Chapter

Systemic Therapy in Thyroid Cancer

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Abstract

The standard treatment for patients with differentiated thyroid cancer (DTC) is a combination of surgery, radioactive iodine (RAI), and long-term thyroid hormone–suppression therapy. Treatment of patients whose diseases persist, recur, or metastasize remains a challenge. The role of cytotoxic chemotherapy in the treatment of thyroid cancer is limited. The key signaling pathways involved in the pathogenesis of thyroid cancers are the RAS/RAF/MEK & PI3K/Akt/mTOR pathways. Systemic therapy in thyroid cancer involves the use of tyrosine kinase inhibitors targeting the above mentioned pathways which are often both effective in controlling disease and have manageable toxicity. Sorafenib and lenvatinib are approved for advanced radioiodine refractory and poorly differentiated thyroid cancers and vandetanib and cabozantinib for recurrent or metastatic medullary thyroid cancers. Cabozantinib is also approved for the treatment of locally advanced or metastatic radioactive iodine–refractory differentiated thyroid cancer that has progressed after prior VEGF-targeted therapy. The combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) is approved for BRAF V600E mutated unresectable locally advanced anaplastic thyroid cancer. Selpercatinib, RET kinase inhibitor is used for advanced and metastatic RET mutated medullary thyroid cancers and advanced and metastatic RET fusion-positive thyroid cancers of any histologic type. Various clinical trials using newer molecules targeting the aforementioned pathways are ongoing.

Keywords: carcinoma thyroid, Iodine refractory, tyrosine kinase inhibitors, anaplastic and medullary thyroid cancer

1. Introduction

The incidence of thyroid cancers is on the rise with over 586,202 new patients diagnosed and greater than 43,646 deaths recorded each year worldwide [1]. Thyroid cancers arise from either of the two cell types, namely follicular and parafollicular cells. Differentiated thyroid cancer (DTC) accounts for 95% of all thyroid cancers [2] and has three subtypes, papillary thyroid cancer (PTC), follicular thyroid cancer

(FTC), and Hurthle cell thyroid cancer (HCTC). The poorly differentiated or undifferentiated category includes anaplastic thyroid cancer (ATC). Differentiated and undifferentiated tumors originate in follicular cells and medullary thyroid cancer (MTC) arises from parafollicular or C cells. While surgery remains the mainstay of the treatment of all different histologies of thyroid cancers, for differentiated thyroid cancers, radioactive iodine and TSH suppression therapy also play an important role in adjuvant management [3]. The prognosis of thyroid cancer, with the exception of anaplastic thyroid cancer is excellent with the standard therapy. Treatment of patients whose diseases persist, recur, or metastasize remains challenging. Cytotoxic chemotherapy has limited role in the treatment of thyroid cancer, hence there was an urgent need for the development of new more effective therapies for that subset of patients. Recent developments in understanding the molecular etiologies of thyroid cancer have led to the identification of novel precision oncological treatments that are significantly improving the outlook for patients with advanced diseases and a new era of treatment options emerged. Targeted therapy with kinase inhibitors has shown promise in management of metastatic and recurrent thyroid cancer. This chapter summarizes the rationale for using systemic therapy and the approved drugs in recurrent or metastatic thyroid carcinoma.

