Immuntherapien und zielgerichtete Therapien beim schlecht-differenzierten und anaplastischen Schilddrüsenkarzinom

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JAHRESTAGUNG

Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie

www.jahrestagung-haematologie-onkologie.com

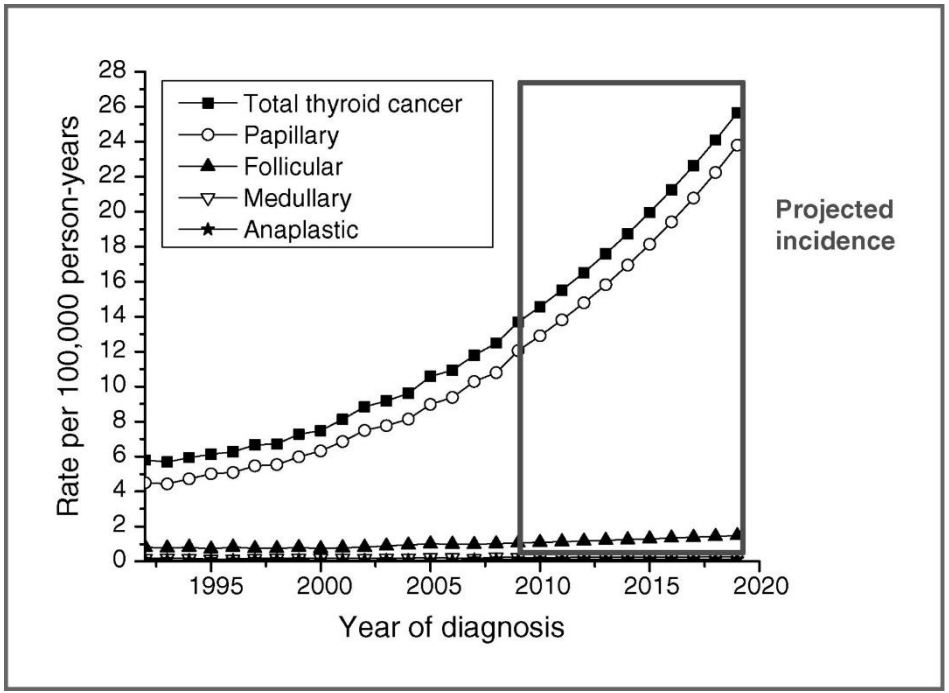
2023 13.–16. Okt. Hamburg

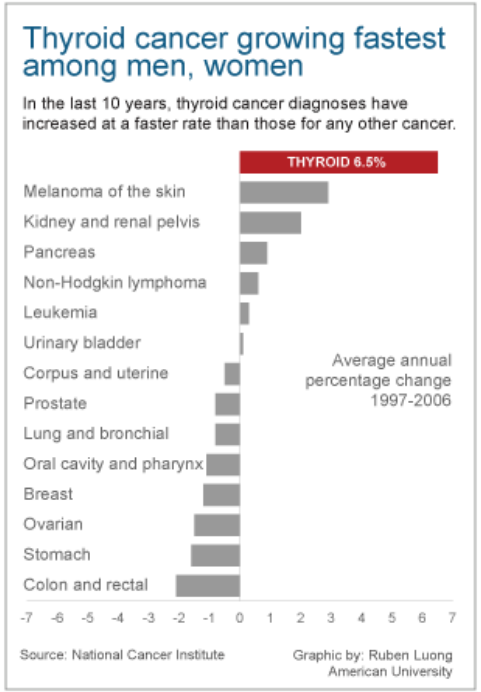
DECLARATION OF INTERESTS

Financial support by BMS

Advisory Board: Eisai, Janssen, Roche

Erhöhte Inzidenz von Schilddrüsen-Karzinomen in Europa, USA und weltweit (15/100.000)





Durone et al., 2017, Bryde et al., 2016

Schilddrüsen-Karzinom Subtypen

Type	%	age	spread	prognosis	10-year survival
Papillary	60-70	20-40	lymphatic	Excellent	74 - 93 %
Follicular	20-25	40-50	blood stream	Good	43 - 94 %
Poorly differentiated	1-3	Elderly	aggressive local, LN	poor	5-9 %
Anaplastic	1-3	>65		very poor	1-3 %
Medullary (C-cells)	10	elderly, but familial cases occur		variable, more aggressive in familial cases	65%

Molekulare Progression

Altered gene	Papillary thyroid carcinoma	Follicular thyroid carcinoma	Poorly differen-tiated thyroid carcinoma	Anaplastic thyroid carcinoma
RET/PTC	20%	0	0	0
TP53	0	0	20–30%	65–70%
BRAF	45%	0	15%	20–25%
RAS	10–15%	45%	30–35%	50–55%
β-Catenin	0	0	20–25%	65%
PAX8:PPAR	0	35%	0	0

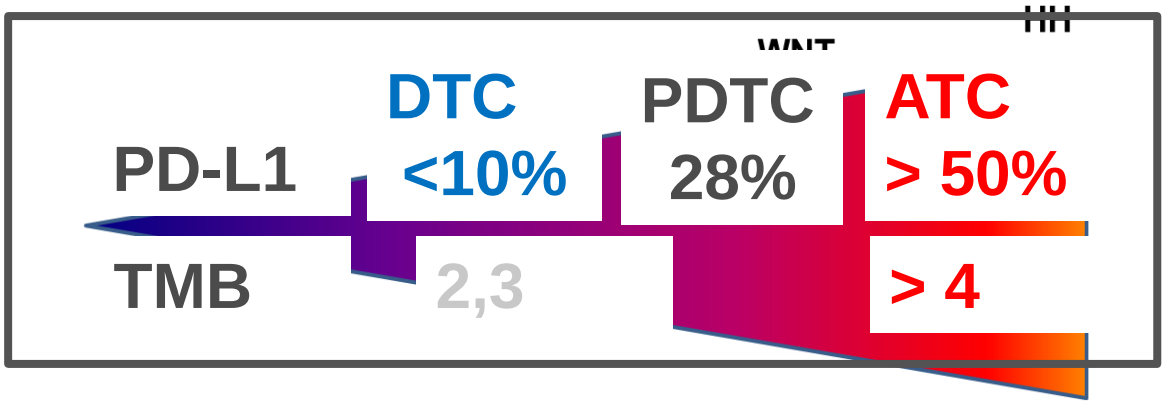
oft > 100 somatische Mutationen

Reddy et al., 2015

Eine Zunahme der Mutationslast ist assoziiert mit einer höheren PD-L1 Expression

Differentiated ⟶ **Anaplastic**

mouse models with consecutive addition of further mutations



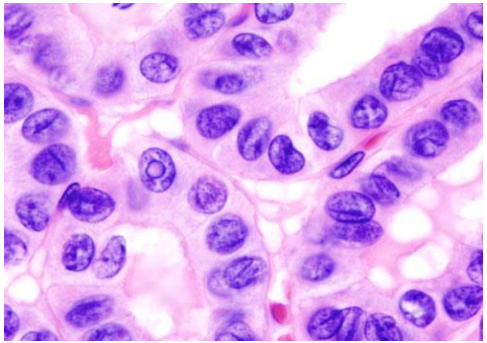
PD-L1 low ⟶ **PD-L1 high**

Biomarkers for treatment response to checkpoint inhibitors:
PD-L1 Expression and TMB (Tumor Mutation Burden)

