Anaplastic thyroid cancer: genome-based search for new targeted therapy options

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Abstract

Objective: Anaplastic thyroid cancer (ATC) is one of the most lethal human cancers with meager treatment options. We aimed to identify the targeted drugs already approved by the Food and Drug Administration (FDA) for solid cancer in general, which could be effective in ATC.

Design: Database mining.

Methods: FDA-approved drugs for targeted therapy were identified by screening the databases of MyCancerGenome and the National Cancer Institute. Drugs were linked to the target genes by querying Drugbank. Subsequently, MyCancerGenome, CIViC, TARGET and OncoKB were mined for genetic alterations which are predicted to lead to drug sensitivity or resistance. We searched the Cancer Genome Atlas database (TCGA) for patients with ATC and probed their sequencing data for genetic alterations which predict a drug response.

Results: In the study, 155 FDA-approved drugs with 136 potentially targetable genes were identified. Seventeen (52%) of 33 patients found in TCGA had at least one genetic alteration in targetable genes. The point mutation BRAF V600E was seen in 45% of patients. PIK3CA occurred in 18% of cases. Amplifications of ALK and SRC were detected in 3% of cases, respectively. Fifteen percent of the patients displayed a co-mutation of BRAF and PIK3CA. Besides BRAF-inhibitors, the PIK3CA-inhibitor copanlisib showed a genetically predicted response. The 146 (94%) remaining drugs showed no or low (under 4% cases) genetically predicted drug response.

Conclusions: While ATC carrying BRAF mutations can benefit from BRAF inhibitors and this effect might be enhanced by a combined strategy including PIK3CA inhibitors in some of the patients, alterations in BRAF WT ATC are not directly targeted by currently FDA-approved options.

Introduction

Anaplastic thyroid cancer (ATC) is one of the most lethal human cancers with a historical median survival of 5–12 months and a 1-year survival rate of 20–60% (1, 2, 3). About 50% of patients have metastatic disease at the time of diagnosis (1) which generally requires a systemic therapy in addition to surgery and/or radiation therapy.

A recent single-institution retrospective study on 479 patients treated at the University of Texas MD Anderson
Cancer Center over 20 years (3) revealed that targeted therapy and immunotherapy play an increasing role, resulting in significantly improved 1- and 2-year survival rates (59 and 42%, respectively). Median overall survival (OS) for patients treated with targeted therapy, regardless of their grouping, was 15.7 months compared with 7.6 months in patients not having received any targeted therapy (3). In another single-institution retrospective study with 120 Korean ATC patients, tyrosine kinase inhibition (TKI) was also associated with favorable OS in a multivariate analysis (4).

Although to date, half of the patients are still receiving cytotoxic chemotherapy (3), first-line therapy is progressively shifting toward targeted therapy options as precision medicine and the increasing role of molecular testing in clinical routine is evolving (5). The Food and Drug Administration (FDA) approval of the combination BRAF/MEK inhibitor therapy for the management of BRAF V600E-positive ATC in 2018 was a major first step in this direction. Besides BRAF (dabrafenib and vemurafenib) and MEK inhibitors (trametinib and cobimetinib), TKI like cabozantinib, lenvatinib, sorafenib and pazopanib, the mTOR inhibitor sapanisertib, PPAR-agonist efatutazone, the ALK inhibitor ceritinib, the VEGF inhibitor bevacizumab and several combined treatment and immunotherapeutic agents (pembrolizumab, ipilimumab, nivolumab, durvalumab, tremelimumab, spartalizumab and atezolizumab) are currently being tested in clinical trials (Table 1) (2).

However, ATC is an orphan disease, accounting for only 3% of thyroid cancers (1). Given the low number of patients that can consequently be recruited for clinical studies, a thorough in silico screening of possible treatment strategies offers an intriguing approach for planning future targeted therapy trials.

The aim of this study is to explore if any of the 155 drugs which have been approved by the FDA for targeted therapy of other solid cancers may play a role in the treatment of ATC based on such an in silico analysis of genetic alterations in ATC.

