AT THE CUTTING EDGE: IL CARCINOMA ANAPLASTICO DELLA TIROIDE

10.20 INQUADRAMENTO CLINICO, DIAGNOSTICO Prof.ssa Laura Fugazzola

10.40 NUOVE TERAPIE E NUOVE SPERANZE DI SOPRAVVIVENZA Prof.ssa Rossella Elisei

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ATC IS A RARE TUMOR

Mean Incidence in Europe:

- **<0.2/100.000/year**

- **Stable over the years**

About 80 cases per year in Italy

	Total number of cases	Age-standardised incidence rates per 100 000 person-years					
		All thyroid cancer types combined	Papillary	Follicular	Medullary	Anaplastic	Other or unknown
Europe							
Northern							
Denmark	823	7·5	5·3	1·41	0·31	0·19	0·32
Ireland	774	9·1	7·1	1·34	0·13	0·18	0·35
Norway	974	10·3	8·6	1·08	0·36	0·11	0·19
UK	8684	7·4	5·3	1·45	0·17	0·10	0·41
Western							
Austria	3807	19·4	16·2	1·84	0·57	0·11	0·68
France	3393	21·8	19·6	1·44	0·44	0·13	0·14
Germany	595	9·9	7·6	1·16	0·37	0·07	0·71
Netherlands	1906	5·6	4·3	0·81	0·24	0·15	0·15
Switzerland	880	16·8	14·0	2·23	0·29	0·11	0·18
Southern							
Croatia	2068	22·3	18·6	1·56	0·56	0·08	1·52
Italy	4029	36·7	32·9	1·84	0·82	0·13	1·03
Slovenia	559	12·9	11·0	1·49	0·29	0·10	0·01
Spain	2597	16·2	13·8	1·77	0·37	0·12	0·16
Eastern							
Lithuania	1556	21·3	18·7	1·56	0·65	0·14	0·28
Bulgaria	1221	7·8	6·7	0·66	0·17	0·04	0·27

Adalberto Miranda-Filho et al. , Lancet E&D, 2021; Lin et al., Am J Transl Res, 2019

Is the prognosis changed over the years?

ANAPLASTIC GIANT-CELL CARCINOMA OF THE THYROID

A Study of Treatment and Prognosis

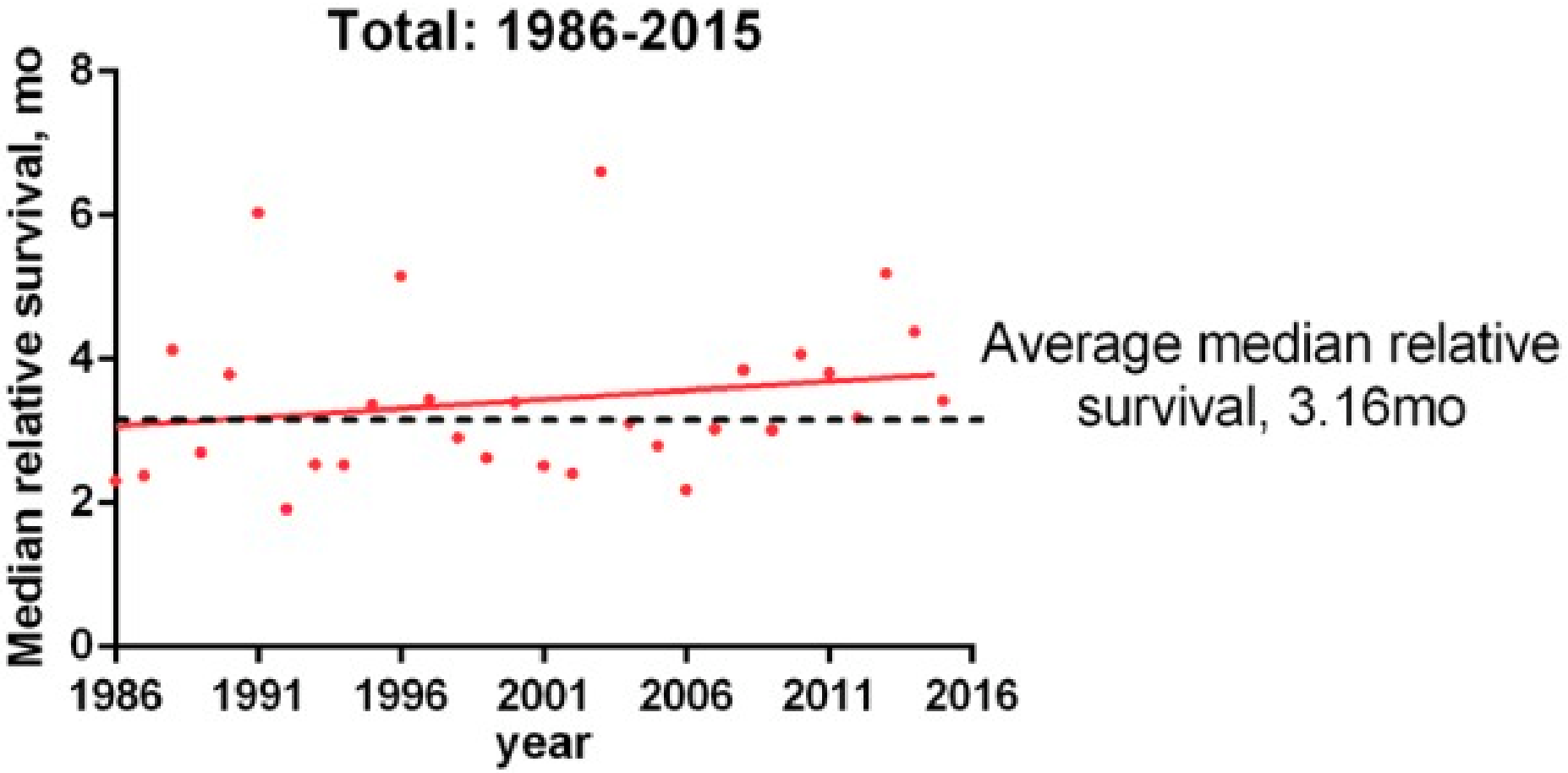
B. JEREB, MD,* J. STJERNSWÄRD, MD,† AND T. LÖWHAGEN, MD‡

In 79 cases of histologically verified anaplastic giant-cell carcinoma, symptoms, treatment, and prognosis were documented. Seventy-eight patients are dead, the mean survival time being 2.5 months. One patient is cured. It was concluded that surgery and/or radiotherapy alone are not sufficient. The results from an additional 8 patients also treated with methotexate indicate a positive therapeutic effect, the mean survival time being 9.4 months. Disappearance of recurrent tumor or pulmonary metastases was noted in 2 patients.

Cancer 35:1293–1295, 1975.

"Fifty percent of the patients died within 3 months and 90% within 6 months of the admission"

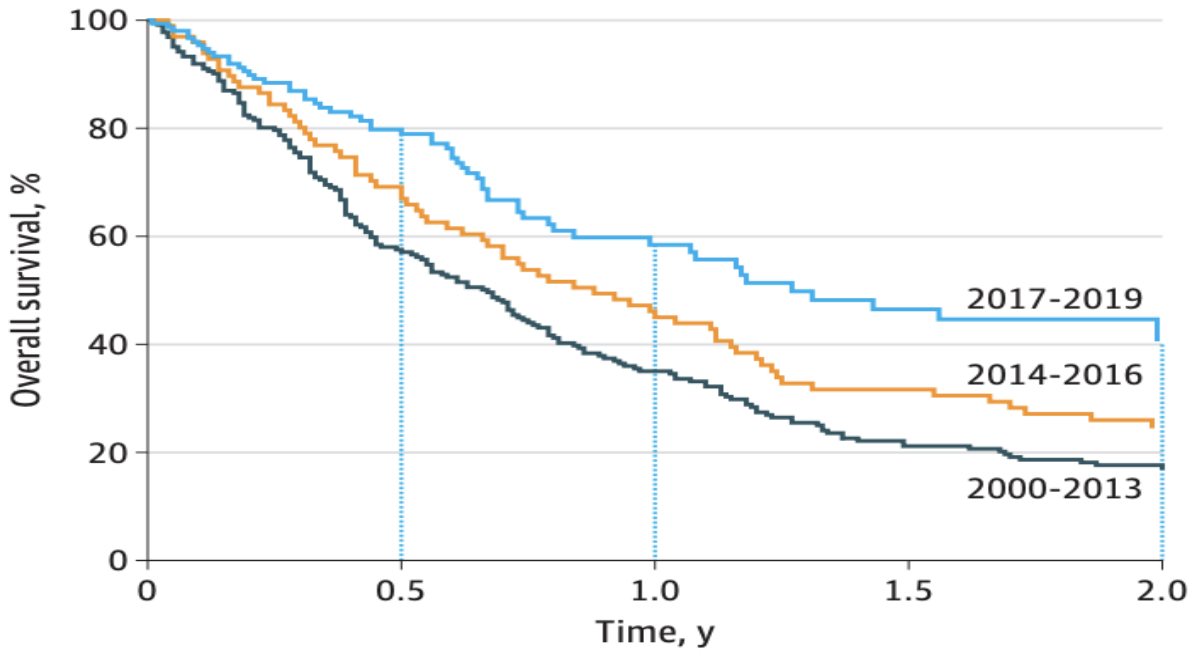
...(1567 patients from SEER database)



Lin et al., Am J Transl Res, 2019

A slightly difference in survival over the year in patients followed in one referral centre

Figure 2. Two-Year Overall Survival (OS) of Patients With Anaplastic Thyroid Carcinoma (ATC) According to Year of Presentation



No. at risk					
2000-2013	225	124	74	44	35
2014-2016	100	63	42	28	21
2017-2019	152	96	43	26	11

For years 2000-2013, the median OS was 0.67 years; for 2014-2016, median OS, 0.88 years; and for 2017-2019, median OS, 1.31 years. The adjusted hazard ratio was 0.77 when comparing the 2000-2013 group with the 2014-2016 group, and 0.50 when comparing the 2000-2013 group with the 2017-2019 group.

Maniakas et al., JAMA Oncol, 2020

What has been changed over the years?

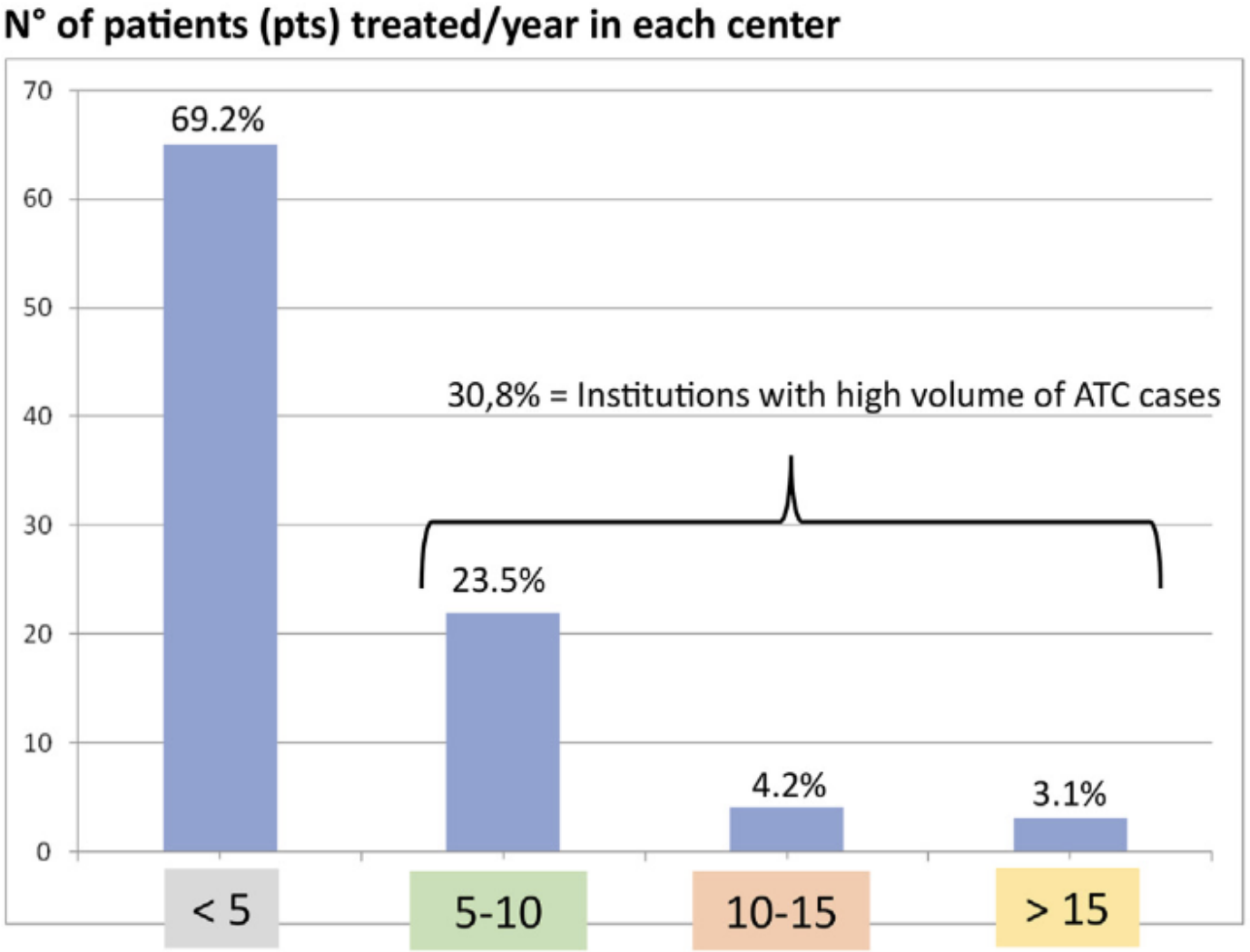
Table 1. Baseline Patient Characteristics

Characteristic	No. (%) All patients (N = 479)	2000-2013 (n = 227)	2014-2016 (n = 100)	2017-2019 (n = 152)	*P* value
Age at diagnosis, median (range), y	65.0 (21.1-92.6)	64.7 (21.1-92.6)	65.7 (32.8-88.6)	65.0 (39.3-92.5)	.74
Male	246 (51)	108 (48)	54 (54)	84 (55)	.29
AACCI					.79
Mean (SD)	2.6 (1.6)	2.7 (1.7)	2.6 (1.5)	2.6 (1.5)	
Median (range)	2 (0-10)	2 (0-10)	2 (0-8)	2 (0-9)	
AACCI Score					.70
0-2	247 (52)	115 (51)	55 (55)	77 (51)	
3-4	177 (37)	83 (37)	33 (33)	61 (40)	
≥5	55 (11)	29 (13)	12 (12)	14 (9)	
Stage					.28
IVA	52 (11)	31 (14)	6 (6)	15 (10)	
IVB	172 (36)	76 (33)	41 (41)	55 (36)	
IVC	255 (53)	120 (53)	53 (53)	82 (54)	
BRAF V600E IHC/NGS					<.001
Tested	268 (56)	38 (17)	82 (82)	148 (97)	
Not tested	211 (44)	189 (83)	18 (18)	4 (3)	
BRAF V600E IHC/NGS tested					.57
Positive/tested	101/268 (38)	12/38 (32)	34/82 (41)	55/148 (37)	
Negative-WT/tested	167/268 (62)	26/38 (68)	48/82 (59)	93/148 (63)	
Targeted therapy	156 (33)	21 (9)	43 (43)	92 (61)	<.001
Immunotherapy	92 (19)	3 (1)	18 (18)	71 (47)	<.001
Cytotoxic chemotherapy	256 (53)	121 (53)	57 (57)	78 (51)	.78
Radiation-locoregional	322 (67)	148 (65)	71 (71)	103 (68)	.47
Radiation-other sites	60 (13)	21 (9)	15 (15)	24 (16)	.09
Clinical trial	102 (21)	21 (9)	30 (30)	51 (34)	<.001
Surgery post neoadjuvant	23 (5)	0 (0)	0 (0)	23 (15)	<.001

Abbreviations: AACCI, age-adjusted Charlson comorbidity index; IHC, immunohistochemistry; NGS, next-generation sequencing; WT, wild type (nonvariant).