2. Molecular pathogenesis of thyroid cancer

Thyroid cancers arise as a result of the accumulation of multiple genetic mutations that cause abnormal cellular proliferation and prolonged survival of malignant cells. Most thyroid cancers arise as a result of aberrant signaling involving the PI3K/Akt/mTOR and MAPK signaling pathways. The PI3K and MAPK pathways are activated by receptor tyrosine kinase (RTK). The PI3K/Akt/mTOR pathway is classically activated by the induction of RTK at the cell membrane. Activated intracellular PI3K then phosphorylates and activates AKT. AKT then travels inside the nucleus to upregulate various other oncogenes as well the mTOR pathway, that later trigger tumorigenesis. MAPK signaling is stimulated first by activation of an RTK similar to the PI3K/Akt/mTOR pathway. RTK then activates multiple other genes, including MEK, ERK, RAS, and BRAF. ERK ultimately enters the nucleus and then promotes tumorigenesis. The most common of genetic changes in Papillary Thyroid Cancers are point mutations in *BRAF* (40%) [4] and *RAS* (38%) genes [5]. Rearrangement of the *RET/PTC* proto-oncogene occurs in ~10–20% of papillary cancers [6]. Genetic rearrangements and mutations in anaplastic lymphoma kinase (*ALK*) [7] and neurotrophic tropomyosin receptor kinase *(NTRK)1-3* are also present [8], but only ~1–2% of cases. Point mutations of *RAS* and rearrangements of *PPARγ/PAX8* genes are the most common oncogenic alteration in follicular thyroid cancers. Mutations in members of the PI3K pathway, such as *PTEN* deletion/mutation and *PIK3CA*, have also been reported at low frequencies [9]. Both Anaplastic and Poorly Differentiated Thyroid Cancers also demonstrate a high prevalence of the *TP53* and *TERT* promoter mutations, which is usually associated with greater aggressiveness [10]. The most common genetic alterations found in Medullary Thyroid Cancer cells are the *RET*-activating point mutations [11], whereas *RAS* mutations, mainly the *HRAS* and *KRAS* mutations, have been reported in ~17%of cases [12].

Angiogenesis, being a very important process in tumor development is another attractive target for cancer therapy [9]. The vascular endothelial growth factor (VEGF) is overexpressed in the setting of intratumoral hypoxia via hypoxia-inducible

factor-1α (HIF1α) and promotes angiogenesis. This transcription factor HIF1α is also upregulated by MAPK and PI3K/AKT pathways. An important target of HIF1α is the MET receptor, which is highly expressed in many thyroid cancers, promoting angiogenesis, cellular motility, invasion, and metastasis [13]. The above mentioned molecular pathways have been the basis for development of newer drugs and their testing in clinical trials in recent years and thereby provide attractive therapeutic targets for thyroid cancer.

3. Systemic therapy in thyroid cancer

3.1 Chemotherapeutic agents

Cytotoxic chemotherapy has limited role in treatment of thyroid cancer, as most trials using cytotoxic chemotherapies in thyroid cancer have shown disappointing efficacy. FDA approved doxorubicin for the treatment of thyroid cancer in 1974. Chemotherapy regimens with doxorubicin have shown 30–45% partial response in differentiated thyroid cancers [14, 15]. The combination of cisplatin and doxorubicin did not result in any additional improvement in overall response compared to doxorubicin alone [16]. Various other combination chemotherapy regimens also have not yielded any encouraging results so far [17, 18]. Chemotherapy is generally not recommended for patients with differentiated thyroid cancers in view of poor response rates, short duration of response, and toxic effects of chemotherapy [19]. Similar to DTC, chemotherapy has a limited role in the treatment of persistent or recurrent MTC due to the poor response rates (10–15% partial response) [20]. Combination chemotherapy regimens based on dacarbazine and doxorubicin have been tried in MTC, but with limited results [21]. In anaplastic thyroid cancers, chemotherapy in addition to surgery and radiation showed longer median survival rates for stage IVA and IVC ATC patients in a US national cancer registry study [22]. Few other studies have also demonstrated the utility of neoadjuvant chemotherapy in patients with stage IVA and IVB tumors allowing them to undergo successful resection [23]. In advanced cases, doxorubicin, taxanes (paclitaxel or docetaxel) and platins (cisplatin or carboplatin) have demonstrated activity with response rates ranging from 15 to 25% [24, 25].

3.2 Targeted therapies

Evolution of targeted therapies in thyroid cancer:

The increasing knowledge about the molecular alterations underlying thyroid cancer has greatly increased the interest in developing new drugs for targeted treatments in the last decade. The families of drugs that have primarily been investigated and most extensively studied for the treatment of thyroid cancer are tyrosine kinase inhibitors (TKIs). The first international clinical trial started in 2005 and explored the efficacy of motesanib diphosphate on 93 patients with progressive, locally advanced or metastatic, radioiodine refractory DTC. The median PFS was estimated to be 40 weeks [26]. The same drug was investigated for the treatment of locally advanced or metastatic, progressive, or symptomatic MTC in another single-arm phase 2 study which enrolled 91 patients. The median PFS was 48 weeks [27]. Despite these promising results, the drug was not FDA approved for these indications. Both studies used a single-arm design and were performed in a relatively small population of patients. Moreover, the lack of a placebo arm is another limitation. Soon after the motesanib