Genetic alterations in anaplastic thyroid cancer
We identified 15 studies that reported genomic data on a total of 809 ATC patients (Table 2). The data set of Landa et al. (7) provides the largest available whole-exome sequencing (WES) data set and we therefore based our drugability estimates on this study. Systematic tumor genomics data of ATC generated mutation significance as indicated by MutSig and putative copy number alterations as indicated by GISTIC 2.0 were extracted from Landa et al. (7). We included datasets of anaplastic thyroid cancers (n = 33) and excluded poorly differentiated thyroid cancers (n = 84 pat). Mutation variants and copy number variations (CNVs) directly or indirectly affecting genes of potentially targeted therapy options were identified. As the validation study for our work, we used the study by Pozdeyev et al. (8), which provides information on the targeted sequencing of 196 ATC tumors.

FDA-approved targeted therapy and their biological targets
In order to find new therapeutic options in anaplastic thyroid cancer, we first identified all FDA-approved drugs for any cancer therapy by searching the databases of National Cancer Institute (https://www.cancer.gov/news-events/cancer-currents-blog/2017/aliqopa-fda-follicular-lymphoma) and MyCancerGenome (https://www.mycancergenome.org/content/page/what-is-my-cancer-genome/), as previously described (6) (database query 09/2021) (Supplementary Table 1 (http://doi.org/10.6084/m9.figshare.14937117), see section on supplementary materials given at the end of this article). We identified 155 FDA/EMA-approved drugs targeting cancer genetic alterations. These drug lists were linked to 136 genes by querying databases of the University of Texas MD Anderson Cancer Center (https://pct.mdanderson.org/) and Drugbank (9), which encode the potential sites of binding and action of each drug (Supplementary Table 1 (http://doi.org/10.6084/m9.figshare.14937117)). Special attention was given to specific genetic alterations resulting in either drug sensitivity or drug resistance to targeted therapy. Hereby the expert-crowdsourced, publication-based databases from MyCancerGenome (https://www.mycancergenome.org/content/page/what-is-my-cancer-genome/), CIViC (10), TARGET (https://software.broadinstitute.org/cancer/cga/target) and OncoKB (11) (Supplementary Table 2 (http://doi.org/10.6084/m9.figshare.14937117)) were mined.
Table 1  Overview of clinical trials involving ATC (data from Al-Jundi et al. (37)). The table lists the clinical trials on BRAF/MEK inhibitors, kinase inhibitors, mTOR inhibitors and combination therapies in anaplastic thyroid cancer in terms of study design, primary outcomes and reported adverse events. Data from Al-Jundi et al. (37) has been updated with current clinical trials still recruiting. Many trials do not focus on ATC exclusively, but rather include ATC among other thyroid cancer types.