39

Schlecht-differenzierte Schilddrüsen-Karzinome (PDTC) entstehen fast immer aus einem differenziertem SD-CA

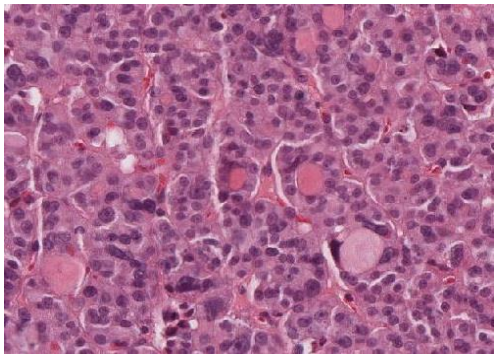
Papillary thyroid carcinoma



50% **B-RAF** mutations
10-20% **RET/**PTC-rearrangements
10% **NTRK**1/3-rearrangement

targetable with **inhibitors**

Follicular thyroid carcinoma

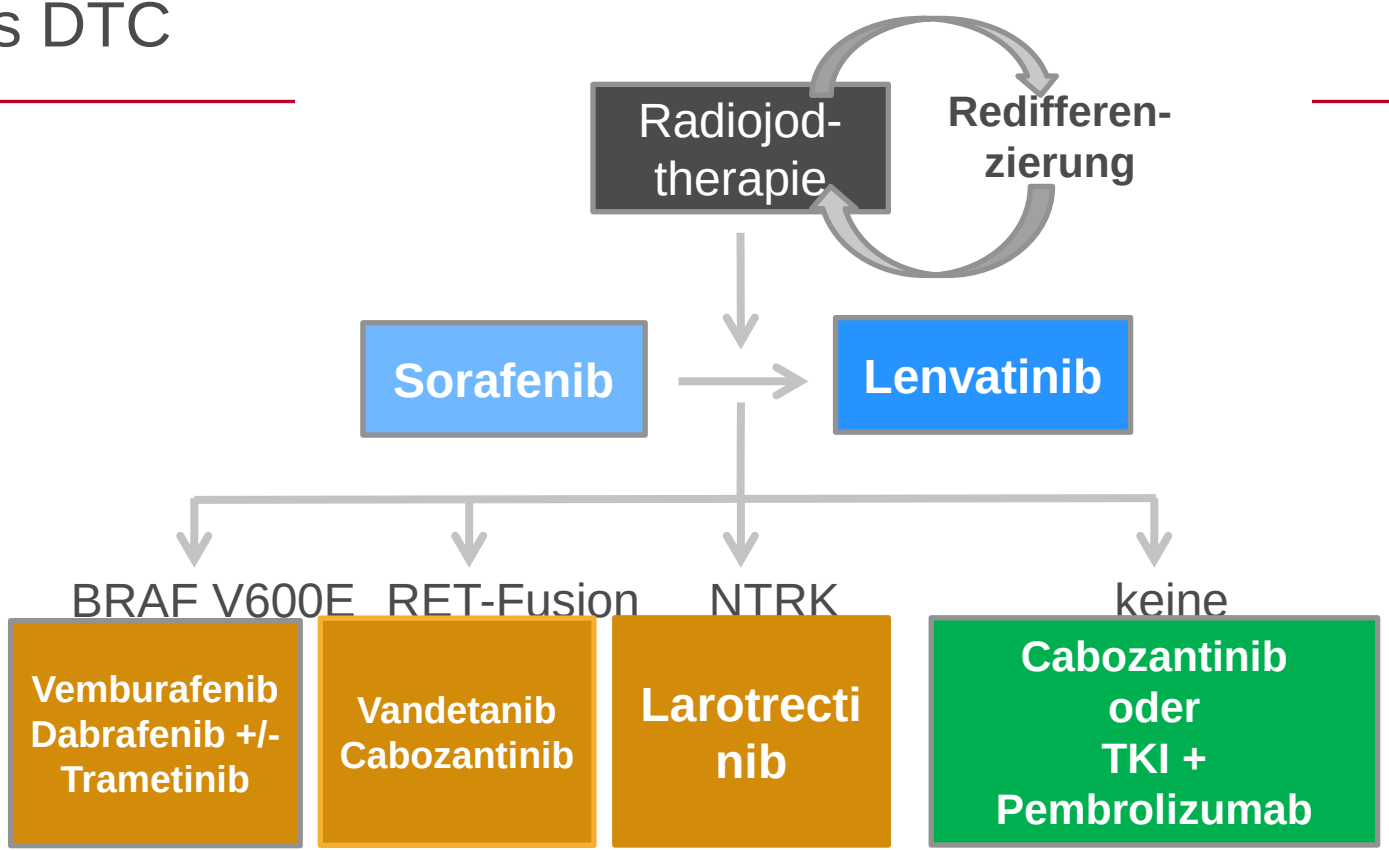


50% RAS mutations
PAX8-rearrangements
FOXO3a mutations
PIK3CA-amplifications

no targetable genetic lesions

Und tragen deren Treibermutationen als potentielle Treatment Targets

Systemtherapie des PDTC entspricht primär der eines DTC



Systemtherapie Anaplastisches Schilddrüsenkarzinom

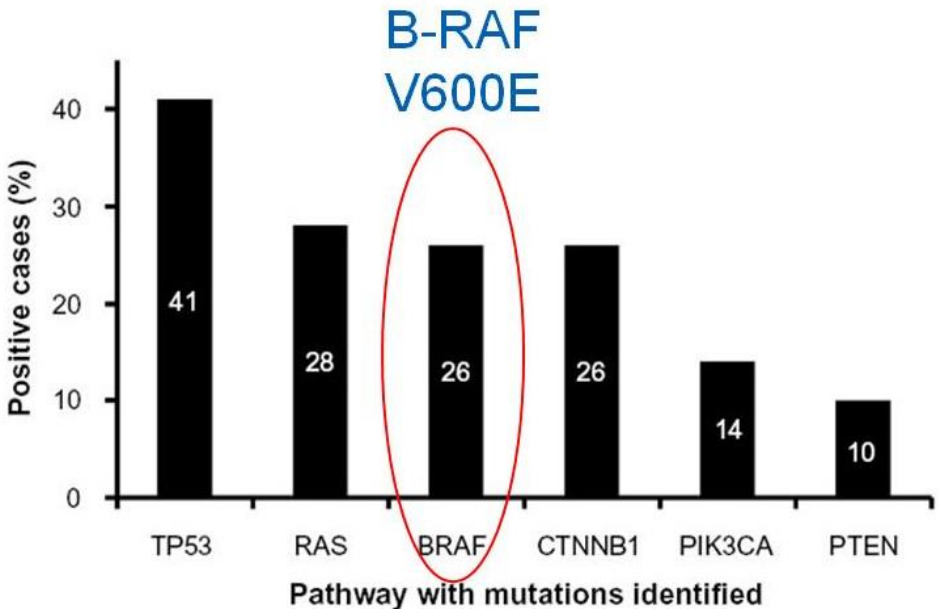
1. Chemotherapie
2. Targeted Therapies: **BRAF** Inhibitoren
3. Andere Targets: **NTRK, RET, EGFR**
4. Immun- Kinase-Inhibitor-Kombination

Therapieoption 1: Chemotherapie

Doxorubicin:	ORR	24%
	PFS	3,4 Monate
Doxorubicin/Cisplatin:	ORR	28%
	PFS	5 Monate
Carboplatin/Taxol:	ORR	27%