study, another, phase 2 study examining the effect of axitinib on 52 cases of locally advanced, unresectable, or metastatic MTC or RAI-R DTC was started. The median PFS and OS was 16.1 months and 27.2 months respectively. As in the previous studies, the single-arm design of this study makes the interpretation of the results rather difficult. Although the results appeared encouraging, no further studies have been planned using this drug [28]. These trials show that targeted therapies could lead to prolonged disease stabilization and objective response in patients with metastatic or recurrent thyroid cancers. Following these multiple other targeted agents soon entered clinical trials and there by a new era of treatment options emerged.

3.2.1 Multikinase inhibitors

Various multikinase inhibitors has proven to be an effective treatment option for metastatic and recurrent Thyroid Cancers, given the activity of the PI3K/Akt/mTOR and MAPK signaling pathways in this disease. Currently, there are four drugs, all oral multikinase inhibitors, approved in the treatment of differentiated and medullary thyroid cancer. Sorafenib is a multikinase inhibitor that targets the VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and RAF. Lenvatinib is another kinase inhibitor that targets VEGFR1–3, fibroblast growth factor receptors (FGFR) 1–4, PDGFRα, RET, and c-Kit signaling pathways. Vandetanib selectively targets RET, VEGFR, and EGFR signaling and cabozantinib is a kinase inhibitor of RET, VEGFR2, and MET. All these kinase inhibitors are antiangiogenic, but they also have additional targets that may contribute to their efficacy. The response rates of the above agents vary from 30 to 50% in various trials.

Sorafenib and lenvatinib are FDA approved for advanced radioiodine refractory and poorly differentiated thyroid cancers and vandetanib and cabozantinib are approved for recurrent or metastatic medullary thyroid cancers.

Role of multikinase inhibitors in differentiated thyroid cancer:

Two randomized placebo-controlled phase III clinical trials that led to US Food and Drug Administration (FDA) approval of TKIs for treatment of progressive RAI-refractory DTC are the DECISION and SELECT trials.

Sorafenib was approved by the FDA in 2013 on the basis of DECISION trial in locally advanced or metastatic radioiodine refractory differentiated thyroid cancer [29]. DECISION, a double-blind, placebo-controlled, phase 3 trial trial reported a significant progression-free survival (PFS) benefit of 5 months with sorafenib. Median progression-free survival in the sorafenib group was 10·8 months vs. 5·8 months in the placebo group ($p < 0{\cdot}0001$). However, the overall response rate [ORR] was 12% in the trial. Sorafenib did not improve overall survival (OS), although PFS was longer with sorafenib. The SELECT trial, a phase 3 randomized double-blind trial investigated lenvatinib versus placebo in patients with progressive iodine-refractory DTC which showed a significant improvement in PFS of 14 months with lenvatinib compared with placebo. The median PFS was 18.3 months in the lenvatinib group and 3.6 months in the placebo group ($P < 0.001$) and lenvatinib had an ORR of 65% [30].

Cabozantinib has shown activity in patients with radioiodine-refractory DTC who have been previously treated with lenvatinib, sorafenib, or both TKIs in COSMIC -311, a double-blind, placebo-controlled, phase 3 trial [31]. The trial showed significant improvement in progression-free survival for cabozantinib over placebo (5·7 versus 1·9 months, $p < 0{\cdot}0001$) and an ORR of 15%.Based on the above trial results, FDA approved cabozantinib for the treatment of locally advanced or metastatic radioactive iodine–refractory differentiated thyroid cancer that has progressed after prior VEGF-targeted therapy in 2021.

Role of multikinase inhibitors in medullary thyroid cancer:

Vandetanib was approved for the treatment of locally advanced or metastatic medullary thyroid cancer based on the ZETA trial, a randomized double blind phase 3 trial that demonstrated a PFS benefit of 11 months ($p < 0.0001$) with vandetanib compared with placebo in patients with MTC. At a median follow up of 24 months, vandetanib demonstrated an ORR of 45% [32]. One major limitation in the design of the study was that there was no requirement for disease progression prior to enrolment in the trial. Because of the above limitation, patients with indolent disease could have been part of this clinical trial.