| Drug/clinicalTrials.gov ID/ reference | Mechanism of action | Enrolled patients* | Primary outcome | Study design | Results | Reported adverse events |
|--------------------------------------|---------------------|-------------------|----------------|-------------|---------|--------------------------|
| **BRAF inhibitors**                  |                     |                   |                |             |         |                          |
| Vemurafenib                          | BRAF<sup>V600E</sup> | ATC: 7 (multiple BRAFV600E mutant tumors) | ORR            | Phase II, basket trial | PR: 14%  
CR: 14% | Rash, fatigue, arthralgia |
| Hyman et al. (38)                    |                     |                   |                |             |         |                          |
| **BRAF/MEK inhibitor combination**   |                     |                   |                |             |         |                          |
| Dabrafenib and Trametinib            | Dabrafenib: BRAF<sup>V600E</sup> 
Trametinib: MEK1, MEK2 | ATC: 16 locally advanced or metastatic BRAF<sup>V600E</sup> mutant disease | ORR            | Phase II, single arm, open label | PR: 63%  
CR: 6% | Skin papilloma hyperkeratosis, alopecia, fatigue, fever, diarrhea, acneiform rash |
| Subbiah et al. (17)                  |                     |                   |                |             |         |                          |
| Trametinib and Dabrafenib            |                     | BRAF-positive ATC, neoadjuvant estimated enrolment: 18 | ORR            | Phase II, single arm, open label, recruiting | N/A  
estimated end date: 01/26  
(clinicaltrials.gov) | N/A |
| NCT04739566                          |                     |                   |                |             |         |                          |
| **Tyrosine kinase inhibitors**       |                     |                   |                |             |         |                          |
| Axitinib                             | VEGFR, PDGFR, KIT   | DTC: 45 (resistant to or not appropriate for RAI) 
MTC: 11 
ATC 11 | ORR            | Phase II, single arm, open label | ORR of 30% 
SD for _ 16 weeks: 38% 
PFS: 18.1 months | Fatigue, diarrhea, nausea, anorexia, hypertension, stomatitis |
| Cohen et al. (39)                    |                     |                   |                |             |         |                          |
| Lenvatinib                           | VEGFR, PDGFR, EGFR, RET, KIT | Enrolled all types of thyroid cancer, but results reported one cohort for 17 patients with ATC | Serious/ non-serious AE | Phase II, single arm, open label | Median PFS: 7.4 months 
Most frequent AE (decreased appetite, 82%; HTN, 82%; fatigue, 59%; nausea, 59%; proteinuria, 59%) | Hypertension, diarrhea, fatigue, anorexia, weight loss, nausea |
| Tahara et al. (28)                   |                     |                   |                |             |         |                          |
| Lenvatinib                           |                     | ATC estimated enrolment: 39 | OS             | Phase II, single arm, open label | N/A  
completed 03/20, no results published yet | Fatigue, skin and hair hypopigmentation, diarrhea, nausea |
| NCT02726503                          |                     |                   |                |             |         |                          |
| Pazopanib                            | VEGFR, FGFR, PDGFR, RET, KIT | ATC: 15 (advanced or metastatic disease) | Tumor response rate | Phase II, two arms, open label | No response | Fatigue, skin and hair hypopigmentation, diarrhea, nausea |
| Bible et al. (27)                    |                     |                   |                |             |         |                          |
| Selpercatinib                        | VEGFR, FGFR, RET    | Thyroid cancer with RET alterations (including ATC) estimated enrolment: 30 | ORR            | Phase II, single arm, open label, recruiting | N/A  
estimated end date: September 24 (clinicaltrials.gov) | N/A |
| NCT04759911                          |                     |                   |                |             |         |                          |

(Continued)
### Table 1 (Continued).