	PFS	4,5 Monate

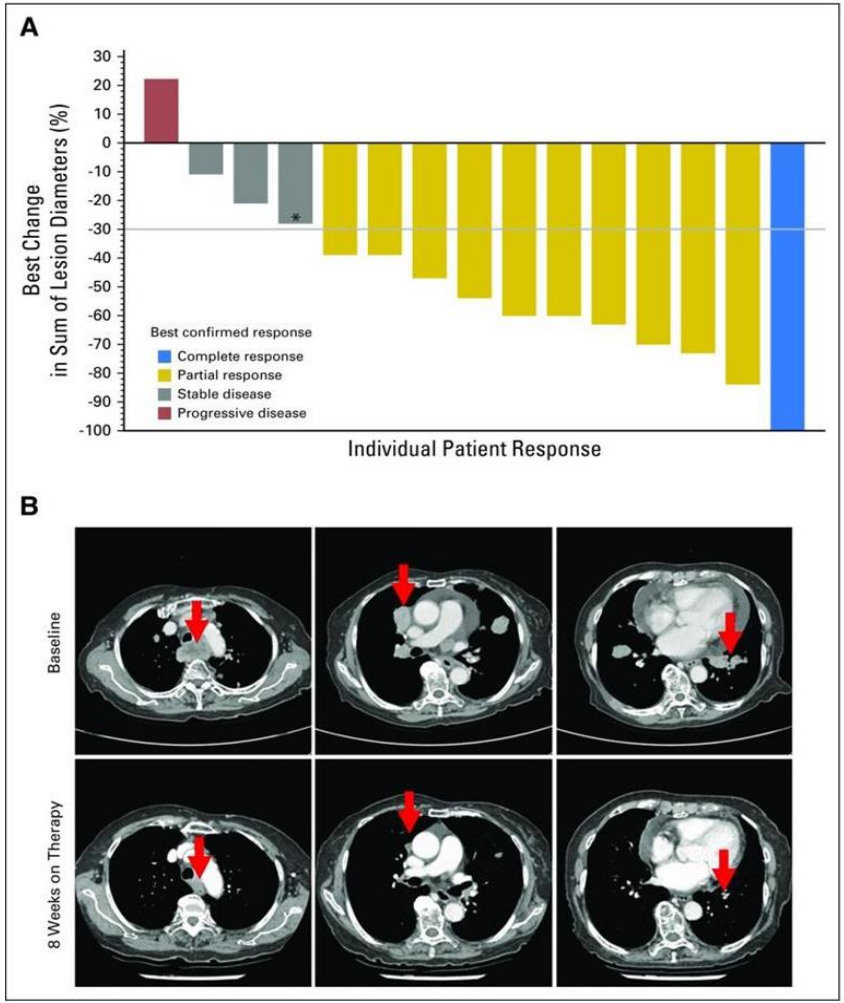
- ältere unfitte Patienten eher Doxo oder Taxol mono
- fitte Patienten Carboplatin/Taxol

Therapieoption 2: Molekulare Targets



Dabrafenib + Trametinib

n = 16 patients
Dabrafenib 150 mg 1-0-1
Trametinib 2 mg 1-0-0



Subbiah et al., 2018

Dabrafenib+Trametinib in BRAF V600E mutiertem ATC

Table 2. Best Overall Response to Therapy in Anaplastic Thyroid Cancer

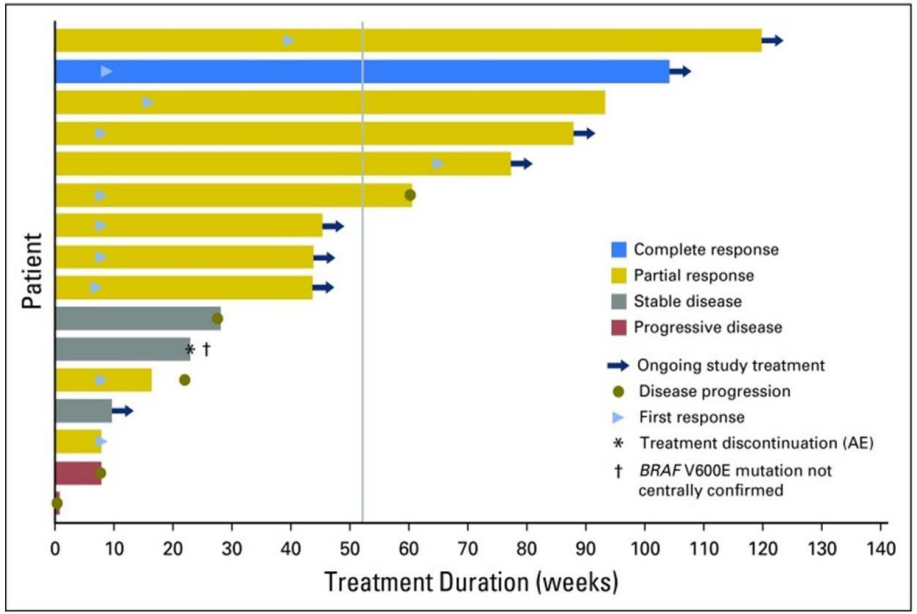
Radiology Review Type	Intent-to-Treat (n = 16)		*BRAF* V600E Centrally Confirmed Patient Population (n = 15)	
	Investigator	Independent	Investigator	Independent
Best response*				
Complete response	1 (6)	0	1 (7)	0
Partial response	10 (63)	10 (63)	10 (67)	10 (67)
Stable disease	3 (19)	3 (19)	2 (13)	2 (13)
Progressive disease	2 (13)	3 (19)	2 (13)	3 (20)
Not evaluable	0	0	0	0
Overall response rate [95% CI]†	11 (69) [41.3 to 89.0]	10 (63) [35.4 to 84.8]	11 (73) [44.9 to 92.2]	10 (67) [38.4 to 88.2]

