

## THEMATIC REVIEW

# Redifferentiation-facilitated radioiodine therapy in thyroid cancer

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## Abstract

Based on experimental data, the inhibition of the MAPkinase pathway in patients with radioiodine-refractory thyroid cancer was capable of inducing a redifferentiation. Preliminary data obtained in a small series of patients were encouraging and this strategy might become an alternative treatment in those patients with a druggable mutation that induces a stimulation of the MAP kinase pathway. This is an active field of research to answer many still unresolved questions.

### Key Words

- ▶ thyroid cancer
- ▶ refractoriness
- ▶ radioiodine
- ▶ redifferentiation

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## Introduction

Since the '40s, the treatment of distant metastases from differentiated thyroid cancer is based on the administration of a high activity of <sup>131</sup>I and this was the first available targeted therapy for metastatic disease that provided long-term benefits in a significant percentage of patients (Hertz & Roberts 1946, Seidlin *et al.* 1946, Coliez *et al.* 1951). Also, the short-term toxicity rate was lower than that observed with other cancer treatment modalities; and on a long-term basis, an increased risk of secondary leukemia and cancers was observed only in a few patients following the administration of high cumulative activities of <sup>131</sup>I (>22GBq) (Rubino *et al.* 2003, Verburg *et al.* 2020).

However, large retrospective studies have shown that two-thirds of metastatic patients became refractory to radioiodine treatment (Durante *et al.* 2006, Schlumberger *et al.* 2014), and this is mainly due to a loss of differentiation of the thyroid cancer cells with an impairment of iodine metabolism. The life expectancy in these refractory patients can be as low as <10% in 10 years (Durante *et al.*

2006, Schlumberger *et al.* 2014) and they might need other treatment modalities.

The improved knowledge on the biology of thyroid cancer has led to therapeutic trials for redifferentiating refractory thyroid cancer that might permit an effective treatment with radioactive iodine. This exciting field of research led to several prospective phase 2 trials and was recently the topic of reviews and editorials (Wirth 2019, Buffet *et al.* 2020, Jhiang *et al.* 2020).

## Abnormalities of iodine metabolism in differentiated thyroid cancer tissue

The two major steps of iodine metabolism – uptake and organification – are altered in thyroid cancer tissues, resulting in an impaired uptake and in a short effective half-life of iodine in the cells (Schlumberger *et al.* 2007). These abnormalities are related to abnormal

expression of thyroid functional genes (Lazar *et al.* 1999, Bidart *et al.* 2000, Lacroix *et al.* 2001): sodium/iodide symporter (NIS) and thyroid peroxidase (TPO) mRNA expression being strongly reduced in most differentiated thyroid cancers.

Immunohistochemistry confirmed that NIS protein expression is profoundly decreased in differentiated thyroid cancer tissues and, in positive samples, NIS protein is detected in only a few malignant cells and appears to be confined to the basolateral membrane (Caillou *et al.* 1998). Other studies suggested that the NIS protein is present in the intra-cellular compartments in some thyroid cancer tissues but is not transported to the cell membrane, and this may explain why it is not biologically active (Dohán *et al.* 2001). TPO biological activity is reduced (Fragu & Nataf 1977) and TPO immunostaining is weak or absent in most carcinomas (Di Cristofaro *et al.* 2006).

The expression of NIS and of most thyroid functional genes is increased following TSH stimulation, and prolonged and intense TSH stimulation should be performed before any administration of  $^{131}\text{I}$  in thyroid cancer patients.

Furthermore, several alterations in the post-translational modification and targeting of NIS protein to the plasma membrane and in its degradation can have an impact on the capability of thyroid cells to concentrate iodine. Dimerization of NIS molecules might be critical for its trafficking to the plasma membrane (Thompson *et al.* 2019). Pituitary tumor transforming gene 1 (PTTG1) binding factor overexpression in thyroid cancers results in decreased NIS levels (Read *et al.* 2011). ADP-ribosylation factor 4 (ARF4) enhances NIS vesicular trafficking from the Golgi to the plasma membrane and valosin-containing protein (VCP), a principal component of endoplasmic reticulum-associated degradation which governs NIS proteolysis; over-expression of VCP can be reverted by a VCP inhibitor (ebastine or clotrimazole) (Fletcher *et al.* 2020).