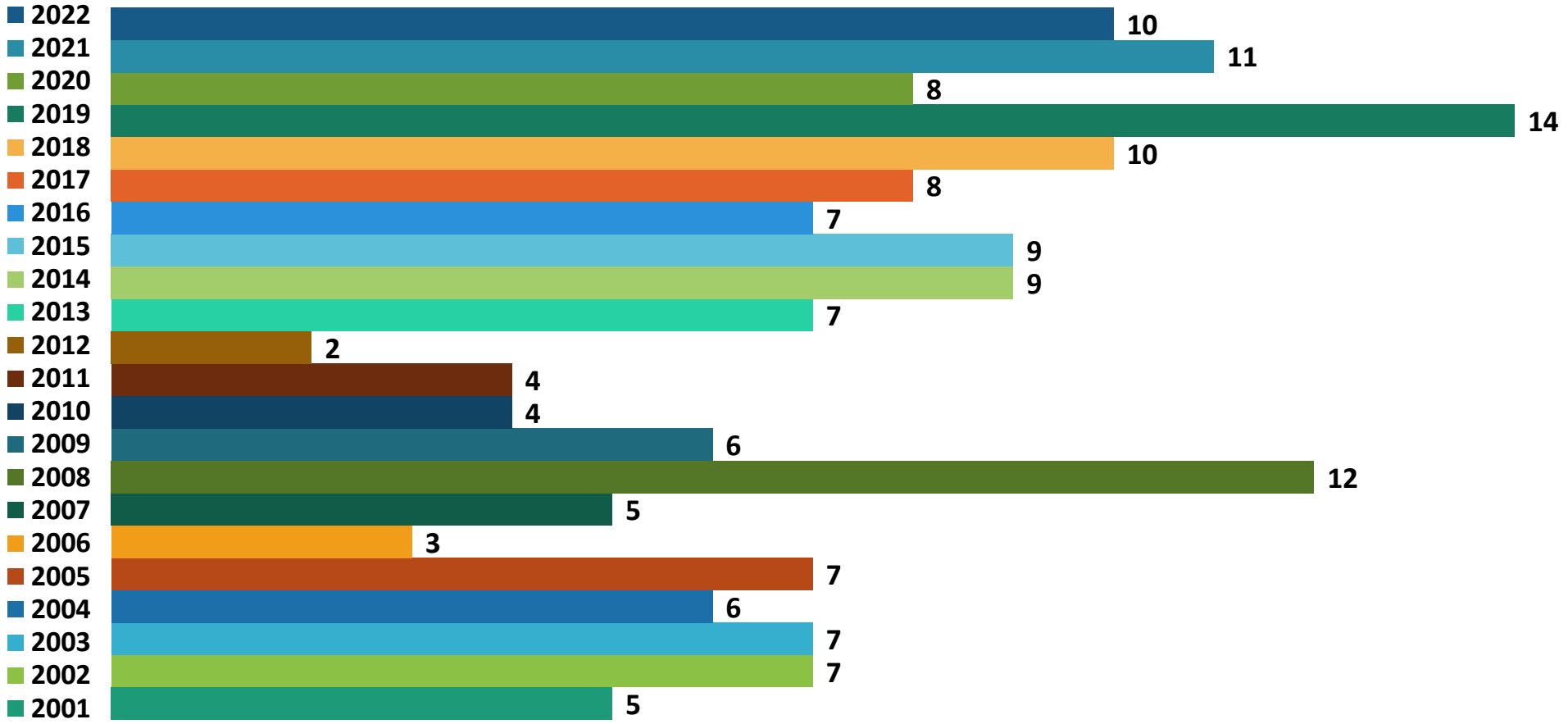
Maniakas et al., JAMA Oncol, 2020

ATC should be treated in referral centres

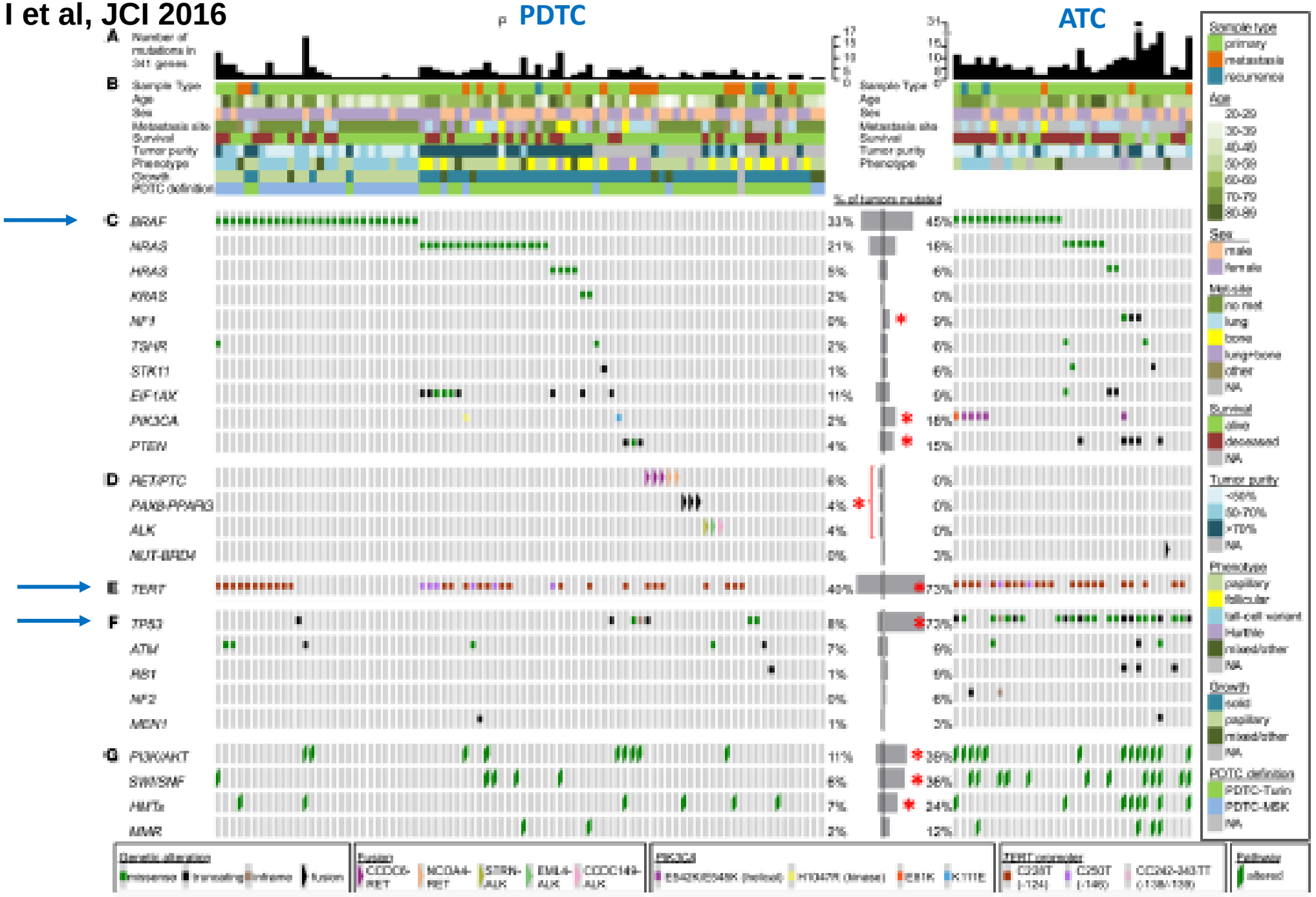


Locati LD et al., EJC, 2023

Pisa's series: Cases per year (2001-2022)
median n/year: 7



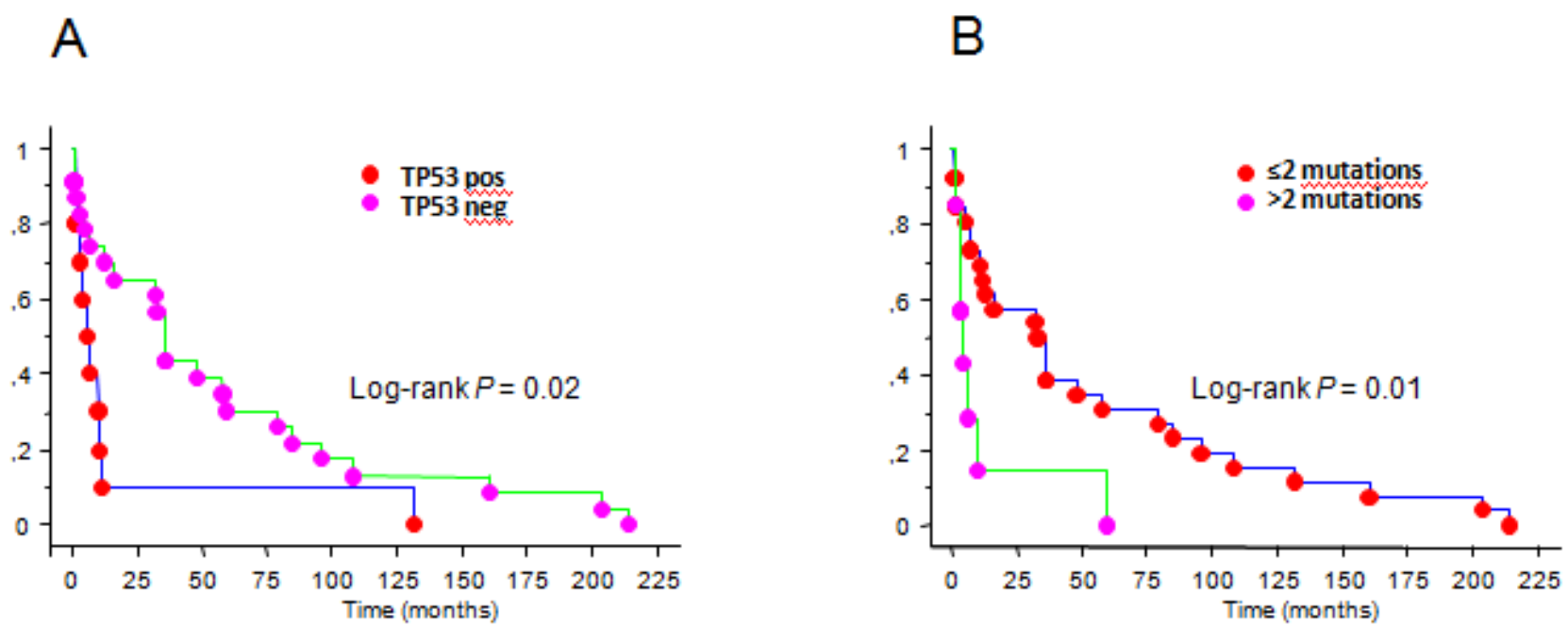
Landa I et al, JCI 2016



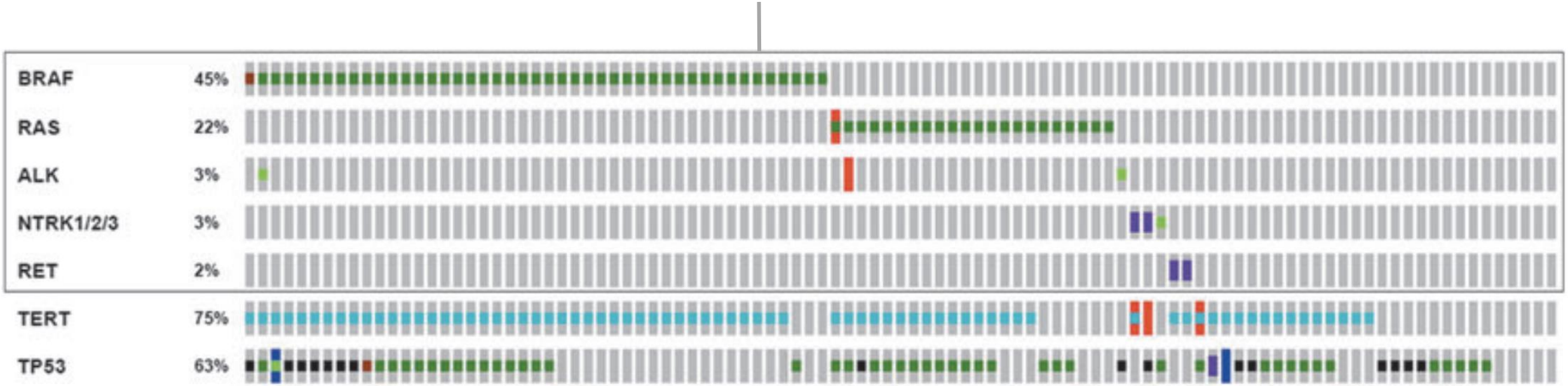
Oncol Lett. 2018 Jun; 15(6): 9174–9182.
Published online 2018 Apr 12. doi: [10.3892/ol.2018.8470]
PMCID: PMC5958691
PMID: 29805648

Clinical, pathological and genetic features of anaplastic and poorly differentiated thyroid cancer: A single institute experience

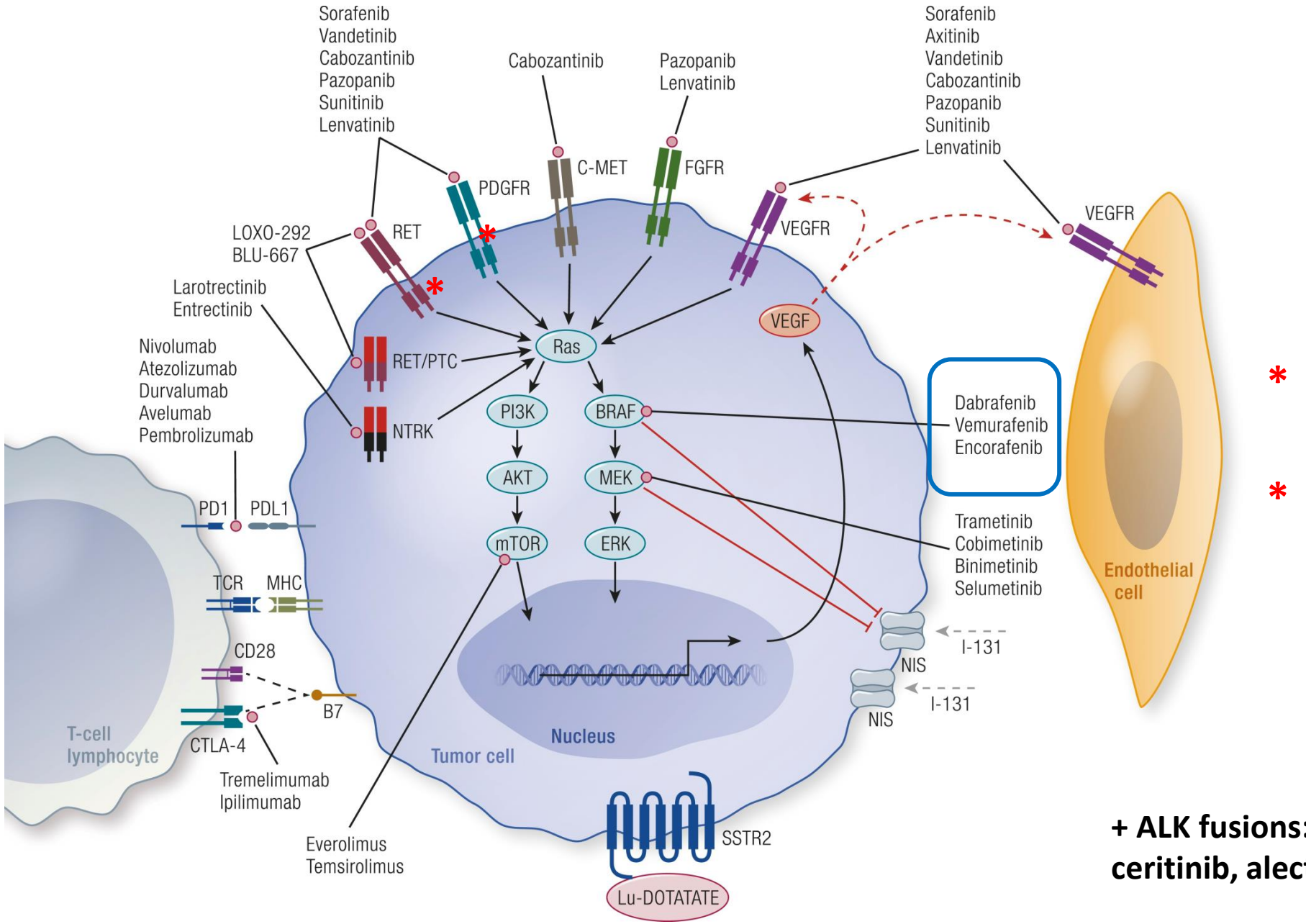
Cristina Romei,[1] Alessia Tacito,[1] Eleonora Molinaro,[1] Paolo Piaggi,[1] Virginia Cappagli,[1] Letizia Pieruzzi,[1] Antonio Matrone,[1] David Viola,[1] Laura Agate,[1] Liborio Torregrossa,[2] Clara Ugolini,[2] Fulvio Basolo,[2] Luigi De Napoli,[2] Michele Curcio,[3] Raffaele Ciampi,[1] Gabriele Materazzi,[2] Paolo Vitti,[1] and Rossella Elisei[1]



DRUGGABLE GENE ALTERATIONS (126 PATIENTS)

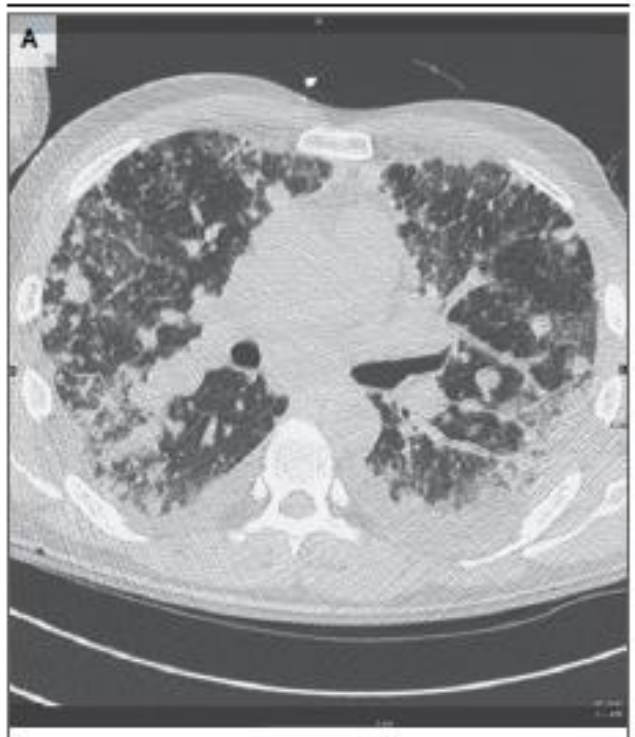


Xu et al., Thyroid, 2022



+ ALK fusions: crizotinib, ceritinib, alectinib

Cabanillas et al., Endocrine Reviews, 2019



BRAF V600E Inhibition in Anaplastic Thyroid Cancer

Michael H. Rosove, M.D.
Parvin F. Peddi, M.D.
John A. Glaspy, M.D.
David Geffen School of Medicine at University of California, Los Angeles