NOTE. Data are given as No. (%) unless otherwise noted.
Abbreviation: *BRAF*, B-Raf kinase.
*Investigator and independent assessment per RECIST v1.1.[16]
†Complete response plus partial response. CIs were estimated by using the exact Clopper-Pearson method.

ORR 69% (1 CR, 10 PR)

Subbiah et al., 2018

Dabrafenib+Trametinib mit PFS 14m



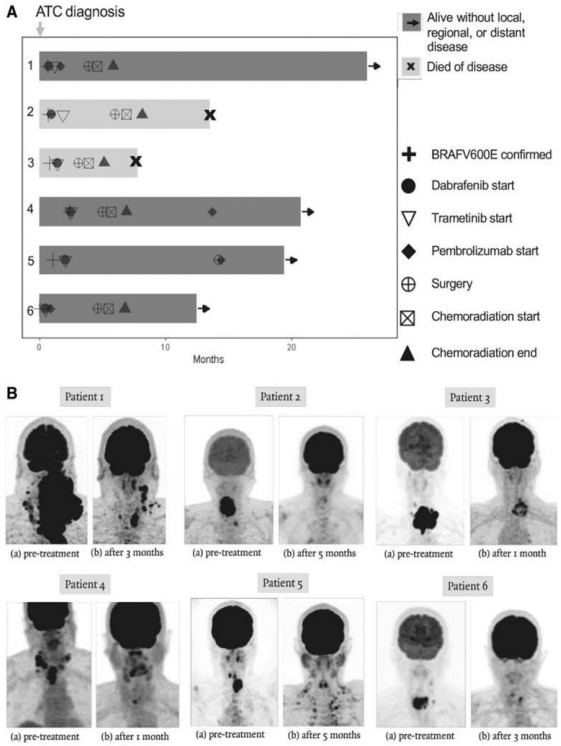
PFS 14 Monate

Subbiah et al., 2018

Neoadjuvante Ansätze mit Dabrafenib + Trametinib in BRAF-mutierten ATC Patienten

n = 6 patients with unresectable tumor

neoadjuvant treatment with D/T followed by resection



Wang et al., 2019

Weitere molekulare Targets in ATC

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1. **RET-Fusionen:** Selpercatinib, 2 Pt Libretto Trial
2. **NTRK Fusionen:** Larotrectinib/Entrectinib
3. **EGFR Mutationen:** Erlotinib, Gefitinib, …
4. **MET-Mutationen:** Crizotinib, Cabozantinib

PDTC/ATC: Entwicklungen aus dem Molekularen Tumorboard

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Tumor properties

- **highly proliferative** (constitutive kinase activation)
- **increased neoangiogenesis** (VEGF/FGFR-sig.)
- **high mutation frequency** (TMB)
- **high PD-L1 expression** (10 - 90% TPS)

Lenvatinib
(blocks proliferation and VEGFR/FGFR signaling)

+

Pembrolizumab
(immune checkpoint inhibitor)

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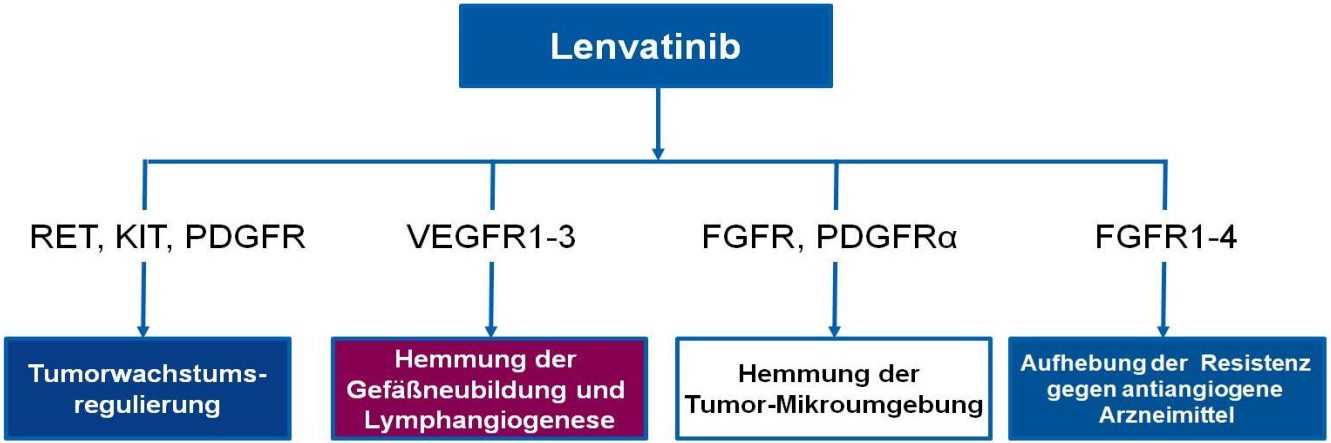
Lenvatinib: Wirkprinzip



