Speicheldrüsenkarzinome –
Präzisionsonkologie im Lichte der neuen Leitlinien

Prof. Dr. Dr. Sacha Rothschild
Chefarzt Onkologie/Hämatologie

Kantonsspital Baden
KSB

Offenlegung Interessenkonflikte

Anstellungsverhältnis oder Führungsposition
Kantonsspital Baden, Schweiz

Beratungs- und Gutachtertätigkeit
Astra-Zeneca, Bayer, BMS, Boehringer-Ingelheim, Eisai, Eli Lilly, Janssen-Cilag, Merck Serono, MSD, Novartis, Otsuka Pharmaceutical, Pfizer, PharmaMar, Roche, Sanofi-Aventis, Takeda (sämtliche Honorare an die Institution)

Besitz von Geschäftsanteilen, Aktien oder Fonds
keine

Patent, Urheberrecht, Verkaufslizenz
keine

Honorare
Astra-Zeneca, BMS, Boehringer-Ingelheim, MSD, Novartis, Roche (sämtliche Honorare an die Institution)

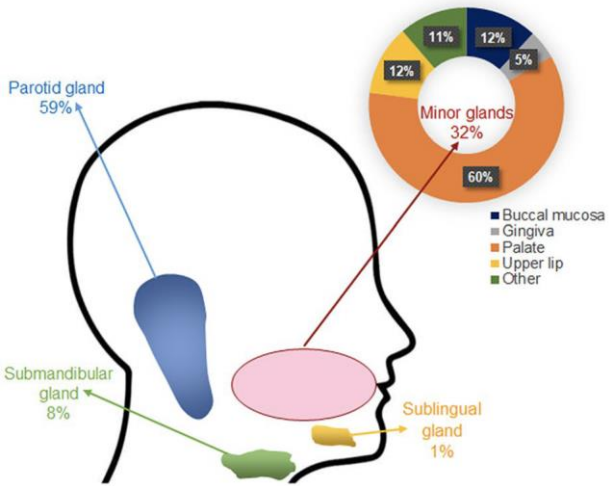
Finanzierung wissenschaftlicher Untersuchungen
AbbVie, Astra-Zeneca, BMS, Boehringer-Ingelheim, Merck, Roche

Andere finanzielle Beziehungen
keine

Immaterielle Interessenkonflikte
Vize-Präsident Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK); Gewähltes Mitglied der Eidgenössischen Arzneimittelkommission des Bundesamtes für Gesundheit

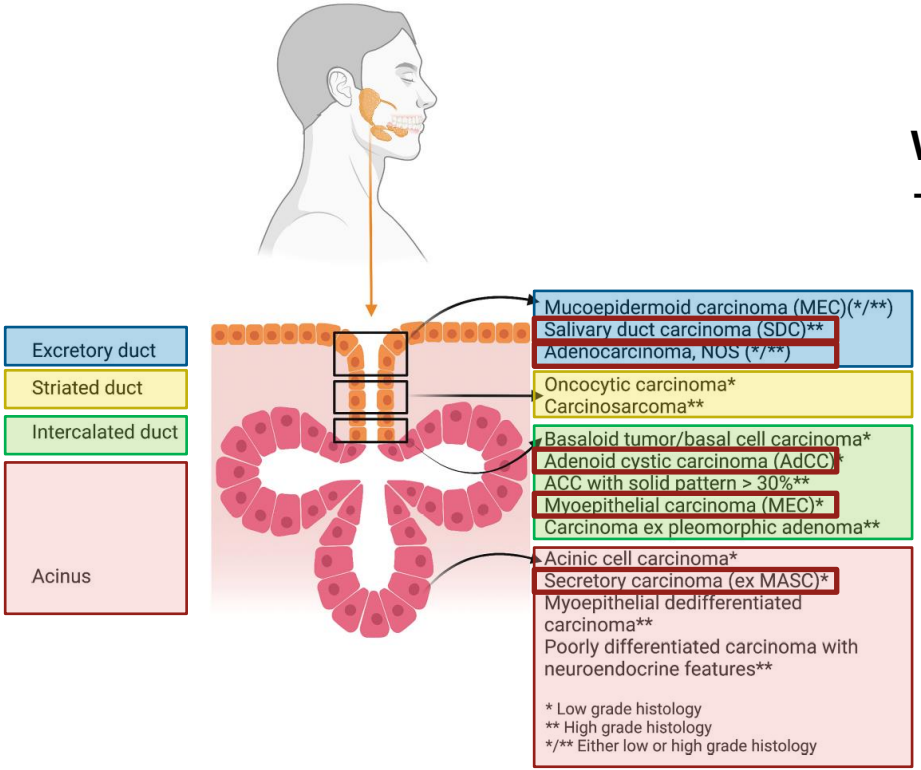
Epidemiologie

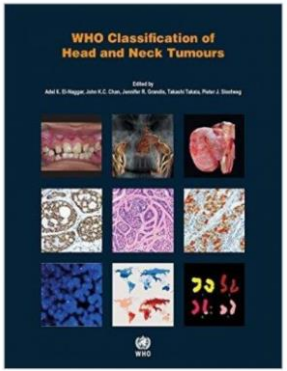
- Inzidenz: 1.3 / 100‘000 / Jahr
  - 53.583 neue Fälle in 2020 weltweit (WHO Globocan)
- 5% aller Kopf-Hals-Tumoren



https://gco.iarc.fr; Alsanie I, et al. Head Neck Pathol 2022;16:1043-54

Histologische Subtypen





WHO-Klassifikation 2022
→ 22 maligne Subtypen

Malignant epithelial tumours

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Secretory carcinoma
- Microsecretory adenocarcinoma
- Polymorphous adenocarcinoma
- Hyalinizing clear cell carcinoma
- Basal cell adenocarcinoma
- Intraductal carcinoma
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Mucinous adenocarcinoma
- Sclerosing microcystic adenocarcinoma
- Carcinoma ex pleomorphic adenoma
- Carcinosarcoma of the salivary glands
- Sebaceous adenocarcinoma
- Lymphoepithelial carcinoma
- Squamous cell carcinoma
- Sialoblastoma
- Salivary carcinoma, NOS and emerging entities

Colombo E, et al. Front Oncol 2022;12:1032471; WHO classification 2022

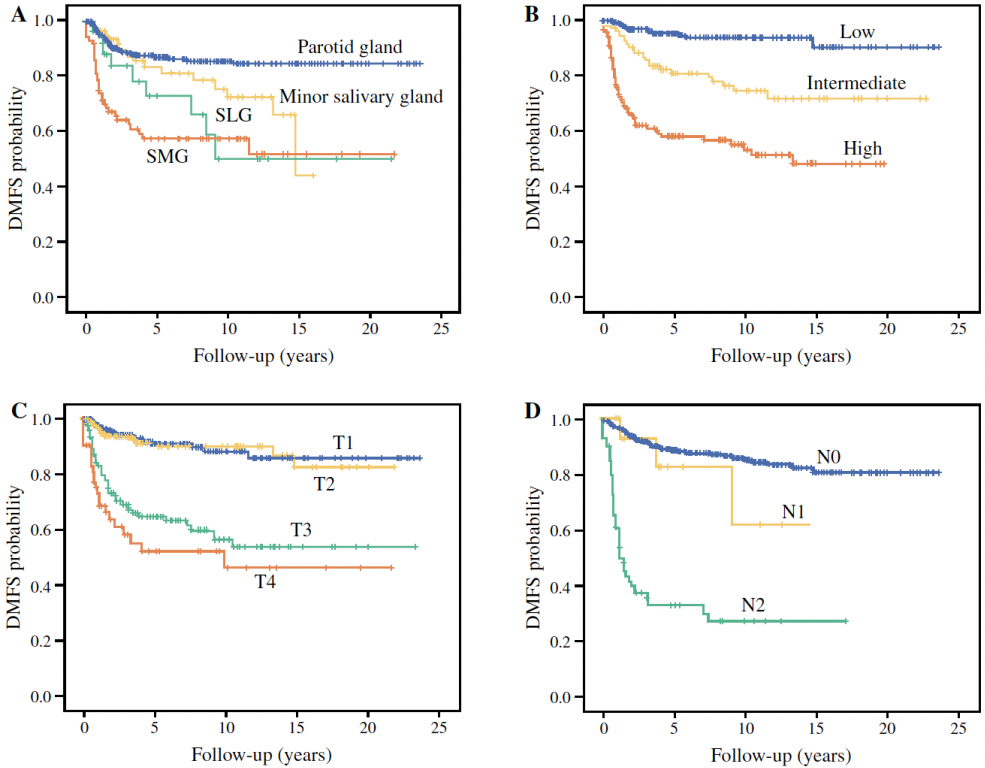
Rezidive nach lokaler Therapie

	Number of patients	Type of recurrence			
		Local	Regional	Distant	Multiple
ACC	1475	34.8%	7.1%	31.1%	25.3%
SDC	172	15.8%	4.2%	49.5%	36.8%
MEC	379	25.3%	14.7%	44.0%	29.3%
SC	229	70.7%	19.5%	9.8%	17.1%

Abbreviations: ACC, adenoid cystic carcinoma; MEC, mucoepidermoid carcinoma; SC, secretory carcinoma; SDC, salivary duct carcinoma.

Mannelli G, et al. Head Neck 2022;44:1961-75

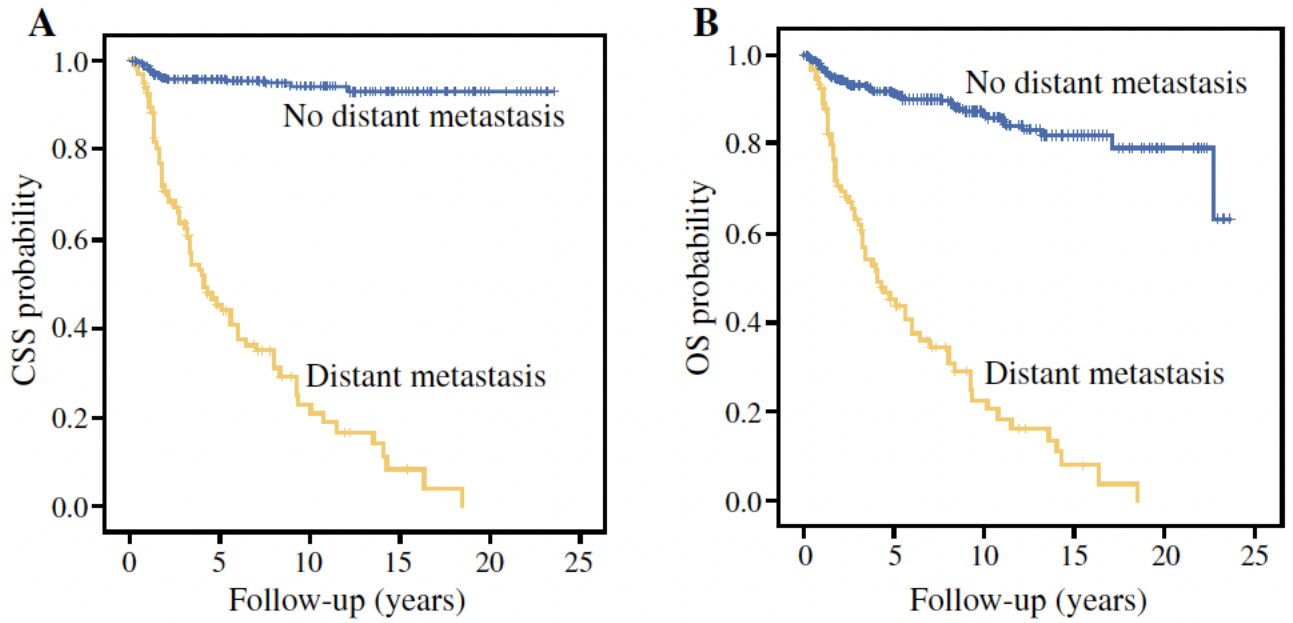
Fernmetastasen bei Speicheldrüsenkarzinomen



- N=454
- 20.9% M1
  - 7.4% initial
  - 92.6% follow-up (median: 100 Mte.)
- 67.4% Befall eines Organs
- Lunge am häufigsten (77.9%)
- Unabhängige Risikofaktoren
  - Nicht-parotidealer Primarius
  - Grading
  - Pn1
  - T3-4
  - N2-3
- Medianes Überleben für M1: 15 Mte.

