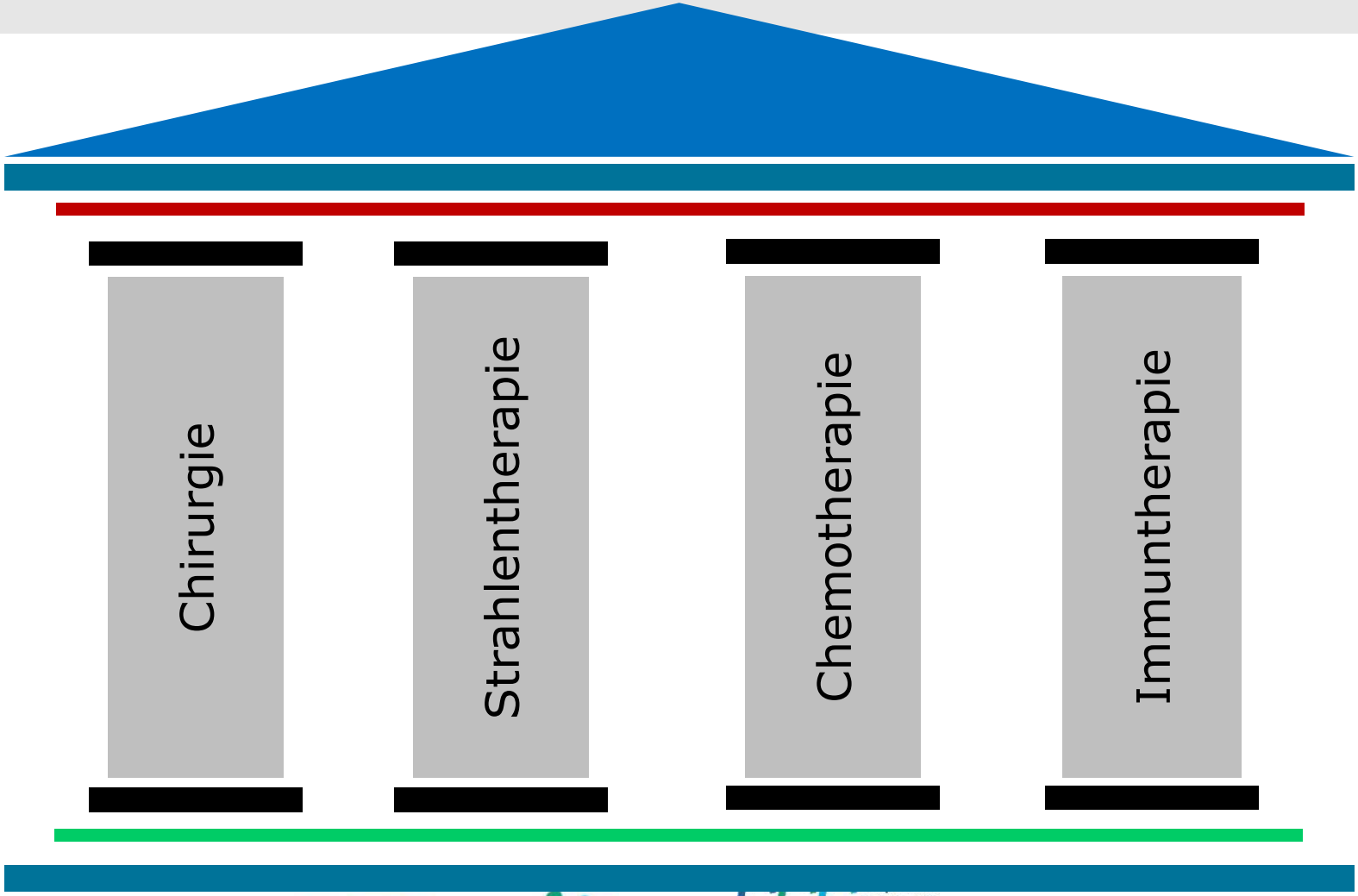
Disease burden of HNSCC

- H&N cancer is the 7th most common cancer globally[1]
- HNSCC accounts for 90–95% of all head and neck cancers[2]



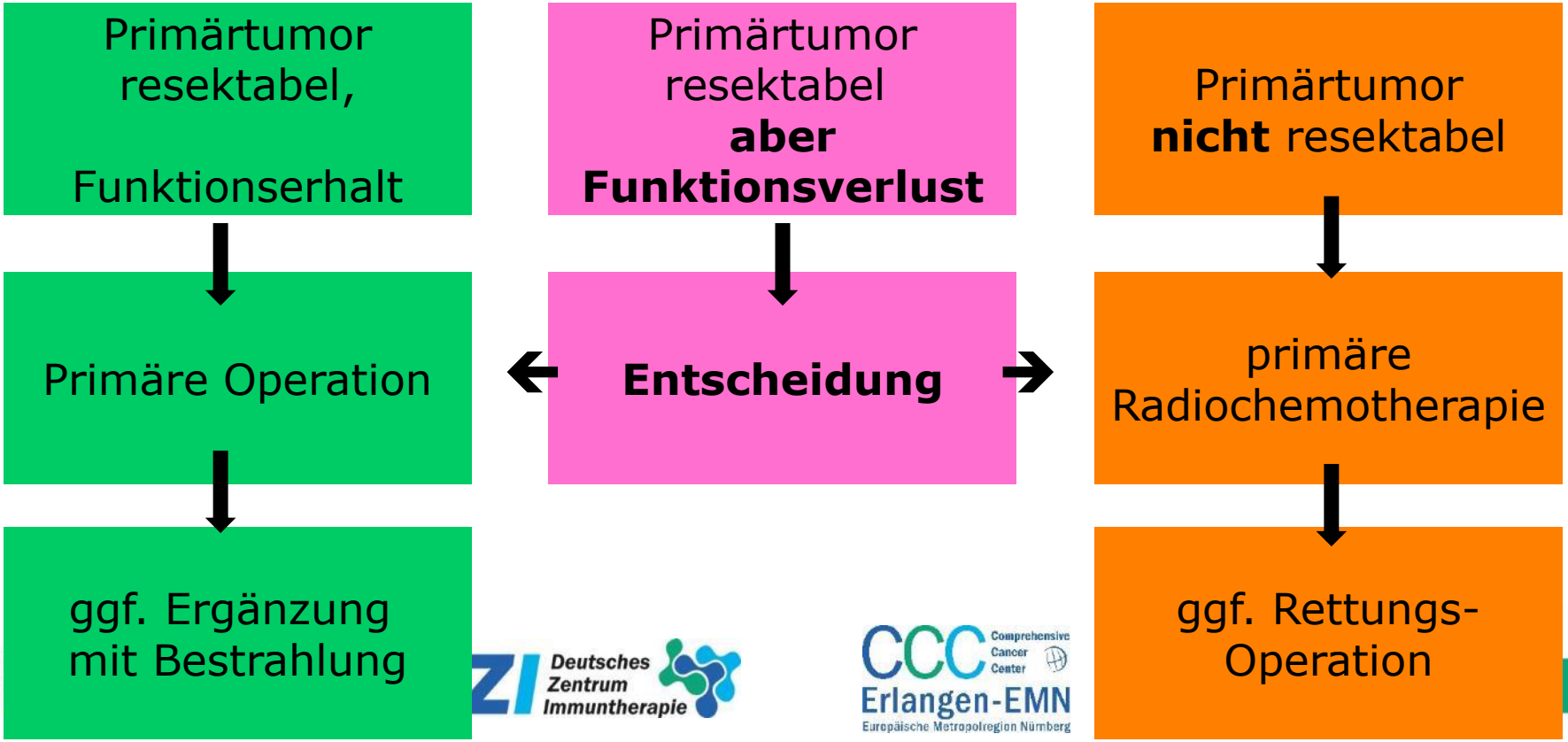
[a]Stage III–IV SCCHN in oral cavity, oropharynx, hypopharynx or larynx with no distant metastases. [b]Relative survival in patients with HNSCC. [c]OS in patients with R/M HNSCC deemed incurable by surgery or radiation therapy.
H&N, head and neck; HPV, human papilloma virus; Int., intermediate; OS, overall survival; R/M, recurrent or metastatic; HNSCC, squamous cell carcinoma of the head and neck; SEER, National Cancer Institute Surveillance, Epidemiology, and End Results programme.
1. GLOBOCAN 2012. Population Fact Sheets (accessed July 2016); 2. Seiwert TY et al. *Nat Clin Pract Oncol.* 2007;4:156–171. 3. Siegel RL et al. CA Cander *J Clin.* 2016;66:7–30. 4. Ho AS et al. *Head Neck.* 2013;36:144–151; 5. Goodwin WJ Jr. *Laryngoscope.* 2000;110:1–18; 6. Ang KK et al. *N Engl J Med.* 2010;363:24–35; 7. SEER Cancer Statistics Factsheets: Oral Cavity and Pharynx Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/oralcav.html (accessed January 2020); 8. Argiris A et al. *Cancer.* 2004;101:2222–2229.