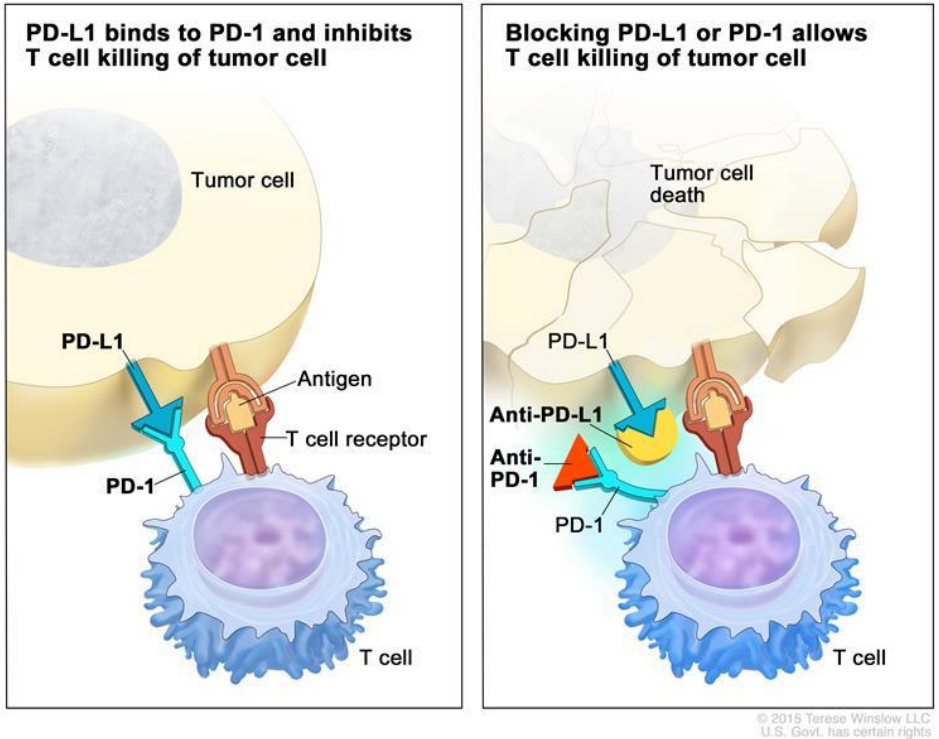
FGFR: Rezeptor des Fibroblasten-Wachstumsfaktors;
PDGFR: Rezeptor des thrombozytären Wachstumsfaktors
VEGFR: Rezeptor des vaskulären endothelialen Wachstumsfaktors
RET: Rezeptor-Tyrosinkinase "rearranged during transfection"
KIT: Stammzellfaktor-Rezeptor (SCFR, CD117)

Stjepanovic N, et al. Biologics. 2014;8:129-139.

Divergent results on lenvatinib monotherapy in ATC:

- neg. results in international trial (Wirth et al., 2021) ORR 3%
- pos. results with ORR 39 % in Japanese trial (Tahara et al., 2019)

Immun-Checkpoint-Inhibition



Biomarkers for response: PD-L1 Expression und Mutationslast

Characteristic	Spartalizumab 400 mg Every 4 Weeks (N = 42)
Central pathology review	
ATC	38 (90.5)
Other	2 (4.8)
Missing	2 (4.8)
Age, years, median (range)	62.5 (46-83)
Sex, male	23 (54.8)
ECOG PS	
0	17 (40.5)
1	25 (59.5)
Prior treatment regimens	
0	17 (40.5)
1	20 (47.6)
≥ 2	5 (11.9)
Prior radiation	
Yes	30 (71.4)
Prior thyroidectomy and/or neck dissection	
Yes	28 (66.7)
Metastatic sites at study entry	
Lung	35 (83.3)
Lymph node	20 (47.6)
Bone	5 (11.9)
Liver	3 (7.1)
BRAF V600 mutation by Cobas 4800	
Mutant	12 (28.6)
Nonmutant	26 (61.9)
Missing	4 (9.5)

Spartalizumab beim ATC

	n = 42	%
ORR	8	19 %
CR	3	7 %
PR	5	12 %
SD	5	12 %
PD	25	69 %
DCR (> 6 mo)	11	31 %

Capdevila et al., JCO 2020

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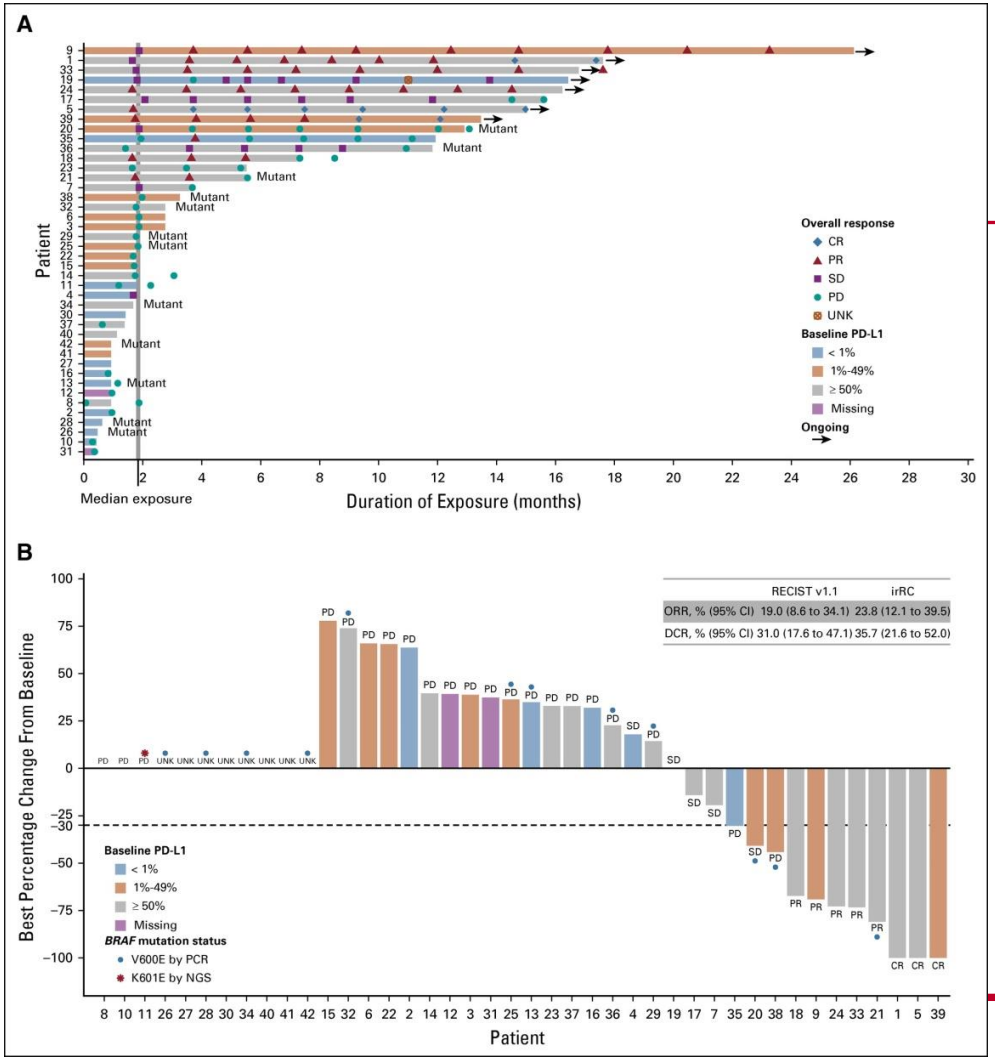
Spartalizumab beim ATC