N ENGL J MED 368;7 NEJM.ORG FEBRUARY 14, 2013

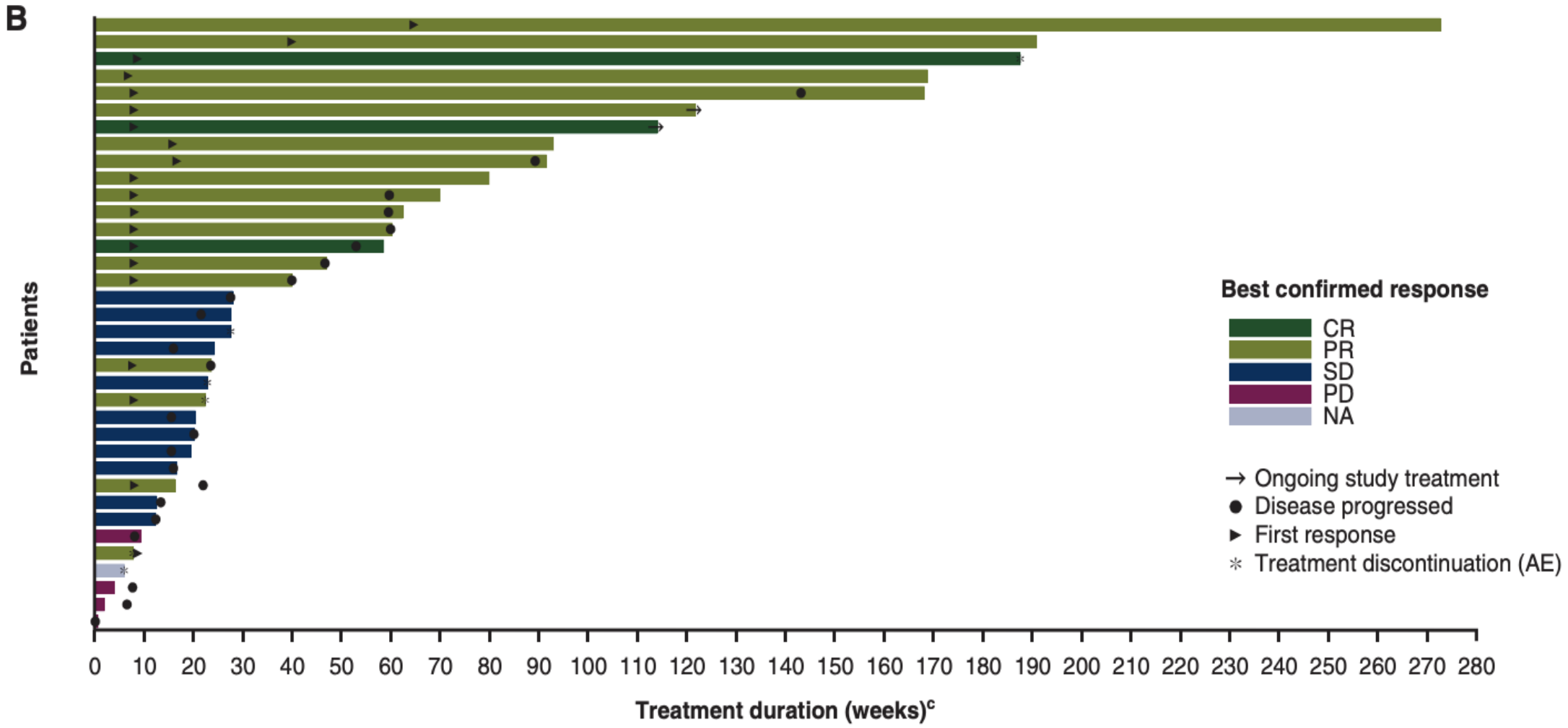
Figure 1. Chest Imaging of the Patient.

Computed tomographic images of the chest on day 10, at the initiation of vemurafenib (Panel A), and on day 38, after 28 days of treatment (Panel B), are shown.

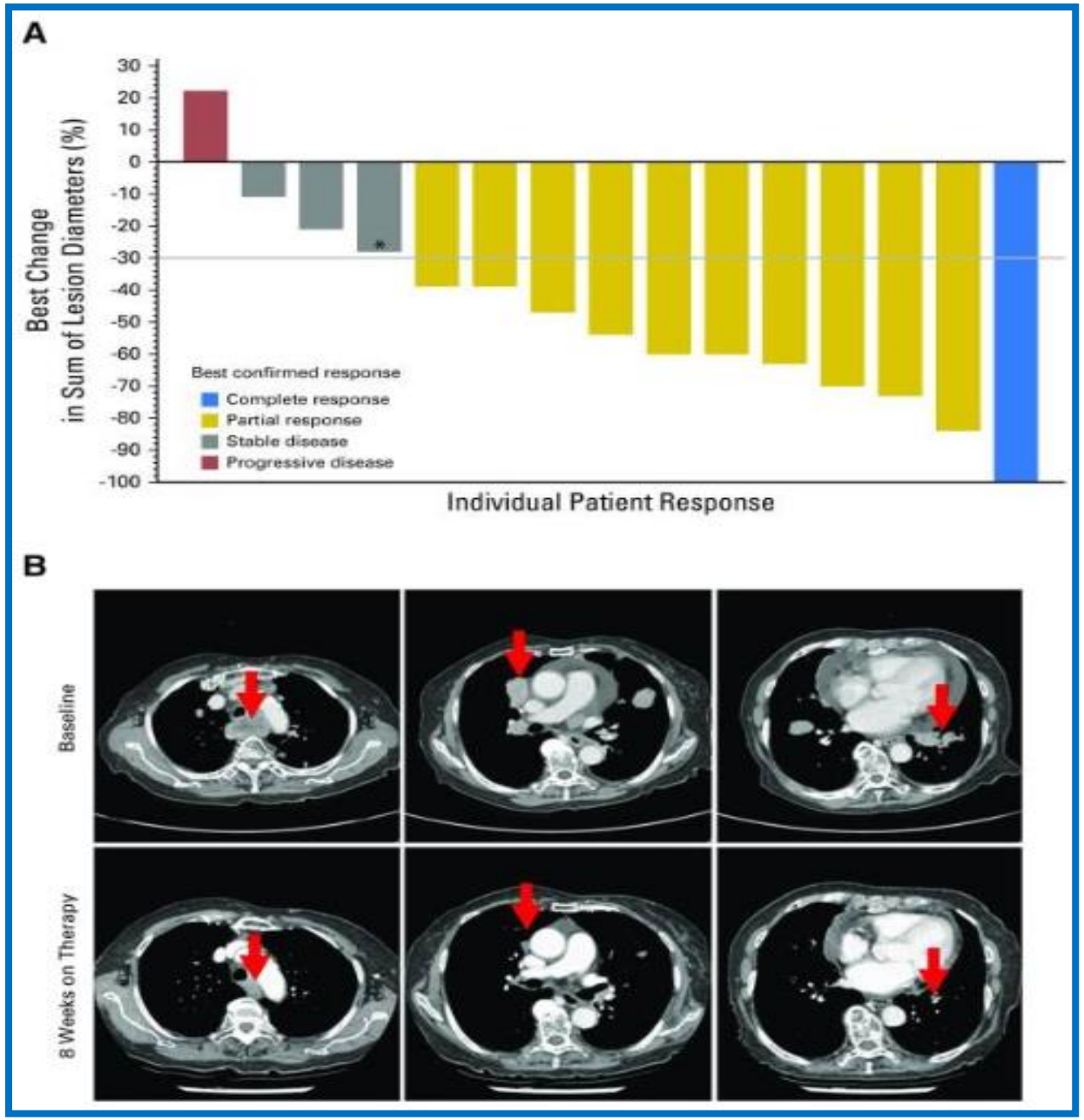
Dabrafenib plus trametinib: phase II ROAR basket study

Subbiah et al., Ann. Of Oncology, 2022

36 PATIENTS WITH ATC



Dabrafenib plus trametinib: phase II ROAR basket study

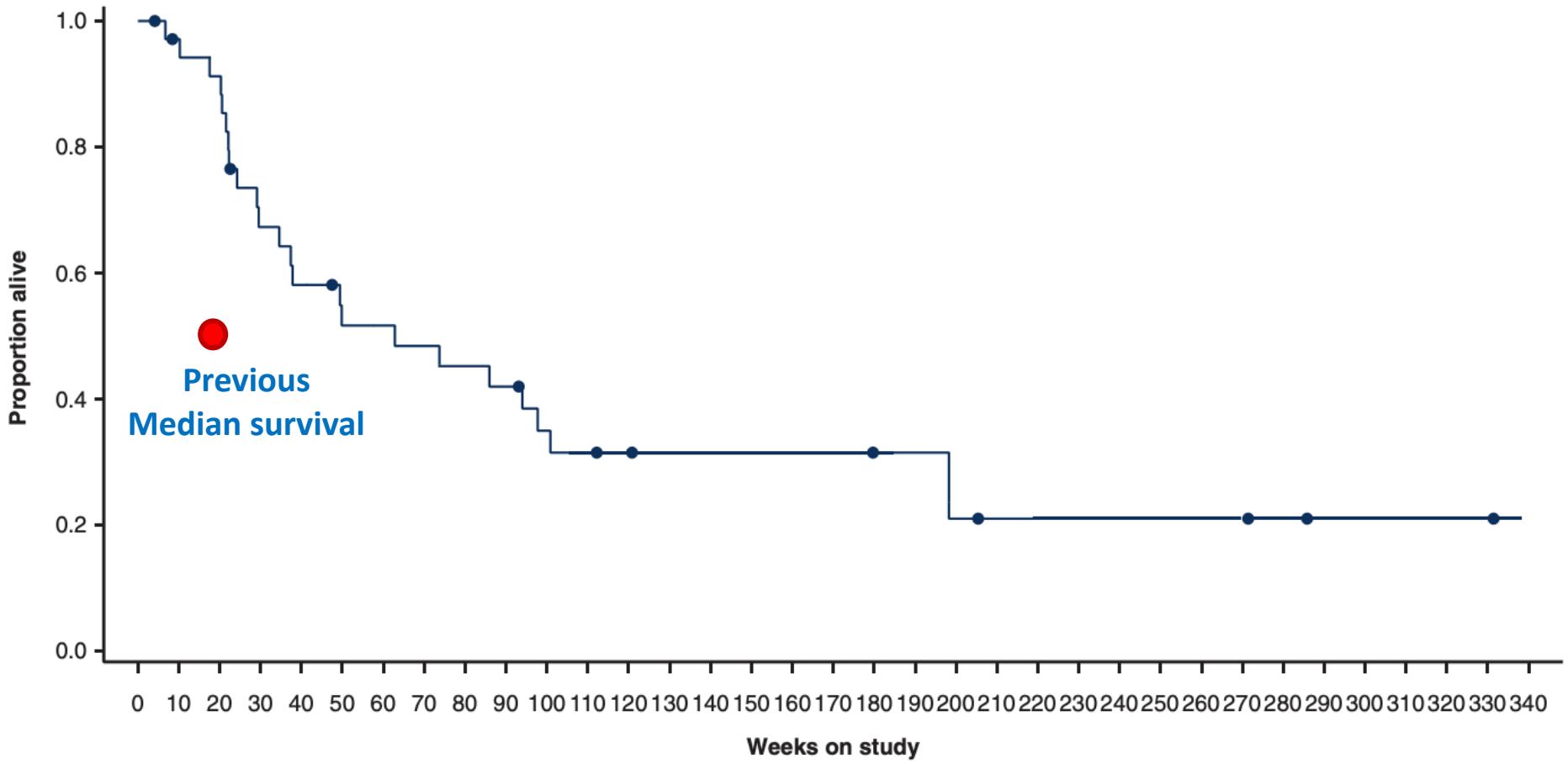


Subbiah et al.,
Ann. of Oncology, 2022

Dabrafenib plus trametinib: phase II ROAR basket study

Subbiah et al., Ann. Of Oncology, 2022

36 PATIENTS WITH ATC



FDA approves dabrafenib plus trametinib for anaplastic thyroid cancer with BRAF V600E mutation

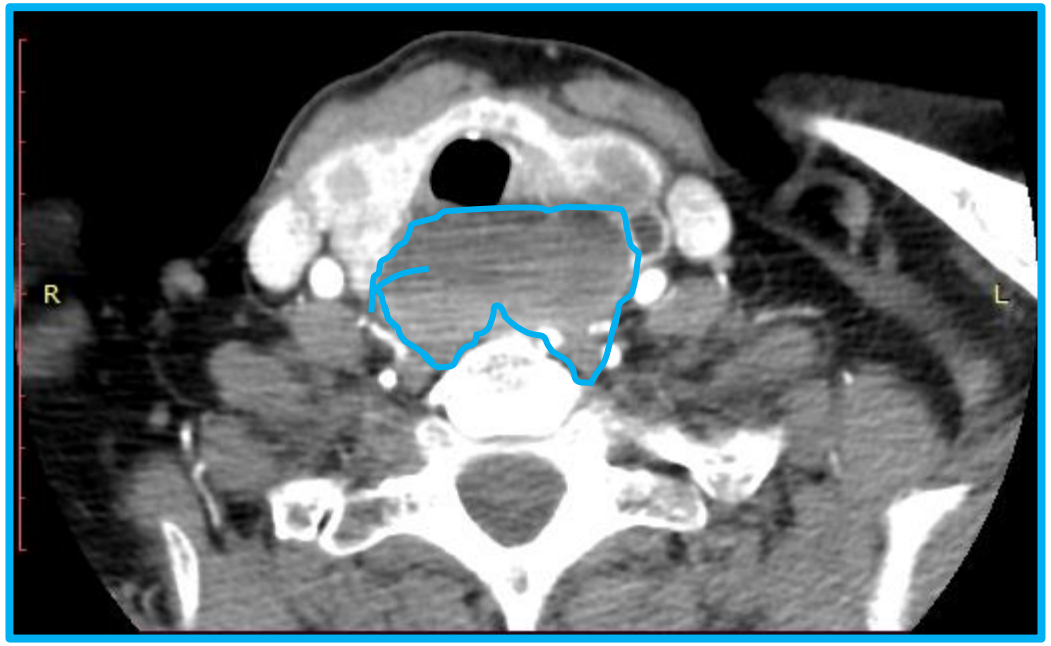
On May 4, 2018, the Food and Drug Administration approved dabrafenib (TAFINLAR®, Novartis Pharmaceuticals Corp.) and trametinib (MEKINIST®, Novartis Pharmaceuticals Corp.) in combination for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Approval was based on a nine-cohort, non-randomized trial, BRF117019 (NCT02034110) enrolling patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic ATC with no locoregional treatment options. The overall response rate was 61% (95% CI: 39%, 80%) in 23 patients with ATC who were evaluable for response. The complete and partial response rates were 4% and 57%, respectively. Response duration was at least 6 months in 64% of responding patients.

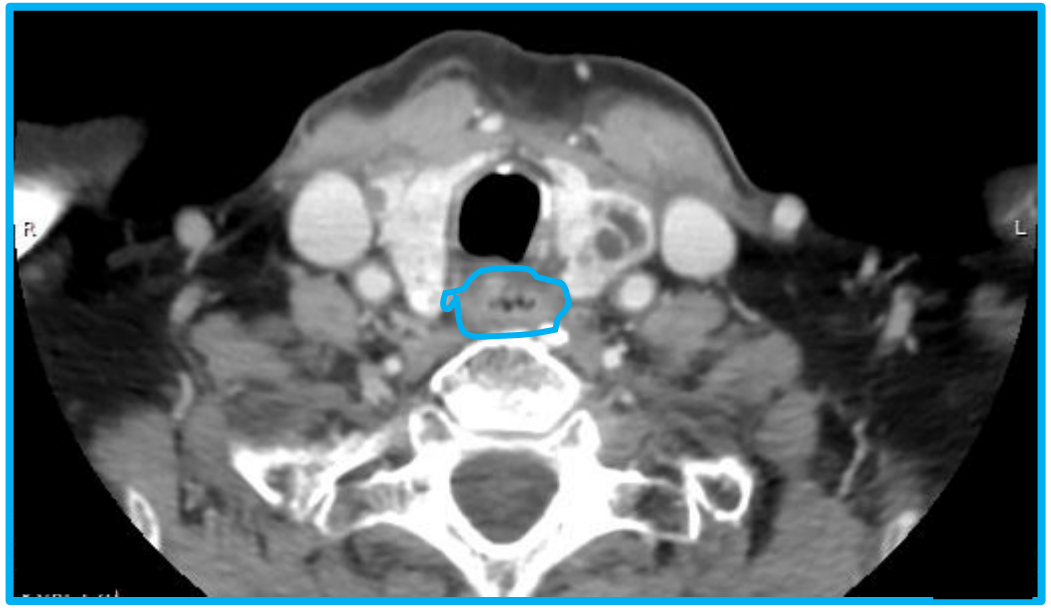
The adverse reaction profile among all patients in the trial and among patients in the ATC cohort was similar to that observed in other approved indications.