| Drug/clinicalTrials.gov ID/ reference | Mechanism of action | Enrolled patients* | Primary outcome | Study design | Results | Reported adverse events |
|--------------------------------------|---------------------|--------------------|-----------------|-------------|---------|-------------------------|
| Sorafenib Capdevila et al. (40)      | VEGFR, PDGFR, RET, KIT, FLT | DTC: 16 MTC: 15 ATC: 3 (metastatic progressive unsuitable for surgery, RAI, or radiotherapy) | ORR | Retrospective, Spanish o_-label-sorafenib-use program | DTC PR: 19% MTC PR: 47% ATC PR: 33% | Hand-foot skin reaction, diarrhea, alopecia, skin rash or desquamation |
| Sunitinib Ravaud et al. (26)         | VEGFR, PDGFR, RET, KIT, FLT | DTC: 41 (RAI resistant) MTC: 26 ATC: 4 (sunitinib as a first-line anti-angiogenic therapy) | ORR | Phase II, single arm, open label | DTC PR: 22% MTC PR: 38.5% ATC: no response | Cytopenia, diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, hypertension |
| **Serine/threonine kinase inhibitors** |                     |                    |                |             |         |                         |
| Abemaciclib NCT04552769             | CDK4 CDK6           | Metastatic or locally advanced anaplastic/undifferentiated thyroid cancer estimated enrolment: 17 | ORR | Phase II, single arm, recruiting | N/A estimated end date: September 23 (clinicaltrials.gov) | N/A |
| **mTOR inhibitors**                 |                     |                    |                |             |         |                         |
| Everolimus Lim et al. (41)          | mTOR               | Thyroid cancer (all subtypes): 38 | Disease control rate (PR + SD > 12 weeks) | Phase II, single arm, open label | PR: 5% (2/38, one PTC patient and one FTC) SD: 76% | Mucositis, anorexia, abnormal, liver enzymes, acneiform rash |
| Everolimus Hanna et al. (42)        |                    | DTC: 33 MTC: 10 ATC: 7 | PFS | Phase II, single arm, open label | DTC: Median PFS 12.9 months, PR 1/38 MTC: Median PFS 13.1 months, PR 1/10 ATC: Median PFS 2.2 months, PR 1/7 | N/A estimated end date: January 22 (clinicaltrials.gov) |
| MLN0128 NCT02244463                |                    | Metastatic ATC estimated ATC: 25 | PFS | Phase II, single arm, open label, recruiting | N/A estimated end date: July 23 (clinicaltrials.gov) | N/A |
| **Combination therapies under investigation** |                     |                    |                |             |         |                         |
| Atezolizumab Bevacizumab Cobimetinib Vemurafenib Paclitaxel Nab-Paclitaxel NCT03181100 | Atezolizumab: PD-1L Bevacizumab: VEGFR Cobimetinib: MEK1, MEK2 Vemurafenib: BRAFV600E Paclitaxel: antimicrotubule agent Nab-Paclitaxel: albumin-stabilized antimicrotubule agent | ATC and poorly differentiated thyroid cancer estimated enrolment: 50 | OS | Phase II, open label, parallel assignment, recruiting | N/A estimated end date: July 23 (clinicaltrials.gov) | N/A |

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| Study design | Primary outcome | Enrolled patients | Mechnism of action | Reported adverse events |
|--------------|----------------|-------------------|-------------------|-------------------------|
| Phase I/ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase I/Ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase I/Ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase I/Ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase I/Ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase I/Ib, open label, parallel assignment, single arm, double-blind, randomized, not recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |
| Phase II, single arm, open label, recruiting | Phase II, single arm, open label, recruiting | N/A | N/A | N/A |

For placebo-controlled studies, only the number for patients enrolled under the treatment arm is mentioned (data from Al-Jundi et al. (37)).
Table 2: Genomic data concerning ATC. The table lists all genomic data found involving anaplastic thyroid cancer. Shown are the number of samples, the main alternated genes in % of the whole sample group and their nationality, gender distribution in % and median age accordingly.

| Study                  | n of samples | Type of sequencing/number of genes | Genes % of total | Genes | Nationality | Gender in % | Median age in years |
|------------------------|--------------|-----------------------------------|------------------|-------|-------------|--------------|---------------------|
| Nikiforova et al. 2013 | 27           | TS 12                             | BRAF 26%         | PIK3CA 11% | USA         | N/A          | N/A                 |
| Jeon et al. 2016       | 11           | WES 520                           | KRAS 9%          | N/A     | Korea       | 27/73        | 75                  |
| Landa et al. 2016      | 33           | TS 341                            | TP53 30%         | N/A     | USA         | 27/24(49)    | 66                  |
| Latteyer et al. 2016   | 30           | TS 9                              | TERT 4%          | N/A     | Germany     | 55/45        | 70                  |
| Tiedje et al. 2017     | 118          | TS 17                             | N/A              | N/A     | Germany     | 48/52        | 65                  |
| Ibrahimpasic et al. 2017 | 57       | TS 410                            | N/A              | N/A     | USA         | 44/56        | >45                 |
| Bonhomme et al. 2017   | 94           | TS 50                             | N/A              | N/A     | France      | 40/60        | 68                  |
| Chen et al. 2018       | 12           | TS 46/50                          | N/A              | N/A     | USA         | 48/52        | 55                  |
| Duan et al. 2019       | 25           | TS 18                             | N/A              | N/A     | USA         | 48/52        | 55                  |
| Yoo et al. 2019        | 13           | WGS                               | N/A              | N/A     | Korea       | 37/63        | 61                  |
| Ravi et al. 2019       | 11           | WES                               | N/A              | N/A     | N/A         | N/A          | N/A                 |
| Xu et al. 2020         | 107          | TS (multiple platforms)           | N/A              | N/A     | USA/Australia | 46/54     | 68                  |
| Lai et al. 2020        | 27           | TS 7                              | N/A              | N/A     | Taiwan      | 49/51        | 75                  |