PFS 1.7 mo

PFS rate at 1 year 17%

DCR 31%

Capdevila et al., JCO 2020

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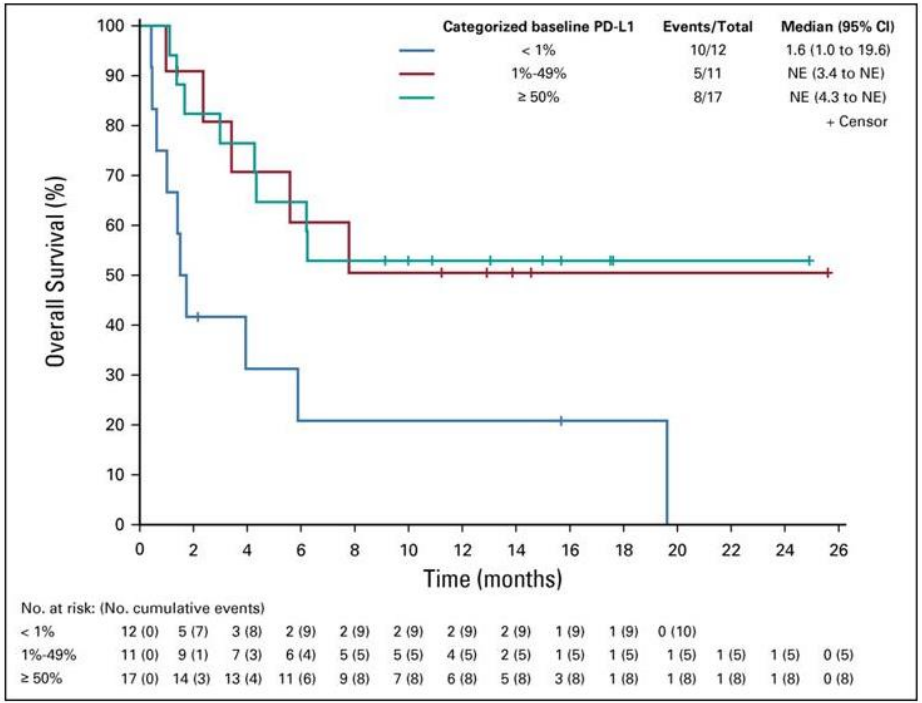
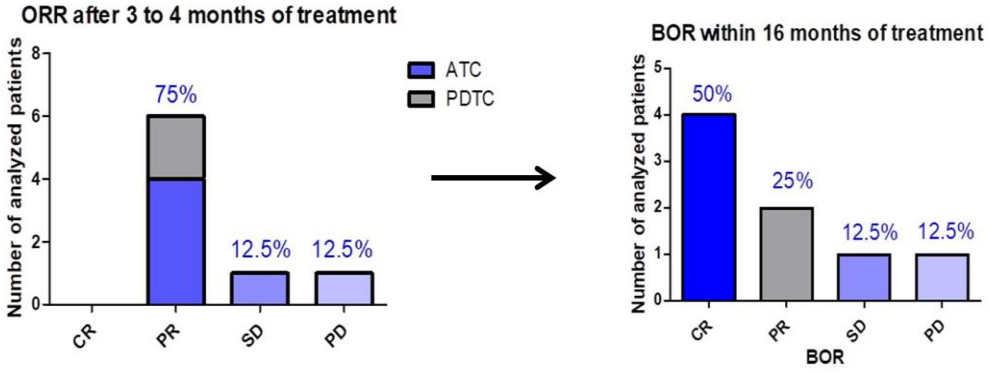
Spartalizumab: Response korreliert Mit PD-L1 Expression im ATC



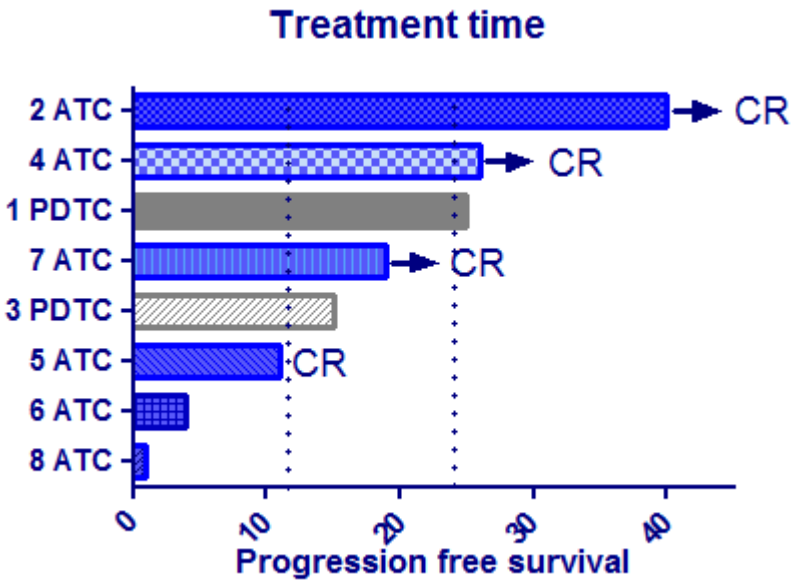
Capdevila et al., JCO 2020

Individuelle Heilversuche mit Lenvatinib und Pembrolizumab



ESMO 2018/2020
Dierks et al., Thyroid 2020

Ansprechen auf Lenvatinib und Pembrolizumab in ATC/PDTC



Gesamt: PFS 17.75 mo, OS 18.5 mo

ATCs: PFS 16.5 mo, OS 17.5 mo

PD-L1 and TMB predict treatment response

OS ATC only

Entity	BOR	PD-L1 in %	CPS	Somatic mutations	TMB (mutations/ MB)
PDTC 1	PR	50	40	106	13.79
ATC 2	CR	60	75	1447	81.87
PDTC 3	PR	10	10	79	4.08
ATC 4	CR	90	100	19	3
ATC 5	CR	80	100	29	3.3
ATC 6	SD	60	65	24	3.58
ATC 7	CR	5	7	138	5.59
ATC 8	PD	1	5	n.a.	n.a.