The recommended doses for ATC are 150 mg of dabrafenib orally twice daily and 2 mg of trametinib orally once daily. Full prescribing information is available at:

Dabrafenib plus trametinib: our experience (woman 80 years old, good health quality, stage 4A)

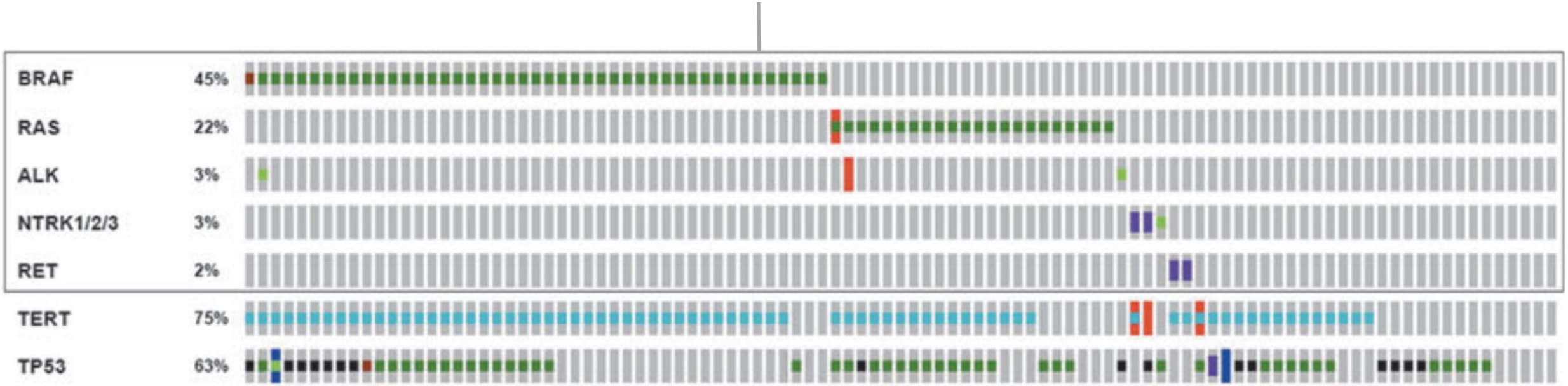


At diagnosis



After 2 years form dabrafenib + trametinib

DRUGGABLE GENE ALTERATIONS (126 PATIENTS)



Xu et al., Thyroid, 2022

ALK INHIBITOR

Crizotinib: a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond

Drug Design, Development and Therapy
23 November 2011

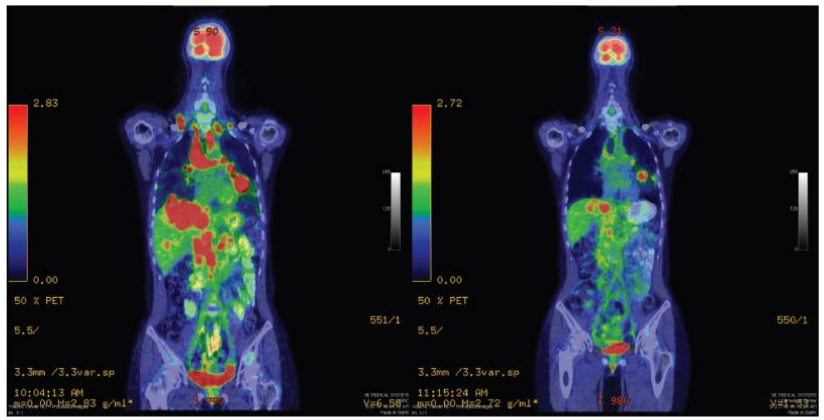


Figure 3 Dramatic response to crizotinib in a ALK-rearranged NSCLC patient.

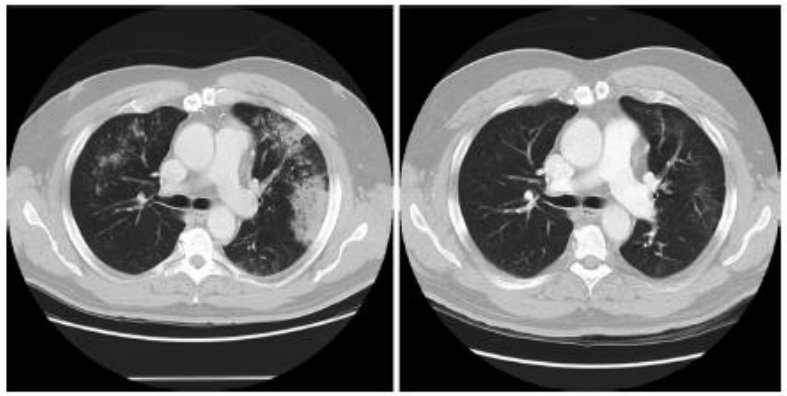


Figure 2 Response of *ALK*-rearranged NSCLC after 2 months of crizotinib.

Table 2 Efficacy of 255 patients with *ALK* rearranged non-small cell lung cancer enrolled in A8081001 and PROFILE 1005[27,29]

Efficacy parameter	A8081001 (n = 119*)	PROFILE 1005 (n = 136)
ORR (CR + PR) [% (95% CI)]	61% (2% + 59%) [52%, 70%]	50% (1% + 49%) [42%, 59%]
Duration of response (months) [range]	11.22 (0.96–17.87)	9.78 (1.45–9.82)

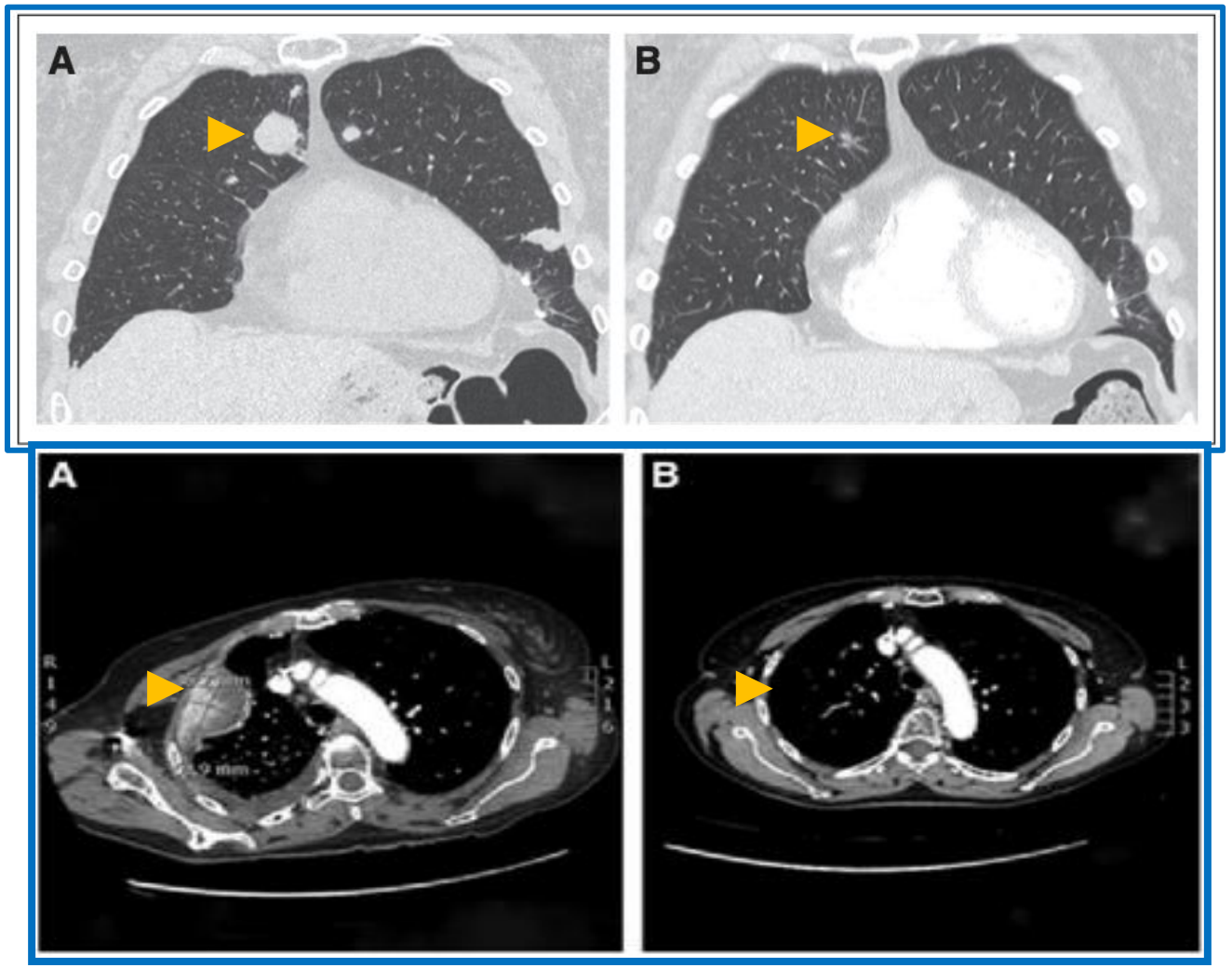
Notes: *119 patients enrolled and 116 evaluable patients. Response rate was calculated based on 116 patients.

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response.