Säulen der Onkologischen Therapie



Therapiekonzepte: „klassisch“

Tumorbeurteilung: Ultraschall, Spiegelung, Bildgebung



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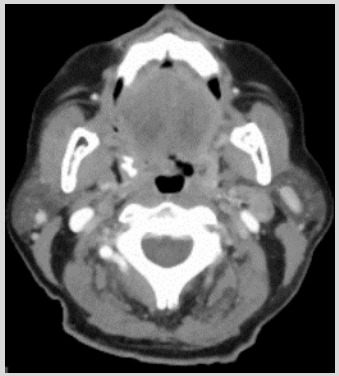
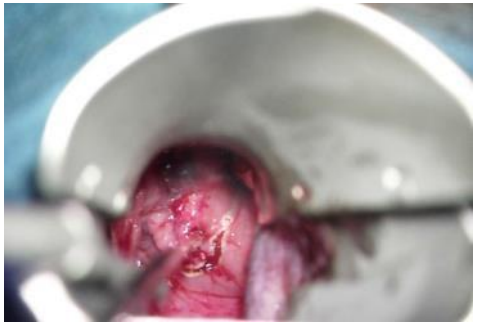
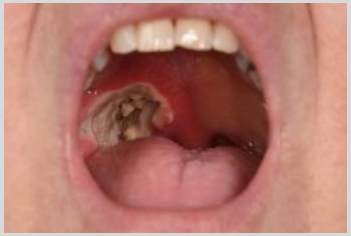
transorale Chirurgie - Oropharynx

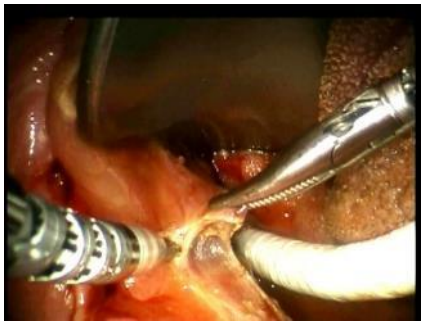


LASER-Chirurgie

Roboter-Chirurgie







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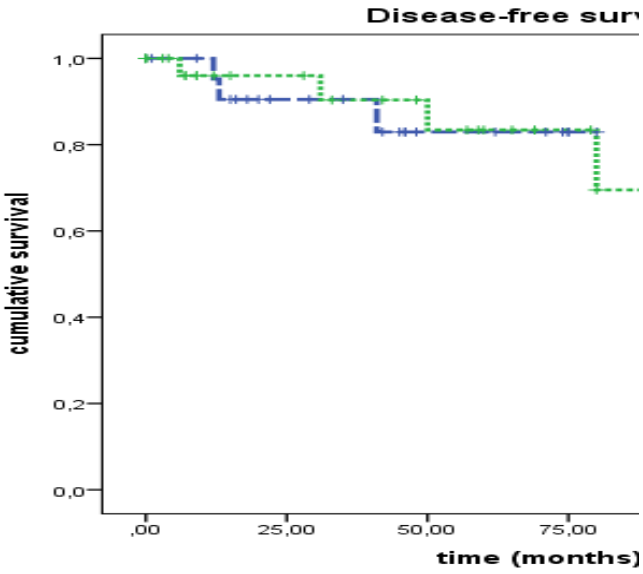
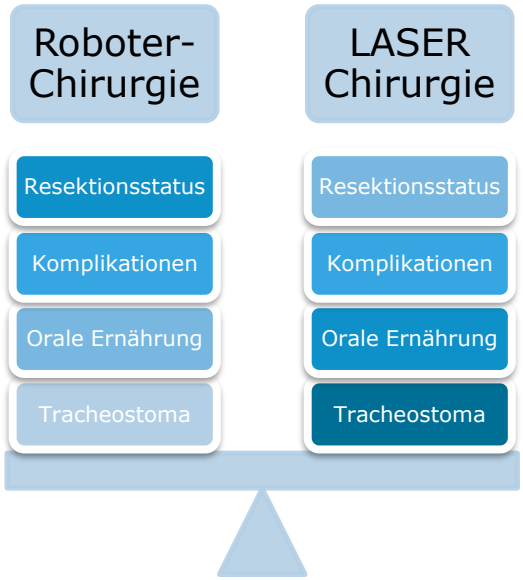
transorale Roboter - Chirurgie - Oropharynx





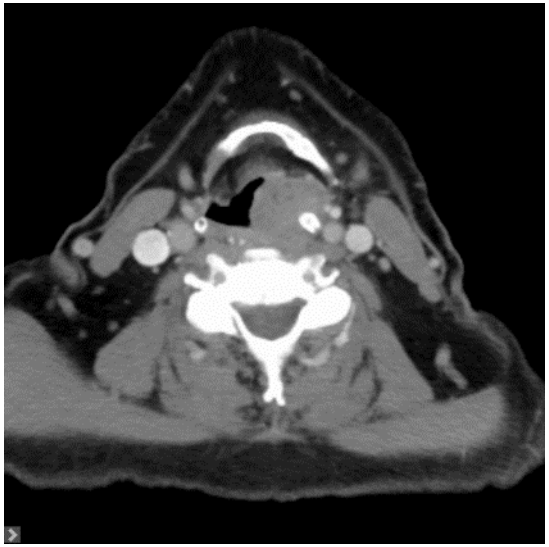
Sievert M, …Gostian AO. 2021

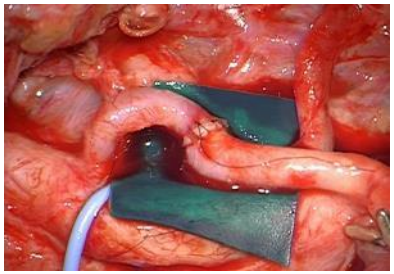
ablative » rekonstruktive Chirurgie - Larynx

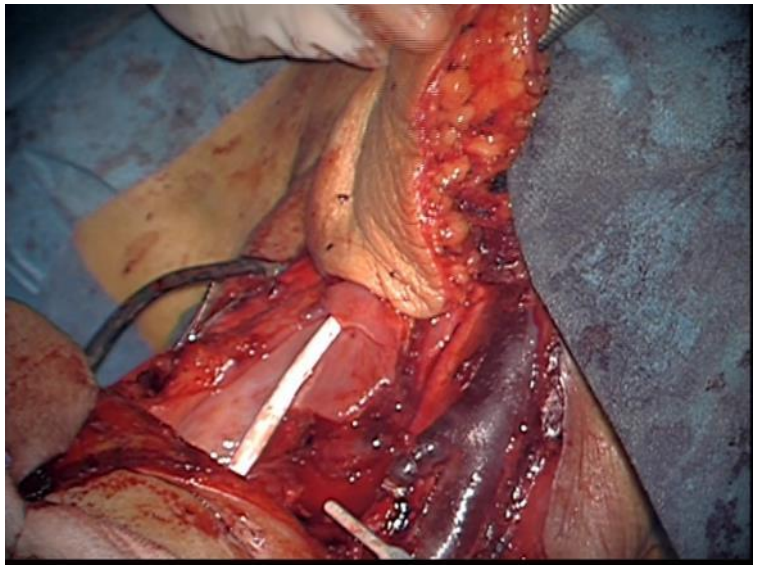
Organerhalt durch Radiochemo-therapie

Organverlust durch Laryngektomie

ablative » rekonstruktive Chirurgie - Larynx

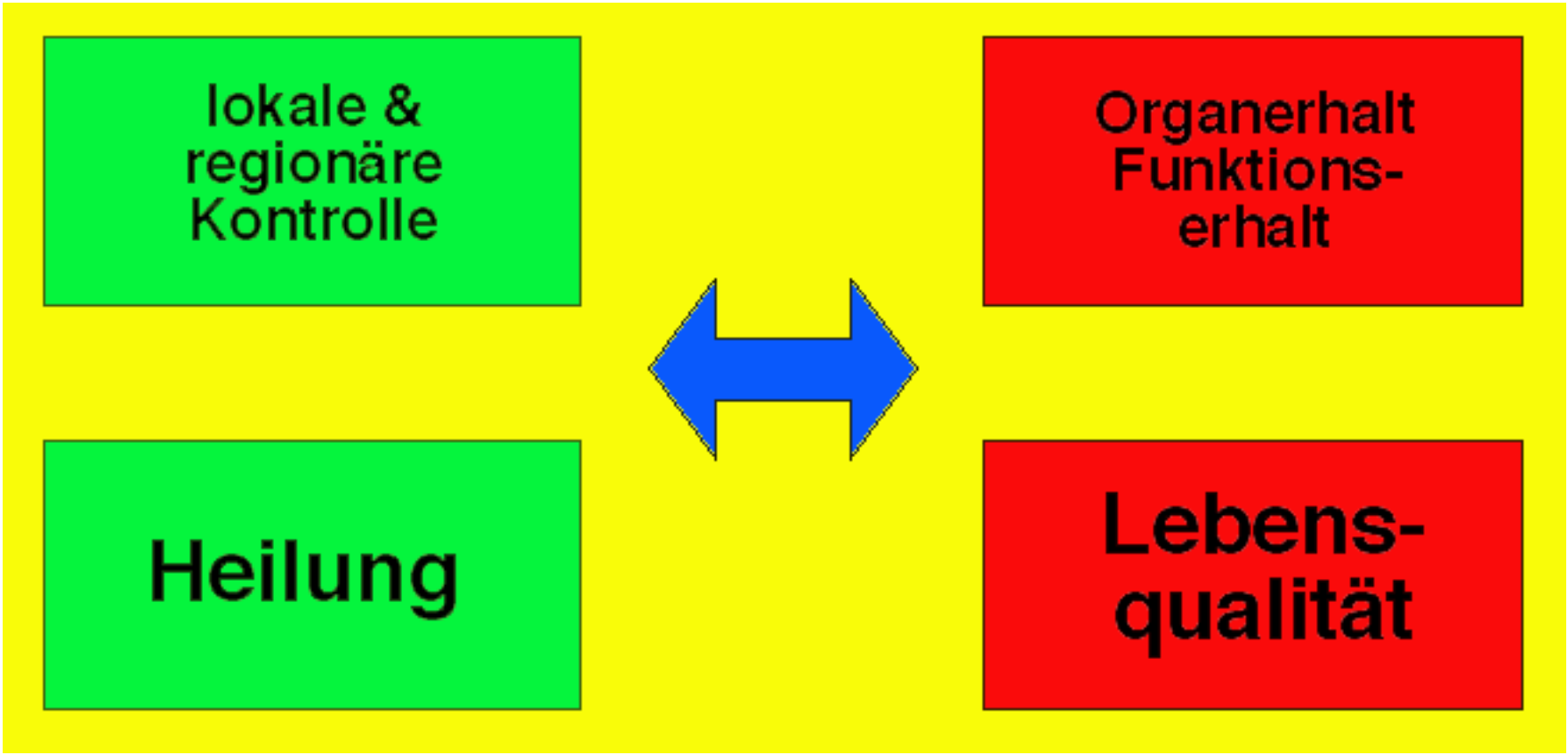






ALT- Transplantat

Ambivalenz des kurativen Therapieansatzes



Comparing Surgical and Nonsurgical Larynx-Preserving Treatments With Total Laryngectomy for Locally Advanced Laryngeal Cancer. Patel et al. Cancer 2019;125:3367-3377.