ESMO 2018/2020

Dierks et al., Thyroid 2020

Erste Daten zu Lenvatinib und Pembrolizumab in ATC/PDTC zeigen gutes Ansprechen

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- PD-1 inhibitors are effective in ATC/PDTC with PD-L1 expression
- PD-1 inhibitors can be used in PD-L1-pos. PDTC
- The Lenvatinib/Pembrolizumab combination is effective in the majority of ATCs, but has more side effects than Checkpoint-inhibition alone

ATC	Spartalizumab ATC	Lenvatinib	Lenvatinib + Pembrolizumab
ORR	26 %	16-40 %	50 %
SD	5 %	40 %	50 %
PD	69 %	30-60 %	0 %
PFS	1,7 mo	2,5 - 6 mo	> 10 mo

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ATLEP trial: Phase II clinical trial with Lenvatinib/Pembrolizumab in patients with ATC/PDTC

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- ATC a has very poor prognosis

- Multimodal therapy in ATC extends survival to 4-5 months

- Chemotherapy is effective in 10-20% of the pts

- 70% of ATC/PDTC pts have no targetable mutation/fusion

- Previous pilot study showed response to Lenvatinib/Pembrolizumab in 75% of PD-L1+ pts. (Dierks et al., Thyroid 2021)

ATLEP: Phase II monocentric trial in Freiburg (and Halle)

Patients with ATC/PDTC (n=35 evaluable pts)

- ≥18 Jahre
- Blood pressure ≤160/90 mmHg
- no previous therapy with Lenvatinib > 10 days or Immun-Checkpoint-Inhibitor

→

Lenvatinib + Pembrolizumab
21-day cycles

Dose level	Lenvatinib	Pembroli-zumab
0	20 mg	200 mg abs. all 21 days
-1	14 mg	
-2	10 mg	

Additional scientific program: PD1/PD-L1, WES

→

Primary Endpoint
- ORR at 3 months

Secondary Endpoint
- PFS
- DCR (ORR + SD)
- BOR
- OS
- Safety

Treatment until IRR-verified disease progression by iRECIST

Cooperation Centers: Diakoniekrankenhaus Stuttgart, LMU München, Würzburg, Klinikum Schwarzwald-Baar, Mainz, Münster, Magdeburg, Göttingen, Essen, Lübeck

=> included in the trial:35/35 patients

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Patient characteristics

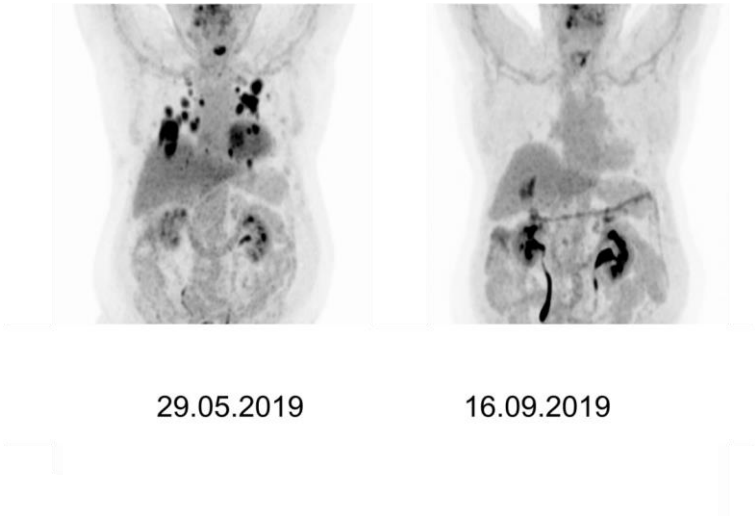
Median age at treatment start, years (range)	**64**	**(39 - 82)**
Gender, n (%)		
Men	**21**	**(60 %)**
Women	**14**	**(40 %)**
Performance status, n (%)		
ECOG 0	**6**	**(17.1 %)**
ECOG 1	**23**	**(65.7 %)**
ECOG 2	**6**	**(17.1 %)**
Pathological diagnosis, n (%)		
ATC	**27**	**(77.1 %)**
PDTC	**8**	**(22.9 %)**
Stage at treatment start, n (%)		
IVB (local relapse)	**1**	**(2.9 %)**
IVC (metastasized)	**34**	**(97.1 %)**
Previous therapy, n (%)		
Surgery	**34**	**(97.1 %)**
Cervical radiation therapy	**28**	**(80 %)**
Chemotherapy	**28**	**(80 %)**
Radioiodine therapy	**7**	**(20.6 %)***

Patients with BRAF mutations excluded!

ATLEP trial: primary endpoint 3 months ORR

Response after 3 months of treatment	Percentage	Patients
ORR (3 mo)	**34.3 %**	12/35
CR (3 mo)	0 %	0/35
PR (3 mo)	34.3 %	12/35
SD (3 mo)	60 %	21/35
PD (3 mo)	5.6 %	2/35