Crizotinib & ceritinib (ALK inhibitors)
ATC case reports

Crizotinib

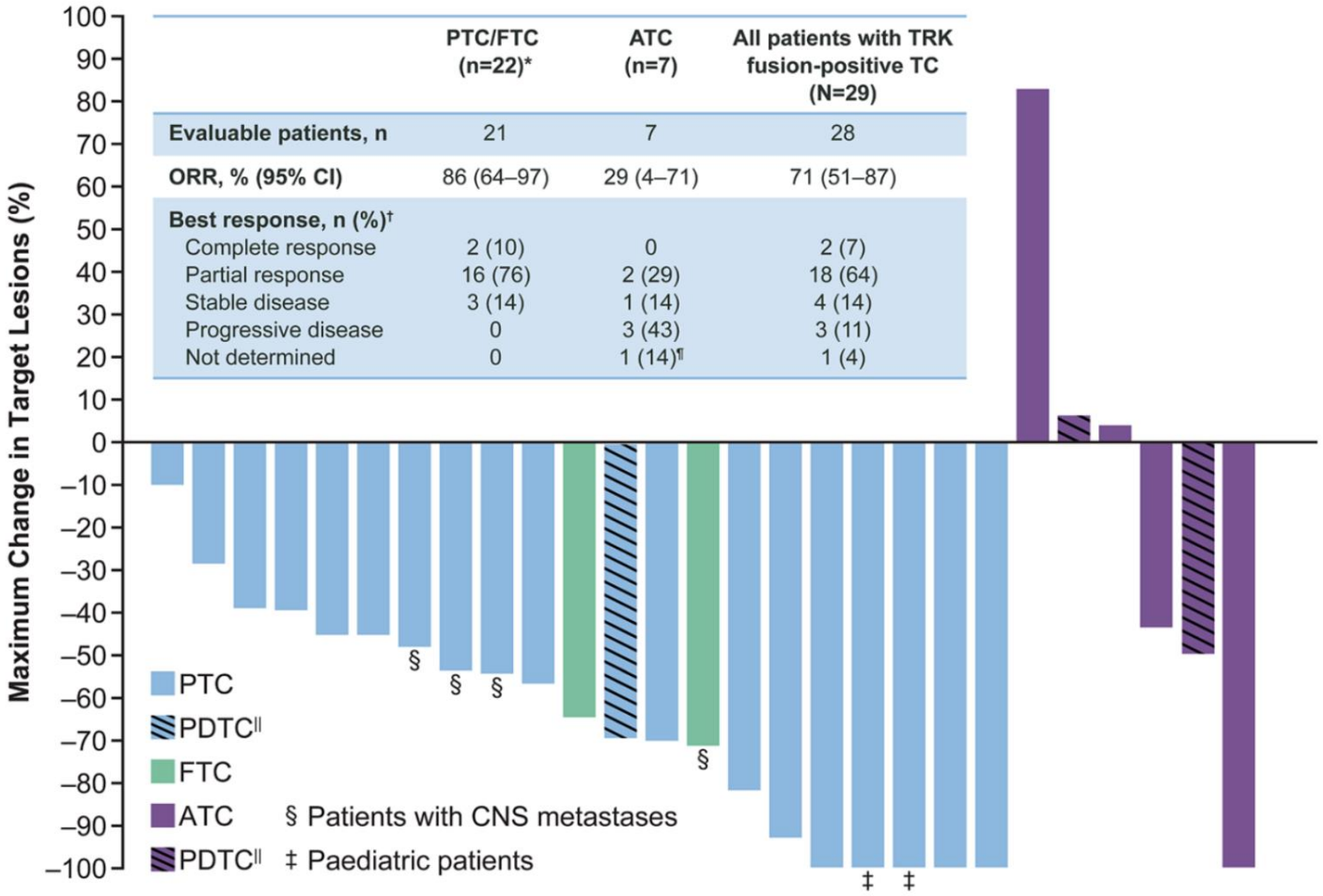
Ceritinib

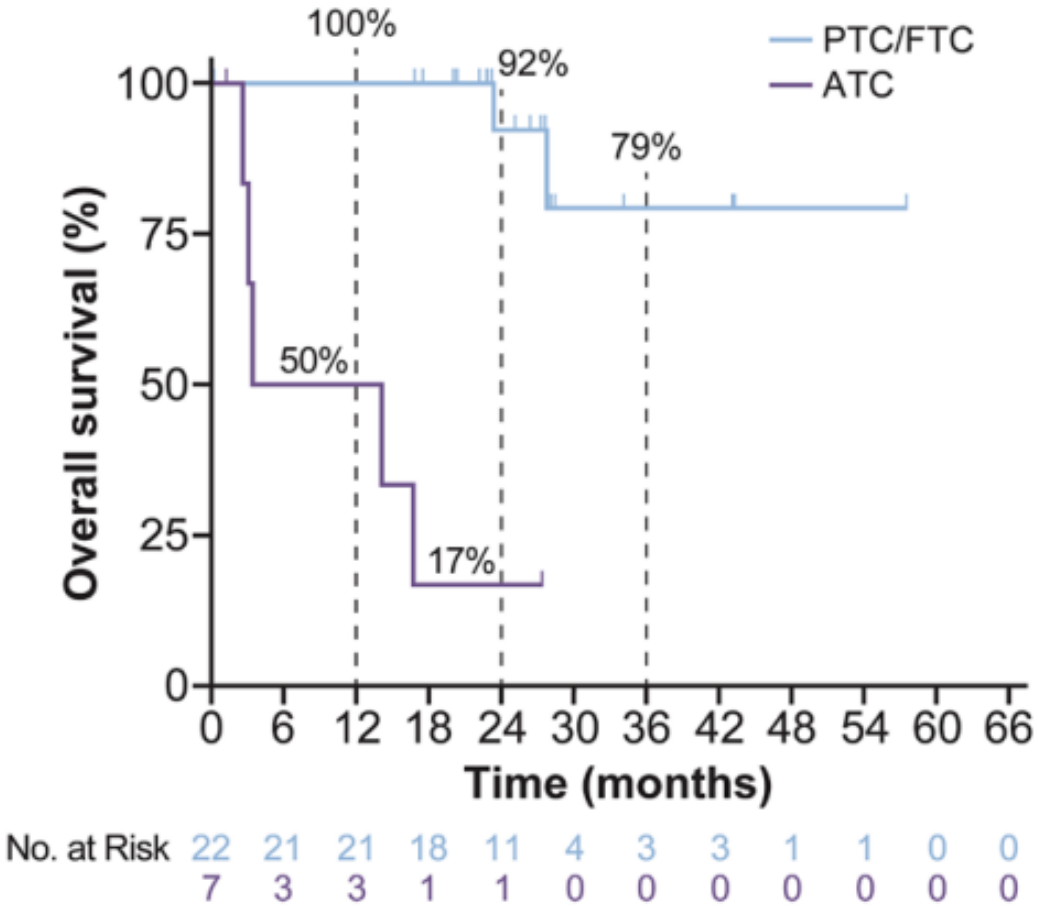


Godbert et al., JCO, 2015; Leroy et al., Thyroid, 2020

Larotrectinib (NTRK inhibitor): phase II NAVIGATE basket trial

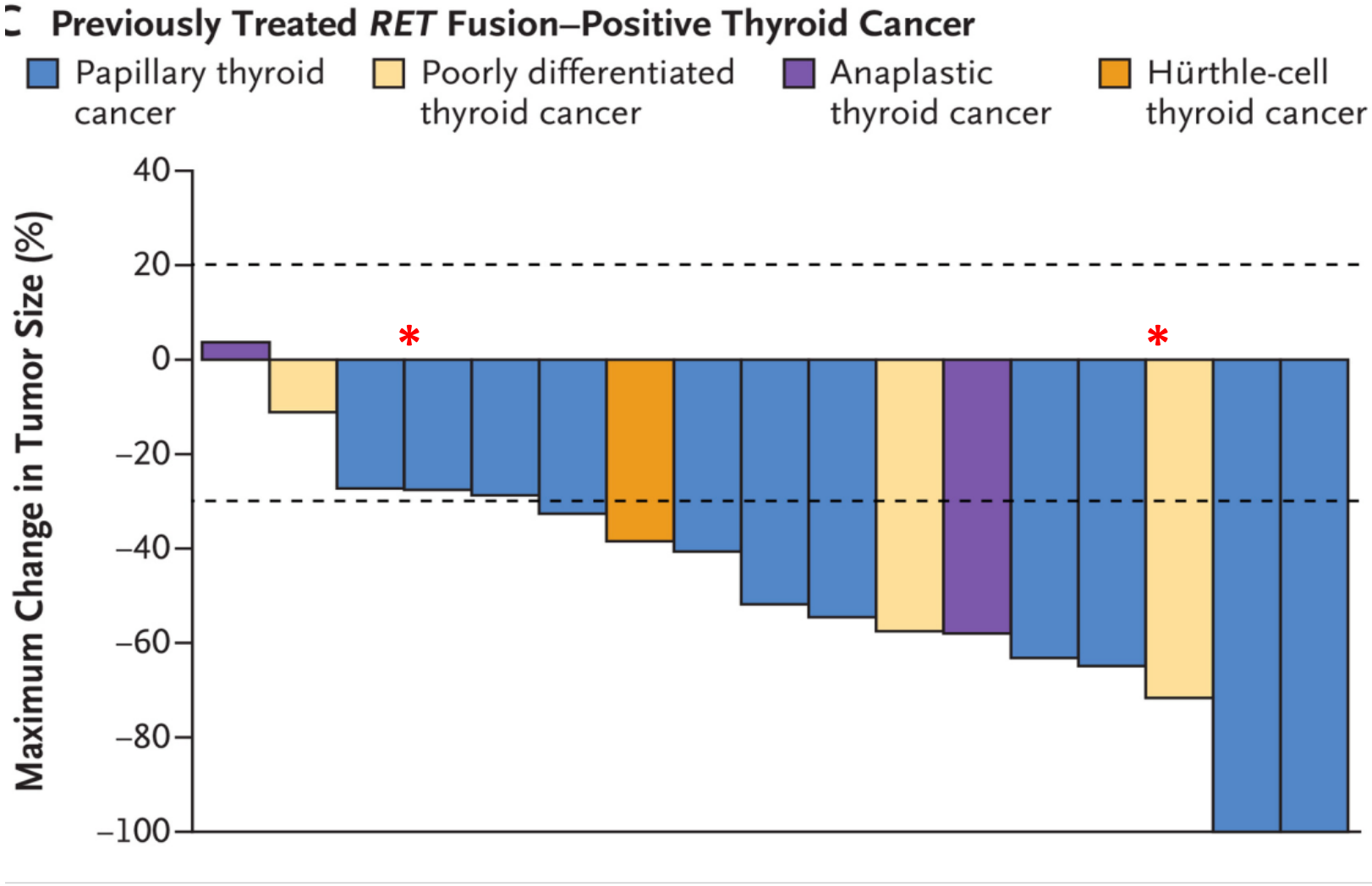
	PTC/FTC (n=22)*	ATC (n=7)	All patients with TRK fusion-positive TC (N=29)
Evaluable patients, n	21	7	28
ORR, % (95% CI)	86 (64–97)	29 (4–71)	71 (51–87)
Best response, n (%)†			
Complete response	2 (10)	0	2 (7)
Partial response	16 (76)	2 (29)	18 (64)
Stable disease	3 (14)	1 (14)	4 (14)
Progressive disease	0	3 (43)	3 (11)
Not determined	0	1 (14)¶	1 (4)





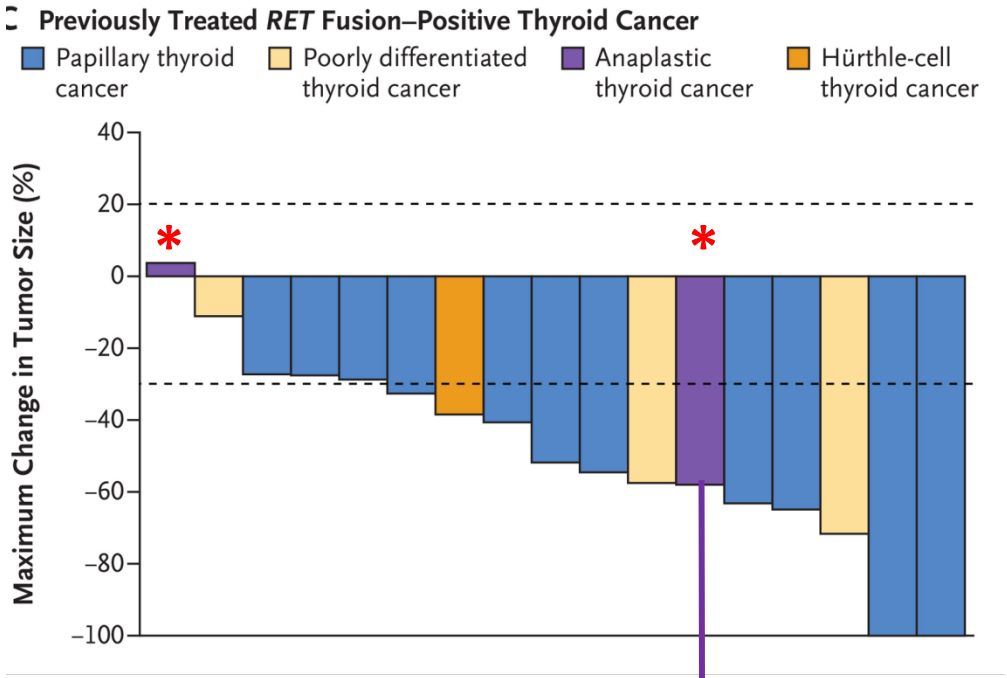
Waguespack *et al., EJE, 2022*

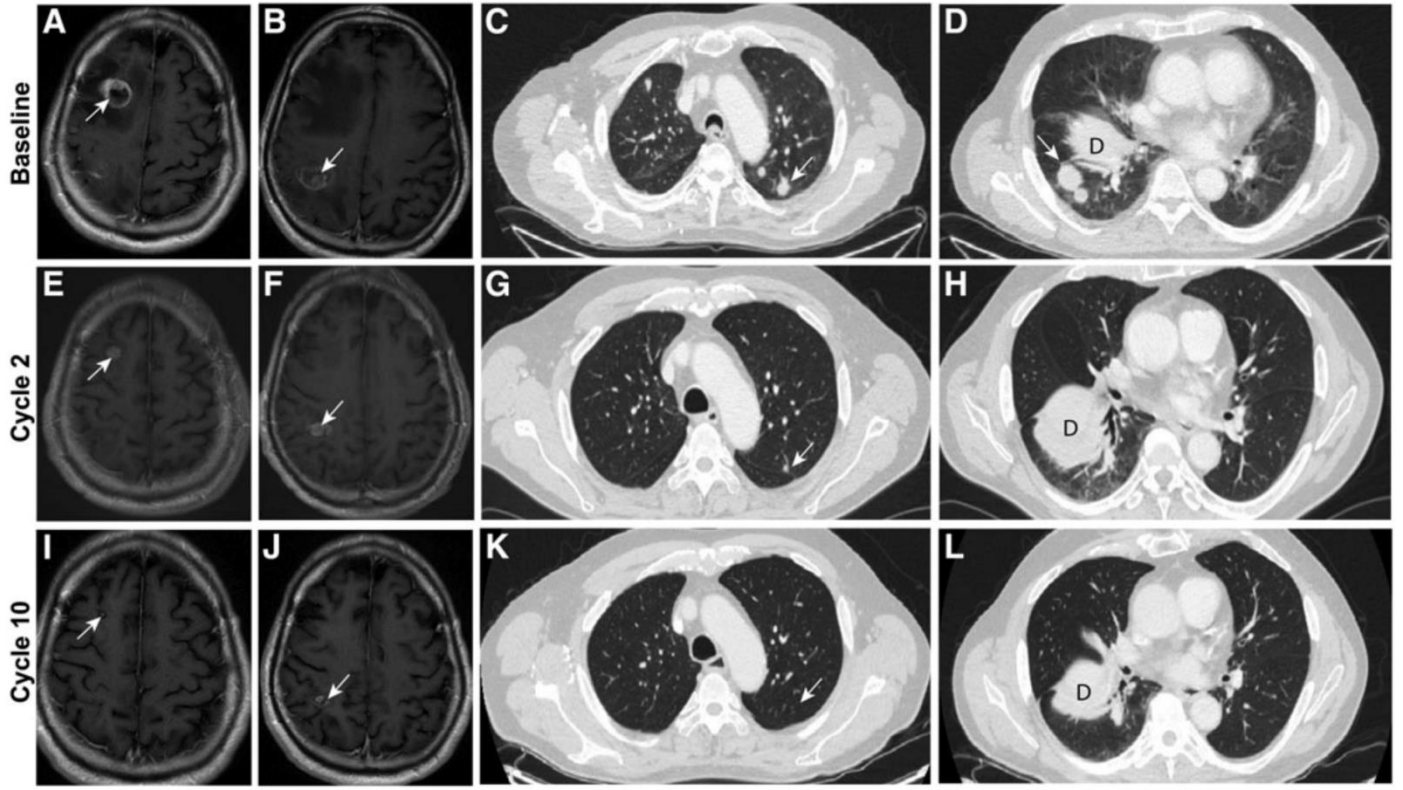
Selpercatinib (RET inhibitor): LIBRETTO-001 phase I/II trial



Wirth *et al., NEJM, 2020*

Selpercatinib: LIBRETTO-001 phase I/II trial

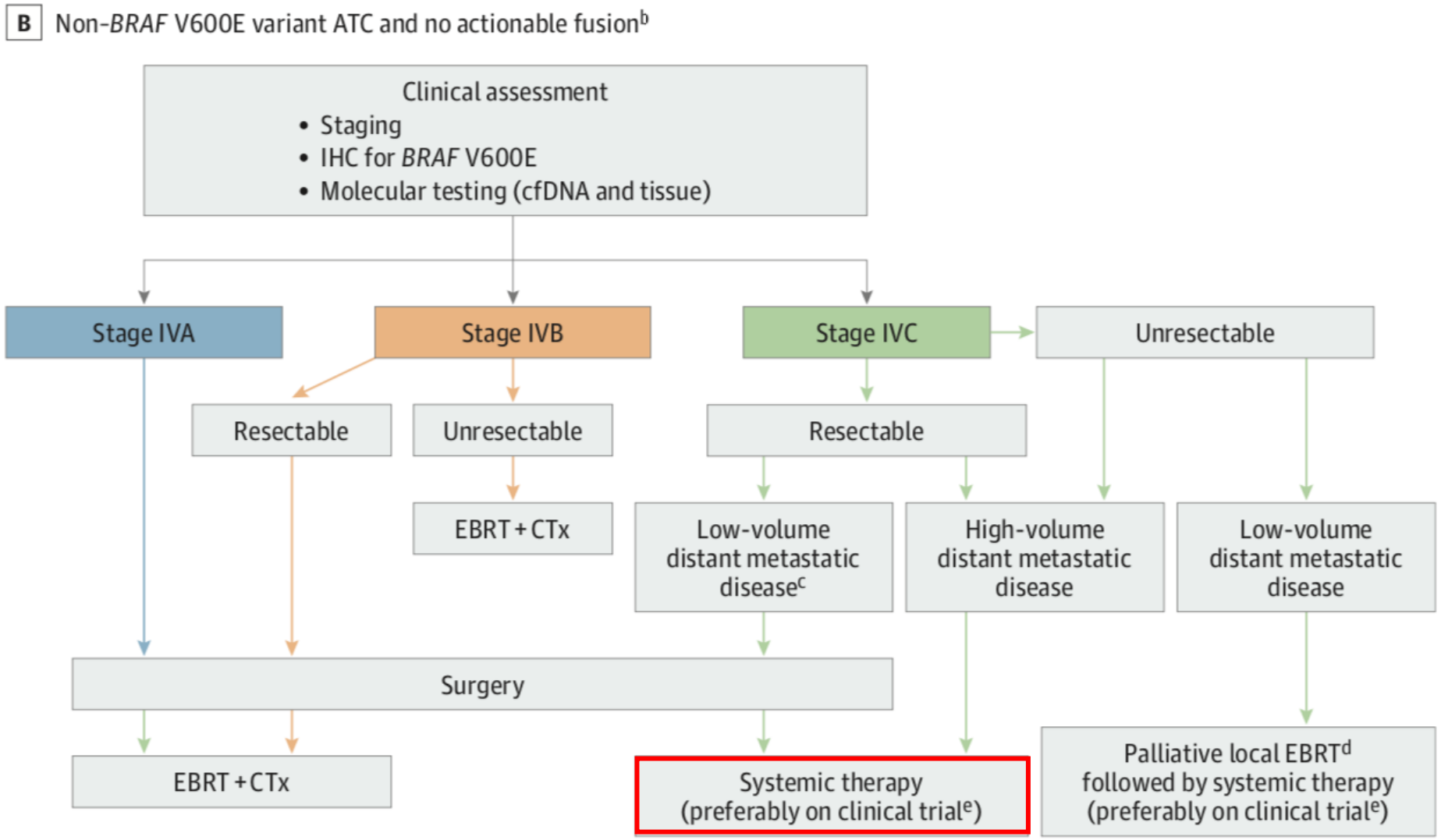




Wirth *et al., NEJM, 2020;*

Dias-Santagata et al., Thyroid, 2020

What about cases without druggable alterations?



Maniakas et al., JAMA Oncol, 2020

PRE CLINICAL STUDIES WITH TKI IN ATC

Antiproliferative and Proapoptotic Activity of

THYROID
Volume 22, Number 7, 2012

DOI: 10.1089/thy.2011.0380

Clin Cancer Res. 2011 April 15; 17(8): 2281–2291. doi:10.1158/1078-0432.CCR-10-2762.

VANDETANIB

Epidermal Growth Factor Receptor (EGFR) Is Overexpressed in Anaplastic Thyroid Cancer, and the EGFR Inhibitor Gefitinib Inhibits the Growth of Anaplastic Thyroid Cancer

Bradley A. Schiff,[2] Andrea B. McMurphy,[2] Samar A. Jasser,[1] Maher N. Younes,[1] Dao Doan,[1] Orhan G. Yigitbasi,[1] Seungwon Kim,[1] Ge Zhou,[1] Mahitosh Mandal,[1] Benjamin N. Bekele,[3] F. Christopher Holsinger,[1] Steven I. Sherman,[4] Sai-Ching Yeung,[5] Adel K. El-Naggar,[1,6] and Jeffrey N. Myers[1,7]

slowed tumor growth in a nude mouse model of thyroid carcinoma cells injected subcutaneously.