TABLE 4. Survival Analysis by Tumor and Lymph Node Classification

Classification[a]	No. of Patients	No. of Events	Median Survival, mo	Actuarial Survival Rate, %		*P*
				3-Year	5-Year	
T2N1 or T3N0-N1 (non-T4, low nodal burden group)[b]						
CRT	2728	1132	71.1	69.4	54.7	.017
PL ± RT or CRT	534	212	89.2	70.5	60.3	
TL ± RT or CRT	938	425	67.1	64.4	52.6	
T2-T3N2-N3 (non-T4, high nodal burden group)[b]						
CRT	1718	835	46.6	56.8	43.0	.033
PL ± RT or CRT	239	126	48.3	55.0	47.6	
TL ± RT or CRT	301	176	34.4	49.4	36.7	
T4N-any[c]						
CRT	853	503	37.8	51.2	37.0	<.0001
PL ± RT or CRT	119	70	29.5	46.6	38.5	
TL ± RT or CRT	1273	613	57.5	60.1	49.1	

- T2-3 – N0/N1 ⇨Laryngektomie ≈ pRCT

- T2-3 – N2/N3 ⇨ pRCT ≥ Laryngektomie

- ≥ T4 – N0-N3 ⇨ Laryngektomie > pRCT

Lebensqualität nach Pharyngolaryngektomie

Quality-of-life and functional outcomes following pharyngolaryngectomy: a systematic review of literature

Mahalingam, S.,*† Srinivasan, R.† & Spielmann, P.*‡

*University of Edinburgh, Edinburgh, UK †Department of Otolaryngology, Head and Neck Surgery, East Surrey Hospital, Redhill, UK
‡Department of Otolaryngology, Head and Neck Surgery, Ninewells Hospital, University Department of Otolaryngology, Dundee, UK

Accepted for publication 3 March 2015
Clin. Otolaryngol. 2016, **41**, 25–43

- Sprachverständnis: 17 Studien – 576 Patienten
- Schluckfunktion: 15 Studien – 1076 Patienten

Stimmrehabilitation mittels Stimmprothese

- ~ 90% gute Stimmqualität

Schluckfunktion

- 14,2 Tage postoperative mittlere Nahrungskarenz
- 6,5% Langzeit- Abhängigkeit von Ernährungssonde
- 11,4 % Strikturen

Ergebnisse nach totaler Laryngektomie sind besser als nach Pharyngo-Laryng-Ektomie

Qualität der Laryngektomie

Association of Hospital Volume With Laryngectomy Outcomes in Patients With Larynx Cancer
Christine G. Gourin, et al.
JAMA Otolaryngol Head Neck Surg. 2019;145(1):62-70.

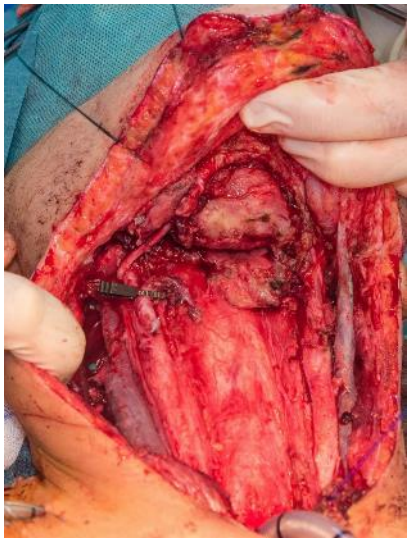
45 156 Patienten - 5516 Krankenhäuser

High-volume Krankenhäuser assoziiert mit

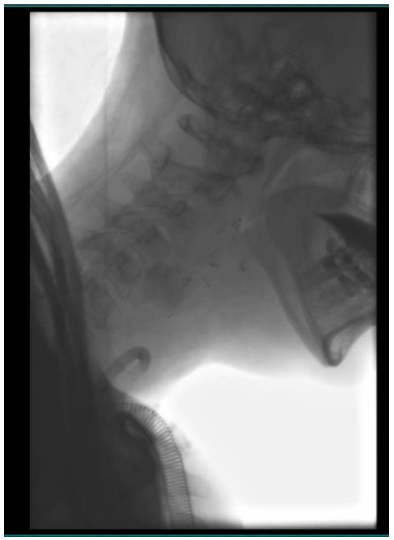
- ► geringere Chance zum Versterben im KH
- ► Weniger postoperativen chirurgischen Komplikationen
- ► akuten medikalen Komplikationen
- ► geringerer Dauer der Hospitalisation
- ► geringeren Behandlungskosten

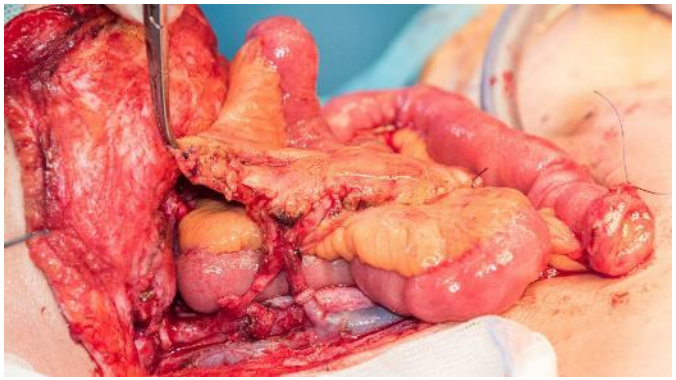
„These data support the concept of centralization of complex care at centers able to meet minimum volume thresholds to improve patient outcomes."

Rettungs - Chirurgie



Z.n. prim. RCT alio loco bei
cT3-4 Hypopharynxkarzinom





Tumortherapie im Kopf-Hals-Bereich I

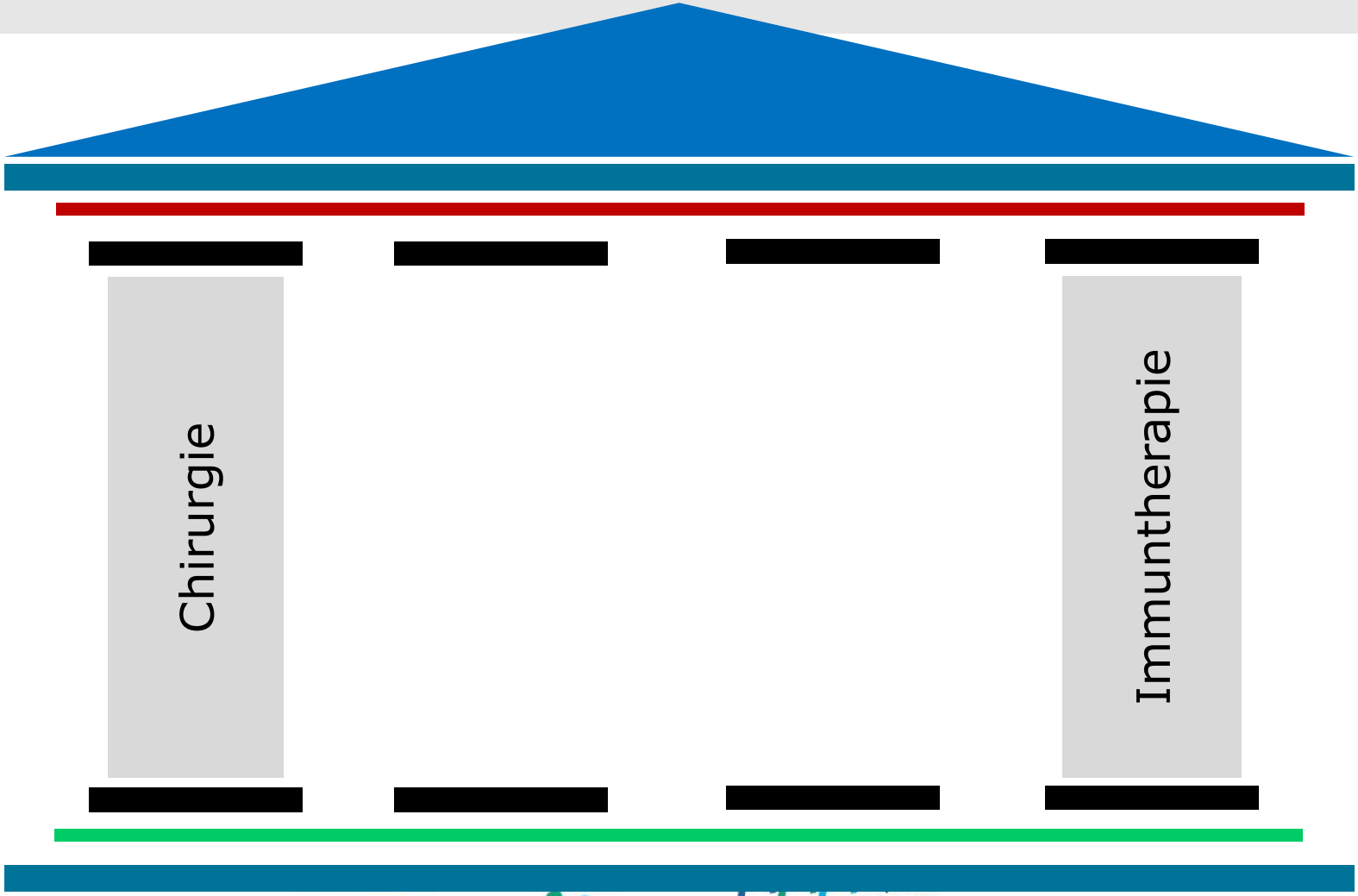
- Chirurgie ist in Frühstadien die Therapie der Wahl