## Radiation and dosimetry concepts

The outcome of  $^{131}\text{I}$  therapy is related to the dose of radiation absorbed by the thyroid cancer cells and to the sensitivity of these cells to radiation. The absorbed dose depends on the initial radioactive concentration of  $^{131}\text{I}$  in the tissue, namely the ratio between total uptake and the mass of thyroid tissue, and on its effective half-life in the tissue (i.e. the time after which radioactivity in the tissue has decreased by a factor of 2). The effective

half-life is composed of its physical half-life (8.02 days) and of its biological half-life, which is related to its elimination from the tissue. The volume in which uptake occurs can be estimated with 3D imaging, using  $^{131}\text{I}$  and single photon emission computed tomography/computed tomography (SPECT/CT). The poor spatial resolution of this imaging technique is a limiting factor for accurate measurement of small volumes as observed in miliary lung metastases. Moreover, the absolute quantification of  $^{131}\text{I}$  concentration in small lesions is challenging because of the complex detection and image reconstruction processes (Dewaraja *et al.* 2013). PET/CT imaging provides a higher spatial resolution and semi-quantitative measurement of radioactivity, and despite complex radiation decay,  $^{124}\text{I}$  can be used for pre-therapeutic dosimetry assessment (Wierds *et al.* 2016). Advanced methods based on a 3D dosimetry calculation using Monte Carlo simulation (Dewaraja *et al.* 2012) can take into account uptake heterogeneity and improve the accuracy of the absorbed dose estimate (Sgouros *et al.* 2006). Most of the absorbed dose is delivered by beta particles that do not penetrate deep into the tissue (maximum of 2.4 mm in depth). As virtually no beta particles escape from large tumor deposits with  $^{131}\text{I}$  uptake, large absorbed doses may be delivered without damaging surrounding tissues. However, in cases of multiple small diffuse lung metastases with  $^{131}\text{I}$  uptake, the absorbed dose delivered to the normal lung tissue might be significant and in some patients with high lung uptake, high  $^{131}\text{I}$  activities led to radiation-induced pneumonitis (Rall *et al.* 1957).

Even though the administered activity is high, the absorbed dose delivered to neoplastic foci might be suboptimal for successful therapy due to a low radioiodine concentration and a short effective half-life in the lesion (Schlumberger *et al.* 2007). Radioiodine uptake and biological half-life not only differ from one patient to another and in a given patient among metastases, but also differ in a given neoplastic focus and can also vary with time, resulting in wide differences in the absorbed doses among various tumor foci among patients and also in a given patient (Sgouros *et al.* 2004, Wierds *et al.* 2016). Dose distribution is also heterogeneous at the cellular level in neoplastic foci, due to the spotty distribution of radioiodine (Caillou *et al.* 1998) and due to the short path of the beta particles emitted by  $^{131}\text{I}$ . This heterogeneity that is not reflected in the absorbed dose estimate provided by scintigraphic methods may explain some pitfalls of radioiodine treatment.

A positive correlation has been shown between the radiation dose delivered to neoplastic thyroid foci and outcome of  $^{131}\text{I}$  therapy in patients with distant metastases.