Nam SJ, et al. Ann Surg Oncol 2016;23:4376-83

Fernmetastasen bei Speicheldrüsenkarzinomen



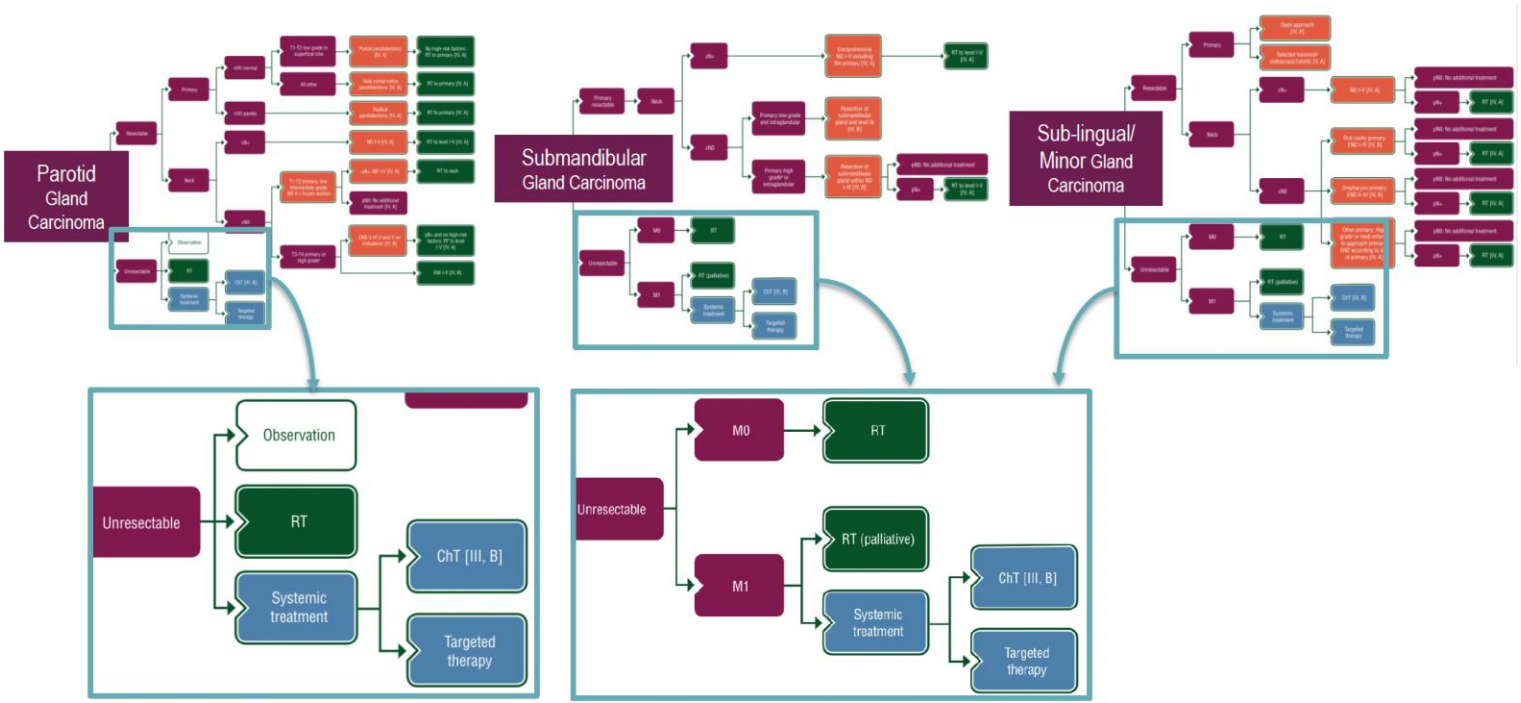
Nam SJ, et al. Ann Surg Oncol 2016;23:4376-83

Chemotherapie beim Speicheldrüsenkarzinom

- Keine Phase III Studien
- **Adenoid-zystisches Karzinom**
  - CAP (Cisplatin/Doxorubicin/Cyclophosphamid: ORR 28%
  - Monotherapie: Epirubicin, Vinorelbin
- **Andere Histologien**
  - Platin + Anthracyclin/Taxan: ORR 30-40%; PFS 4-6 Mte.

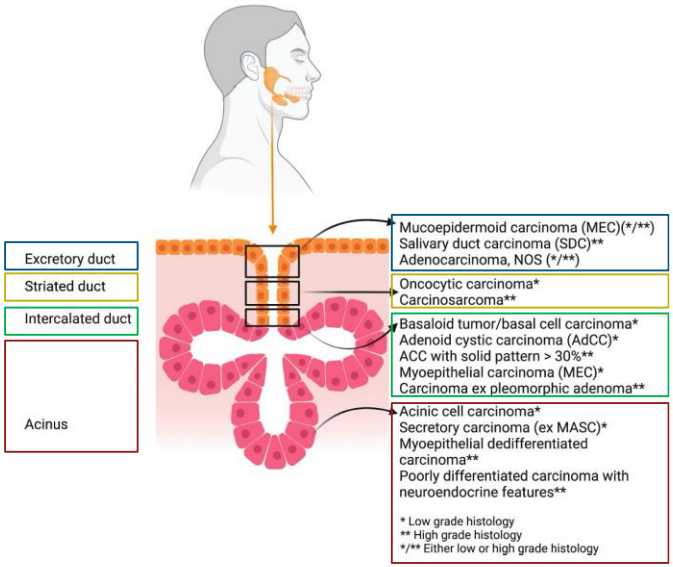
Laurie SA, Licitra L. J Clin Oncol 2006;24(17):2673-8

ESMO Guidelines für metastasierte Speicheldrüsenkarzinome



van Herpen C, et al. ESMO Open 2022;7(6):100602

Genetische Alterationen



	Gene and mechanism	Prevalence
Salivary duct carcinoma	*HER2* amplification	31%
	FGFR1 amplification	10%
	TP53 mutation	56%
	PIK3CA mutation	33%
	HRAS mutation	33%
	AR copy gain	35%
	PTEN loss	38%
	CDKN2A loss	10%
Intercalated duct subtype	*RET* fusions	47%
Myoepithelial carcinoma	*PLAG1* fusions	38%
	EWSR1 rearrangement	13%
	HRAS mutations	78%
Secretory carcinoma	*ETV6-NTRK3* fusion	>90%
	ETV6-RET fusion	2–5%
	ETV6-MET fusion	<1%
	ETV6-MAML3 fusion	<1%
	VIM-RET fusion	<1%
Adenoid-cystic Ca	*MYB* fusion/activation/amplification	~80%
	MYBL1 fusion/activation/amplification	~10%
	NOTCH mutations	14%

Colombo E, et al. Front Oncol 2022;12:1032471;
Skalova A, et al. Head Neck Pathol 2022;16(1):40-53

Speicheldrüsengangkarzinome – prädiktive genomische Alterationen

Table 1. Clinical characteristics and genomic alterations in 10 different salivary gland cancer histologic subtypes

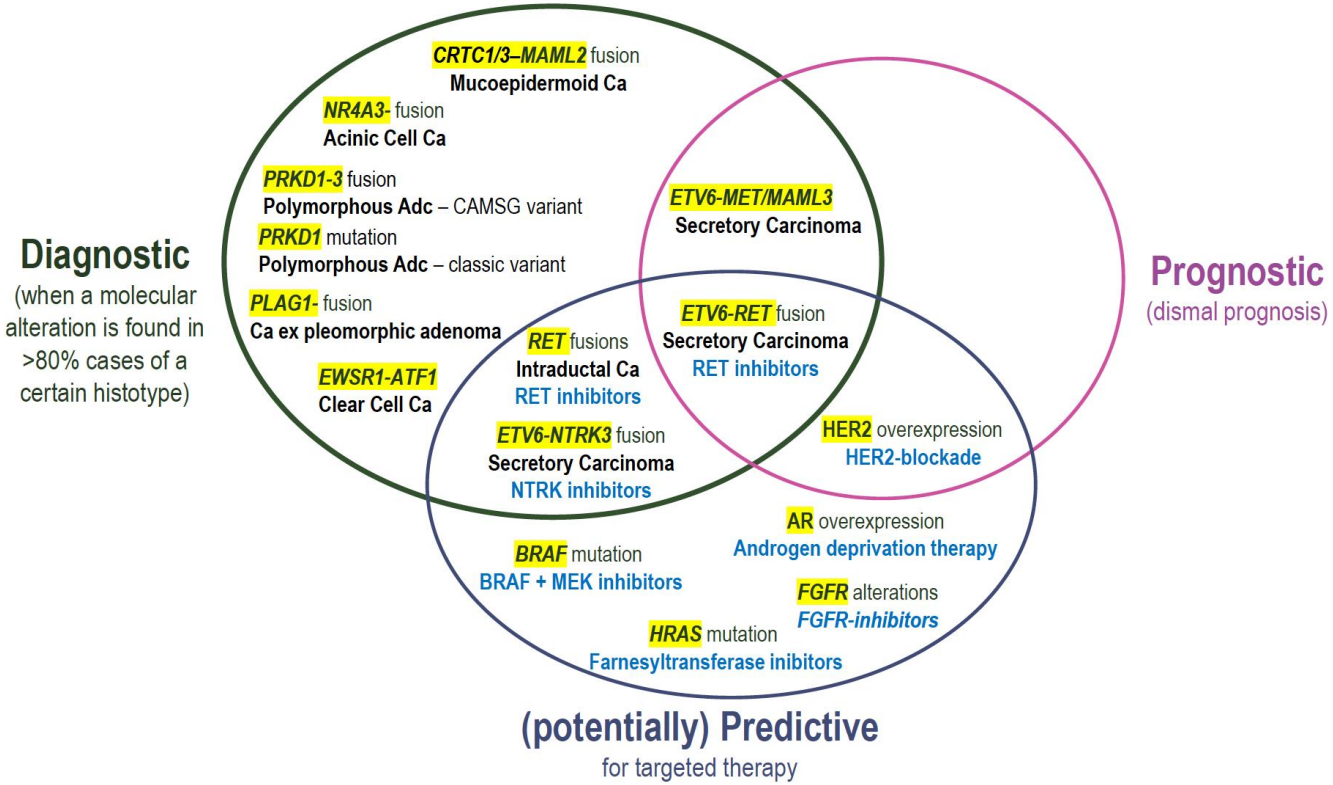
	Typically low-grade salivary gland cancers ($n = 264$)					Typically higher grade salivary gland cancers ($n = 359$)				
	Adenoid cystic carcinoma	Acinic cell carcinoma	Polymorphous low grade adenocarcinoma	Myo-epithelial carcinoma	Mammary analog secretory carcinoma	Muco-epidermoid carcinoma	Salivary duct carcinoma	Adenocarcinoma, not otherwise specified	Carcinoma, not otherwise specified	Carcinoma ex pleomorphic adenoma
Patients (*N*)	154	73	5	20	12	57	44	117	119	22
GAs/tumor	1.6	2.8	1.6	3.6	2.8	4.2	3.6	4.1	5.2	3
Median age in years	55	55	72	56	62	58	67	61	63	62
Gender (% female/% male)	50% F 50% M	54% F 46% M	80% F 20% M	42% F 58% M	38% F 62% M	46% F 54% M	18% F 82% M	26% F 74% M	35% F 65% M	50% F 50% M
Significant GAs (%)	MYB-NFIB (65)	PTEN (10) BRAF (5) NF1 (5)	PTEN (20) TSC2 (20) FGFR1 (20)	PIK3CA (15) RICTOR (15) PTCH1 (10) PDGFRB (5)	ETV6-NTRK3 (100)	PIK3CA (20) ERBB2 (13) BRCA2 (17) FGFR1 (7)	ERBB2 (32) PTEN 17) BRAF (5) PIK3CA (27)	ERBB2 (17) BRAF (5) EGFR (5) PIK3CA (24)	ERBB2 (15) PIK3CA (20) NF1 (8) PTEN (8) NF1 (8)	ERBB2 (32) FGFR1-PLAG (9)
TP53 GA frequency (%)	4	10	0	13	17	43	67	55	48	46
ERBB2 GA frequency (%)	0	0	0	0	0	13	32	17	15	2
PIK3CA GA frequency (%)	5	3	0	15	0	20	27	24	20	0
BRAF GA frequency (%)	0	3	0	5	0	4	5	4	4	0
Tumor mutational burden >10 mut/Mb (%)	1	3	0	5	0	10	14	10	2	12
Potential for targeted therapies	Low	Limited	Moderate	High	High	Moderate	High	Moderate	Moderate	High

GA, Genomic alterations.