- Ablative Chirurgie fortgeschrittener Stadien

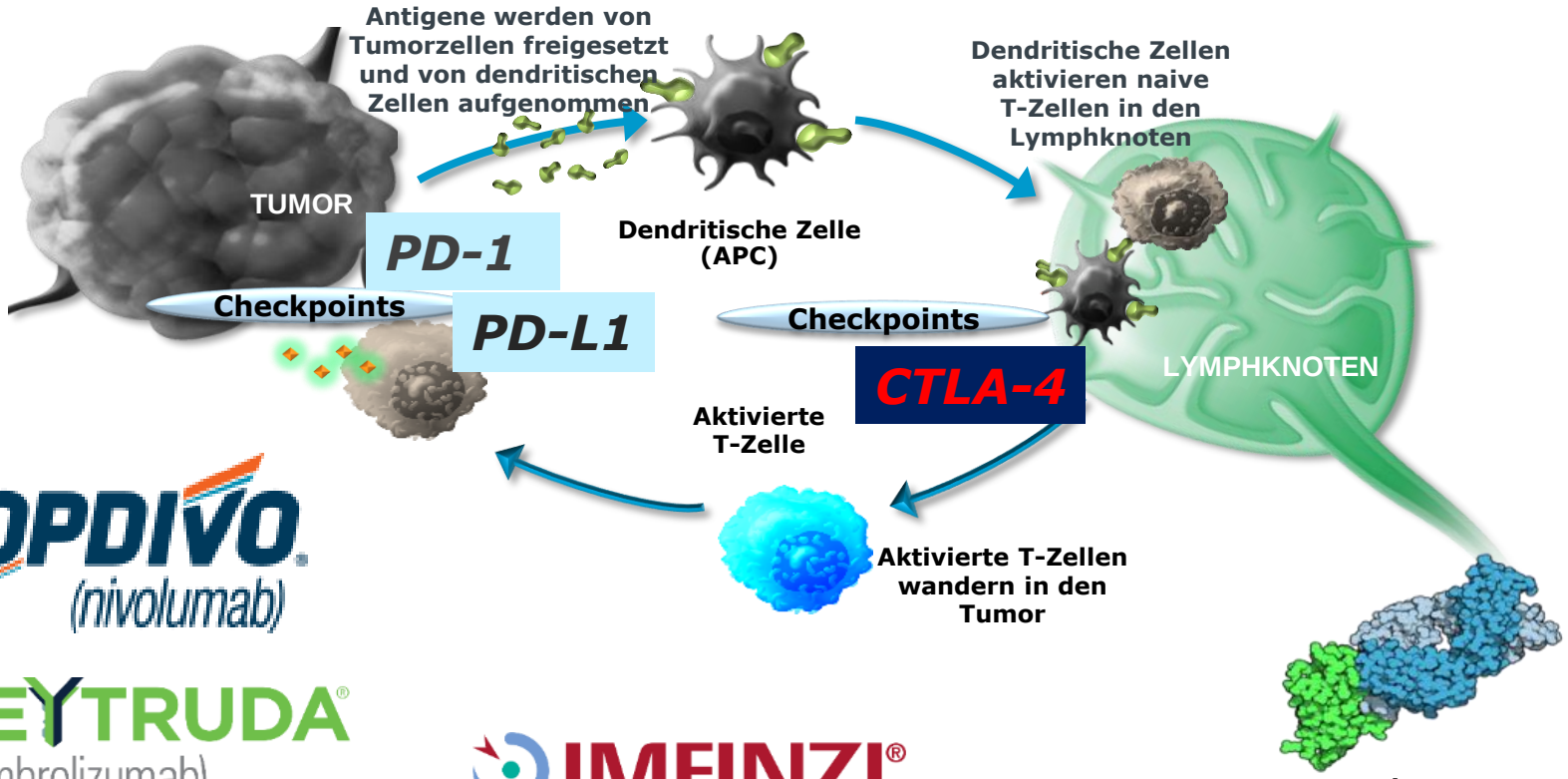
  - kann Lebensqualität erhalten
  - onkologisch effektiv
  - idR in Kombination mit adjuvanter Therapie
  - technisch komplikationsarm durchführbar - Rettungschirurgie

- Definitive Radiochemotherapie

Säulen der Onkologischen Therapie



Immuntherapie durch Immun-Checkpoints - Reduktion der Drosselung der Immunantwort



OPDIVO (nivolumab)

KEYTRUDA (pembrolizumab)

IMFINZI durvalumab

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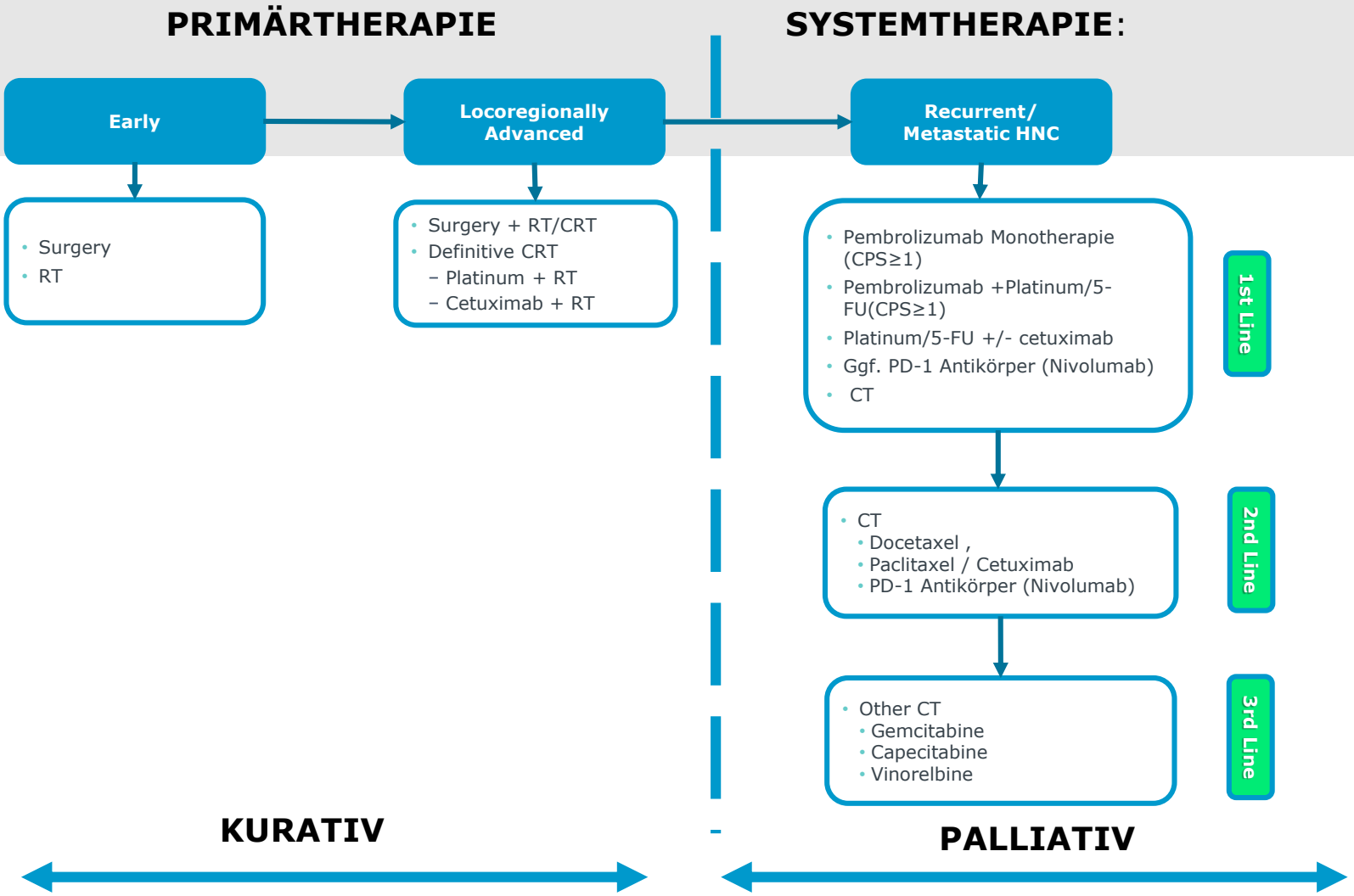


CT = chemotherapy; CRT = chemoradiotherapy; HNC = head and neck cancer; HNSCC = head and neck squamous cell carcinoma; MTX = methotrexate; R/M = recurrent and/or metastatic; RT = radiotherapy.