Conclusions: ATC cells consistently overexpress EGFR, rendering this receptor a potential target for molecular therapy. Gefitinib effectively blocks activation of EGFR by EGF, inhibits ATC cellular proliferation, and induces apoptosis *in vitro*. Our *in vivo* results show that gefitinib has significant antitumor activity against ATC in a subcutaneous nude mouse tumor model and therefore is a potential

Sartini, Alessandro Corti, Simona Piaggi, Gabriele Materazzi, Claudio Spinelli, Gabriella Fontanini, Romano Danesi, Federico Da Settimo, and Paolo Miccoli

THYROID
Volume 23, Number 5, 2013

DOI: 10.1089/thy.2012.0103

Phase II Trial of Sorafenib in Patients with Advanced Anaplastic Carcinoma of the Thyroid

Panayiotis Savvides,[1,2] Govardhanan Nagaiah,[3] Pierre Lavertu,[1,2] Pingfu Fu,[1,2] John J. Wright,[4] Robert Chapman,[5] Jay Wasman,[1,2] Afshin Dowlati,[1,2] and Scot C. Remick[3]

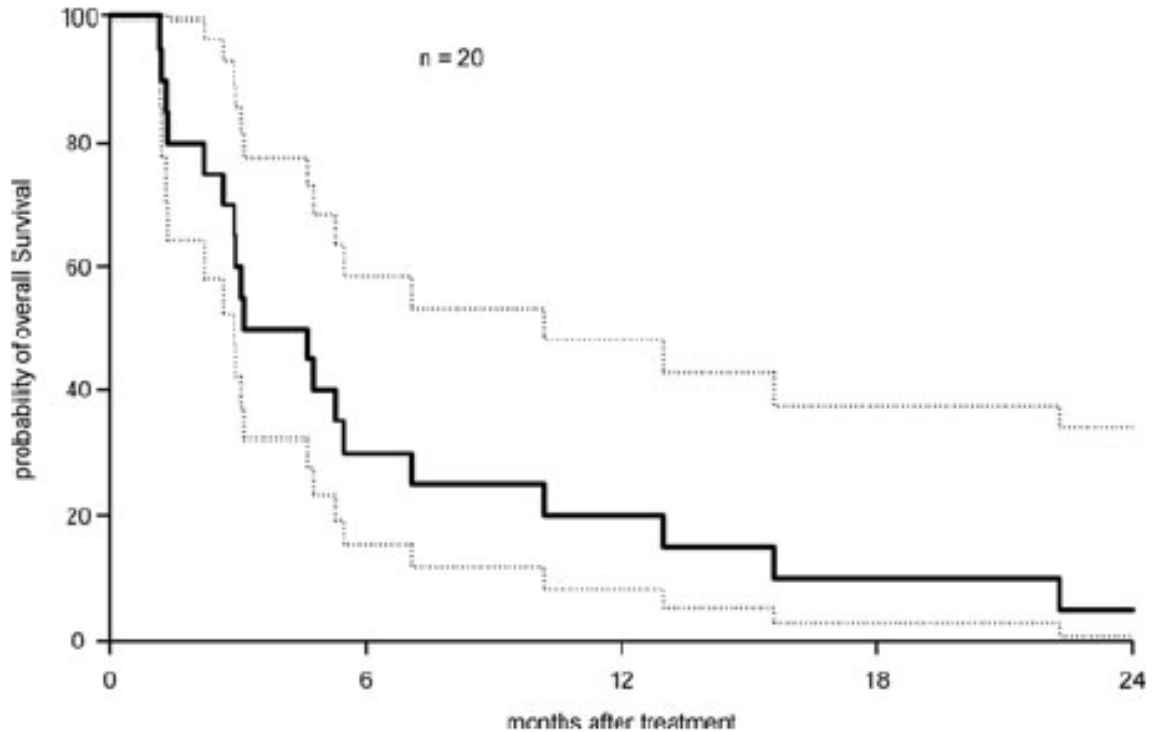
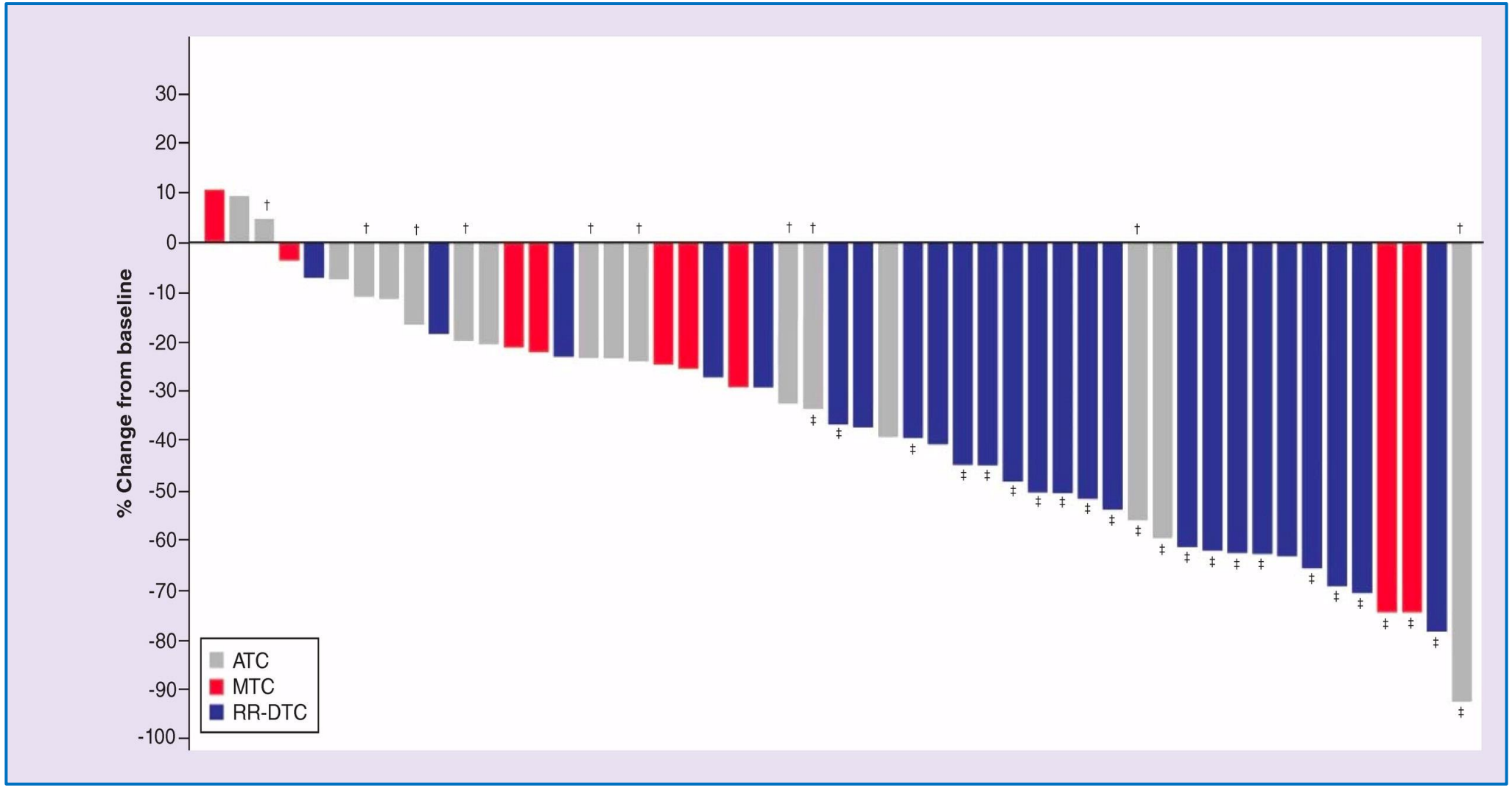


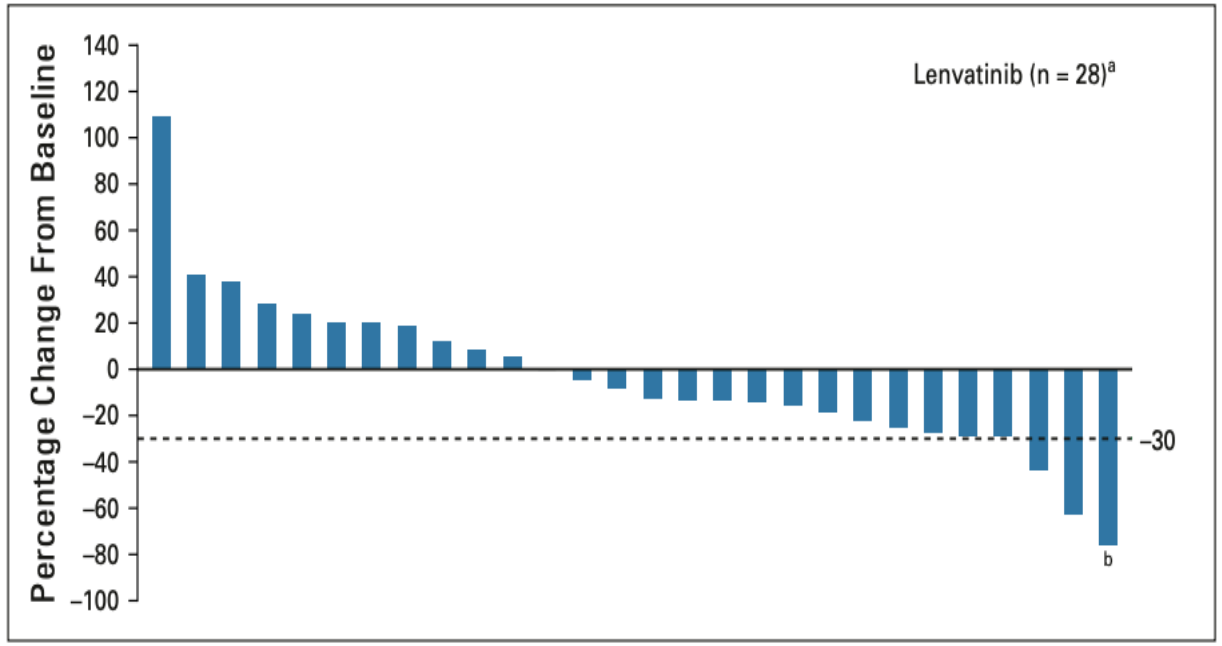
FIG. 1. Kaplan–Meier estimation of overall survival with 95% confidence interval [CI]. The median overall survival time was 3.9 months [CI 2.2–7.1 months].

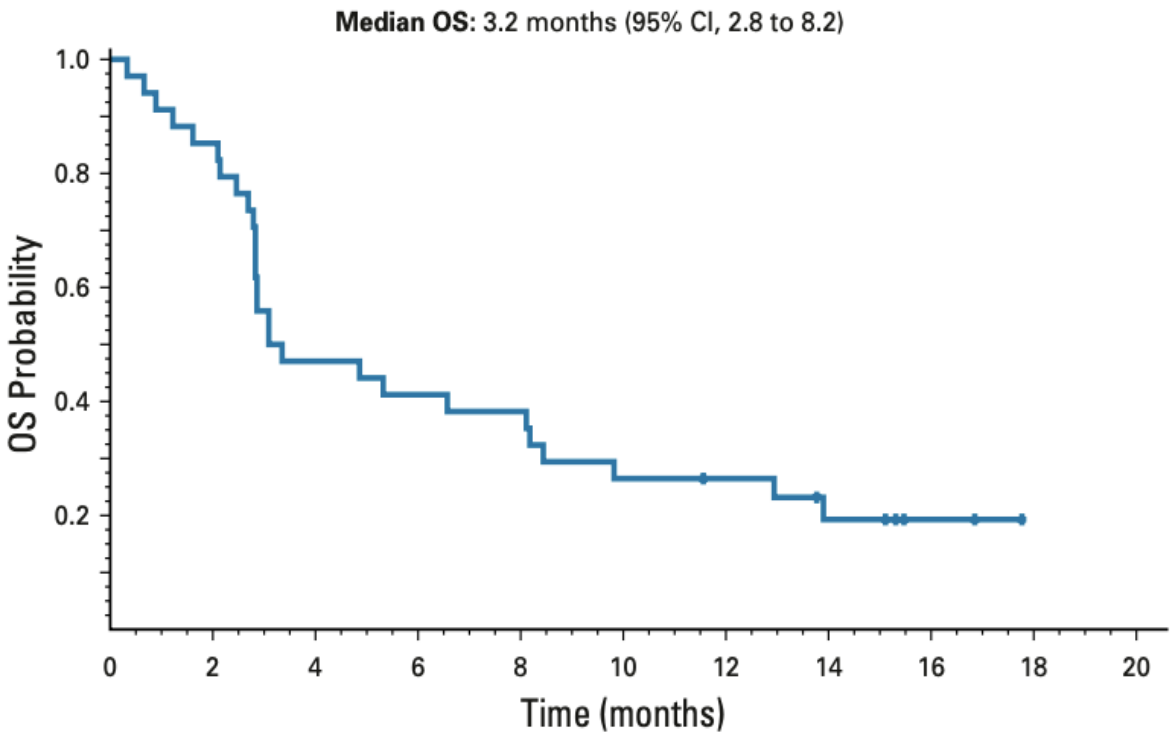
Lenvatinib : Japanese phase II study in thyroid cancers



Takahashi et al., Future Medicine, 2019

Lenvatinib : American phase II study in ATC





The study was halted for futility

Wirth et al., JCO, 2021

Lenvatinib as single treatment

Higashiyama et al., EJC, 2022

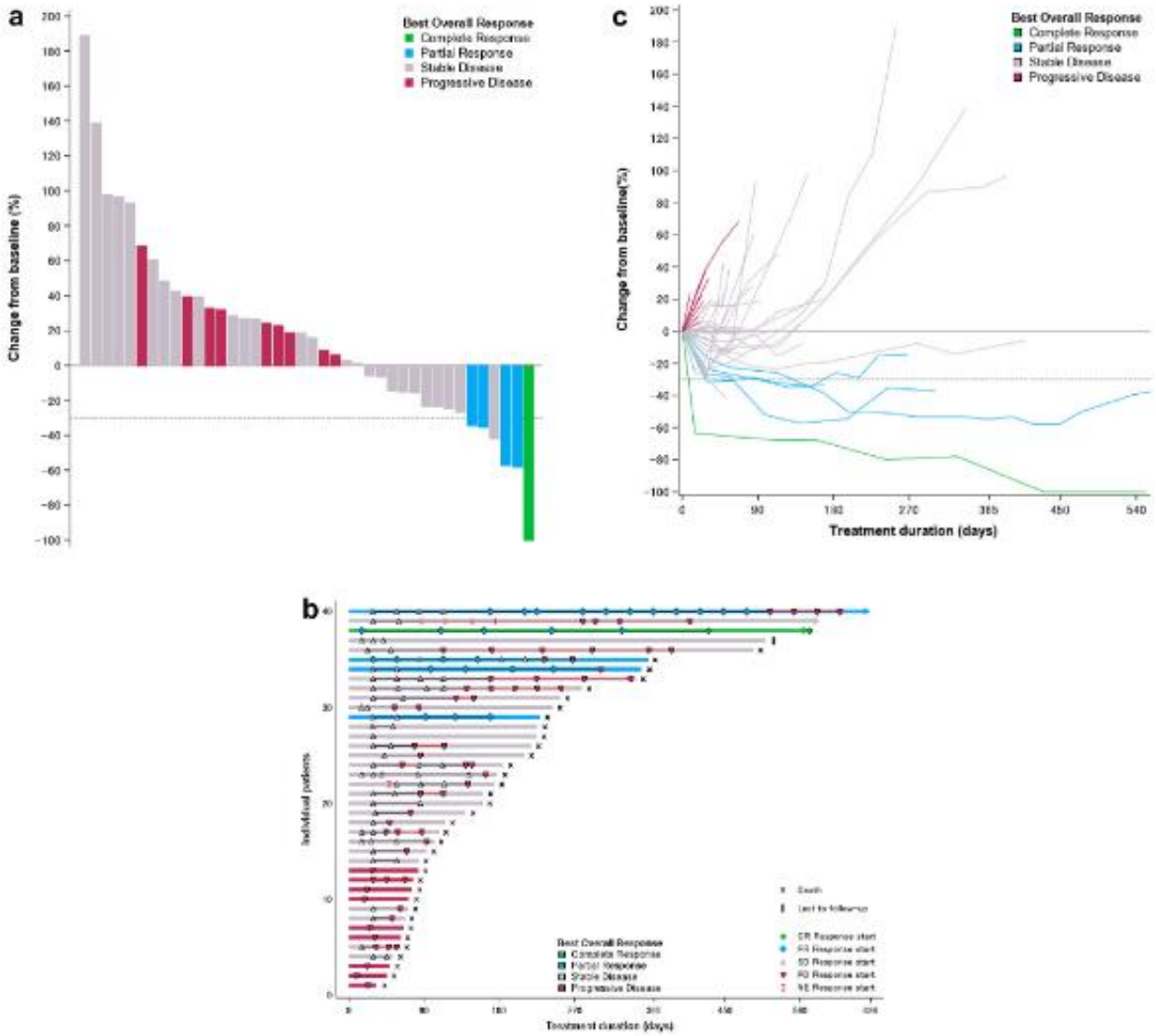
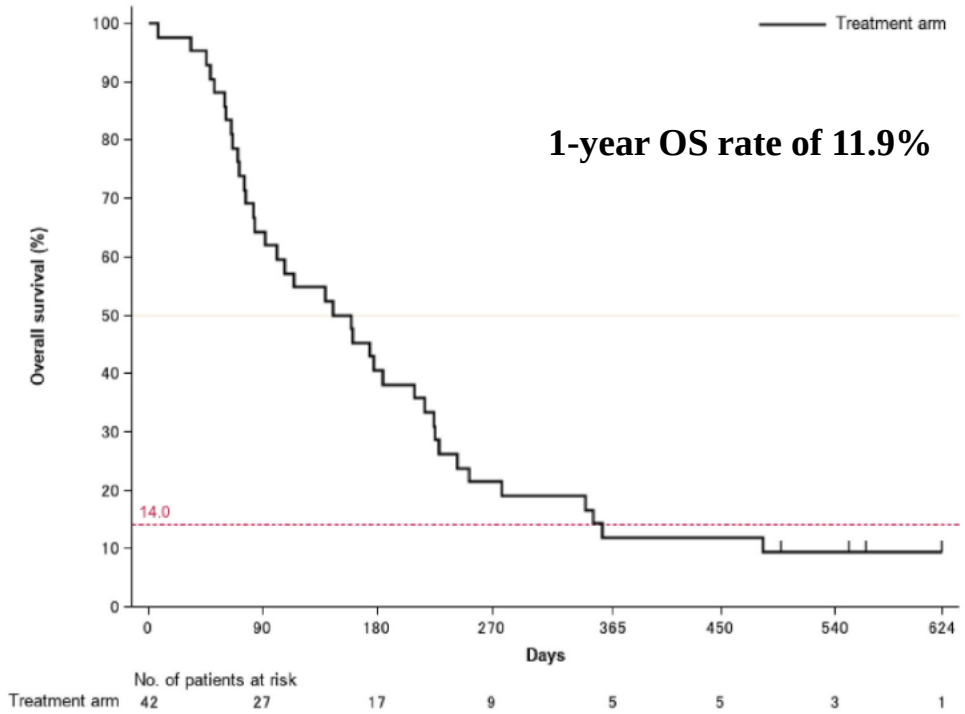


Fig. 2. (2a) Waterfall plot of maximum rate of change in target lesion diameter sum (2b) Swimmer plot of response to treatment of each case (2c) Spider plot of changes in the sum of target lesion diameters. Two patients without tumour evaluation at follow-up were excluded.