ATC, anaplastic thyroid cancer; BRAF, v-Raf murine sarcoma viral oncogene homolog B; f, female; HRAS, gene encoding for the H-Ras (Harvey Rat sarcoma virus) protein; KRAS, gene encoding for the K-Ras (Kirsten rat sarcoma virus) protein; n, number; NRAS, neuroblastoma RAS viral oncogene homolog; N/A, not available; m, male; PIK3CA, gene coding for phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TGS, third generation sequencing; TERT, gene encoding for telomerase reverse transcriptase; TP53, gene encoding for tumor protein p53; TS, target sequencing; WES, whole exome sequencing; WGS, whole genome sequencing.
Drug response prediction

Drug response prediction was calculated as previously described (6). Briefly, the genetic datasets of ATC were searched for (i) gain of function; (ii) CNV-amplification; (iii) specific genetic alterations.

The data on approved drugs and their targets were integrated with data on genomic alterations from patients annotated with the biologically relevant genetic alterations. The prediction of whether a patient might respond to a given drug is based on the following criteria:

(i) The gene underlying the FDA-approved drug target shows a copy number increase in the ATC dataset of the TCGA study.
(ii) The drug targets a gene whose product shows a gain of function in the TCGA dataset.
(iii) The drug shows literature-based effectiveness on a specific alteration found in the TCGA dataset such as indicated in the FDA guidelines (7).

Gain of function

Gene alterations resulting in gain of function were determined by querying the databases OncoKB (11) and CIVIC (10). These databases derive a biological effect score from publications. Gene alterations were defined as ‘gain of function’ according to the OncoKB-score (gain of function or like gain of function), CIVIC score (pathogenetic, likely pathogenetic or positive), as well as mutations affecting Chang’s mutational hotspots (12).

CNV-amplification

The data from cBioPortal (13) is annotated with a copy number analysis algorithm (GISTIC 2.0 (14)), which indicates the copy number level per gene: ‘−2’ deep loose, ‘−1’ shallow loose, ‘0’ diploid, ‘1’ low-level gain and ‘2’ high-level amplification. The threshold of high-level amplification ‘2’ was chosen to signify an occurrence of a copy number increase in each tissue sample.

Specific gene alterations

The expert-crowdsourced, publication-based databases (MyCancerGenome, CIVIC, TARGET and OncoKB) list-specific genetic alterations affecting targeted therapy, which were checked on the dataset of anaplastic thyroid cancer (7).

Mutation hotspot analysis

Since mutation hotspots play an important role in thyroid cancer, the mutation datasets were screened to detect mutation hotspots and their frequency. Mutation variants known to be responsive to FDA-approved drugs according to the database DOCM (15) were also searched.

Analysis of genetic coalterations

A co-alteration analysis was performed by querying cBioPortal (13). All genes which were altered in ≥3 (9%) patients were included in this analysis. χ²-tests were performed to identify different distributions of genetic alterations between BRAF-unaltered and BRAF-alterated groups.

Currently recruiting studies on ATC

The databases of the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good clinical practice network (https://ichgcp.net/clinical-trials-registry) and ClinicalTrials.gov (https://clinicaltrials.gov/) were searched for the following terms to identify trials currently recruiting and including patients with ATC: ‘anaplastic thyroid cancer’, ‘thyroid cancer’ and ‘ATC’.