The mean radiation dose recommended to treat metastases is 100 Gy (Maxon *et al.* 1983, Maxon & Smith 1990). Many attempts have been made to improve the absorbed dose in neoplastic foci. Prolonged withdrawal of thyroid hormone treatment provides higher metastatic uptake than rhTSH injections (Pötzi *et al.* 2006, Plyku *et al.* 2017) and indeed, iodine contamination should be avoided. Two dosimetric methods might optimize the activity to be administered for treatment (Lassmann *et al.* 2010). One is pre-therapeutic lesion dosimetry from repeated 3D imaging with  $^{131}\text{I}$  SPECT/CT or  $^{124}\text{I}$  PET/CT after a tracer administration. It enables reconstruction of the time-activity curve within the lesion and will determine the activity to be administered to deliver an optimal radiation dose to the lesion. However, in addition to the caveats described above, the dose estimated with a low activity may differ from the dose effectively delivered during a treatment with a high  $^{131}\text{I}$  activity due to lower uptake and shorter retention in the lesion induced by high absorbed doses; this dosimetric method needs to be validated in patients. The other method is whole-body/blood clearance dosimetry to determine the maximal activity that can be administered so that absorbed dose to blood does not exceed 200 cGy and whole-body retention does not exceed 2.96 GBq (80 mCi) at 48 h after administration in the presence of iodine-avid diffuse lung metastases, in order to prevent toxic effects on the bone marrow and lungs (Benua *et al.* 1962, Tuttle *et al.* 2006, Bikas *et al.* 2016).

In a study comparing the outcome of patients with distant metastases with  $^{131}\text{I}$  uptake, overall survival was similar among the different groups of patients classified according to prognostic factors (age and size of the metastases) and treated either with a standard activity of 3.7 GBq (100 mCi) every 6–12 months or with higher activities determined with whole-body/blood clearance dosimetry (Deandreis *et al.* 2017). This study has raised concerns, but unfortunately scientific data demonstrating that either method for dosimetry is beneficial for these metastatic patients in terms of efficacy are still controversial (Klubo-Gwiedzinska *et al.* 2011; Wierst *et al.* 2016). However, these methods might be useful in redifferentiation trials for determining the optimal time of treatment and the  $^{131}\text{I}$  activity to be safely administered (see below).

Following  $^{131}\text{I}$  treatment, complete tumor responses were observed in young patients with small metastases from a well-differentiated DTC and with high initial  $^{131}\text{I}$  uptake (Durante *et al.* 2006). Unfortunately, not all tumor foci with  $^{131}\text{I}$  uptake respond to  $^{131}\text{I}$  treatment, and this is the case in older patients with large metastases from a

poorly differentiated thyroid cancer or in the presence of high fluorodesoxyglucose (FDG) uptake on PET/CT (Robbins *et al.* 2006). Sufficient uptake of  $^{131}\text{I}$  for effective treatment of metastases occurs only in two-thirds of patients, and complete responses are achieved in only one-third of patients (Durante *et al.* 2006). Therefore, about two-thirds of patients with extended disease will be considered refractory to  $^{131}\text{I}$  therapy at some point in their life, with a reduced 10-year life expectancy of ~10%, and will then require other treatment modalities (Schlumberger *et al.* 2014).

### Genomic alterations and relationships with functional defects

Genomic alterations have been characterized in differentiated thyroid cancers (Fagin & Wells 2016). In the Thyroid Cancer Genome Atlas based on the analysis of 500 papillary thyroid cancer tissues, one driver alteration was found in 96.5% of tumors and these alterations were mutually exclusive in most tumors (Cancer Genome Atlas Research Network 2014). The *BRAF V600E* point mutation is the most frequent alteration being found in 45–60%, followed by *RAS* and then *TERT* promoter point mutations; gene fusions (*TRK 1/3*, *RET*, *ALK*, *BRAF*) are found in 15% of tumor samples. Aberrant activation of the MAPK pathway is present in 85% of papillary thyroid cancers.

In advanced follicular cancers, *RAS* mutations are the most frequent (25%), followed by *TERT* promoter, *TP53*, *EIF1AX*, *PTEN*, *RBI*, *GNAS* point mutations and *PAX8-PPARG*, *ALK*, *NTRK 1/3*, *RET* fusions are also found (Yoo *et al.* 2016, Pozdeyev *et al.* 2018). In Hürthle cell carcinoma, the spectrum of mutations is different (Ganly *et al.* 2018). In poorly differentiated thyroid cancers, the density of mutations is higher, and *BRAF* and *RAS* point mutations are the most frequent alterations (Landa *et al.* 2016).