- N=623

Ross JS, et al. Ann Oncol 2017;28:2539-46

Bedeutung genetischer Alterationen



Mueller SK, et al. J Clin Med 2022;11(3):720; Colombo E. ESMO workshop on rare cancers 2022

ESMO Empfehlungen

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score[a,b]
Androgen receptor in salivary duct carcinoma or adenocarcinoma	IHC	Androgen receptor blocker + gonadotropin-releasing hormone agonist[92]	II-B[92]
HER2 in salivary duct carcinoma or adenocarcinoma	IHC for HER2 protein expression (3+) or FISH for *HER2* gene amplification	Anti-HER2 antibodies (e.g. trastuzumab)[93]	II-B[93]
NTRK fusion in secretory carcinoma	NGS or WGS	TRK inhibitors (e.g. entrectinib, larotrectinib)[94-96]	I-C[94-96]

van Herpen C, et al. ESMO Open 2022;7(6):100602

MyPathway – Phase II Studie

Table 1. Baseline demographics and clinical characteristics by patient

Pt	Sex	Age, years	Race	ECOG PS	Histology	Grade	Stage	Alteration	Testing platform[a]	Previous lines of therapy[b]	Sites of metastasis
HER2 amplification and/or overexpression: treated with pertuzumab + trastuzumab											
1	M	59	White	0	Salivary duct adenocarcinoma	G3	IV	*HER2* amplification	NGS (copy number = 15)	1	Brain, lung, LN
2	M	80	White	1	Adenocarcinoma	G2	IVA	HER2 overexpression	IHC (3+)	1	Bone, LN
3	M	55	Black/African American	2	Unspecified carcinoma	G3	IVA	HER2 amplification + overexpression	FISH/CISH (ratio = 7.3), IHC (3+)	2	Bone, lung, LN
4	M	70	White	1	Invasive ductal carcinoma	G4	IV	HER2 amplification + overexpression	FISH/CISH (ratio = 2.4), IHC (3+)	1	Bone, liver, LN
5	M	73	White	1	Adenocarcinoma	G3	IV	HER2 amplification + overexpression	FISH/CISH (ratio = 9.9), IHC (3+)	1	Bone, LN, spleen
6	M	47	White	1	Adenocarcinoma	G3	IVC	HER2 amplification, overexpression + mutation	NGS (copy number gain; L755F and D769H mutations), IHC (3+)	0	Bone, LN
7	M	61	White	1	Unspecified carcinoma	G3	III	HER2 amplification + overexpression	NGS (copy number = 94); IHC (3+)	0	Liver, lung
8	F	54	White	0	Adenocarcinoma	G3	IV	HER2 amplification + overexpression	NGS (copy number = 104), IHC (3+)	0	Liver, LN
9	M	54	Other	1	Unspecified carcinoma	G3	III	*HER2* amplification + mutation	FISH/CISH (ratio = 5.5), NGS (G776V mutation)	0	Bone, lung, LN
10	F	75	Asian	0	Adenocarcinoma	G3	IVA	*HER2* amplification	NGS (copy number gain)	0	Lung
11	M	70	White	1	Unspecified carcinoma	G1	IVC	*HER2* amplification	NGS (copy number = 60)	2	Bone, liver, lung, LN, intraorbital
12	M	37	White	1	Adenocarcinoma	GX	IV	HER2 overexpression	IHC (3+)	1	Bone, liver
13	M	62	American Indian or Alaska native	1	Mucoepidermoid carcinoma	G3	III	HER2 amplification + overexpression	FISH/CISH (ratio = 7.8), NGS (copy number = 20), IHC (3+)	3	Adrenal gland, liver, lung, LN
14	M	48	Asian	1	Invasive ductal carcinoma	G4	IVA	HER2 amplification + overexpression	FISH/CISH (ratio = 7.2), IHC (3+)	1	Brain, lung, LN
15	F	44	White	2	Adenocarcinoma	G3	IV	*HER2* amplification	NGS (copy number = 15)	2	Brain, chest wall, left eye, liver, LN, neck (subcutaneous tissue), parapharyngeal mucosa
***HER2* mutation: treated with pertuzumab + trastuzumab**											
16	M	68	White	0	Adenocarcinoma	G3	III	*HER2* mutation	NGS (S310F mutation)	0	Lung, LN, mediastinum
Hh alteration: treated with vismodegib											
17	M	65	White	0	Mucoepidermoid carcinoma	G3	II	Hh alteration	NGS (*PTCH-1* Q400* mutation)	0	Lung
***BRAF* V600 mutation: treated with vemurafenib**											
18	M	51	White	1	Mucoepidermoid carcinoma	G3	IV	*BRAF* mutation	NGS (V600E mutation)	1	Liver, lung, LN
High TMB: treated with atezolizumab											
19	M	82	White	1	Mucoepidermoid carcinoma	G3	IVA	High TMB	NGS (31 mutations/Mb)	0	Adrenal gland, LN, skin

- N=19
- HER2 Alteration
  - Pertuzumab + Trastuzumab
- PTCH-1/SMO Mutation
  - Vismodegib
- BRAF V600E Mutation
  - Vemurafenib
- High TMB
  - Atezolizumab

Kurzrock R, et al. Ann Oncol 2020;31(3):412-22

MyPathway – Phase II Studie

Table 2. Clinical outcomes by patient

Pt	Alteration	Time on treatment, months	Best response	Duration of response, months	Duration of SD, months	Best change in target lesion size from baseline, %	PFS, months	OS, months
HER2 amplification and/or overexpression: treated with pertuzumab + trastuzumab								
1	*HER2* amplification	16.5+	CR	15.2+	–	−91.7[a]	16.5+	16.5+
2	HER2 overexpression	26.1+	PR	19.7+	–	−33.3	25.2+	26.1+
3	HER2 amplification and overexpression	12.6	PR	9.2	–	−62.5	13.4	20.4
4	HER2 amplification and overexpression	8.3	PR	7.3	–	−100.0[b]	8.6	14.9+
5	HER2 amplification and overexpression	10.6+	PR	7.2+	–	−66.7	8.5+	10.6+
6	HER2 amplification, overexpression, and mutation (L755F and D769H)	19.8	PR	4.2	–	−85.7	5.6	21.2
7	HER2 amplification and overexpression	4.1+	PR	2.8+	–	−73.0	4.0+	4.1+
8	HER2 amplification and overexpression	4.1[c]	PR	2.7	–	−68.2	9.1	9.1
9	*HER2* amplification and mutation (G776V)	3.5+	PR	1.4+	–	−55.7	2.8+	3.5+
10	*HER2* amplification	11.2	SD	–	11.7	−27.9	11.7	14.0+
11	*HER2* amplification	3.5	SD	–	3.9	−25.6	3.9	10.4
12	HER2 overexpression	2.9+	SD	–	2.9+	−24.3	2.9+	2.9+
13	HER2 amplification and overexpression	2.1	SD	–	2.3	1.4	2.3	8.2
14	HER2 amplification and overexpression	0.7	PD	–	–	3.6	1.5	8.3
15	*HER2* amplification	0.7	PD	–	–	22.5	1.4	3.1
***HER2* mutation: treated with pertuzumab + trastuzumab**								
16	*HER2* mutation (S310F)	10.4	SD	–	11.0	−12.8	11.0	13.7+
Hh alteration: treated with vismodegib								
17	Hh alteration (*PTCH-1* Q400*)	14.4	PR	10.7		−55.6	14.3	17.3+
***BRAF* V600 mutation: treated with vemurafenib**								
18	*BRAF* mutation (V600E)	16.8	PR	15.1	–	−43.4	18.5	20.1
High TMB: treated with atezolizumab								
19	High TMB (31 mutations/Mb)	5.7+	PR	0.03+	–	−56.0	5.5+	5.7+

- ORR: 60%
- PFS: 8.6 Mte.
- OS: 20.4 Mte.

Kurzrock R, et al. Ann Oncol 2020;31(3):412-22

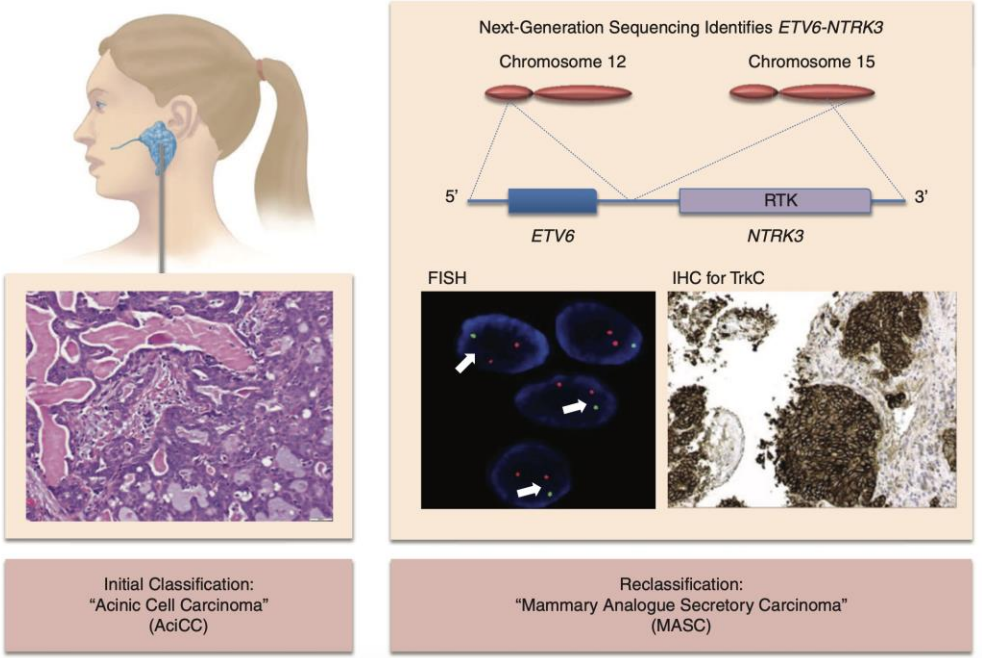
NTRK-Fusion bei Speicheldrüsenkarzinomen

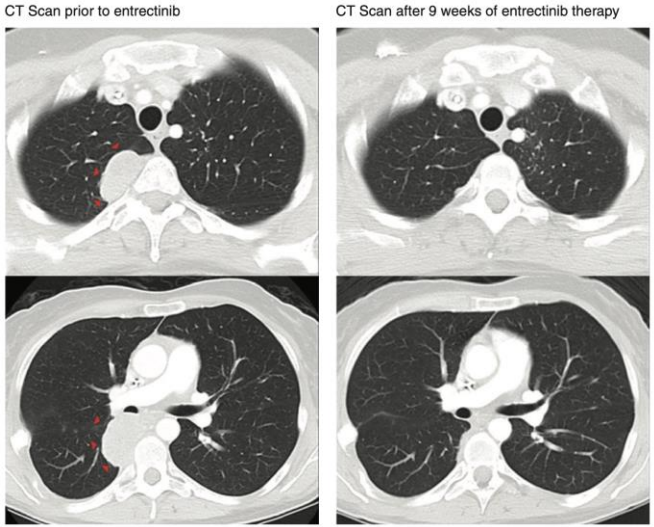
ESMO 2022 Guidelines: In patients with secretory carcinoma and NTRK gene fusions, treatment with a TRK inhibitor (**entrectinib** or **larotrectinib**) is recommended [III, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: 3; **ESCAT score: I-C**]

van Herpen C, et al. ESMO Open 2022;7(6):100602

NTRK beim sekretorischen Karzinom

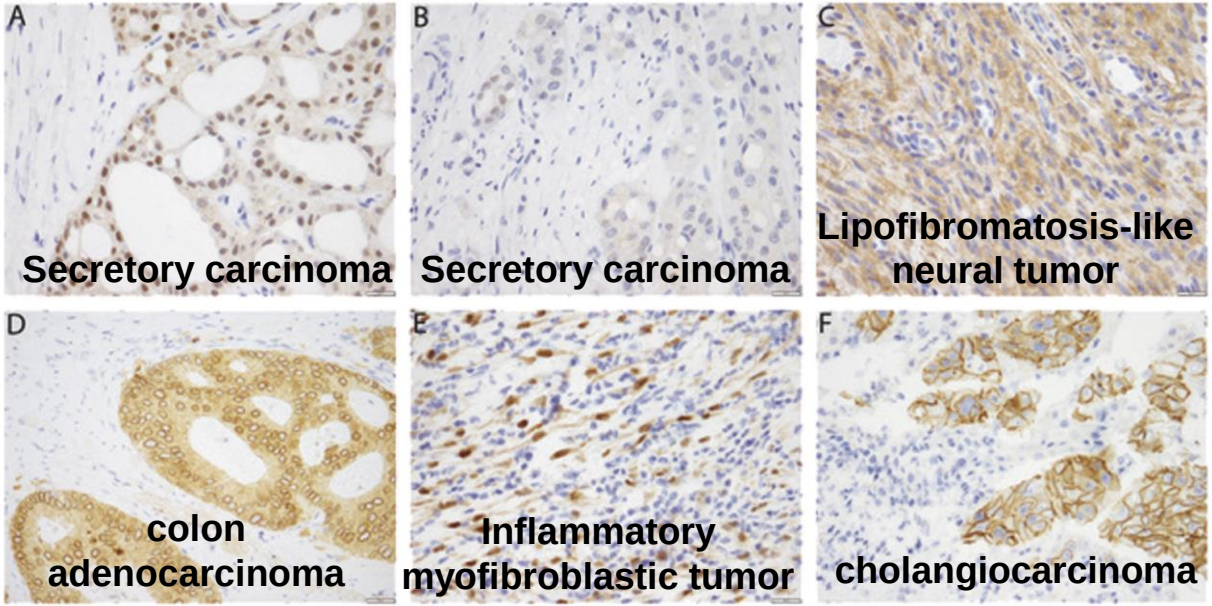
Frühere Nomenklatur: mammary analogue secretory carcinoma (MASC)