Results

Genetic alterations in targeted genes

To date there are 155 already FDA-approved targeted drugs which could potentially aid ATC patients. According to the National Cancer Institute (https://www.cancer.gov/news-events/cancer-currents-blog/2017/aliqopa-fda-follicular-lymphoma) and MyCancerGenome (https://www.mycancergenome.org/content/page/what-is-my-cancer-genome/) databases, these 155 approved drugs target 136 genes (Supplementary Table 1 (http://doi.org/10.6084/m9.figshare.14937117)).
Twenty-six (79%) of 33 ATC patients from Landa et al. (7) had at least one genetic alteration in the target genes; there were 53 genetic alterations in 24 (17.6%) of 136 targetable genes, with 23 putative driver genetic alterations in 4 genes (BRAF, PIK3CA, ALK and SRC – Fig. 1A). Activating point mutations in the oncogene BRAF were seen in 15 (45.5%) of 33 cases – in all cases occurring as a BRAF V600E mutation. Putative driver PIK3CA mutations were seen in 18% of cases. A similar prevalence of alterations in BRAF and PIK3CA is reported for the 196 tumors examined by Pozdeyev et al. (8) (41 and 14% respectively, Table 2). Genetic alterations in BRAF and PIK3CA were not mutually exclusive (P = 0.13) and occurred in 15% of all and 33% of BRAF-mutated cases. Amplifications of ALK and SRC were detected in 3% of cases respectively (Fig. 1).

**Mutational hotspot analysis**

The most frequently affected pathway was the RAS pathway, including the BRAF V600 mutational hotspot (45%), followed by the NRAS Q61 (18.2%, 6/33 cases). The PIK3CA pathway was affected by activating mutations in 6 (18%) of 33 cases, including PIK3CA E545 (9.1%, 3/33 cases), PIK3CA E542 (6%, 2/33 cases) and PIK3CA E81K (Fig. 1B).

**Analysis of genetic co-alterations**

In the BRAF-mutated group, TERT-alterations were significantly more common than in the WT group (93.3% vs 55.6%, P = 0.0183). In the WT group TP53 (88.9% vs 53.3%, P = 0.029), NRAS (33.3% vs 0%, P = 0.017) and PTEN (27.8% vs 0%, P = 0.036) alterations were significantly more frequent (Fig. 1C).

**Potential drug options**

We predicted the drug response in the ATC tumor samples as previously described (6). The in silico analysis specifically identified BRAF inhibitors (selective BRAF inhibitors or multikinase i.a. BRAF inhibitors). The PIK3CA-inhibitor copanlisib showed a predicted response in 18% of cases. The 146 remaining drugs showed no or low (under 4% cases) genetically predicted drug response in ATC (Fig. 2).

**Discussion**

Several randomized and non-randomized clinical trials have been conducted in ATC during the last years (Table 1). While in 2019 the Surveillance, Epidemiology, and End Results database still reported no improvement in OS.
between 1986 and 2015 (16) there are clear signs of progress. In 2020, a retrospective analysis of 479 patients treated at the MD Anderson Cancer Center over the course of 20 years revealed a significant increase in BRAF screening from 17% between 2000 and 2013 to 97% between 2017 and 2019. Further, the number of patients receiving targeted therapy increased from 9 to 61% and the median OS for patients treated with targeted therapy increased from 7.6 months in patients not having received any targeted therapy to 15.7 months for the same time-frames (3). Targeted therapies administered to patients at MD Anderson included dabrafenib, trametinib, vemurafenib, cobimetinib, larotrectinib, everolimus, pazopanib, bevacizumab, lenvatinib, selpercatinib, lenalidomide and cetuximab. The median OS increased regardless of the specific therapy scheme (3).

The focus of the present study was to screen targeted cancer drugs approved by the FDA for other solid cancers and to identify those that may play any role in ATC based on its genetic alterations. Since these drugs are already approved, the side-effect profile is known which would lead to a faster approval in another cancer moiety such as ATC. While ATC prognosis is particularly poor, it is also relatively seldom, accounting for only 3% of all thyroid cancer (1). This hinders recruitment for clinical studies, and we consequently tried to build a systematic, in silico theoretical framework for future clinical targeted therapy research.