In the EXAM trial a double-blind, phase III trial, which investigated cabozantinib versus placebo in locally advanced or metastatic medullary thyroid cancer, patients were required to have disease progression at the time of study entry. At a median follow-up of 13.9 months, the trial showed that the placebo arm had a much shorter PFS of 4 months compared with 11 months for those in the cabozantinib arm ($p < .001$), with an ORR of 28% [33]. The below table summarises the four approved kinase inhibitors used in thyroid cancers (**Table 1**).

Drug	**Sorafenib (DECISION TRIAL) [29]**	**Lenvatinib (SELECT trial) [30]**	**Vandetanib (ZETA trial) [32]**	**Cabozantinib (EXAM trial) [33]**	**Cabozantinib (COSMIC trial) [31]**
Tumor	DTC -Radioiodine refractory	DTC -Radioiodine refractory	Medullary Thyroid cancer	Medullary Thyroid cancer	DTC -Radioiodine refractory progressing following VEGFR targeted therapy
Targets	VEGFR,c-Kit, RET, PDGFR, RAS	VEGFR,c-Kit, RET, PDGFR, FGFR	VEGFR,c-Kit, RET, EGFR	VEGFR,c-Kit, RET, ERT, MET	VEGFR,c-Kit, RET, ERT, MET
No of patients	417	392	331	330	187
PR%	12.2%	64.8%	45%	28%	15%
Median PFS (Months)	10.8	18.3	30.5	11.3	5.7
Side effects	Palmer-plantar erythro dysesthesia, Diarrhea, alopecia,skin rash, fatigue, weight loss, anorexia, hypertension	Hypertension, Fatigue, Diarrhea, Anorexia, Weight loss, Nausea, Stomatitis	Diarrhea, Skin rash, Nausea, Hypertension Qt-prolongation	Diarrhea, Palmer-plantar erythro dysesthesia, weight loss, anorexia, Nausea, Fatigue, Gi ulcers & hemorrhage	Diarrhea, Palmer-plantar erythro dysesthesia, weight loss, anorexia, Nausea, Fatigue, Gi ulcers & hemorrhage

Table 1.
Four approved kinase inhibitors based on their phase 3outcomes.

3.2.2 Selective inhibitors

3.2.2.1 BRAF and/or MEK inhibitors

Role of BRAF and/or MEK inhibitors in Anaplastic thyroid cancer:

BRAF inhibitors alone, or in combination with MEK inhibitors, have been extensively studied in *BRAF* mutated thyroid cancer. Dabrafenib (BRAF inhibitor) and trametinib (MEK1/2inhibitor) was FDA approved for BRAFV600E mutated ATC based on the safety and efficacy data in a phase II, open-label BRF117019 trial in which 16 patients with BRAF V600E mutant ATC were enrolled [34]. At a median follow-up of 47 weeks, the ORR was 69%. Seven of the 16 patients had continued response to therapy. Median overall survival and progression free survival were not reached in the study. The common adverse effects observed in the study were fatigue, pyrexia, and nausea.

The outcomes of a series of six initially unresectable *BRAF* V600E mutated ATC patients who received neoadjuvant dabrafenib and trametinib followed by a R1 or R0 surgical resection was reported by Wang et al. All six patients continued treatment with dabrafenib and trametinib after surgery. All six patients could undergo complete surgical resection. Analysis of the surgical specimen revealed 0–5% viability in five patients, whereas it was 50% viable in one patient. OS at 6 months and 1 year was 100% and 83%, respectively and loco-regional control rate was 100% in the series [35]. In a large single-institution cohort study at MD Anderson Cancer Center on 479 patients with ATC treated from 2000 to 2019, there were 20 patients treated with BRAF directed neoadjuvant targeted therapy followed by surgery. The 1-year overall survival was 94% in this group [36].