Drilon A, et al. Ann Oncol 2016;27:920-6

NTRK Immunhistochemie



- **Speicheldrüsenkarzinom:**
  - **Sensitivität: 88.9%**
  - **Spezifität: 52%**

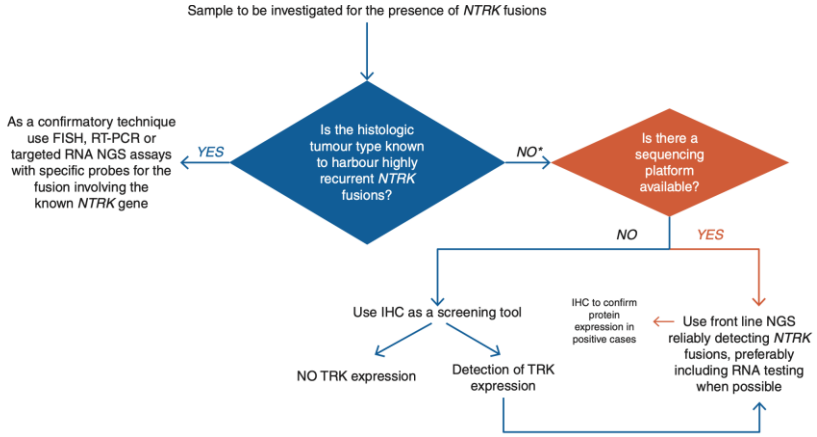
Solomon JP, et al. Mod Pathol 2020;33(1):38-46

NTRK Diagnostik – ESMO Empfehlungen

Table 1. Summary of main features, strengths and weaknesses of all available techniques to detect *NTRK* rearrangements

Method	Sensitivity	Specificity	Detection of all fusion genes	Detection of partner	Detection of expression	Screening
IHC	High[a]	High[b]	Yes	No	Yes	Yes
FISH[c]	High	High	One per probe	No	No	No
RNA seq NGS	High	High	Yes	Yes	Yes	Yes
DNA seq[c]	Moderate	High	Yes	Yes	No	Yes

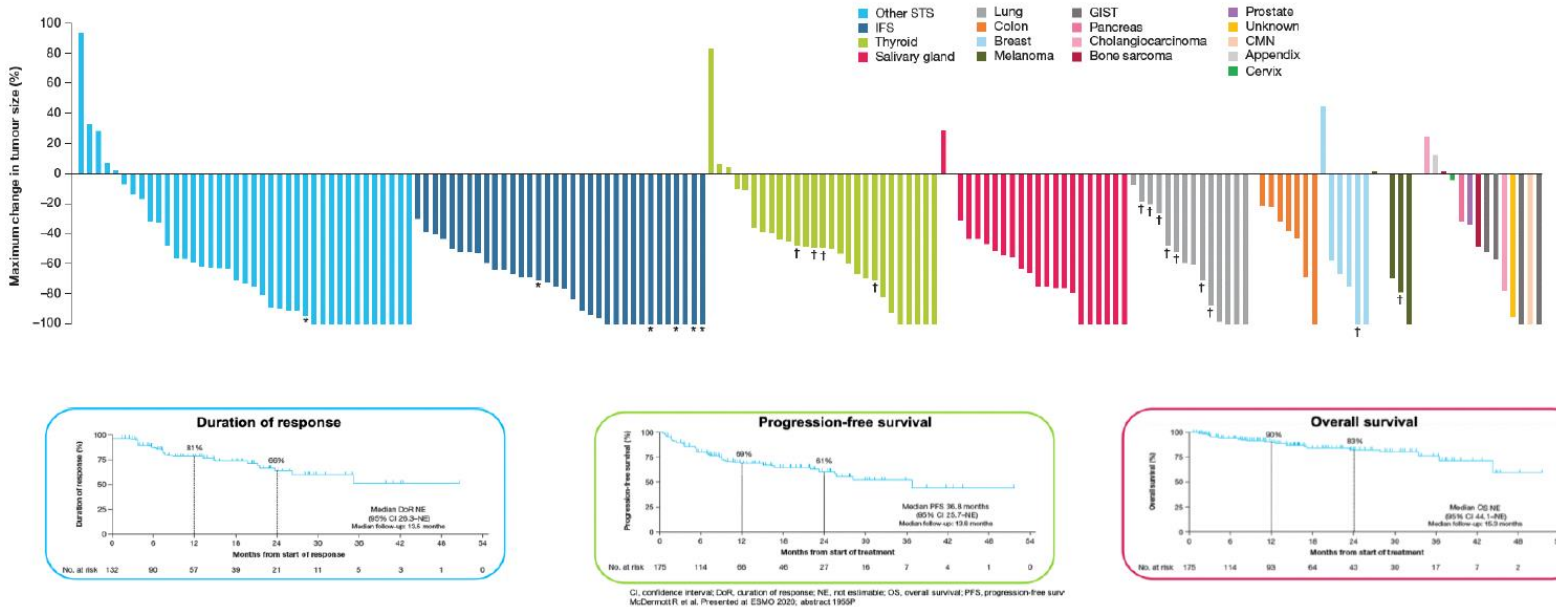
[a]False negatives reported mainly in *NTRK3* fusions.
[b]In the absence of smooth muscle/neuronal differentiation.
[c]Detected rearrangements by DNA-based assays may not result in fusions, correlation with surgical pathology and predicted transcript (for sequencing) is needed.



Marchio C, et al. Ann Oncol 2019;30:1417-27

Larotrectinib für TRK-positive Tumoren

N=55 (Speicheldrüsentumoren: n=12 (22%))
ORR: 75%



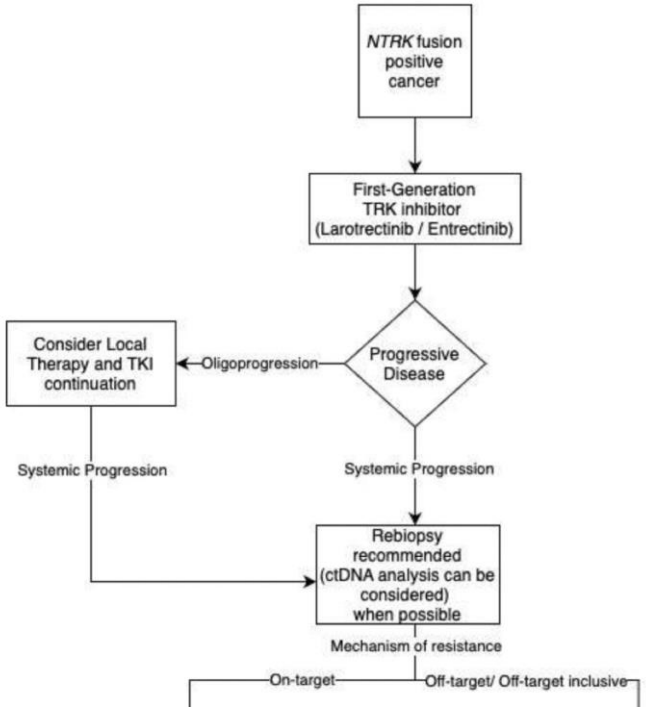
Drilon A, et al. NEJM 2018;378:731-9

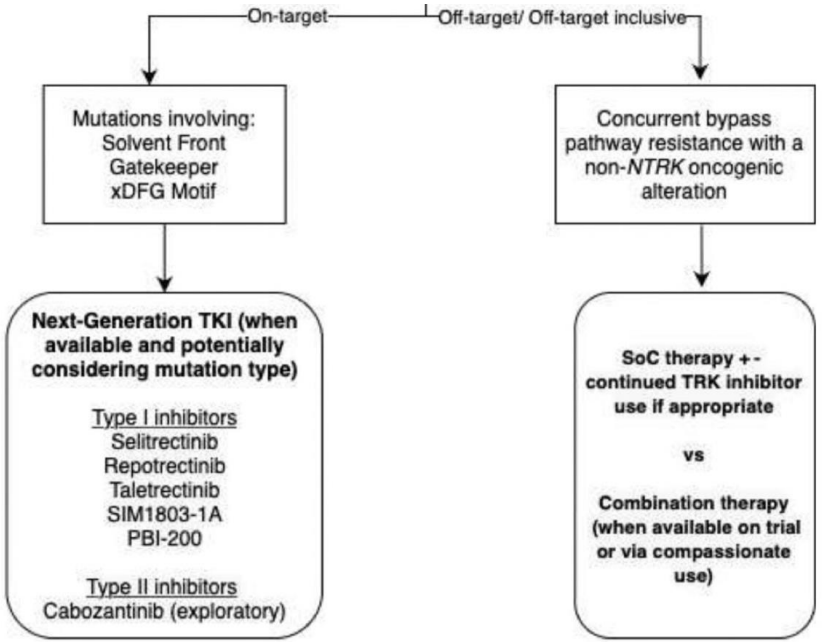
NTRK-Inhibitoren

	Clinical Trials	Medication	n. SGC	Outcomes
1st generation NTRKi	Hong et al, Lancet Oncol 2020 – update of a pooled analysis of: **NCT02576431** **NCT02122913** **NCT02637687**	**Larotrectinib** TrkA/B/C	20	**ORR** 90% (95% CI 69 – 99) **Median duration of response in the SGC cohort** 35.2 months (95% CI 13.3 – not estimable)
	Doebele et al, *Lancet Oncol* 2020 – pooled analysis of: **ALKA-372-001** **STARTRK-1** **STARTRK-2**	**Entrectinib** TrkA/B/C ROS1 ALK	7	**ORR** 83% (95% CI 36–100) **In the whole study population:** **ORR** brain mets 55% (23.4 – 83-3) **Median DoR** 10 months (7.1 – NE)
2nd generation NTRKi	Besse et al, *Mol Cancer Ther* 2021 – update on dose-escalation phase I/II clinical trial **TRIDENT-1** **NCT03093116**	**Repotrectinib** TrkA/B/C ROS1 ALK	UKN	**in TRK TKI–naïve cohort** ORR 63% mDoR 1.9–7.4+ months **In TRK TKI-pretreated cohort** ORR 47% mDoR 1.9–15.1+ months
	NCT03215511 NCT03206931	**Selitrectinib** TrkA/B/C	UKN	**TRK TKI-pretreated cohort** ORR 45%

Hong DS, et al. Lancet Oncol 2020;21(4):531-40; Doebele RC, et al. Lancet Oncol 2020;21(2):271-82

NTRK-Inhibitoren – Resistenz





Harada G, Drilon A. Cancer Genet 2022;264-265:33-39

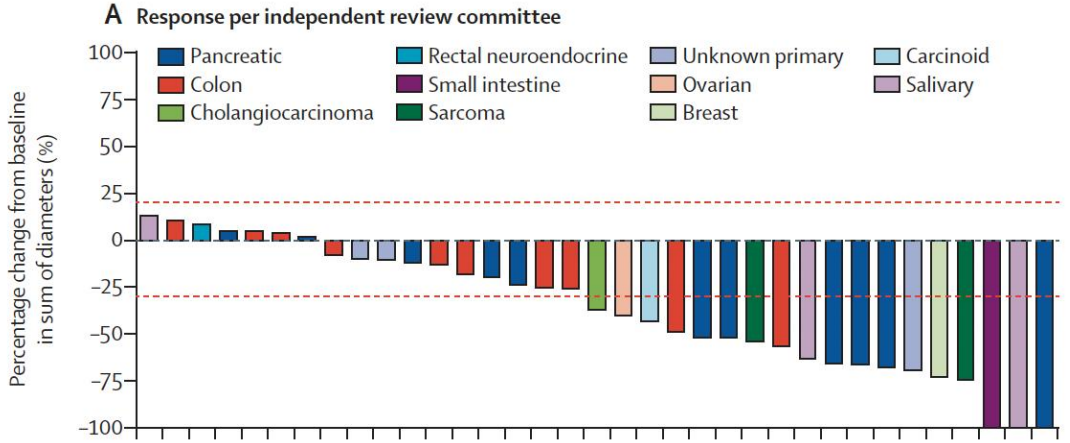
LIBRETTO-001 – Selpercatinib für RET-positive Tumoren

- N=45 (4 (9%) Speicheldrüsenkarzinome)
- ORR: 43.9% (Speicheldrüsenkarzinome: 50%)
- DoR: 24.5 Mte.
- PFS: 13.2 Mte.