1. Adapted from Cohen E. Presented at: New Horizons in Immuno-therapy for HNC 2015: Newberg, OR.

Aktuelle Immuntherapien beim r/m HNSCC

- 1rst line Studien[3]:

Immune checkpoint inhibitor	Phase	Setting	Intervention/drug	Primary end point
Pembrolizumab KEYNOTE 048	III	R/M HNSCC first line	Pembrolizumab vs cetuximab+platinum/5-FU Pembrolizumab+platinum/5-FU vs cetuximab+platinum/5-FU	PFS and OS
Nivolumab Checkmate 651 (BMS)	III	R/M HNSCC, first-line	Nivolumab+Ipilimumab vs SOC (cetuximab+cisplatin/carboplatin +5-FU)	OS and PFS
Durvalumab KESTREL (AstraZeneca)	III	R/M HNSCC, first-line	Durvalumab ± Tremelimumab vs SOC (EXTREME regimen)	PFS and OS

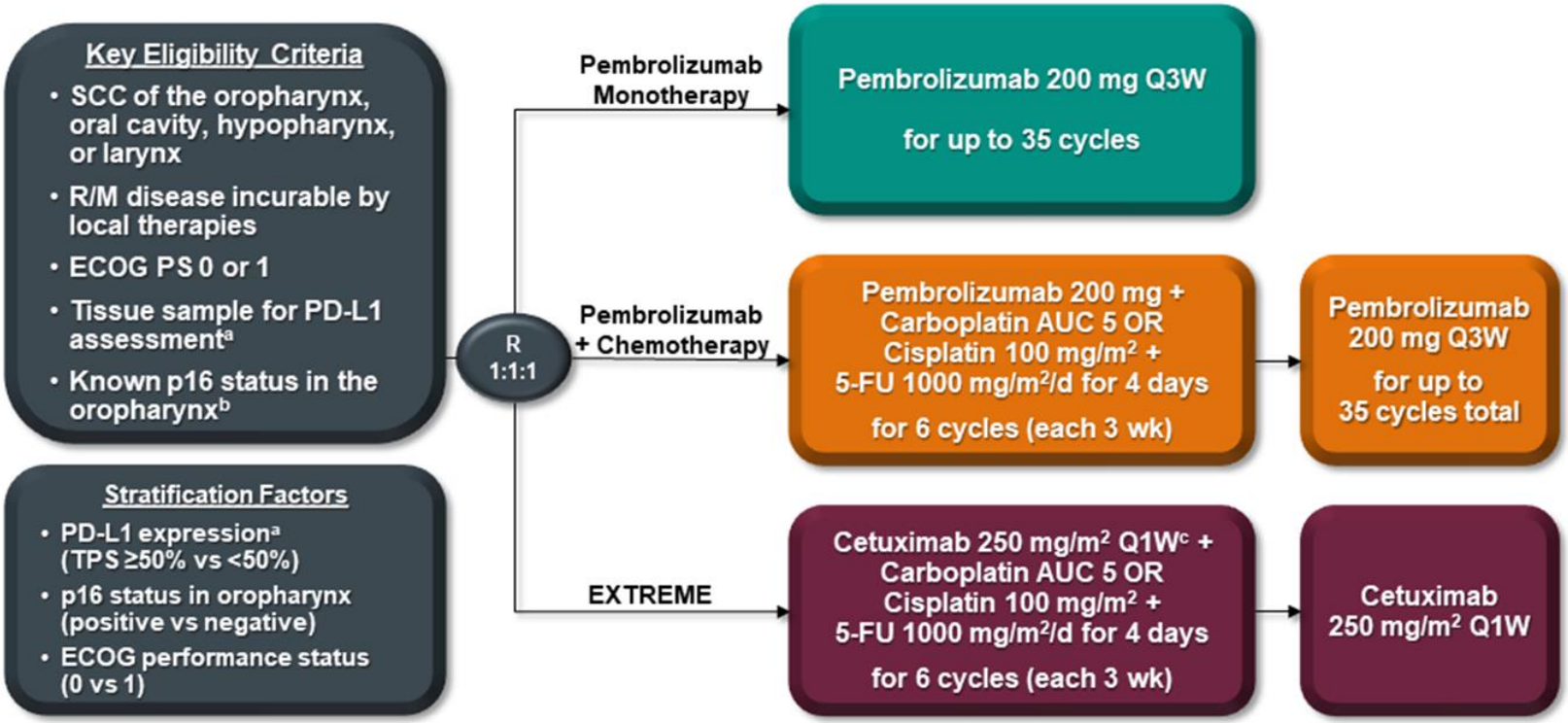
EMA Zulassung 1rst-line seit 20.11.2019 mit Biomarker (CPS ≥1)

ESMO 2021
„the study did not meet its primary endpoints"

05.02.21 – AstraZeneca press release
„did not meet the primary endpoint of improving overall survival "

1. Fachinformation KEYTRUDA°, Stand November 2019, 2. Fachinformation OPDIVO Stand Oktober 2019, 3. modif. nach Samra B, et al. J Investig Med 2018;0:1–8.

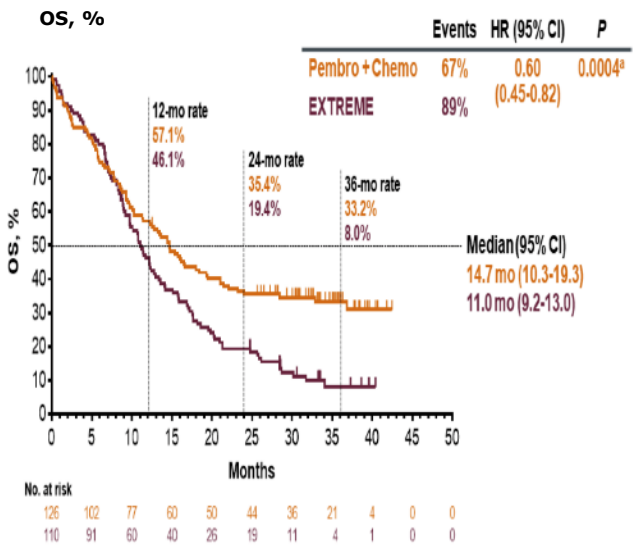
KEYNOTE-048 Study Design (NCT02358031)



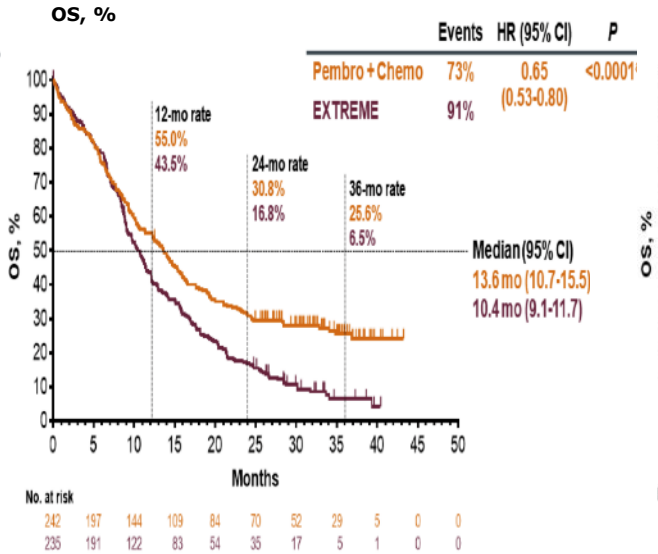
[a]Assessed using the PD-L1 ICH 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint für positivity = 70%. [c]Following a loading dose of 400 mg/m²

KEYNOTE-048: Overall Survival
Pembrolizumab + Chemotherapy vs EXTREME

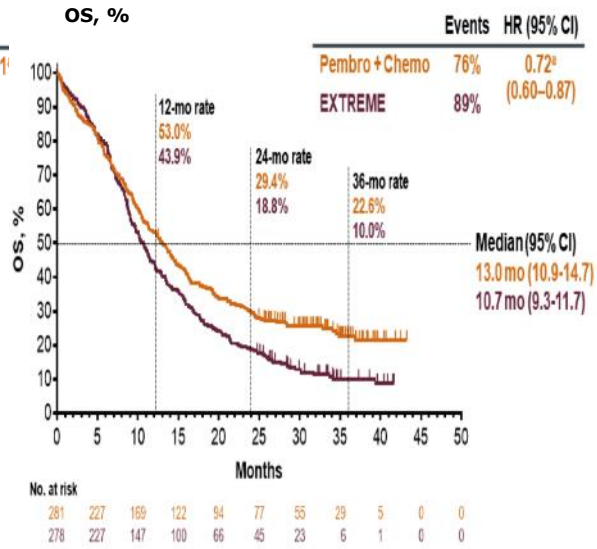
CPS≥20



CPS≥1



Total



Data cutoff date: Jun 25, 2019

Dany Rischin et al., Keynote-048 presented at ASCO 2019, Barbara Burtness et al., Keynote-048 presented at ESMO 2018
Burtness et al., www.thelancet.com Published online October 31, 2019

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Folgekonzepte

Table 5. Future developments with new IO agents and new combinations in R/M pretreated patients.