Fifteen studies covering more than 800 ATC samples were identified (Table 2). The largest WES dataset (7) was used for the discovery of druggability and the largest ATC cohort based on targeted sequencing (8) was defined for validation. Potentially targetable genes of FDA-approved targeted therapy included BRAF, PIK3CA, ALK and SRC (Fig. 1A). It needs to be mentioned that in 13 (39.4%) of 33 patients, the data set of Landa et al. (7) did not cover the whole gene set of 136 druggable genes. Therefore, some genes could be underrepresented (Supplementary Table 6).

The in silico analysis identified BRAF inhibitors, in particular the PIK3 inhibitor copanlisib, the VEGFR-2/c-SRC inhibitor apatinib, and the ALK inhibitors brigatinib, ceritinib, crizotinib and lorlatinib as possible targeted therapy agents for ATC (Fig. 2) (21). Although NRAS-Q61 was the second-highest frequency mutation hotspot (Fig. 1B and C), there are currently no FDA-approved drugs targeting this specific mutation. Besides BI1701963 targeting KRAS and Tipifarnib targeting HRAS (both being tested in ongoing studies), to the best of our knowledge, there is currently no drug targeting NRAS.

For the treatment of the BRAF-mutant ATC, the approval of combined BRAF and MEK inhibition with dabrafenib and trametinib in 2018 represented a major breakthrough with an objective response rate (ORR) of 69% and a stable disease (SD) rate of 19%, although almost all patients experienced adverse events (AE) and 42% grade ≥3 AEs (17). Heterogeneous mechanisms of resistance can modulate the efficacy of BRAF-inhibition, including activation of ERBB3, EGFR, PI3K, IL6, HGF/MET and the reactivation of the MAPK pathway through an acquired KRAS G12D mutation. Inhibition of ERK, a strategy for overcoming BRAF and MEK inhibition resistance in melanoma still needs to be tested in ATC (8).
Due to the coexistence of BRAF and PIK3CA mutations in 15% of tumors, future clinical trials might consider synchronous or metachronous combination therapies with PIK3 inhibitors, as described by Gibson et al. (18). The authors performed a multiregional genomic analysis of an exceptional responder to dual inhibition and demonstrated that this exceptional response was due to coexisting alterations in the MAPK and PI3K/AKT pathways. The PIK3CA inhibitor copanlisib has recently proved very successful in recurrent, indolent non-Hodgkin lymphoma (CHRONOS-3 study (19)) and is currently being tested in trials on radioiodine refractory thyroid cancer in order to improve radioiodine response (NCT04462471). To our best knowledge, there are no current trials testing copanlisib in combined treatments for ATC (Table 1).

ALK overexpression and mutation have been described in 11–20% of ATC patient samples (20, 21). In the TCGA data, only amplifications of ALK were detected in 3% of ATC cases (7). The use of ceritinib, a well-tolerated, highly potent oral ALK-inhibitor, is documented in case reports (22) and is currently being tested in a multicenter, open-label trial (NCT02289144, Table 1).

There are case reports, describing the pre- (23) and postoperative (24) use of the selective VEGFR-2/c-SRC inhibitor apatinib in single patients, but no clinical studies have thus far been published.

BRAF inhibitors provide a good option in patients displaying this mutation. Small studies have used multikinase inhibitors for BRAF V600 WT patients. Sorafenib however exhibited a low ORR (10%), short median progression-free survival (PFS) (1.9 months) and OS (3.9 months) (25). In phase 2 trials, both sunitinib and pazopanib showed no overall response (26, 27). In phase 2 trials including 5–17 patients with ATC, there were PRs of 24–60% under lenvatinib treatment (28, 29). Thus, the two first-line agents for differentiated thyroid cancer (DTC) sorafenib and lenvatinib seem to have a poor response in ATC.