	Number of patients per primary diagnosis	Independent review committee assessment		Investigator assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)	Objective response rate (95% CI)	Median duration of response, months (IQR)
All *RET* fusion-positive solid tumour types	41	43·9% (28·5–60·3)	24·5 (9·2–NR)	43·9% (28·5–60·3)	18·4 (9·8–22·6)
Pancreatic	11	54·5% (23·4–83·3)	NR (NR–NR)	55·5% (23·4–83·3)	NR (12·0–NR)
Salivary	4	50·0% (6·8–93·2)	NR (5·7–NR)	25·0% (0·6–80·6)	5·7 (5·7–5·7)
Breast	2	100·0% (15·8–100·0)	17·3 (17·3–17·3)	100·0% (15·8–100·0)	18·4 (18·4–18·4)
Sarcoma	2	50·0% (1·3–98·7)	14·9 (NR–NR)	50·0% (1·3–98·7)	14·9 (NR–NR)
Xanthogranuloma*	2	NA	NA	50·0% (1·3–98·7)	22·9 (NR–NR)
Carcinoid	1	100·0% (2·5–100·0)	24·1 (NR–NR)	100·0% (2·5–100·0)	18·6 (18·6–18·6)
Ovarian	1	100·0% (2·5–100·0)	14·5 (NR–NR)	100·0% (2·5–100·0)	14·5 (NR–NR)
Small intestine	1	100·0% (2·5–100·0)	24·5 (24·5–24·5)	100·0% (2·5–100·0)	22·6 (22·6–22·6)
Cholangiocarcinoma	1	100·0% (2·5–100·0)	5·6 (NR–NR)	0% (0·0–97·5)	NA
Pulmonary carcinosarcoma	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Rectal neuroendocrine	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Carcinoma of the skin	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA

NA=not applicable. NR=not reached. *Xanthogranuloma skin cancer could not be evaluated by the independent review committee because of the committee's scope of images not allowing for assessment of skin findings.

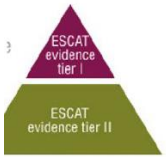
Table 3: Objective response rate and duration of response by tumour type



Subbiah V, et al. Lancet Oncol 2022;23:1261-73

Androgendeprivation

SGC histologies with AR+	%
Salivary duct carcinoma	75
Adenocarcinoma, NOS	21

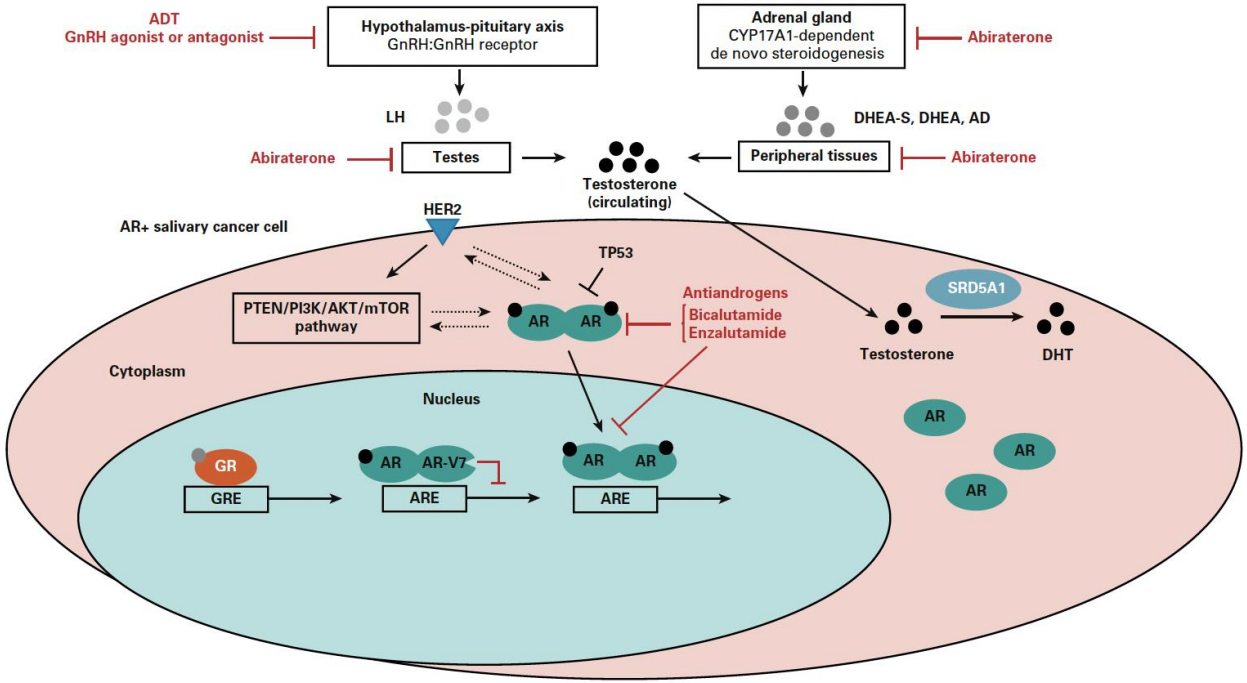


ESMO Guidelines 2022: In case of androgen receptor positivity **(> 70% by IHC)** consider Androgen Deprivation Therapy (combined antihormonal or antiandrogen as single agent) [III, B; **ESCAT score: II-B**]

→ *increased responsiveness and outcome in prospective trials*

van Herpen C, et al. ESMO Open 2022;7(6):100602

Androgen-Rezeptor Signalweg beim Speicheldrüsenkarzinom



Ho A, et al. J Clin Oncol 2021;39(36):4069-72

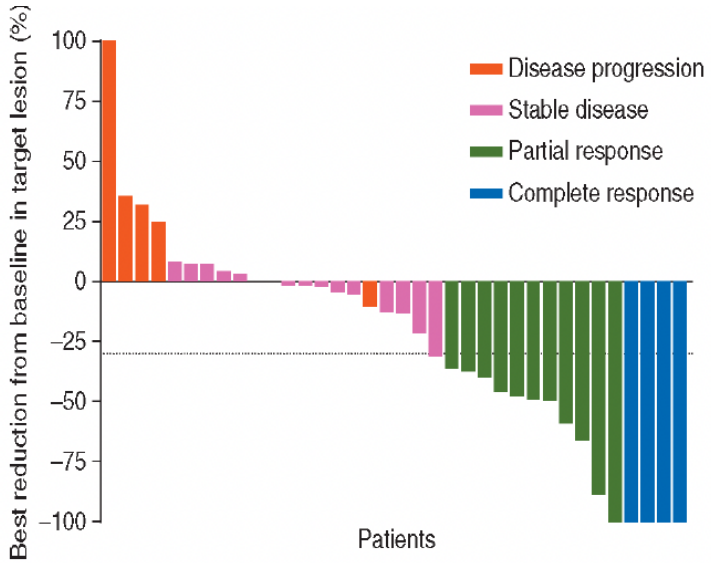
ADT beim Speicheldrüsenkarzinom

ADT						
Fushimi *et al.*[29]	Phase II study	36	Bicalutamide + leuprorelin	41.7% (25.5–59.2)	8.8 (6.3–12.3)	30.5 (16.8–NR)
Locati *et al.*[30]	Retrospective study	17	Bicalutamide + Leuprorelin	64.7% (38.3–85.8)	11 (8–24)‡	44 (23–60)‡
Boon *et al.*[6]	Retrospective study	35	28: Bicalutamide, 7; Bicalutamide + Leuprorelin	17.1%	4 (3–5)	17 (10–24)
Viscuse *et al.*[31]	Retrospective study	20	ADT§	55%	8 (5–12)‖	25 (18–64)‖
Locati *et al.*[32]	Phase II study	24$	Abiraterone + LHRH	21%	3.65 (1.94–5.89)	22.47 (6.74–NR)
Ho *et al.*[33]	Phase II study	46	Enzalutamide	4.3% (10.9%*)	5.6 (3.7–7.5)	17.0 (11.8–30.0)
Kawakita *et al.*	This study	134	Bicalutamide + leuprorelin	28% (21–37)	6 (5–7)	27 (23–38)

Kawakita D, et al. Ther Adv Med Oncol 2022;14:1-17

Androgendeprivation: Leuprorelin + Bicalutamid

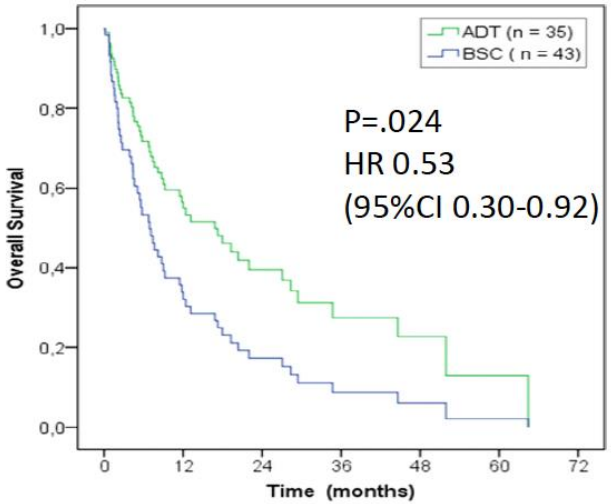
- N=36 (SDC: 94%; ADC NOS: 6%)
- Leuprorelin 3.75 mg s.c. q4w + Bicalutamid 80 mg/d
- ORR: 41.7%
- CBR: 75.0%
- PFS: 8.8 Mte.
- OS: 30.5 Mte.



Fushimi C, et al. Ann Oncol 2018;29:979-84

ADT – Verbesserung des Überlebens?

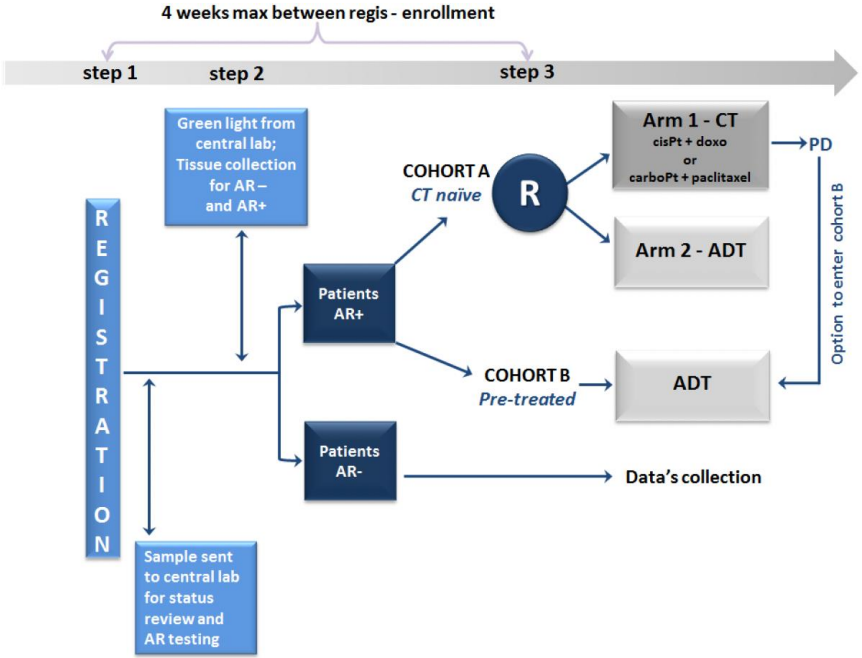
- N=35 (n=28 ADT, n=7 CAB)
- ORR: 18%
- CBR: 50%
- PFS: 4 Mte.
- OS: 17 Mte.
- Vergleich mit historischer Kontrolle
  - BSC: OS 5 Mte.



(Cox regression model: no confounders)

Jaspers HCJ, et al. JCO 2011;29(16):e473-6; Boon E, et al. Head Neck, 2017;40:605-13

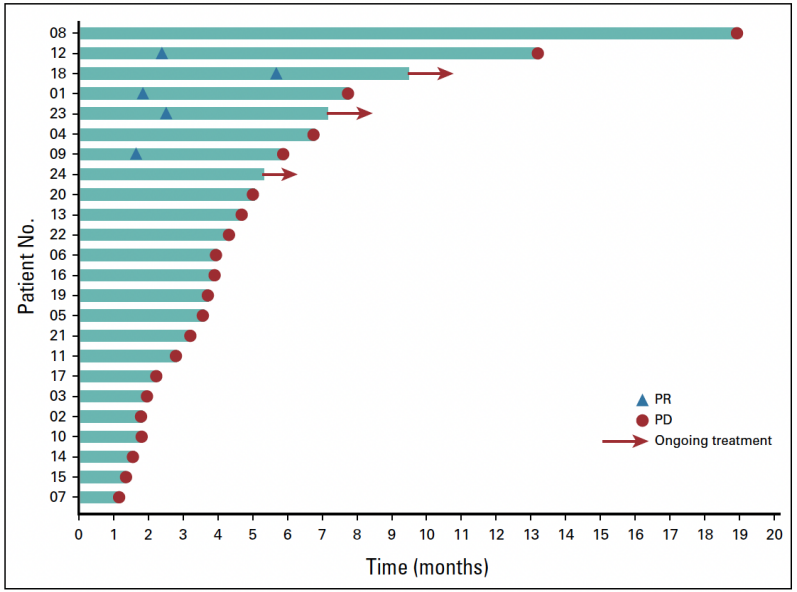
EORTC 1206 – Randomisierte Phase 2 Studie



- N=152
- Primäre Endpunkte:
  - PFS Kohorte A
  - ORR Kohorte B

Kastrationsrefraktäre Situation: Abirateron

- N=24 (SDC: 79%; ADC NOS: 21%)
- PD unter ADT; supprimiertes Testosteron
- Abirateron 1 g/d + Prednison 10 mg/d + LHRH-Agonist
- ORR: 21%
- DCR: 62.5%
- DoR: 5.82 Mte.
- PFS: 3.65 Mte.
- OS: 22.47 Mte.