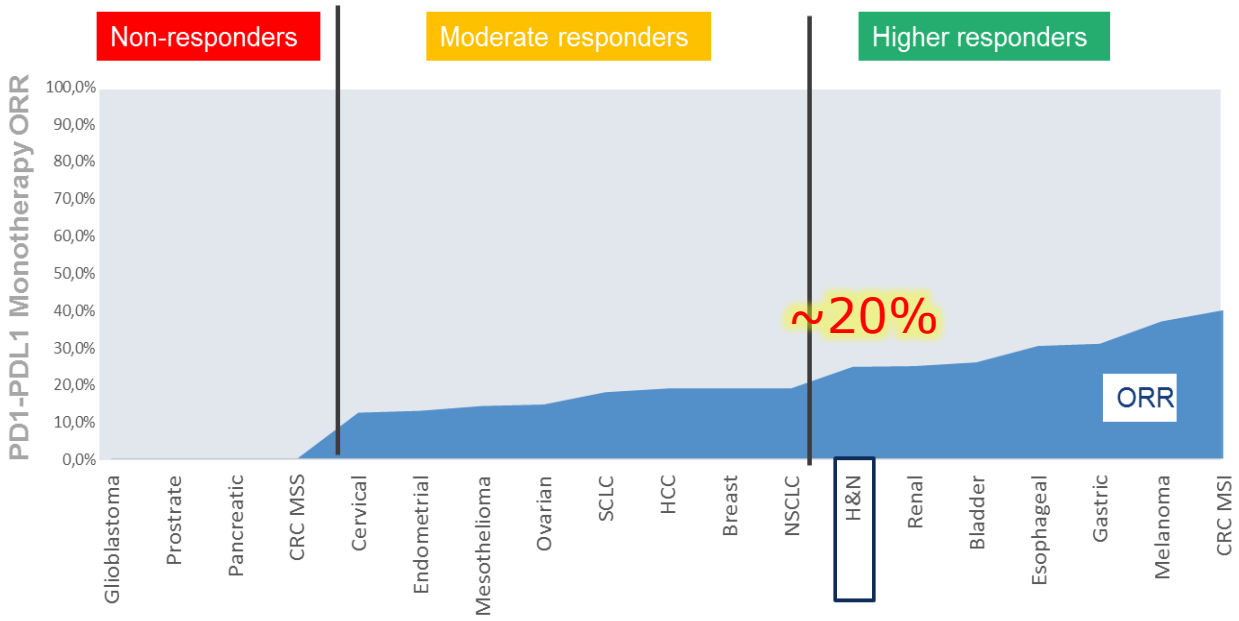
Study	IO Agents + Targeted Therapy	Pts Characteristics.	Nb of Pts	ORR (95%CI)	DCR (95%CI)	PFS Median (95% CI)	OS Median (95%CI)	Related Grade≥3 Toxicity	Consecutive Phase III
INDUCE-1		anti-PD-(L)1 naïve		24%	68%	4.2 mo	13.1 mo		INDUCE-3: –
NCT02723955 [49]	GSK 609 + pembro.	pretreated: 52%	34	(10.7–41.2)	(49.5–82.6)	(2.4–6.2)	(6.7–20)	6%	Pembro +/ GSK609 INDUCE-4: Pembro + CT+/− GSK609
NCT02643550	Monalizumab +	Platinum and		20%				42%	INTERLINK-1: –
Expansion cohort 2 [50]	Cetuximab	Anti-PD-(L)1 pretreated	40	(10.5–34.8)	57.5%			2% related to monalizumab	cetuximab +/ monalizumab
NCT02501096	Pembro.	HNSCC cohort		46%		4.7 mo			LEAP-010 study
[51]	+ lenvatinib	Phase II ≤2 prior lines	22	(24.4–67.8)	90.9%	(4.0–9.8)		67%	NCT04199104

IO: Immuno Oncology; Nb of pts: Number of Patients; ORR: Overall Response Rate; DCR: Disease Control Rate; PFS: Progression Free Survival; OS: Overall Survival;. Pembro: pembrolizumab; CT: chemotherapy.

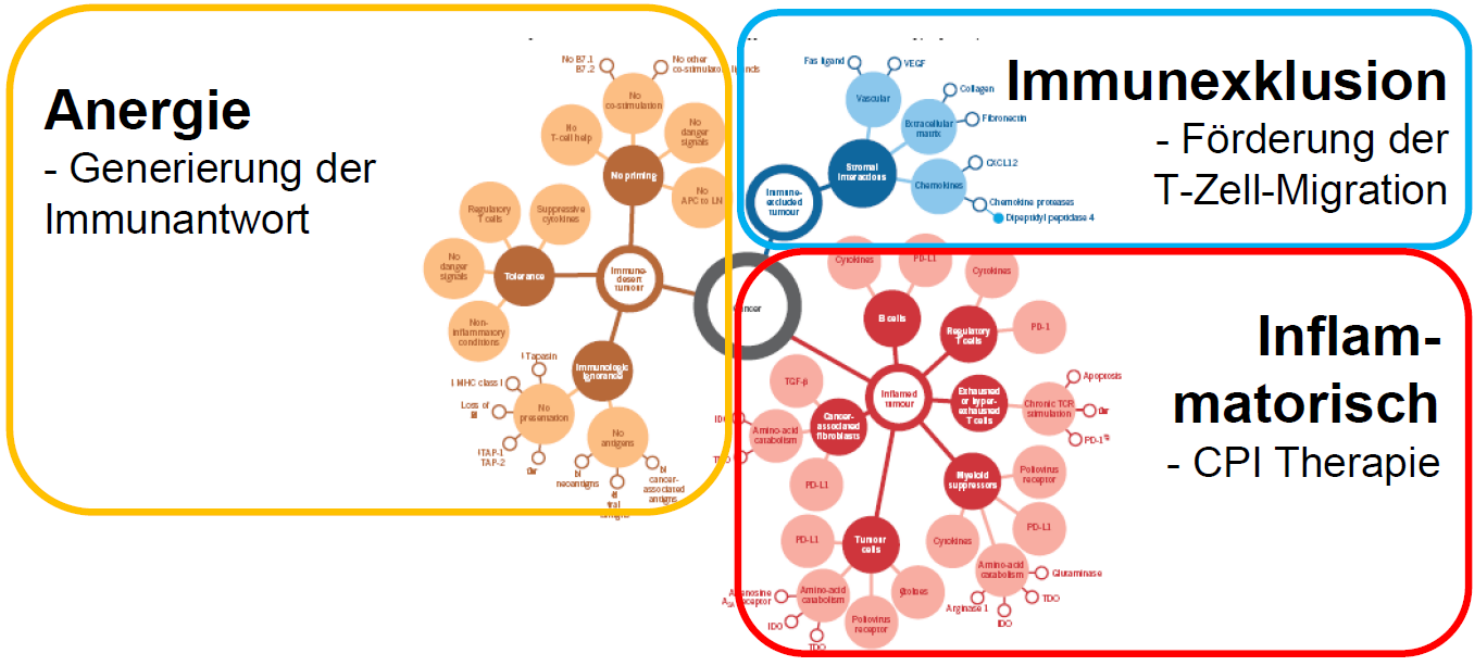
Borel C, Jung AC, Burgy M. Cancers (Basel). 2020

Selektion in der Immuntherapie

Objektive Ansprechraten (ORR) verschiedener Entitäten auf Anti-PD-1/PD-L1



Nicht alle Kopf-Hals-Tumore sind immunogen



Chen, Mellmann – Nature (2017)

Selektion von Patienten sinnvoll und notwendig

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Biomarker

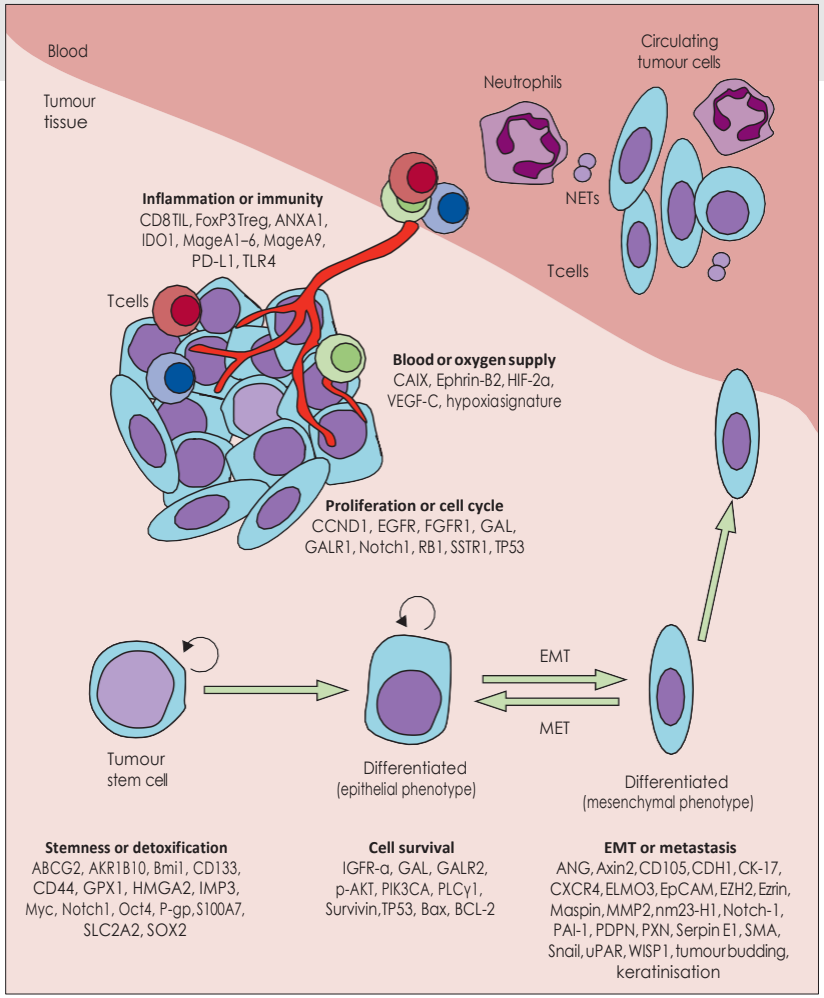

Figure 2: **Prognostic biomarkers in squamous cell carcinoma of the head and neck**
EMT=epithelial to mesenchymal transition. MET=mesenchymal to epithelial transition.NETs=neutrophil extracellular traps.TIL=tumour-infiltrating lymphocytes. TP53=cellular tumor antigen p53. Treg=regulatory T cells.