1-year OS rate of 11.9%

Fig. 1. OS curve estimated by the Kaplan–Meier method.

LENVATINIB MAY BE BENEFICIAL FOR SELECTED PATIENTS

younger than 70 years and without a large, rapidly progressive primary tumour may be preferable candidates

THYROID
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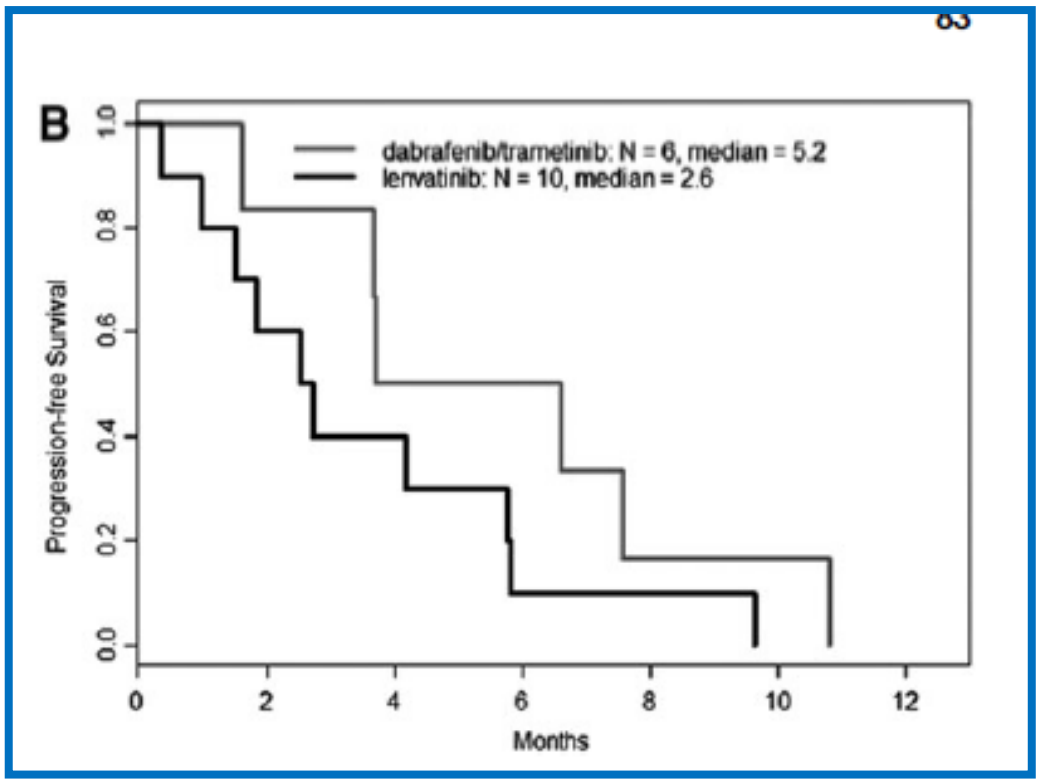
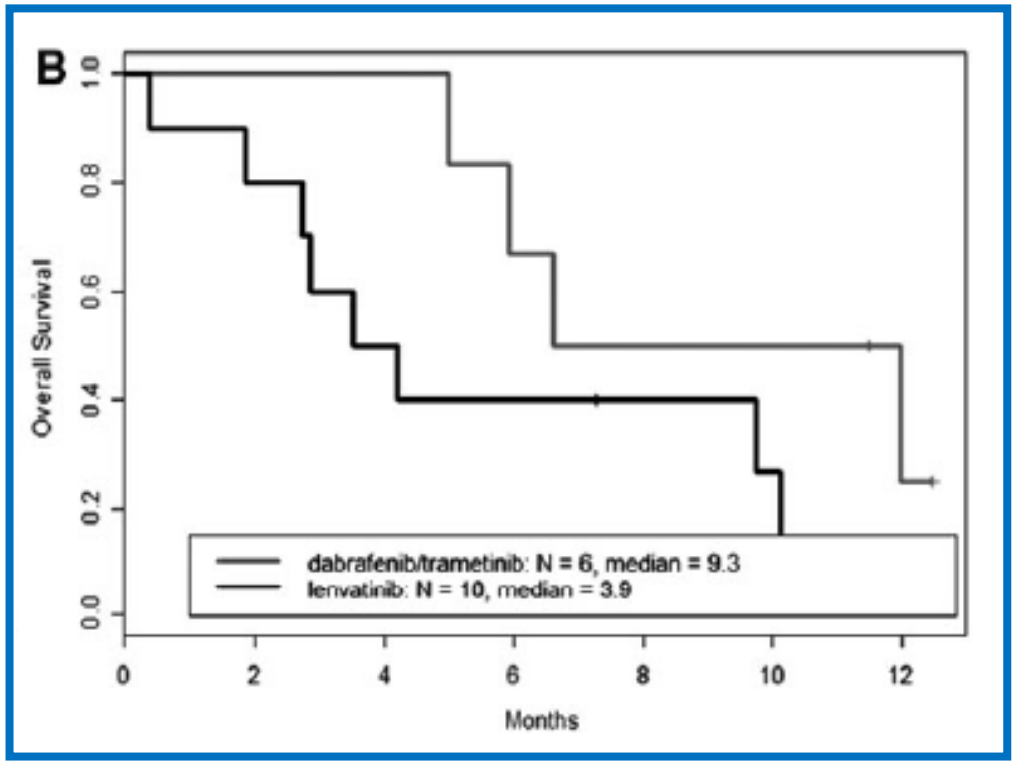
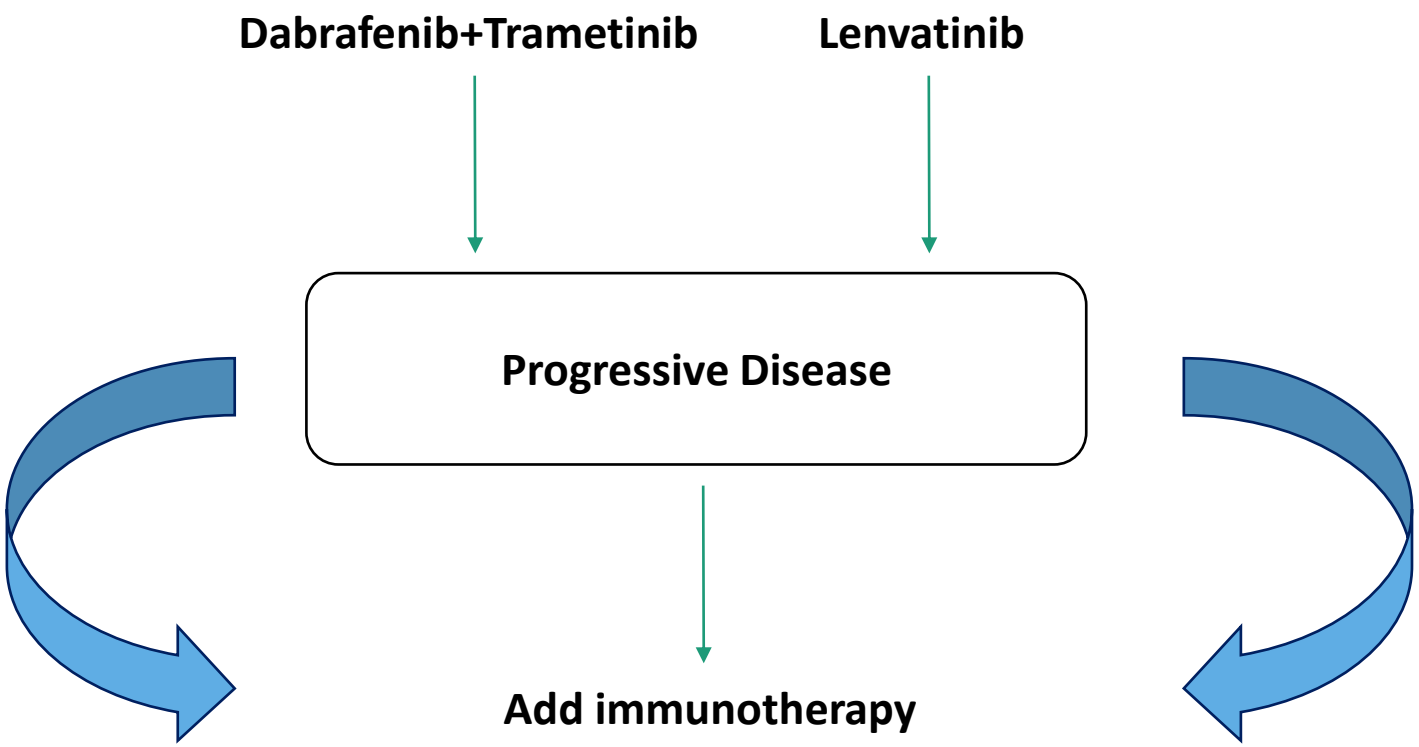
Real-World Experience with Targeted Therapy for the Treatment of Anaplastic Thyroid Carcinoma

Priyanka C. Iyer,[1,2] Ramona Dadu,[1] Renata Ferrarotto,[3] Naifa L. Busaidy,[1] Mouhammed A. Habra,[1] Mark Zafereo,[4] Neil Gross,[4] Kenneth R. Hess,[5] Maria Gule-Monroe,[6] Michelle D. Williams,[7] and Maria E. Cabanillas[1]



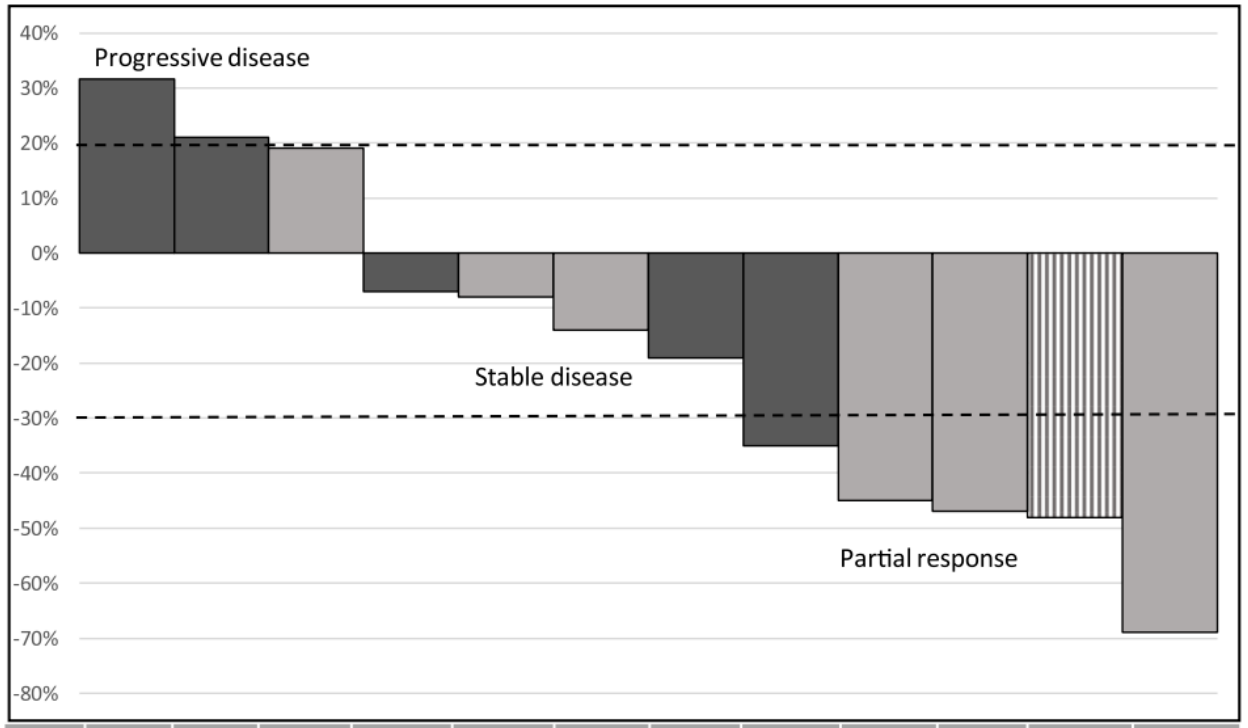


Multimodal therapy



Iyer et al., Journal for ImmunoTherapy of Cancer, 2018

Multimodal therapy



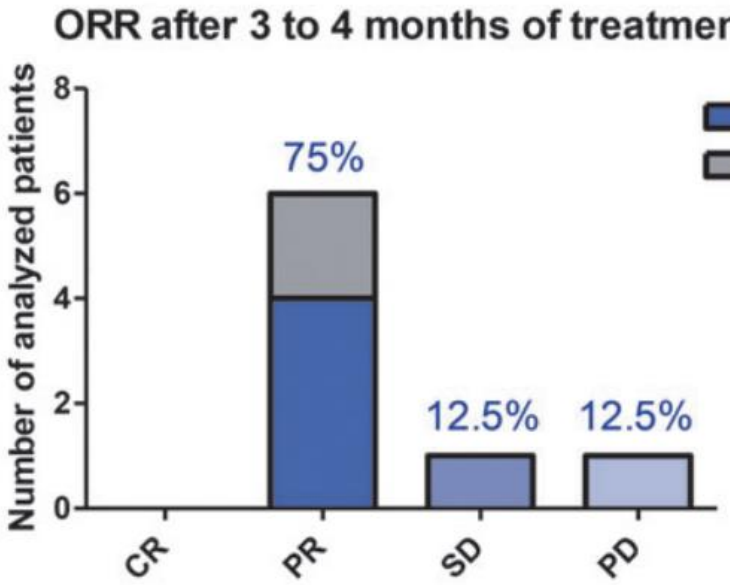
Pt No.	1	2	3	4	5	6	7	8	9	10	11	12
PD-L1	5%	30%	80%	5%	50%	60%	N/A	>95%	10%	N/A	20%	90%

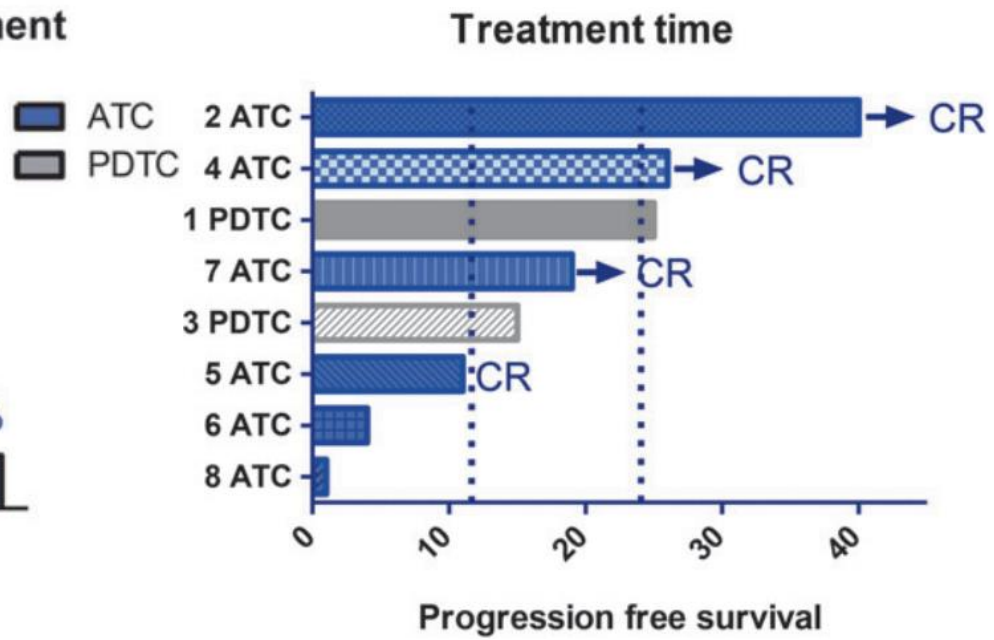
Fig. 1 Waterfall plot demonstrating response to combination of kinase inhibitor therapy and pembrolizumab: A partial response was observed in 5/12 (42%), stable disease in 4/12 (33%) and progressive disease in 3/12 (25%). The box below the patient number describes the PD-L1 status on the tumor tissue

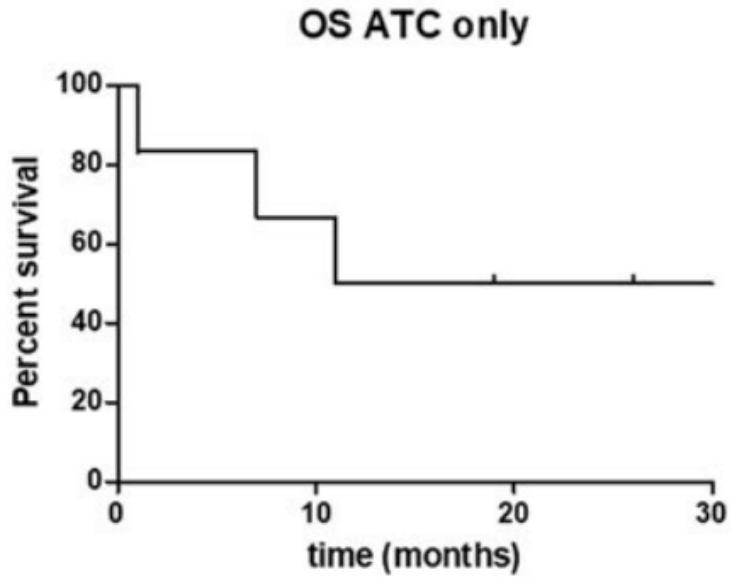
Iyer et al., Journal for ImmunoTherapy of Cancer, 2018

Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma

Dierks et al., Thyroid , 2021





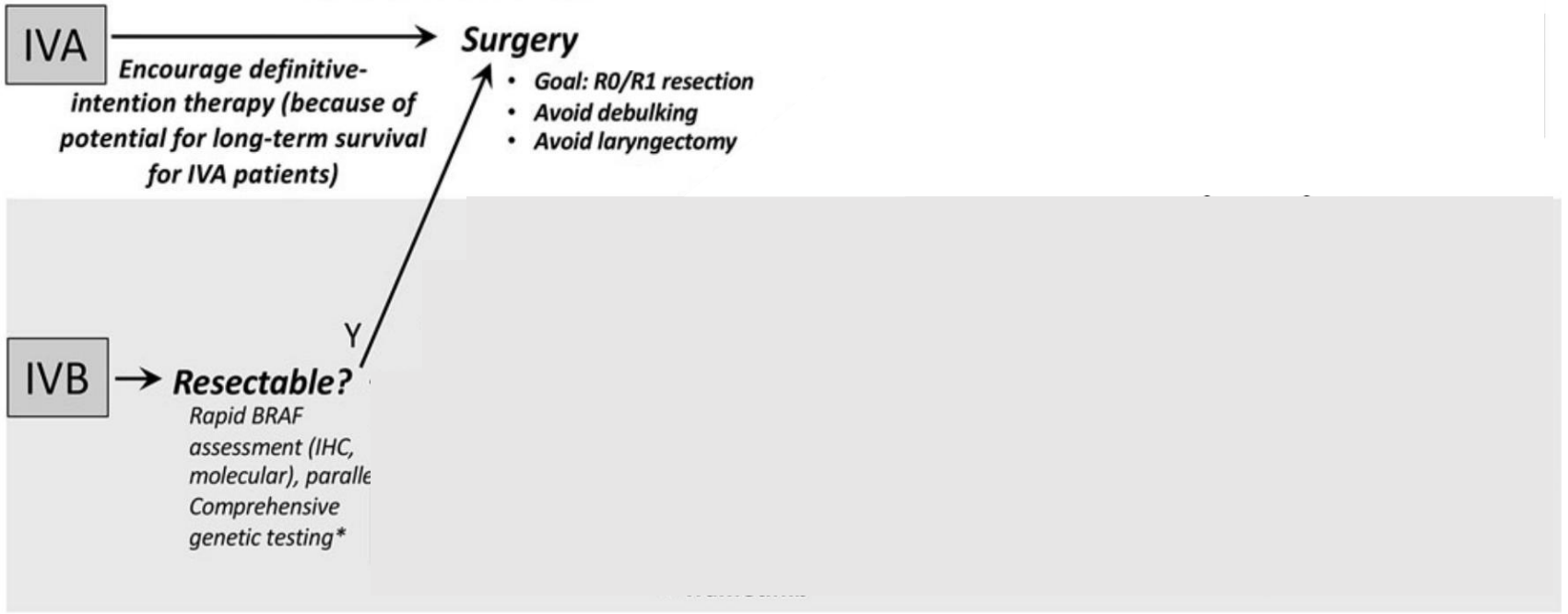


The median OS was 18.5 months, with three ATC patients being still alive without relapse (40, 27, and 19 months) despite metastatic disease at the time of treatment initiation (UICC and stage IVC).
All patients with long-term (>2 years) or complete responses (CRs) had either increased TMB or PD-L1 TPS >50%.

Linee guida americane

Bible et al., Thyroid, 2021

Linee guida americane



Bible et al., Thyroid, 2021

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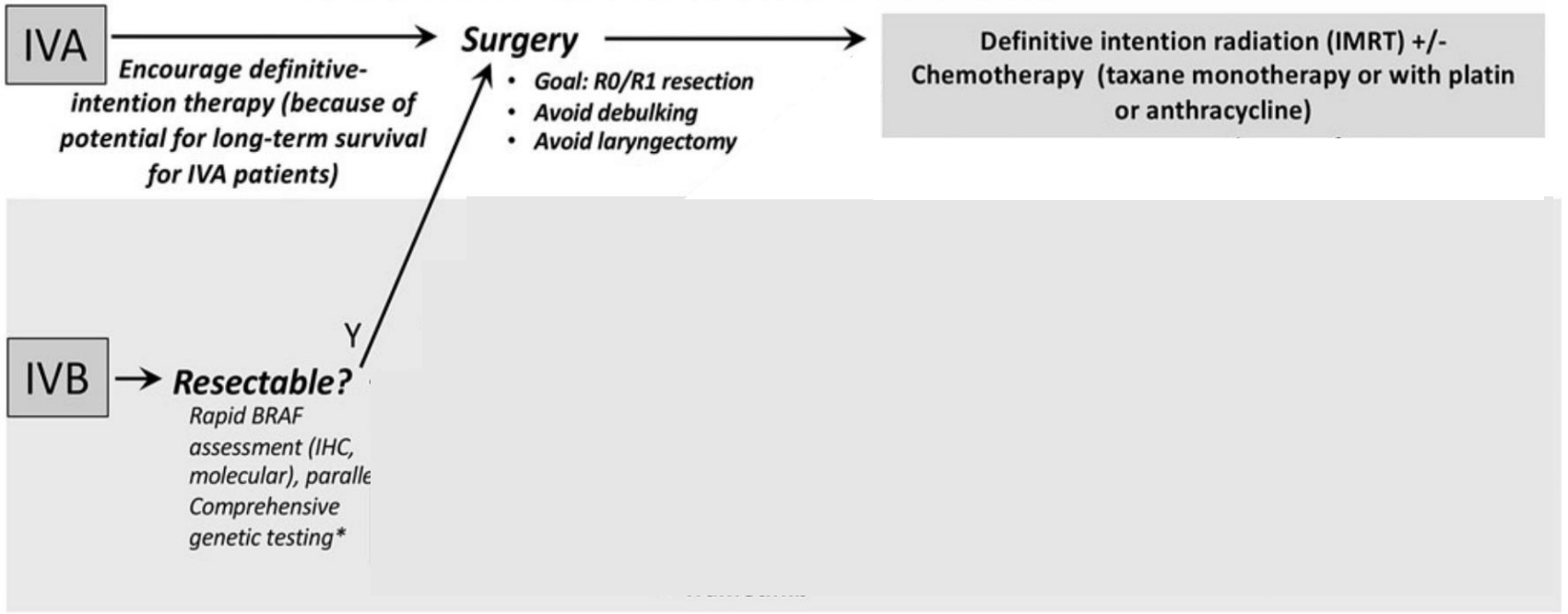

Bible et al., Thyroid, 2021

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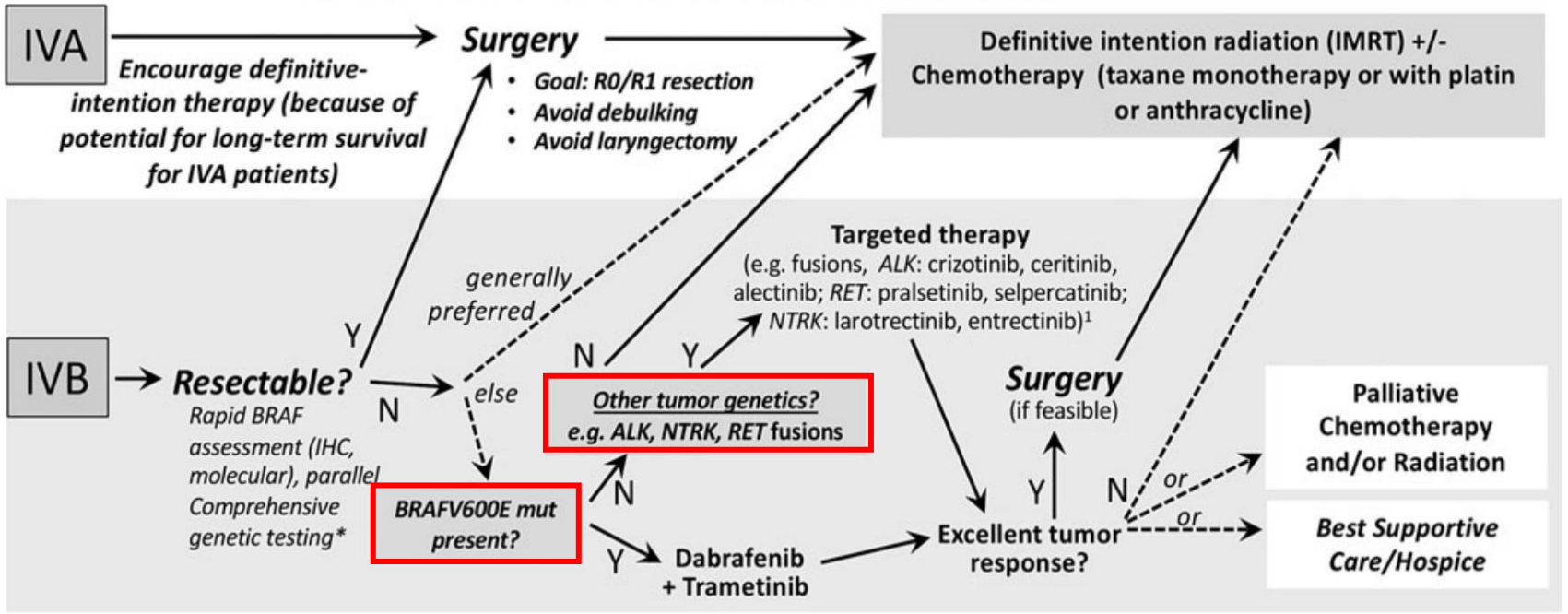

Bible et al., Thyroid, 2021

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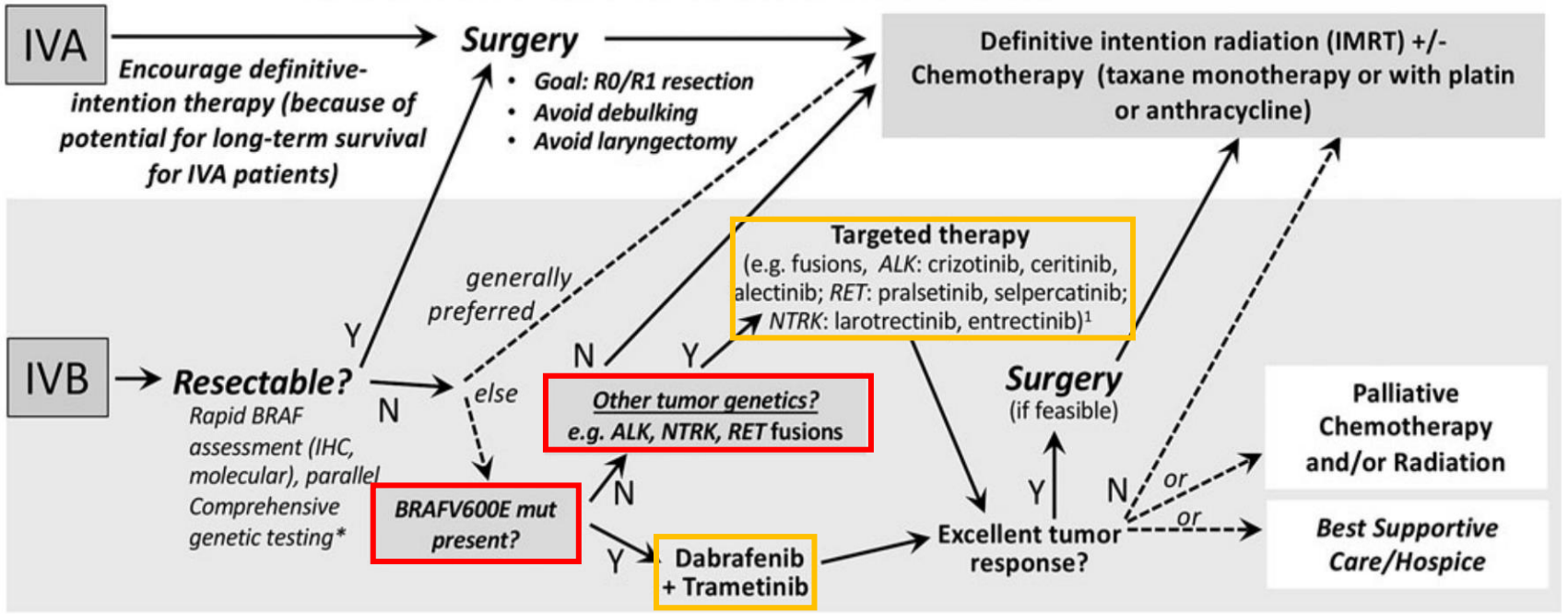

Bible et al., Thyroid, 2021

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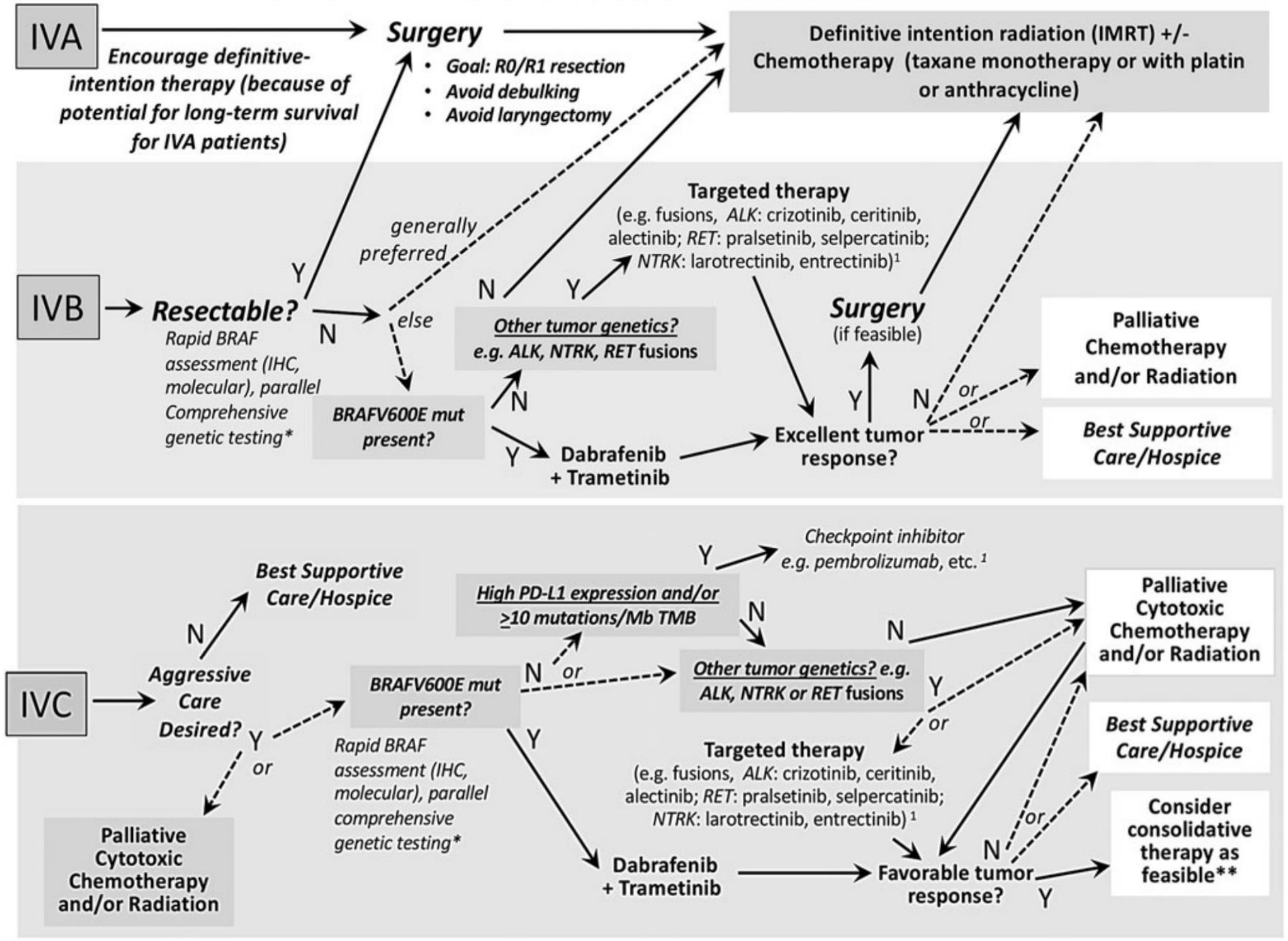

Bible et al., Thyroid, 2021

Conclusions

- **ATC is still a lethal disease with a very short median time of survival**
- **TKI can improve ORR and change the natural course of the disease**
- **In referral center the median time of survival is a little increased but there is still an unmet need to prolong the ATC patients' survival**
- **The target therapy seems to play an important role especially when combined with immunotherapy but we are still missing evidences from prospective and randomized studies that are very difficult to be performed in ATC patients.**

GRAZIE PER L'ATTENZIONE

Dr Alessandro Prete e Drssa Elisa Minaldi