Role of BRAF and/or MEK inhibitors in differentiated thyroid cancer:

BRAF inhibitiors (vemurafenib or dabrafenib) alone or in combination with MEK inhibitors are effective for differentiated thyroid cancers. Vemurafenib was tested in 51 patients with BRAF V600E mutated PTC in a non-randomized, open-label phase II study. 10 of 26 patients who were VEGFR tyrosine kinase inhibitor-naive had partial response (PR) rates of 38.5%, and a majority had at least stable disease (SD) (57.5%). Median PFS was 18.2 months and Median OS was not reached [37]. In another phase II, randomized study, patients with BRAFV600E mutated PTC were randomized to dabrafenib monotherapy or dabrafenib with trametinib. 10 of 26 patients, who received dabrafenib monotherapy, had RECIST defined partial response, while nine of 27 in the combination arm had a partial response of the disease. A total of 50% and 54% in monotherapy and combination, respectively, had at least 20% decrease in target lesions. Median PFS for dabrafinib and trametinib combination was 15.1 months vs. 11.4 months for dabrafenib alone [38].

Mammalian target of rapamycin (mTOR) inhibitors:

The PI3K/Akt/mTOR pathway is downstream of RAS and activation of this pathway mostly occurs in advanced thyroid cancers. Everolimus and temsirolimus are drugs that are inhibitors of the mTOR pathway. These drugs have been studied in several phase 2 clinical trials of all thyroid cancer subtypes.

50 patients (33 DTC, including 13 HCTC; 10 MTC; and 7 ATC) were enrolled in the most recently published everolimus trial by Hanna *et al.* Disease progression within previous 6 months was an inclusion criterion for enrollment to the trial. Six percent of patients in the trial achieved partial response and 74% of patients experienced stable disease. The median PFS was 12.5 months for the entire cohort of patients in the trial. The median PFS in DTC and MTC was 12.9 and 13.1 months, respectively [39].

The combination of everolimus with other targeted agents has also been tried. In a trial combining everolimus and sorafenib, 55% of patients achieved partial response, which is higher than single-agent sorafenib reported in literature [40].

Similarly, when a combination of sorafenib and temsirolimus was studied in follicular-derived thyroid cancer, partial response was seen in 22% patients [10]. Adverse effects of m-TOR inhibitors include mucositis, anorexia, pancytopenia, hyperglycemia, liver function test abnormalities, and rarely pneumonitis.

3.2.2.2 Selective RET inhibitors

Selpercatinib is an oral selective RET kinase inhibitor for RET mutated MTC and RET fusion-positive thyroid cancers. The safety and efficacy of selpercatinib (160 mg twice daily) in patients with RET-mutant MTC was evaluated in the phase I/II LIBRETTO-001 trial. The ORR was 69% among 55 patients previously treated with TKIs including cabozantinib and vandetinib. Among 88 TKI naïve subjects, ORR was 73% and ORR was 62% in a cohort of patients with RET-fusion positive thyroid cancer [41]. Selpercatinib is well tolerated with very few adverse effects reported like fatigue, diarrhea, constipation, dry mouth, nausea, and dyspnea. Pralsetinib, is a second potent RET-inhibitor with activity in RET-fusion positive MTC. ARROW is a phase I/II trial of pralsetinib for RET-mutated cancers. Among 13 RET- fusion positive thyroid cancer patients enrolled in the trial, overall response rates were 91% and all patients had at least stable disease. For RET-mutated treatment naïve MTC patients, overall response rates were 74%, while overall response rates of around 60% were reported for previously treated patients [42]. Pralsetinib is also well tolerated like selpercatinib, with constipation, elevated liver enzymes, hypertension, fatigue, and peripheral oedema being the most common side effects.

3.2.2.3 Other selective inhibitors

The existence of gene fusions in *NTRK*, *ALK*, and *ROS1* in a subgroup of patients with PTC, PDTC, and ATC has added to the understanding of the genetic basis of thyroid cancer and such patients may have more aggressive disease. Larotrectinib is a selective pan-NTRK (A, B, and C) inhibitor. Larotrectinib has been studied in cancer patients that harbor NTRK fusions, including in those with NTRK fusion–positive DTC and ATC [43]. In a study of 28 patients with TRK fusion–positive iodine-refractory DTC, ORR was 75% [44]. Overall, larotrectinib was well tolerated and the most common adverse effects reported were fatigue, nausea, vomiting, abnormal liver function tests and dizziness.

Entrectinib is a potent inhibitor of NTRK like larotrectinib, but it also targets ROS1 and ALK [45]. NCT02568267, an open-label, multicenter, global, phase 2 basket study of entrectinib is enrolling patients with thyroid tumors (including PTC) harboring gene rearrangements in *NTRK*, *ROS1*, or *ALK*.