Budach V, Tinhofer I. Review. Lancet Oncology. 2019

Selektion in der Immuntherapie - CheckRad-CD8

(NCT03426657)

Lokal fortgeschrittene Kopf-Hals-Karzinome

Doppel-Checkpoint Block

- CTLA4 Trem
- PD-L1 Durva

Selektion

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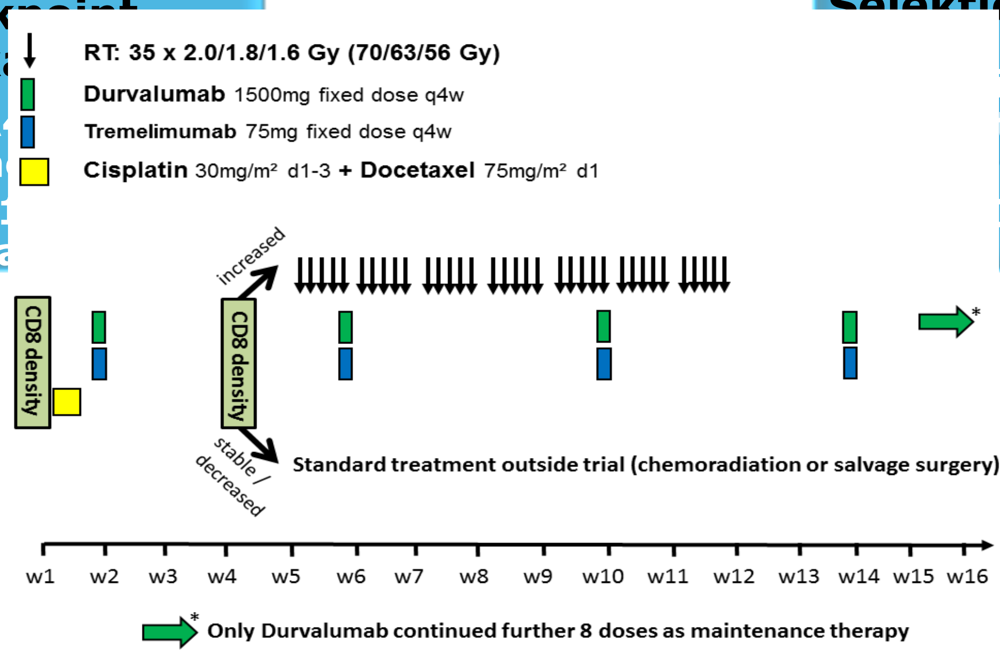
therapie
tion
CD8-



Strahlenklinik
Prof. Dr. R. Fietkau
PD Dr. M. Hecht
HNO
PD Dr. A. Gostian
Pathologisches Institut
Prof. Dr. A. Hartmann
Dr. M. Eckstein

Hecht M, Gostian AO, Eckstein M. J Immunother Cancer. 2020.

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Selektion in c ‹Rad-CD8

(NCT03426657)

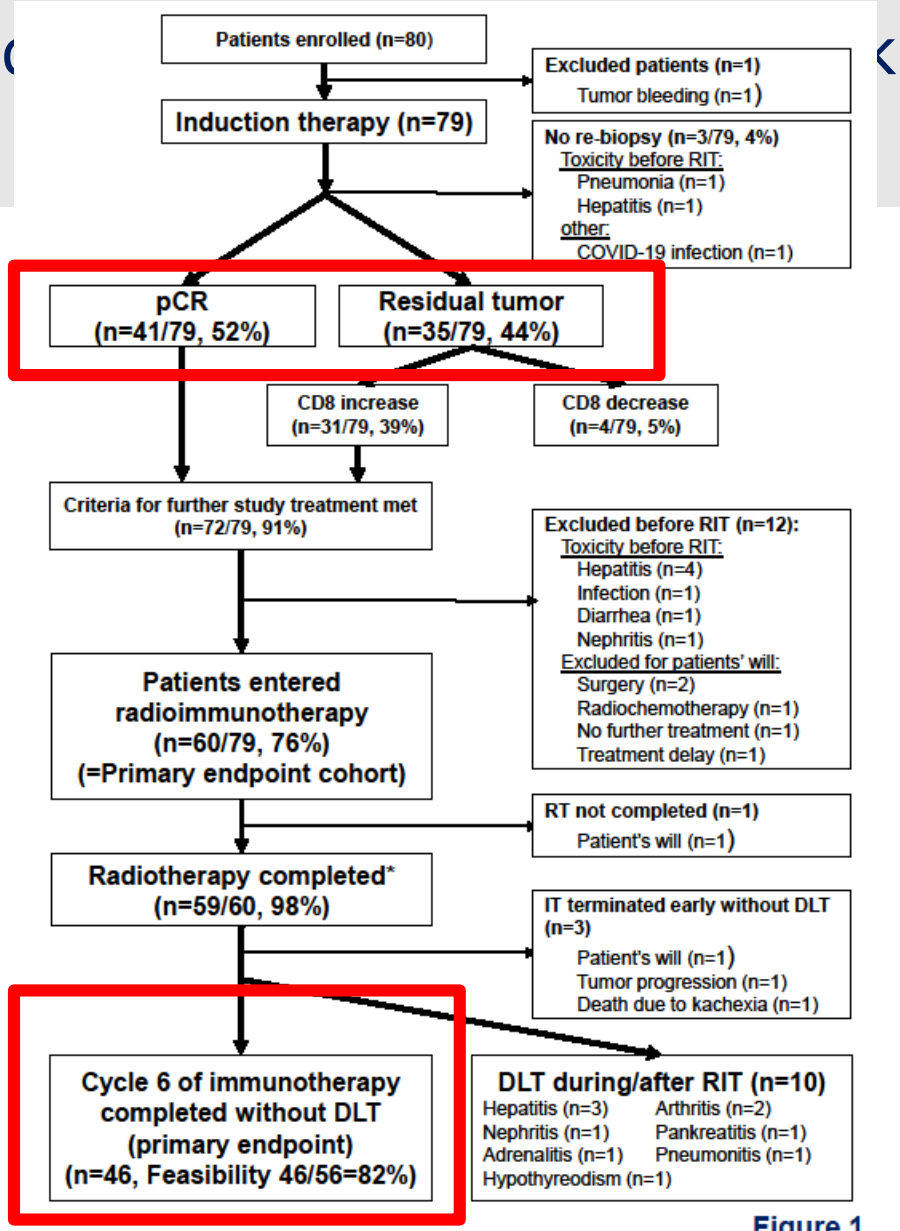

Figure 1

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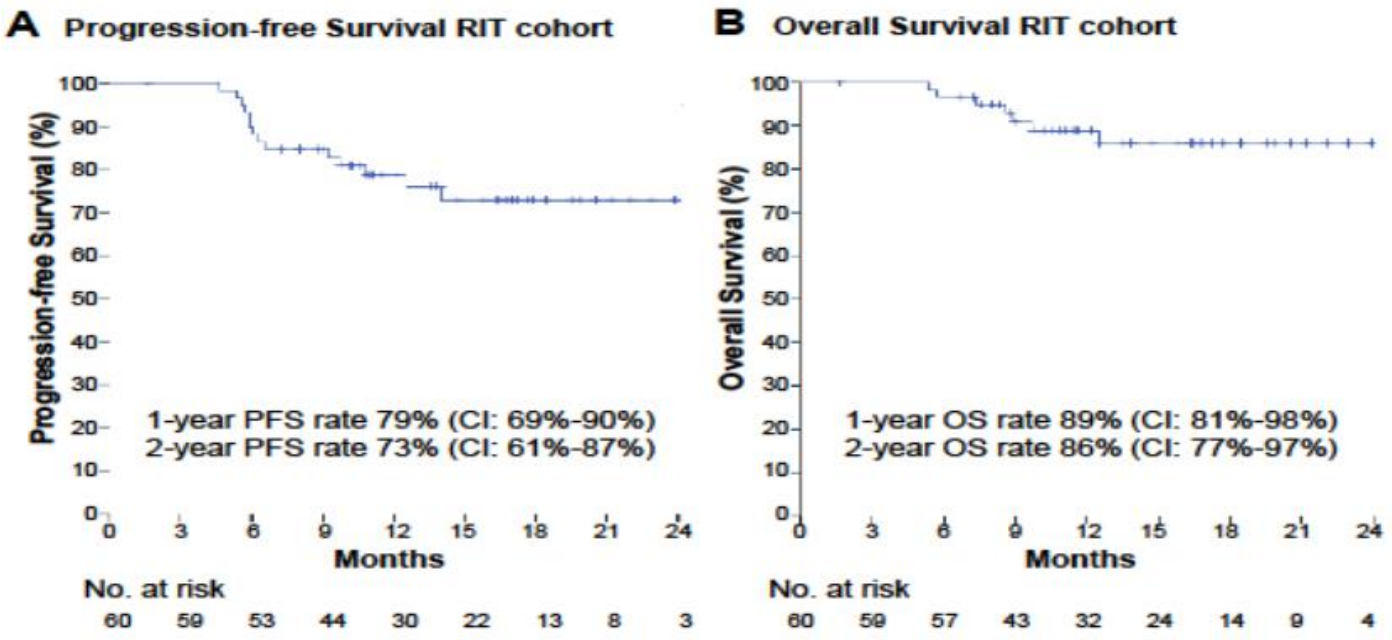
Selektion in der Immuntherapie - CheckRad-CD8