Histological and genomic characteristics have a prognostic impact and may guide the treatment of thyroid cancer. PTC classified as *BRAF*-like tumors are less differentiated than *RAS*-like PTC (Cancer Genome Atlas Research Network 2014). *RAS* mutations are more frequently found in tumors with a follicular pattern (Landa *et al.* 2016), and metastases with RAI uptake are enriched in *RAS*-mutated tumors (Sabra *et al.* 2013). PTC patients with a *BRAF V600E* mutation have a poor clinical outcome, especially if a *TERT* promoter mutation is also present (Xing *et al.* 2013, 2015), and the expression of thyroid functional genes is decreased or absent (Durante *et al.* 2007,

Romei *et al.* 2008). As already reported, about 30% of patients with distant metastases do not demonstrate any radioiodine uptake (Durante *et al.* 2006), and this percentage increases to 70% when *BRAF V600E* is present and to 97% when both *BRAF V600E* and *TERT* promoter mutations are present, whereas it is only 20% in the absence of these two mutations (Liu *et al.* 2020). These data suggest that genomic studies should be performed in all patients with extended thyroid cancer before any systemic treatment, and that whenever mutations are found, they should be taken into account for optimizing the treatment protocol.

### Mechanisms of dedifferentiation

An induced expression of *BRAF V600E* in thyroid cells impaired the expression of thyroid functional genes, which was restored by ceasing its expression or by suppressing the MAPK pathway with a BRAF or a MEK inhibitor (Knauf *et al.* 2005, Chakravarty *et al.* 2011). Similarly, in thyroid cells expressing *RET-PTC1* or a *RAS*-mutated gene, NIS expression was increased following treatment with a MEK inhibitor (Knauf *et al.* 2003). The reversibility of these effects suggests that the inhibition of the expression of thyroid functional genes is related to epigenetic changes.

Loss of differentiation features correlates with the degree of MAPK activation, which is higher in tumors with *BRAF V600E* mutation than in those with receptor tyrosine kinase (*RET*, *TRK* or *ALK*) or *RAS* mutations. In fact, in rat thyroid cells expressing *BRAF V600E* and in an *in vivo* mouse model with *BRAF V600E*-induced thyroid cancer, a small increase in ERK inhibition translates into a markedly increased expression of thyroid functional genes and an increased iodide accumulation in cancer cells (Nagarajah *et al.* 2016, Oh *et al.* 2018). In cases of *BRAF* mutation, the BRAF protein is activated as a monomer and does not respond to the negative feedback of ERK activation, whereas in *RAS*-mutated tumors, the BRAF protein still acts as a dimer sensitive to the negative feedback of ERK activation (Poulikakos *et al.* 2011). In human *BRAF*-mutated thyroid cancer cell lines, the combination of BRAF and MEK inhibition synergistically increased radioiodine uptake, possibly through an inhibition of the rebound of ERK1/2 activation observed with only one drug (Lito *et al.* 2012, Zhang & Chen 2018). Hence, inhibition of MEK-1 and -2 downstream of RAF with drugs such as selumetinib or trametinib could redifferentiate RAI-refractory thyroid cancer. Indeed, the addition of a BRAF inhibitor such as vemurafenib or dabrafenib in cases of *BRAF* mutation

will reinforce the inhibition of the MAPK pathway and will avoid its reactivation due to the disappearance of negative feedback.

One mechanism for the inhibition of the expression of NIS and of other thyroid functional genes is that MAPK pathway activation stimulates transforming growth factor beta (TGFB) secretion that, in turn, stimulates the SMAD pathway that increases the expression of the NADPH oxidase NOX4 (Weyemi *et al.* 2010). NOX4 will then produce ROS that will induce epigenetic changes, such as histone acetylation or methylation at the promoter regions of thyroid functional genes that might reduce their expression (Venkataraman *et al.* 1999, Xing *et al.* 2003, Riesco-Eizaguirre *et al.* 2009, Russo *et al.* 2013, Azouzi *et al.* 2017). All these steps offer the opportunity to use specific inhibitors that might reinduce RAI uptake and organization in thyroid tumor cells.