Locati LD, et al. J Clin Oncol 2021;39:4061-8

Neuere anti-Androgene – negative Studien

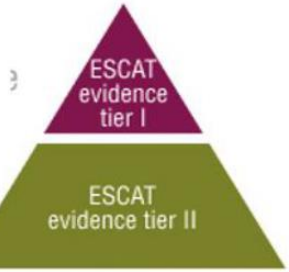
- Enzalutamid[1]
  - N=46 (13 in 2nd line)
  - ORR: 4.3% (15.7% nicht-bestätigte ORR)
  - SD: 52.2%
- Apalutamide + LHRH-Agonist[2]
  - N=31 (24)
  - 6/24 PR
  - Median PFS: 7.43 months

[1]Ho AL, et al. J Clin Oncol 2022;40(36):4240-9; [2]Honma, et al. ASCO 2022

HER2-Überexpression

Histologie	Häufigkeit
Speicheldrüsengangkarzinom	30-70%
Adenokarzinom, NOS	17%
Karzinom aus pleomorphem Adenom	17%
Mukoepidermoid-Karzinom (high-grade)	13%

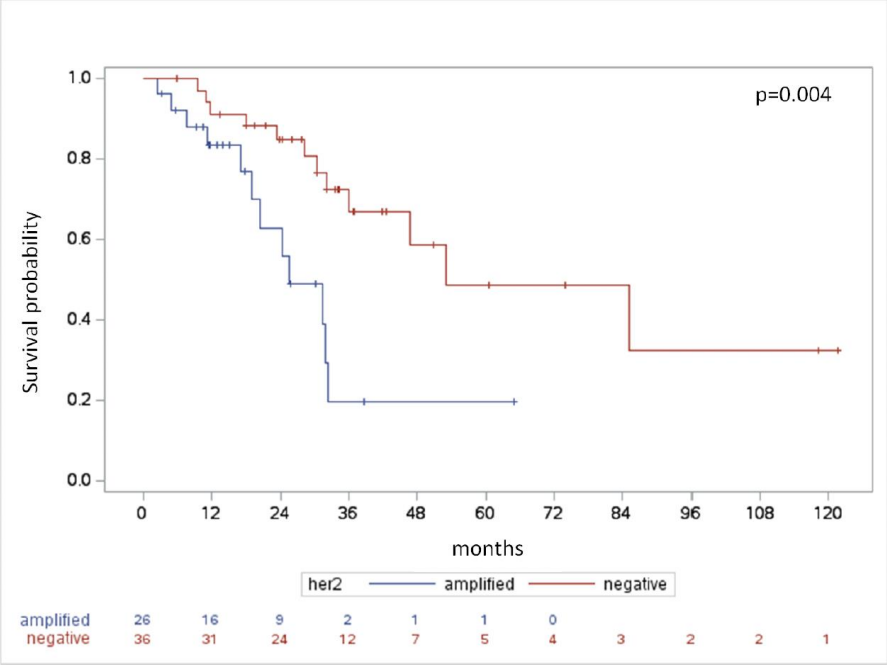
Co-Expression von AR und HER2 in 35-60% der Speicheldrüsengangkarzinome



ESMO-EURACAN Guidelines 2022: In case of HER2 positivity (**IHC score 3+ or FISH positivity**) consider Docetaxel-trastuzumab or T-DM1 [III, B; **ESCAT score: II-B**]

Colombo E. ESMO workshop on rare cancers 2022

HER2-Überexpression und AR-Expression – Prognose



- N=74
- AR pos.
- HR für Rezidiv: 2.97
- HR für Tod: 3.22
- Höhere Prävalenz von ZNS-Metastasen (40% vs. 24%)

Cavalieri S, et al. Front Oncol 2023;12:1096068

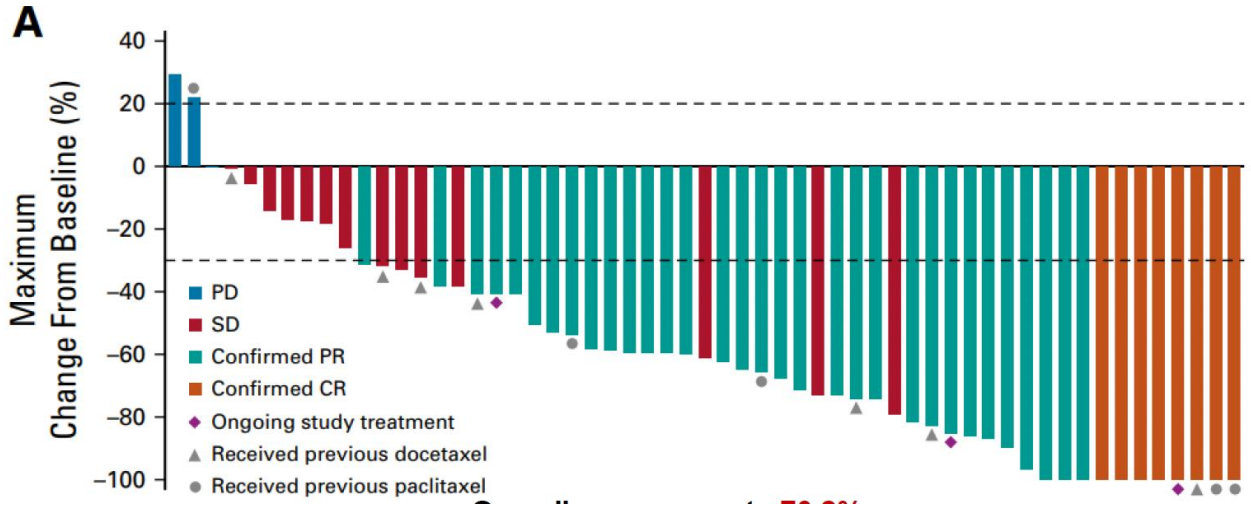
HER-2 gerichtete Therapie

Author	Study design	*n*	Drugs	ORR % (95% CI)	Median PFS months (95% CI)	Median OS months (95% CI)
HER2-targeted therapy						
Haddad *et al.*[21]	Phase II study	13	Trastuzumab	7.9%	4.2	NA
Takahashi *et al.*[22]	Phase II study	57	Trastuzumab + docetaxel	70.2% (56.6–81.6)	8.9 (7.8–9.9)	39.7 (NR)
Kinoshita *et al.*[23]	Phase II study	16	Trastuzumab + docetaxel	60.0% (32.3–83.7)	8.5 (6.0–12.7)	33.8 (16.9–NR)
Kurzrock *et al.*[24]	Phase II study	15	Trastuzumab + pertuzumab	60% (32–84)	8.6 (2.3–NR)	20.4 (8.2–NR)
Uijen *et al.*[25]	Retrospective study	13	Trastuzumab + pertuzumab + docetaxel	58%	6.9 (5.2–8.5)	42.0 (13.8–70.1)
Li *et al.*[26]	Phase II study	10	Ado-trastuzumab emtansine	90% (56–100)	NR (4–22+)	NA
Jhaveri *et al.*[27]	Phase II study	3	Ado-trastuzumab emtansine	66.7%	NA	NA
Uijen *et al.*[25]	Retrospective study	7	Ado-trastuzumab emtansine	57%	4.4 (0–18.8)	NA
Bando *et al.*[28]	Phase I study	17	Fam-trastuzumab deruxtecan-nxki	47.4% (23.0–72.2)	14.1 (5.6–NR)	NA
Kawakita *et al.*	This study	111	Trastuzumab + docetaxel	72% (63–80)	9 (8–11)	38 (33–49)

Kawakita D, et al. Ther Adv Med Oncol 2022;14:1-17

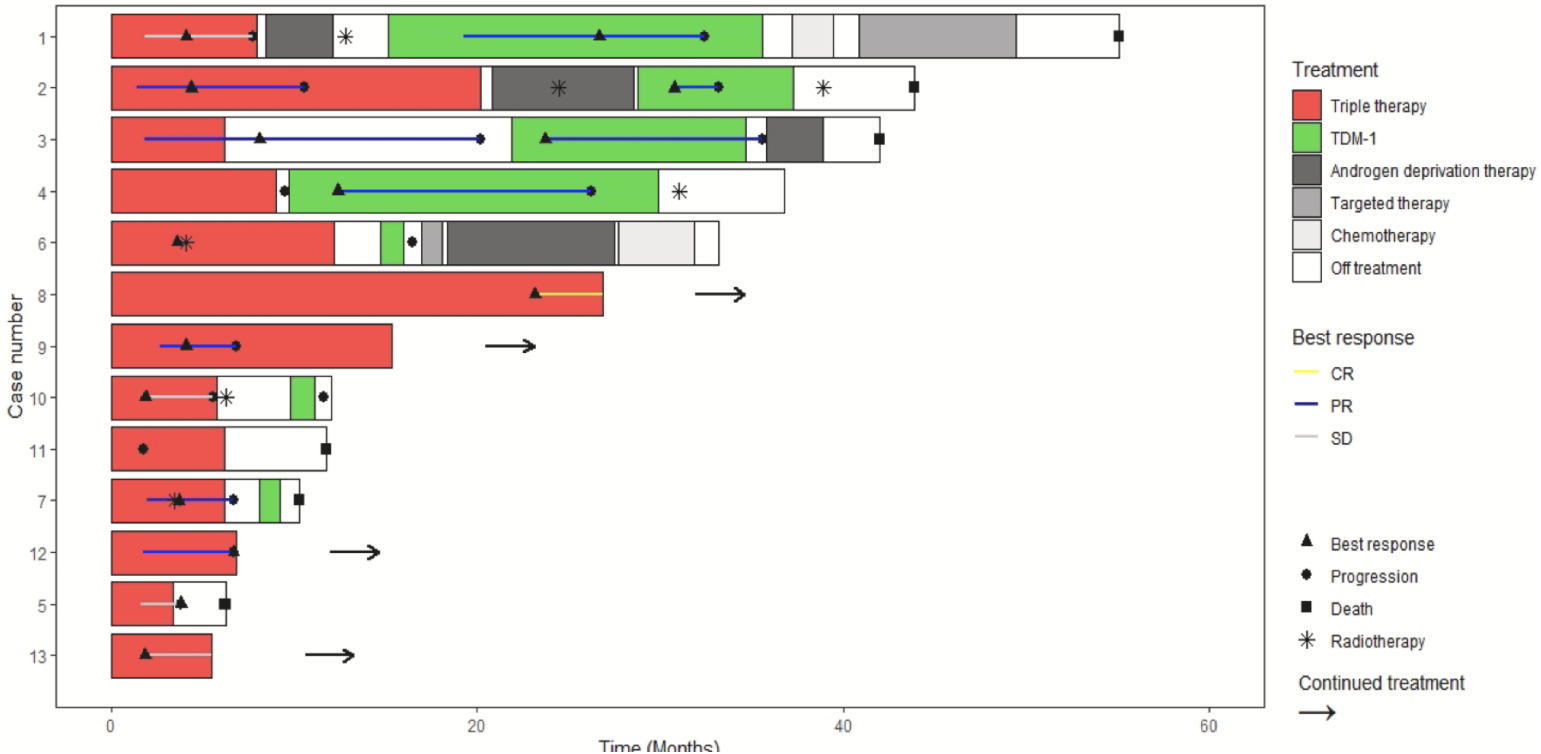
Trastuzumab + Docetaxel beim HER2-positiven Speicheldrüsengangkarzinom

- N=57 (91% HER2 3+)
- ORR: 70.2%
- CBR: 84.2%
- PFS: 8.9 Mte.
- OS: 39.7 Mte.