(NCT03426657)



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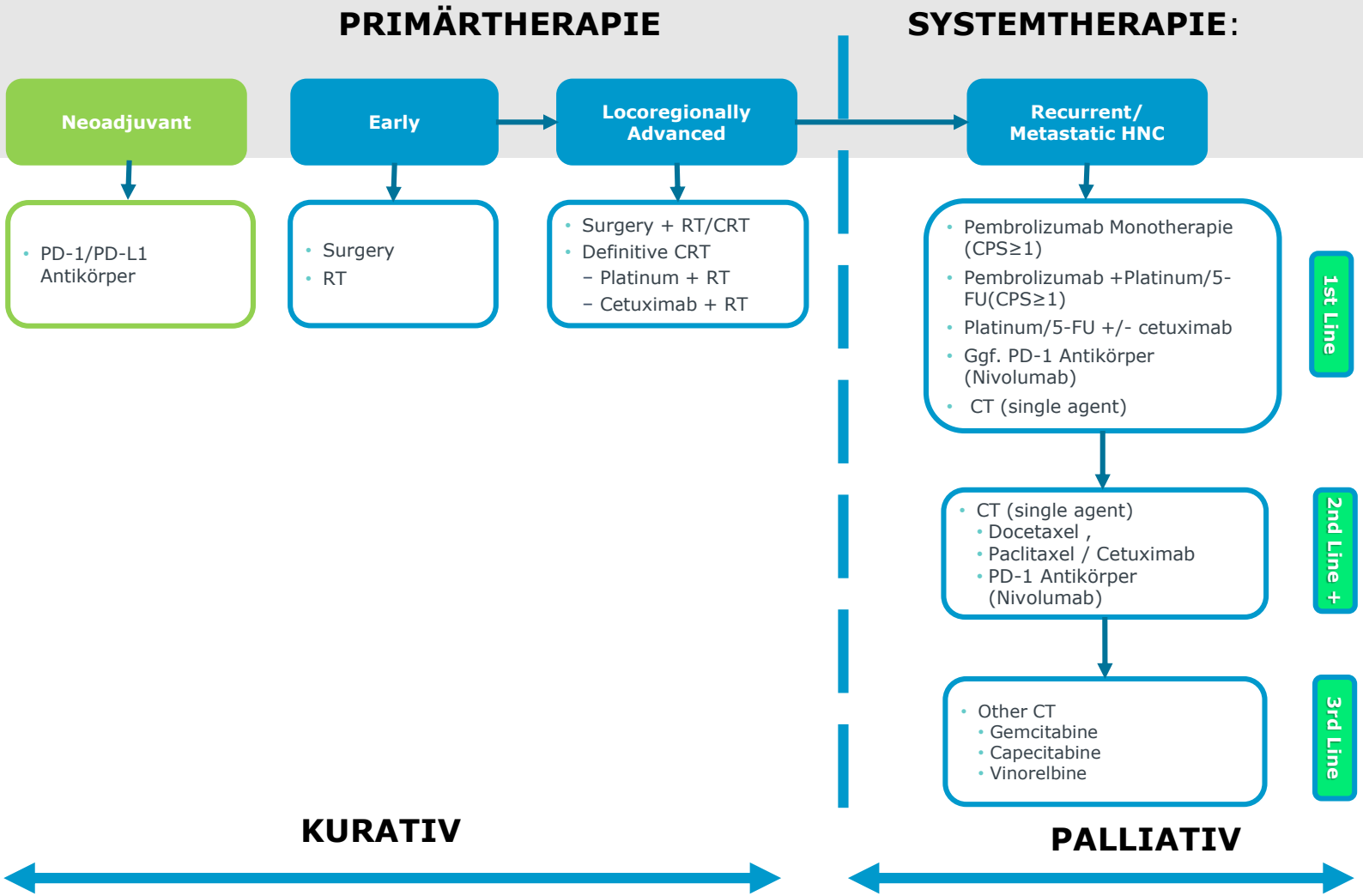


CT = chemotherapy; CRT = chemoradiotherapy; HNC = head and neck cancer; HNSCC = head and neck squamous cell carcinoma; MTX = methotrexate; R/M = recurrent and/or metastatic; RT = radiotherapy.

1. Adapted from Cohen E. Presented at: New Horizons in Immuno-therapy for HNC 2015: Newberg, OR.

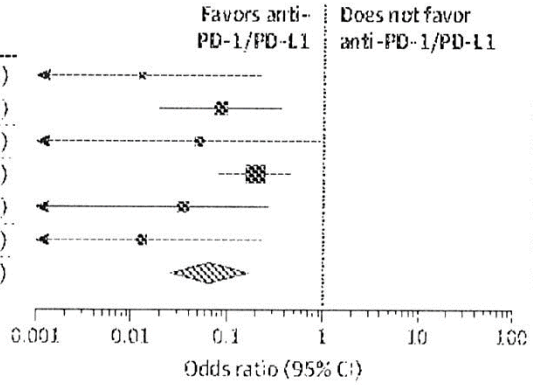
Resektable Tumore - Neo-adjuvante Immuntherapie

A Pathological complete response

Study or subgroup	Log (odds ratio)	SE	Odds ratio (95% CI)	Weight, %
CheckMate 358 study,[16] 2021	-4.317	1.424	0.01 (0.00-0.22)	1.6
CIAO study,[15] 2019	-2.442	0.737	0.09 (0.02-0.37)	22.8
Horton et al,[14] 2019	-2.944	1.451	0.05 (0.00-0.90)	8.8
Kim et al,[18] 2021	-1.609	0.447	0.20 (0.08-0.48)	35.2
Schoenfeld et al,[17] 2020	-3.332	1.018	0.04 (0.00-0.26)	15.2
Uppaluri et al,[12] 2020	-4.29	1.424	0.01 (0.00-0.26)	9.0
Total (95% CI)			0.07 (0.03-0.18)	100.0

Heterogeneity: $\tau^2 = 0.43$; $\chi^2 = 7.61$, $df = 5$ ($P = .18$); $I^2 = 34\%$

Test for overall effect: $z = 5.65$ ($P < .001$)

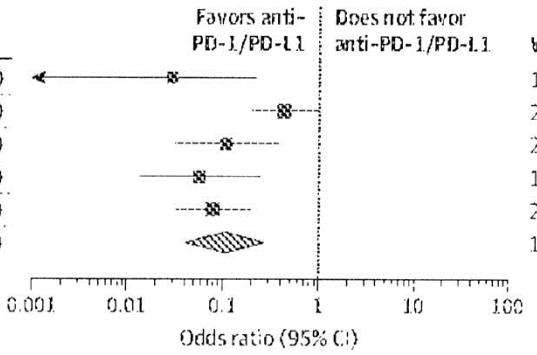


B Major pathological response

Study or subgroup	Log (odds ratio)	SE	Odds ratio (95% CI)	Weight, %
CheckMate 358 study,[16] 2021	-3.497	1.015	0.03 (0.00-0.22)	12.9
IMCISION trial,[13] 2020	-0.799	0.401	0.45 (0.20-0.99)	24.8
Schoenfeld et al,[17] 2020	-2.159	0.61	0.12 (0.03-0.38)	20.2
Uppaluri et al,[12] 2020	-2.833	0.728	0.06 (0.01-0.25)	17.8
Wise-Draper et al,[11] 2021	-2.512	0.424	0.08 (0.04-0.19)	24.3
Total (95% CI)			0.11 (0.04-0.29)	100.0

Heterogeneity: $\tau^2 = 0.78$; $\chi^2 = 13.90$, $df = 4$ ($P = .01$); $I^2 = 71\%$

Test for overall effect: $z = 4.55$ ($P < .001$)



Masarwy R, JAMA Otolaryngol Head Neck Surg. 2021.

Tumortherapie im Kopf-Hals-Bereich II

- Rezidivierte/metastasierte Kopf-Hals-Tumore
  - Immuntherapie als Standard in der 1st line
  - Kombination mit Chemotherapie / Radiotherapie steigert Effektivität
- Resektable, fortgeschrittene, Tumore
  - erste Ergebnisse neoadjuvanter Konzepte sind vielversprechend
  - stärkere Verzahnung mit der Chirurgie
- Selektion der Patienten durch Biomarker
- Effektive Tumortherapie im Kopf-Hals-Bereich ist und bleibt multimodal

Qualitätskonferenz des Bayerischen Krebsregisters
Online-Veranstaltung in Kooperation mit dem Bayerischen Zentrum für Krebsforschung (BZKF) und dem Comprehensive Cancer Center (CCC) Erlangen-EMN

Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit

Tumortherapi… …Bereich

Vielen Dank für Ihre Aufmerksamkeit

…tian

…ais-Nasen-Ohren-Klinik, Kopf- und Halschirurgie

Universitätsklinikum Erlangen

Direktor: Prof. Dr. med. Dr. h. c. Heinrich Iro

FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG MEDIZINISCHE FAKULTÄT

DZI Deutsches Zentrum Immuntherapie

CCC Comprehensive Cancer Center Erlangen-EMN Europäische Metropolregion Nürnberg

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