The genetic RET/PTC and NTRK rearrangements observed in papillary thyroid cancer have also been described in ATC (30). Selective RET inhibitors such as selpercatinib and pralsetinib have been approved by the FDA for RAI-refractory RET fusion thyroid cancer. Phase I–II trials including previously treated non-medullary TC (n = 19) report a high response rate (79%) and a 1-year PFS of 64% (31). However, only 2 of the 19 non-medullary TC samples were anaplastic. RET mutations occur rather rarely in ATC (32). Instead, TRK fusions have been reported in 25% of ATC (32). For larotrectinib, a highly potent and selective inhibitor of all TRKs approved for the treatment of adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusions, the reported objective response rate for ATC pooled from available phase I/II trials was 29% (33). Additionally, larotrectinib was very well tolerated.

In the study by Pozdeyev et al. (8), TERT promoter mutations were common (65%). The reported coexistence with DTC (34, 35) suggests that they might contribute to the more aggressive DTC phenotype which is prone to conversion to ATC when an ATC-related ‘second hit’ genetic event occurs (8). Whether telomerase inhibitors like INOS401, Telomelysin and Imeltestat, which are currently being tested on myeloid malignancy, might also play a role in the treatment of ATC in the future is still unclear.

Since TP53 seems to be mutated in 9–73% of ATCs (Table 2), p53-activating compounds that are currently being tested on myeloid neoplasms and sarcomas (36) might also offer an option in the future.

The better understanding of the genetic basis of ATC with the identification of BRAF-mutant ATC led to an improvement for the treatment of some ATC patients, however, the median survival of 1.3 years is still quite poor and there is still no satisfying treatment for BRAF WT patients. Here we present the first systematic analysis of all currently available FDA-approved drug options in ATC based on genomic alterations reported from ATC tumor sequencing studies. We restricted this first in silico analysis on already FDA-approved studies as the hurdle to progress to further studies would be relatively low with a drug that has already been approved through clinical trials. However, our data show no new or surprising candidate drug. This could be due to the limited dataset of only 33 patients. We restricted our analysis to these 33 patients as these patients could be clearly identified as having ATC as opposed to poorly differentiated thyroid cancer or other types of TC. It would be interesting to repeat this analysis as more tumor samples are sequenced and are deposited on databases. Further, the drug panel could be expanded significantly beyond FDA-approved drugs in order to identify drugs that could be tested in ATC cell lines as a screening tool before going into cell lines and then patients. Lastly, our software algorithm considers only direct gene targets rather than pathways. Therefore, drugs acting indirectly (like the MEK inhibitor selumetinib for NF1 alterations) might not have been considered sufficiently.

**Conclusion**

Based on the currently available genomic data, targeted therapy options for ATC are limited. PIK3 inhibition might...
be an option for combined strategies with BRAF inhibitors. Few patients might also benefit from VEGFR-2 or ALK inhibitors. However, even this limited dataset identified significant heterogeneity amongst tumor samples. Targeting treatment for BRAF WT tumors seems to be very limited and much more challenging.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0624.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data availability
The datasets generated during and/or analyzed during the current study are available in the figshare repository, http://doi.org/10.6084/m9.figshare.14937117.

Code availability
The codes generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution statement
Daniel Hescheler and Hakan Alakus designed the computational model and framework. Daniel Hescheler, Hakan Alakus and Costanza Chiapponi carried out the implementation. Daniel Hescheler, Milan Hartmann, Burkhard Riemann, Maximilian Michel, Christiane Bruns, Hakan Alakus and Costanza Chiapponi contributed to the interpretation of the results. Daniel Hescheler, Milan Hartmann, Burkhard Riemann, Maximilian Michel, Christiane Bruns, Hakan Alakus and Costanza Chiapponi contributed critical feedback and helped shape the research, analysis and manuscript. Costanza Chiapponi and Daniel Hescheler wrote the first draft of the manuscript, and all authors critically revised the manuscript. All authors approved the final version of the manuscript. All authors decided to submit this study and agreed to be accountable for all aspects of the work as recommended by the ‘International Committee of Medical Journal Editors’ (ICMJE) authorship criteria.

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