Activation of the PI3K-AKT pathway was also shown to downregulate iodide uptake and metabolism in thyroid cells. *In vitro* inhibition of the PI3K-AKT pathway induced NIS expression and iodide uptake in human thyroid cancer cells, and also the expression of TSHR, TPO and Tg (Hou *et al.* 2010).

### Manipulating NIS expression gene reactivation and gene therapy

In the past, lithium salts have been used for increasing the effective half-life of <sup>131</sup>I in neoplastic thyroid cells, but their clinical efficacy is still not proven (Luo *et al.* 2018).

Retinoids act on nuclear receptors and activate the transcription of their target genes. Prospective clinical trials failed to demonstrate the clinical utility of isotretinoin (13-cis-retinoic acid) (Short *et al.* 2004, Handkiewicz-Junak *et al.* 2009).

Histone deacetylase inhibitors (Sherman *et al.* 2013) did not induce clinical benefits in patients with radioiodine-refractory thyroid cancer, and clinical trials with methylation inhibitors are still lacking.

Inhibition of BRAF kinase with sorafenib, a weak BRAF inhibitor, did not reinduce significant <sup>131</sup>I uptake in 20 patients evaluated for redifferentiation (Hoftijzer *et al.* 2009).

### Gene therapy

Transfection of NIS cDNA into malignant non-thyroid cells enabled the transfected cells to take-up radioiodine (Shimura *et al.* 1997, Mandell *et al.* 1999, Boland *et al.* 2000,

Spitzweg & Morris 2002). However, NIS-infected tumor cells do not organify iodide efficiently, and this results in a short half-life in the cells and in insufficient radiation doses for treatment efficacy (Magnon *et al.* 2007).

## Current treatment of advanced refractory thyroid cancer

When there is no radioiodine uptake in the metastases or when metastases progress despite the presence of uptake, the disease is considered refractory and radioiodine administration is abandoned (Schlumberger *et al.* 2014). Systemic treatment is currently based on tyrosine kinase inhibitors (TKI). Two phase 3 trials with anti-angiogenic TKI, one with sorafenib and the other with lenvatinib, showed significant improvement of median progression free survival (PFS) over placebo and this led to their approval by the FDA and EMA (Brose *et al.* 2014, Schlumberger *et al.* 2015). Other anti-angiogenic TKIs have been effective in phase 2 trials, such as cabozantinib (Cabanillas *et al.* 2017), pazopanib (Bible *et al.* 2010) and axitinib (Locati *et al.* 2014), which might be used as second line treatment. Unfortunately, the benefits of these TKIs are transient in most patients with no demonstrated benefits on overall survival, except for elderly patients treated with lenvatinib (Brose *et al.* 2017). Furthermore, efficacy appears somehow less important in real-life settings (Berdelou *et al.* 2018, Locati *et al.* 2019) and the long-term use of these TKIs is associated with toxic effects that may be fatal in some (Lamartina *et al.* 2016). More recently, the use of specific inhibitors directed against fusions such as *RET*, *TRK* or *ALK* has produced profound tumor responses in a large proportion of treated patients (Drilon *et al.* 2018, Wirth *et al.* 2020). In patients with a *BRAF V600E* mutation, a *BRAF* inhibitor (dabrafenib) alone or in association with a MEK inhibitor (trametinib) induced a tumor response in up to 54% of patients when administered on a long-term basis (Shah *et al.* 2017). The toxicity profile of these selective TKIs is often more favorable than that observed with anti-angiogenic TKIs. Therefore, the presence of selectively druggable abnormalities should be screened in patients with extended disease, and whenever present, a specific inhibitor might be considered.