Takahashi H, et al. J Clin Oncol 2019;37(2):125-34

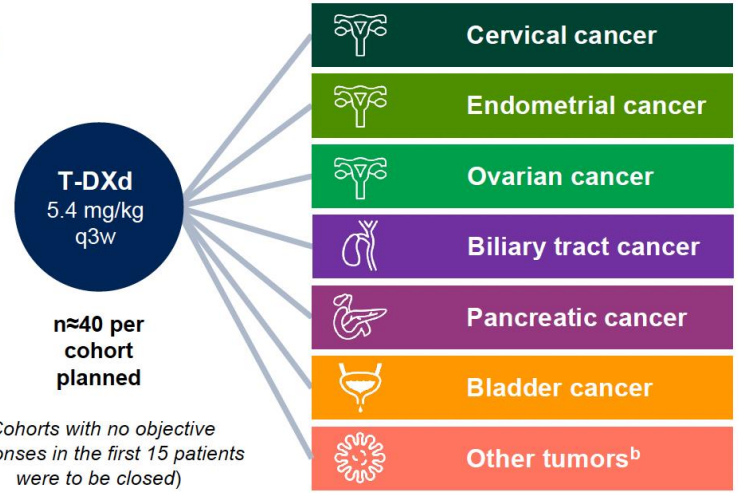
Behandlungssequenz?



Uijen MJM, et al. Oral Oncol 2022;125:105703

DESTINY-PanTumor02 – Trastuzumab-Deruxtecan

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

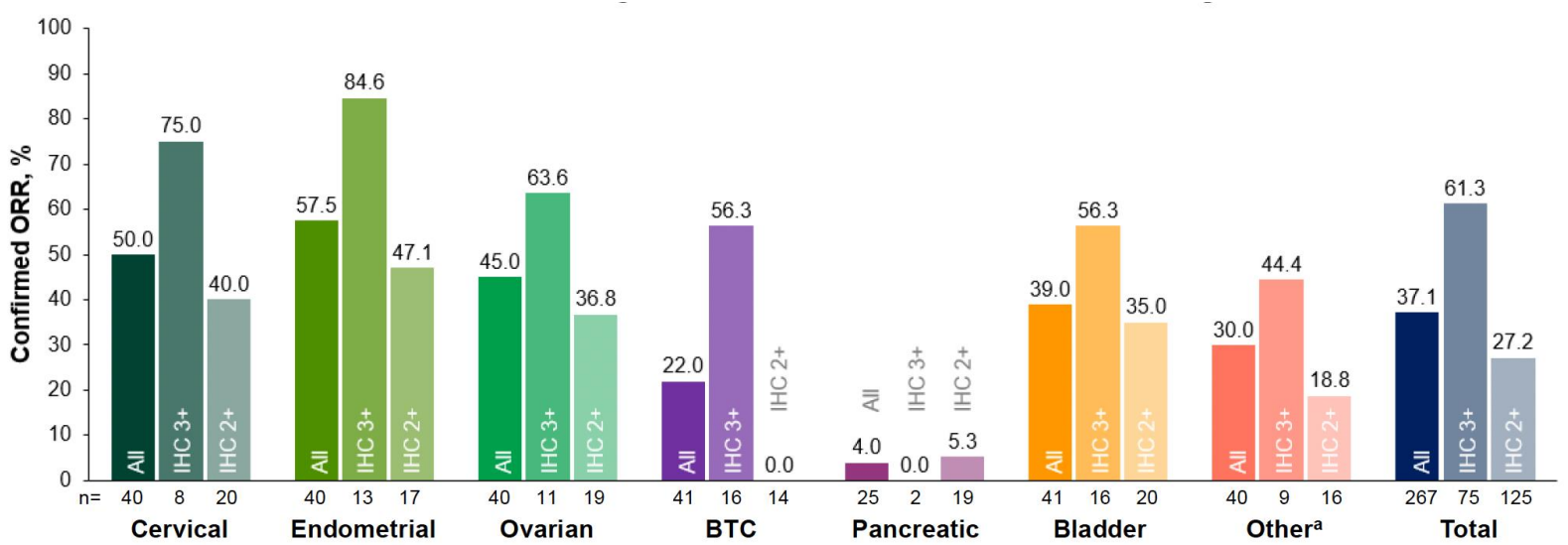
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Meric-Bernstam F, et al. ASCO 2023;LBA 3000

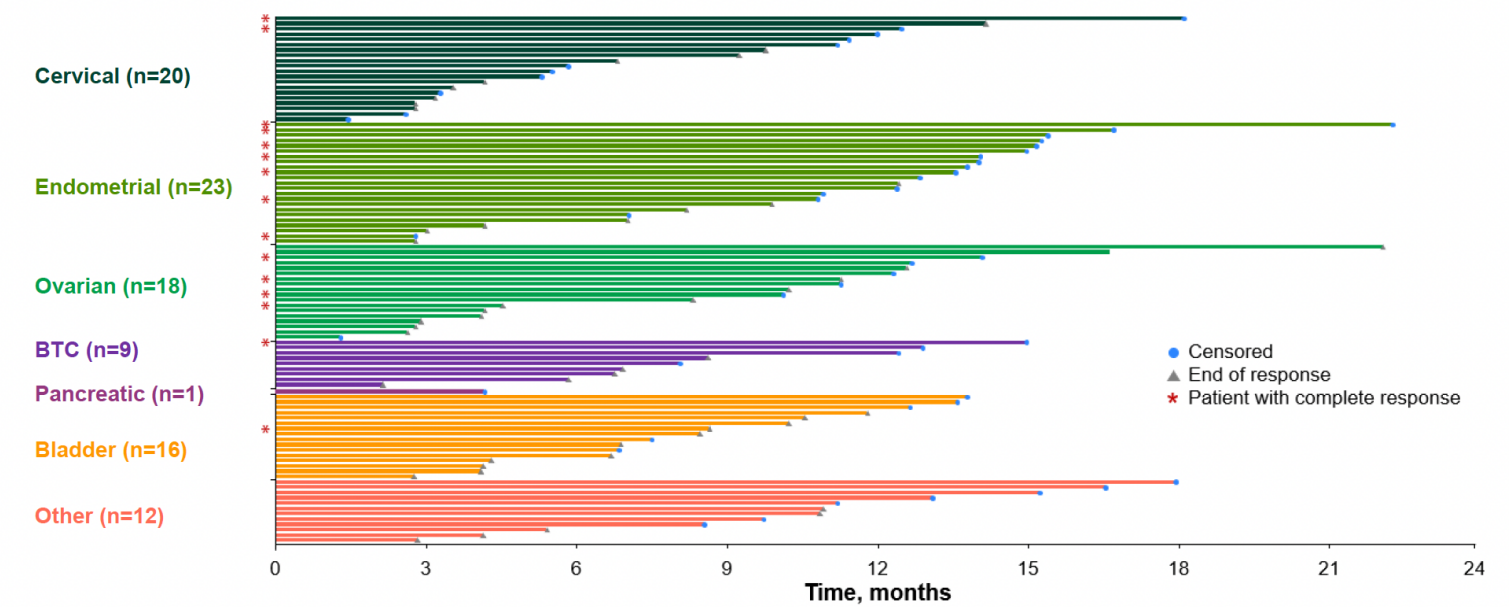
DESTINY-PanTumor02 – Trastuzumab-Deruxtecan



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Meric-Bernstam F, et al. ASCO 2023;LBA 3000

DESTINY-PanTumor02 – Trastuzumab-Deruxtecan

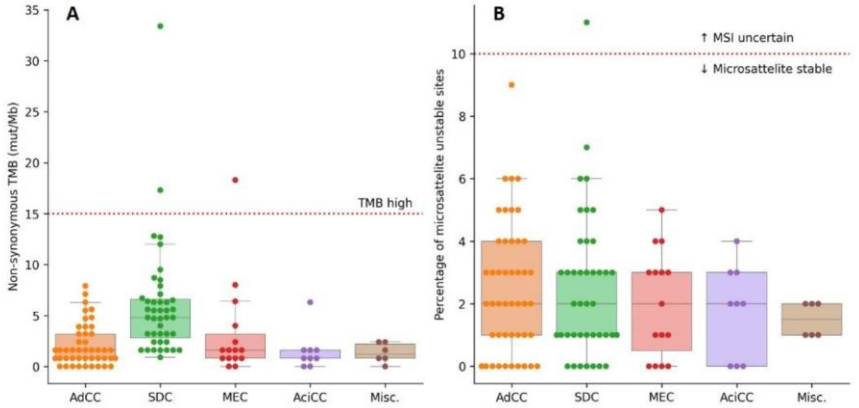


Kaplan-Meier estimate of response at 12 months (%)	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
	47.6	72.3	45.8	41.7	0	23.2	53.6	49.6

Meric-Bernstam F, et al. ASCO 2023;LBA 3000

Immuntherapie?

- Speicheldrüsengangkarzinome
  - Höhere Tumormutationslast (TMB) als andere Speicheldrüsenkarzinome
  - PD-L1 Expression: 26%
  - Dichtes Immuninfiltrat



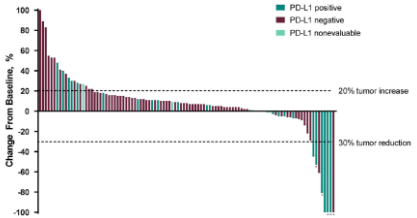
Dalin MG, et al. Clin Cancer Res 2016;22:4623; Hamza A, et al. Ann Diagn Pathol 2019;40:49-52; Linxweiler M, et al. Clin Cancer Res 2020;26(12):2859-79; Lassche G, et al. Cancers 2022;14(17):4156

Immuntherapie – Pembrolizumab Monotherapie

- KEYNOTE-158: Pembrolizumab Monotherapie
- N=109 (25.7% PD-L1 positiv)
  - 54.1% Adenoidzystisches Karzinom
  - 22.9% Adenokarzinom

Antitumour activity of pembrolizumab, according to RECIST version 1.1 criteria, as assessed by blinded independent central radiologic review.[a]

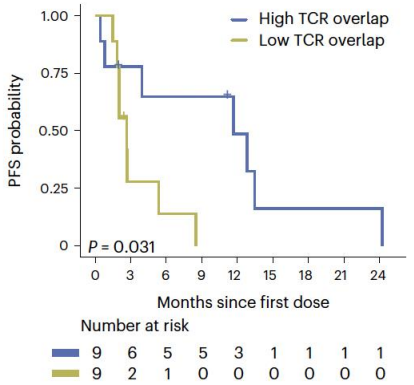
Assessment	All patients (N = 109)	Patients with PD-L1–positive tumours[a] (n = 28)	Patients with PD-L1–negative tumours[a] (n = 77)
ORR, n (95% CI)[b]	4.6 (1.5–10.4)	10.7 (2.3–28.2)	2.6 (0.3–9.1)
Best overall response, n (%)			
CR	1 (0.9)	0	1 (1.3)
PR	4 (3.7)	3 (10.7)	1 (1.3)
SD[c]	53 (48.6)	9 (32.1)	43 (55.8)
Non-CR/non-PD	1 (0.9)	0	1 (1.3)
PD	42 (38.5)	11 (39.3)	29 (37.7)
Not evaluable[d]	5 (4.6)	4 (14.3)	0
No assessment[e]	3 (2.8)	1 (3.6)	2 (2.6)
Time to response, median (range), months	2.0 (1.9–4.2)	–	–
DOR, median (range), months	Not reached (25.1–40.8+)	–	–
Patients with response ≥24 months, n (%)	5 (100.0)	–	–

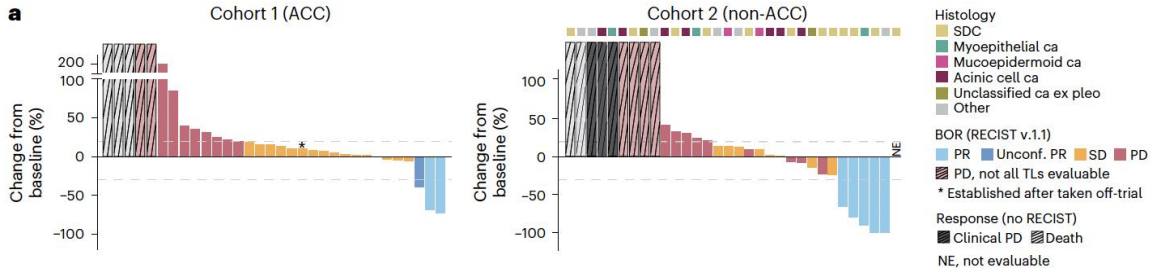


Even C, et al. Eur J Cancer 2022;171:259-68

Immuntherapie – Ipilimumab + Nivolumab

- N=64
  - Kohorte 1: Adenoid-zystisches Karzinom (n=32)
  - Kohorte 2: andere Histologien (n=32)
- ORR
  - Kohorte 1: 16% (5/32)
  - Kohorte 2: 6% (2/32)
- PFS
  - Kohorte 1: 4.4 Mte.
  - Kohorte 2: 2.2 Mte.