3 months

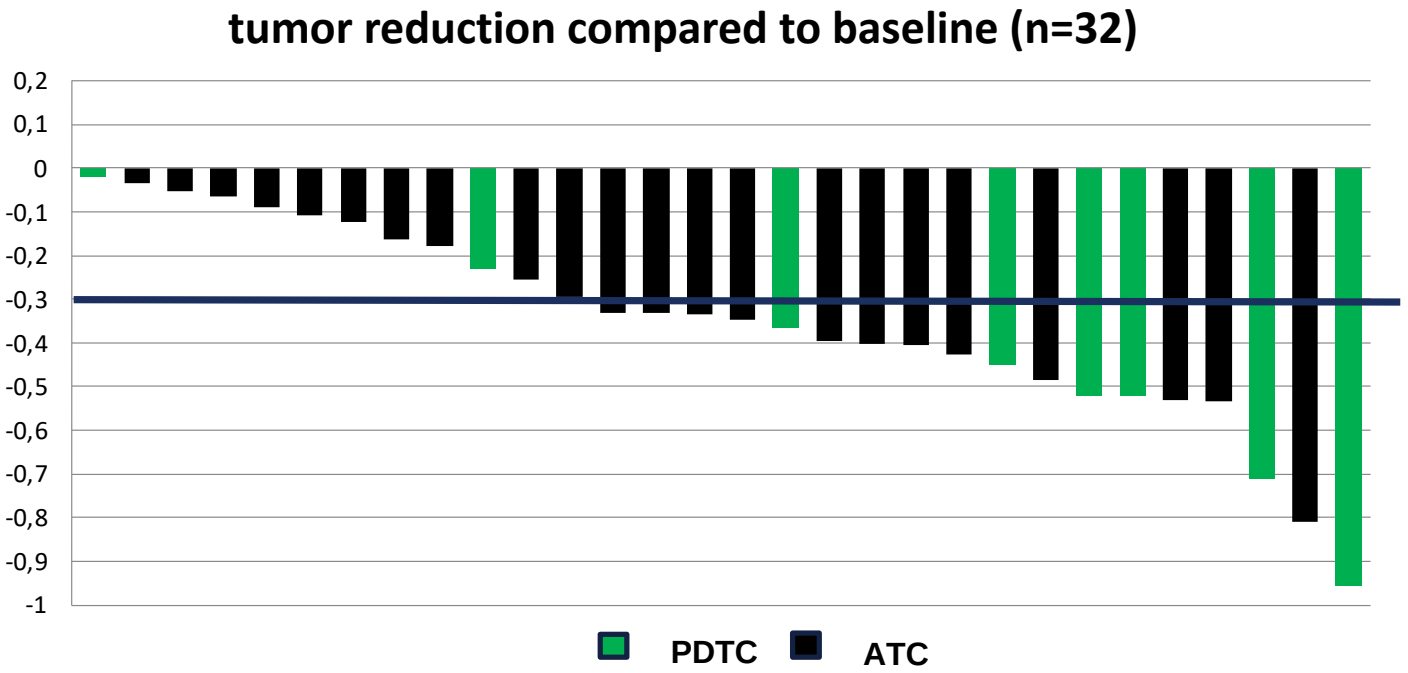


ATLEP trial: BOR for Len/Pem in ATC and PDTC

BOR within 2 years	ATC %	ATC pts
CR	0%	0/27
PR	51.9 %	14/27
SD	48.1 %	13/27
PD	0 %	0/27
ORR	**51.9%**	14/27
CBR	**100%**	27/27

BOR within 2 years	PDTC %	PDTC pts
CR	0%	0/8
PR	75 %	6/8
SD	25 %	2/8
PD	0 %	0/8
ORR	**75 %**	6/8
CBR	**100%**	8/8

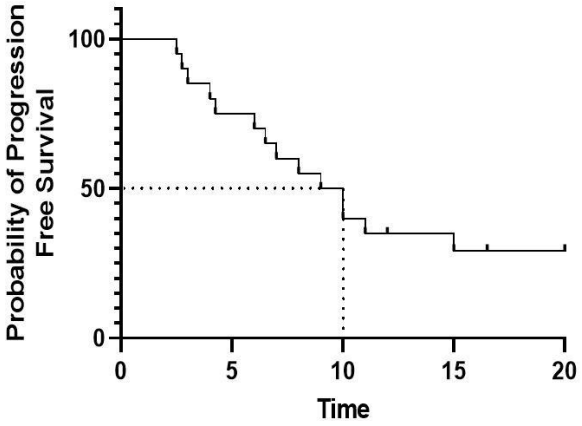
ATLEP trial: Reduction in Tumor Size



ATLEP trial: PFS and OS in ATC pts

PFS

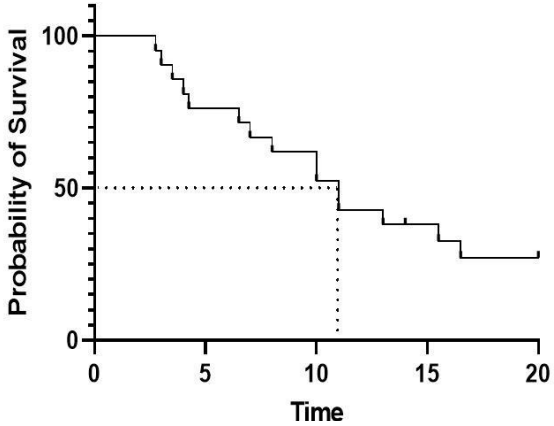
PFS proportions: ATC pts



Median PFS: 10 mo
PFS 12 mo : 41.2 %

OS

Survival proportions: ATC pts



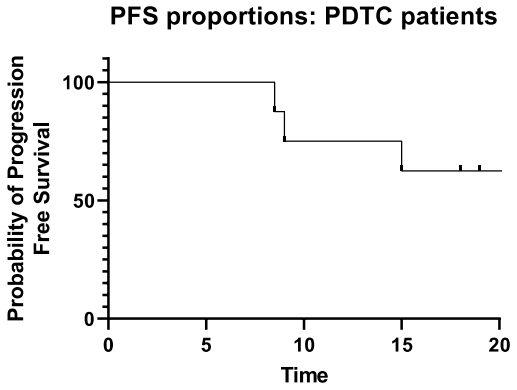
Median OS: 11 mo
OS 12 mo: 44 %

25% of the patients have remissions longer than 20 months

ATLEP trial: PFS and OS in PDTC pts

PFS

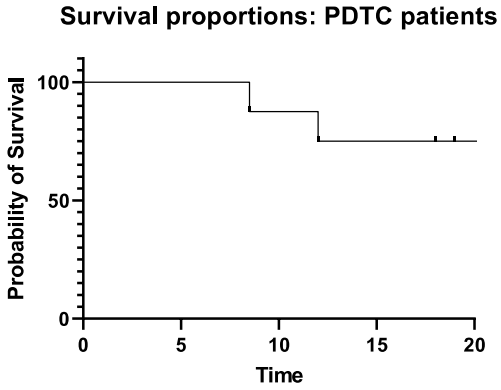
PFS proportions: PDTC pts



Median PFS > 20 mo
PFS 12 mo : 75 %

OS

Survival proportions: PDTC pts



Median OS: not reached
OS 12 mo: 75 %

ATLEP trial: Adverse events

CTCAE °II-IV most frequent hypertension (71.4 %), mucositis (74.2 %), hand-foot-syndrom (45.7 %)

AE	°III /IVAE
Fistula development	4 (11 %)
Arterial Hemorrhage	4 (11 %)
Sepsis	3 (8.3 %)
Pneumonia	1 (5.6 %)
Aspergillus pneumonia	4 (11 %)
Lung embolia	2 (5.6 %)
other thrombosis	3 (8.3 %)
Autoimmune hepatitis	2 (5.6 %)
Diarrhea	3 (8.3 %)
PRES	1 (2.8 %)

Prophylactic treatments:

Ampho-moronal 3 x daily
Cotrim 3 x weekly
Aciclovir 200 mg daily

ATLEP trial: Conclusion

1. **The Lenvatinib/Pembrolizumab combination is effective in ATC and PDTC pts.**
2. The **primary endpoint** of the trial was reached (ORR at 3 months > 30%).
3. **Len/Pem improves ORR** (52 %), **CBR** (100%), median **PFS** (10 mo) and **OS (**11 mo) in ATC compared to historic controls, **and 25% have long-term responses over 2 years.**
4. ATC-specific **serious adverse events:** aspergillus pneumonia, fistulas and bleeding complications, but also general side effects of immunotherapy.
5. **Biomarkers:** Current data shows no correlation of PD-L1 status with OS and PFS, subanalysis and RNAseq/WES is onging.

Thanks to our patients and their relatives, and to all involved scientists and phycisians

Main collaboration centers

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