There is one case report reported in literature of an ATC patient with an *ALK* rearrangement, who has been successfully treated with crizotinib (an ALK inhibitor) after failing standard therapy [46]. An open-label study of ceritinib, an ALK inhibitor, recruiting ATC patients (NCT02289144) is currently ongoing.

3.3 Immunotherapy

Immuno-oncology is another area that is gaining momentum in advanced thyroid cancer, including immune checkpoint blockade. Inhibition of programmed cell death

Study number	Treatments	Thyroid cancer type	Status
NCT04400474 [47]	Cabozantinib with Atezolizumab	ATC	Phase II, Recruiting
NCT04238624 [48]	Cemiplimab with Dabrafenib and Trametinib	ATC	Phase II, Recruiting
NCT03360890 [49]	Pembrolizumab and Chemotherapy	ATC	Phase II, Recruiting
NCT04171622 [50]	Lenvatinib and Pembrolizumab	ATC	Phase II, Not yet recruiting
NCT03181100 [51]	Atezolizumab with Chemotherapy	ATC/PDTC	Phase II, Recruiting
NCT03914300 [52]	Cabozantinib, Nivolumab, and Ipilimumab	Advanced DTC	Phase II, Suspended (scheduled interim monitoring)
NCT04061980 [53]	Encorafenib and Binimetinib and/or Nivolumab	BRAF V600Epositive DTC	Phase II, Recruiting
NCT04675710 [54]	Pembrolizumab, Dabrafenib, and Trametinib	ATC, PDTC	Phase II, Recruiting
NCT02973997 [55]	Lenvatinib and Pembrolizumab	DTC, PDTC	Phase II, Active, Not recruiting
NCT04731740 [56]	Pembrolizumab and Lenvatinib or Chemotherapy	PDTC, ATC	Phase II, Suspended (Financial problems)
NCT03246958 [57]	Nivolumab and Ipilimumab	DTC, MTC, ATC	Phase II, Active, Not recruiting
NCT04524884 [58]	Toripalimab and Surufatinib	MTC, DTC	Phase II, Not yet recruiting
NCT04521348 [59]	Camrelizumab and Famitinib	MTC, ATC, DTC	Phase II, Recruiting
NCT03753919 [60]	Durvalumab with Tremelimumab	ATC, DTC, MTC	Phase II, Recruiting

Table 2.
Ongoing clinical trials of immuno-oncology treatments for thyroid cancer.

protein (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and other proteins in the checkpoint cascade, is currently being investigated as new molecular targets in patients with advanced thyroid cancers (**Table 2**). Updated guidelines that incorporate testing for immuno-oncology markers may need to be developed depending on the results of these trials.

4. Conclusions

Recent understanding on the molecular basis of thyroid cancers have led to newer advances in treatment approaches for patients with advanced and recurrent disease. Patients with advanced radioiodine refractory DTC, PDTC were considered to have poor prognoses until recently. The role of cytotoxic chemotherapy in treatment of thyroid cancer is limited. Sorafenib and lenvatinib are approved for advanced

radioiodine refractory and poorly differentiated thyroid cancers and vandetanib and cabozantinib for recurrent or metastatic medullary thyroid cancers. Cabozantinib is also approved for the treatment of locally advanced or metastatic radioactive iodine–refractory differentiated thyroid cancer that has progressed after prior VEGF-targeted therapy. The combination of the BRAF inhibitor, dabrafenib and MEK inhibitor, trametinib, is approved for *BRAF* V600E mutated; unresectable locally advanced anaplastic thyroid cancer. Selpercatinib, RET kinase inhibitor is used for advanced RET mutated medullary thyroid cancers and RET fusion-positive thyroid cancers of any histologic type. Due to the availability of drugs that target specific molecular alterations for the treatment of thyroid cancers, optimal molecular testing to identify suitable candidates for such therapies is warranted. The knowledge of the molecular profile of the tumor allows informed treatment decisions to be made, though optimal therapeutic sequencing of targeted therapy or their combination with immunotherapy is not yet known. More data from ongoing clinical trials might help to document the optimal therapeutic sequencing of available molecular therapies.

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