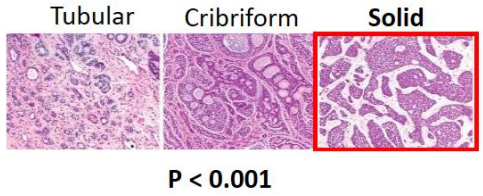
Vos JL, et al. Nat Med 2023; doi: 10.1038/s41591-023-02518-x. Oline ahead of print

Zielgerichtete Therapie beim Adenoid-zystischen Karzinom

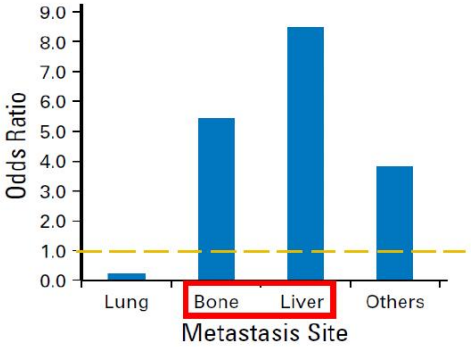
Author, aa	Drug	Phase	N° pts	RR	SD	mPFS, mos
Guigay, 2007	Imatinib (KIT)	II	21	2/17	6/17	NA
Ghosal, 2010	Imatinib + plat KIT	II	28	3/28	19/28	NA
Dillon PM, 2013	Dovitinib (FGFR)	II	21	2/19	9	NA
Thomson DJ, 2013	Sorafenib (BRAF; VEGFR)	II	23	0	13/19	11.3
Locati LD, 2016	Sorafenib	II	19/37	2/19	11/19	8.9
Wong SJ, 2013	Dasatinib (Src)	II	40	0	21	4.8
Ho A, 2016	Axitinib (VEGFR)	II	33	3	25	NA
Guigay, 2016	Pazopanib	II	49	0		
Rodriguez, 2018	Eribulin	II	29 (11 ACC)	3/29 (2 ACC)	8	3.5
Locati LD, 2018	Lenvatinib (VEGFR2, FGFR, PDGFR)	II	28	3/26	20/26	9
Tchekmedyian V, 2019		II	33	5/33	24/33	16.4
Bhumsuk K, ASCO 2020	Axitinib (VEGFR)	IIR	54	0	100% vs 51.9%	10.8 vs 2.8

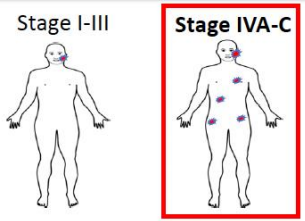
Licitra L. ESMO 2021

NOTCH1-Mutation beim Adenoid-zystischen Karzinom

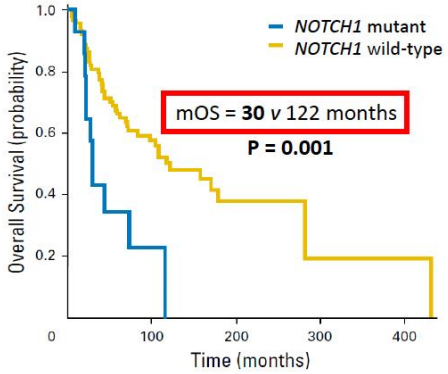


P < 0.001





P=0.02

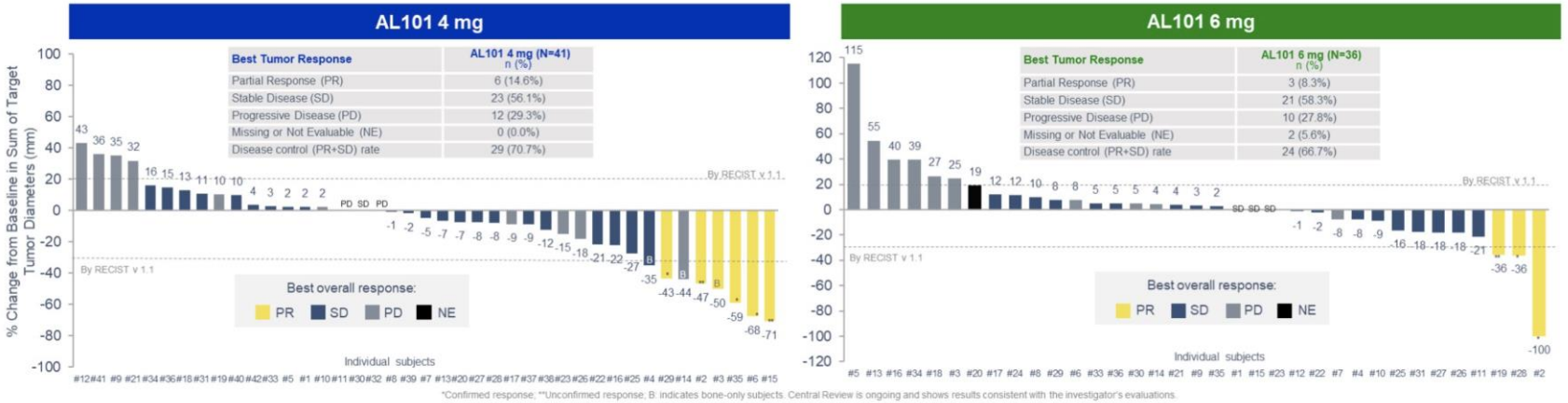


- N=102
- NOTCH1-Mutation: 14.7% (15/102)

Ferrarotto R, et al. J Clin Oncol 2017;35(3):352-60

AL101: Gamma-Secretase-Inhibitor – ACCURACY Phase 2 Studie

- N=82
- ORR: 12%
- DCR: 69%



Ferrarotto R, et al. ASCO 2022; Abstract 6046

MYB-NFIB Fusion beim Adenoid-zystischen Karzinom

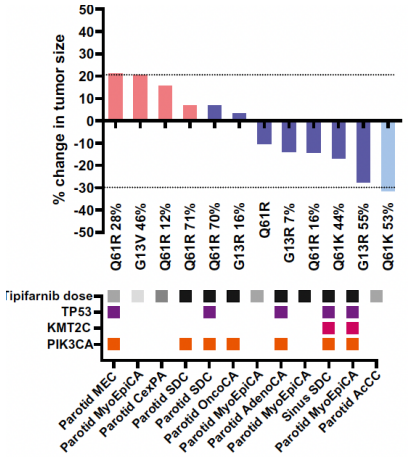
- Präklinische Evidenz
  - Bcr-MYB (MYB-Inhibitor): antiproliferativer Effekt auf ACC-Zellen
  - Proteasomen-Inhibitoren (z.B. Oprozomib) interferieren mit MYB-Signalweg
  - Tretinoin (ATRA) hemmt MYB Expression in myeloiden Leukämien
- Klinische Evidenz
  - ATRA: ORR 9% (n=18), mPFS 3.2 Mte.
- Zukünftige Entwicklungen
- IGF1R/AKT-Inhibition
- ATR Kinase-Inhibitor

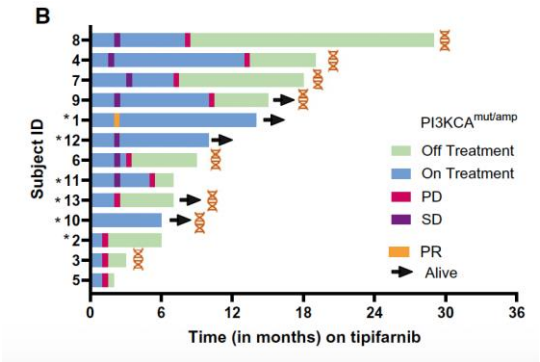
Miller LE, et al. Cancer 2022;16(4):992

HRAS-Mutation – nächste Generation der zielgerichteten Therapie

- 22% der Speicheldrüsengangkarzinome haben eine HRAS-Mutation[1]
  - 100% AR-Überexpression
  - 93% Co-Mutation mit PIK3CA

- Tipifarnib[2]
  - N=13
  - 1-3 Vortherapien
  - ORR: 7%
  - DCR: 65%
  - PFS: 7 Mte.
  - OS: 18 Mte.

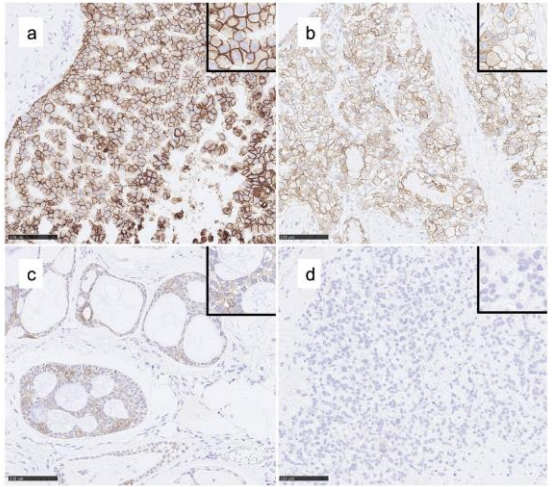




[1]Mueller SA, et al. Modern Pathol 2020;33(10):1896-1909; [2]Hanna GJ, et al. Cancer 2020;126:3972-81

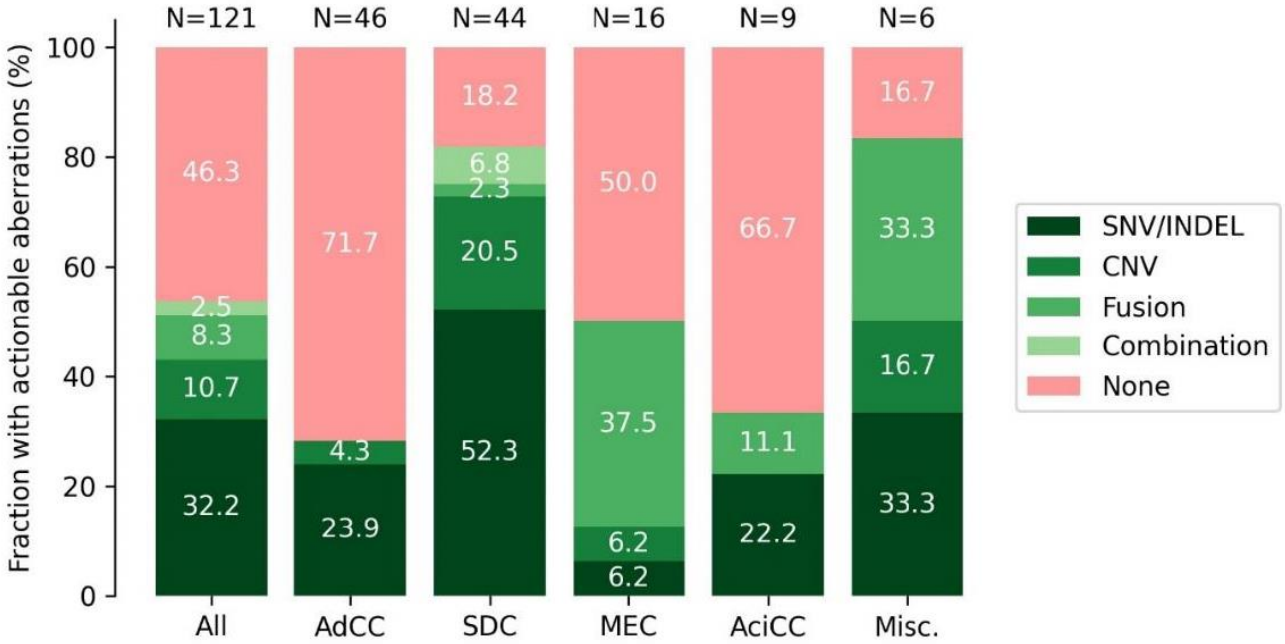
TROP-2 – Ein möglicher therapeutischer Ansatz

- N=114
  - Parotis: 90.4%
- TROP-2 Expression: 92%
  - Hoch: 44%
  - Moderat: 38%
  - Schwach: 10%
- MALDI-Massenspektrometrie: 80% Nachweis von TROP-2



Wolber P, et al. Head Neck Pathol 2021;15:1147-55

Präzisionsonkologie beim Speicheldrüsenkarzinom



Lassche G, et al. Cancers 2022;14(17):4156

Zusammenfassung

- **Speicheldrüsengangkarzinom**
  - AR+ (>70%): ADT / Kombinierte Androgenblockade
  - HER2+ (ICH 3+ / FISH pos.): Docetaxel + Trastuzumab / T-DM1
- **Sekretorisches Karzinom**
  - NTRK-Fusion: NTRK-Inhibitor (Larotrectinib / Entrectinib)
  - RET-Fusion: RET-Inhibitor (Selpercatinib, Pralsetinib)
- **Adenoid-zystisches Karzinom**
  - Platin-basierte Chemotherapie / Angiogenese-Inhibitor
  - Studie mit NOTCH1-Inhibitoren

Zusammenfassung

- Speicheldrüsenkarzinome sind eine heterogene Gruppe von Erkrankungen (22 histologische Subtypen)
- Neue systemische Behandlungsstrategien für einige Subtypen abhängig vom molekularen Profil
  - Immunhistochemie
  - Genomische Analyse (Sequenzierung)
- Verbesserung der Prognose für einige molekular definierte Subgruppen

Vielen Dank!

Fragen?