Because of their toxicity and the absence of demonstrated benefits on overall survival, the use of multikinase inhibitors is often limited to patients with radioiodine-refractory DTC who have large tumor burden, with symptoms or risk of local complications and clinically

meaningful disease progression. Patients with radioiodine-refractory DTC who are asymptomatic and have a low tumor burden and a slowly progressive disease are often followed with active surveillance alone. However, their disease-specific survival is not favorable, and a treatment approach that would be more effective than active surveillance is clearly needed.

## Redifferentiation: current experience

Based on experimental data, inhibition of the MAPkinase pathway might be used on a short-term basis (4–6 weeks) to induce redifferentiation of thyroid tumor cells. Then, in case of reappearance of a significant tumor uptake following rhTSH stimulation, <sup>131</sup>I treatment is administered (Ho *et al.* 2013). Prospective trials are ongoing to evaluate the benefits of this strategy in DTC patients with advanced RAI-refractory (RAI-R) disease, to ascertain the absence of significant toxicity and to evaluate the global cost of this strategy (Table 1).

In the first clinical study, 24 patients with advanced RAI-R DTC were treated with selumetinib (a MEK inhibitor) for 4 weeks and then submitted to <sup>124</sup>I PET-CT following rhTSH stimulation to estimate the activity of <sup>131</sup>I required to deliver an arbitrary dose of 2000 cGy and above to the metastatic lesions (Ho *et al.* 2013). If it appeared that at least one lesion could be treated with an activity of less than 300 mCi, the patient was then treated with <sup>131</sup>I. Of the 20 evaluable patients, selumetinib increased radioiodine uptake in 12. Of these 12 patients, eight reached the dosimetry threshold for radioiodine therapy and were treated with <sup>131</sup>I. Seven of these 8 patients had a confirmed RECIST 1.1 partial response 6 months after radioiodine therapy, but the duration of response was not reported. The eight patients who reached the dosimetry threshold included all five patients with *NRAS* mutation but only one of the nine patients with *BRAF V600E* mutation. This led to the hypothesis that in *BRAF V600E*-mutant tumors, pre-radioiodine treatment by a more robust MAPK inhibition might be needed to effectively induce redifferentiation. To confirm these preliminary data, a multicenter UK single arm phase II trial (SEL-I-METRY, ISRCTN17468602) is ongoing with a similar design (treatment with selumetinib for 4 weeks) and patients showing a significant iodine uptake following rhTSH stimulation are treated with a fixed activity of 150 mCi of <sup>131</sup>I; the potential role of lesion dosimetry is assessed but is not taken into account for treatment decision (Brown *et al.* 2019).

**Table 1** Trials and clinical case reports with redifferentiating strategy with MAPK inhibitors.

Study	TKI/Duration of treatment	Evaluable patients (n)	Restoration of RAI uptake (n)	Treatment (n)	Outcome
Ho <i>et al.</i> 2013	Selumetinib/4 weeks	20	12	8: 5/5 NRAS; 1/9 BRAF; 1/3 RET/PTC; 1/3 WT	At 6 months: 5 PR, 3 SD
Rothenberg <i>et al.</i> 2015	Dabrafenib/6 weeks	10 BRAF V600E	6	6	At 3 months: 2 PR, 4 SD
Dunn <i>et al.</i> 2019	Vemurafenib/4 weeks	10 BRAF V600E	6	4	At 6 months: 2 PR, 2 SD
Jaber <i>et al.</i> 2018	Dabrafenib or vemurafenib +/- trametinib/1–76.4 months	13 with RAI uptake on long-term TKI	13	9: 3/3 RAS, 5/9 BRAF, 1/1 WT. 8 PR, 1 PD on long-term TKI	At 8.3 months: 3 PR, 6 SD
Iravani <i>et al.</i> 2019	Dabrafenib +/- trametinib or vemurafenib + cobimetinib/4 weeks	6	4	4: 1/3 NRAS, 3/3 BRAF	At 3 months: 3 PR, 1SD
Huillard <i>et al.</i> 2017	Vemurafenib/8 months and then dabrafenib/3 months	1 BRAF V600E	1	1	1 PR after each treatment
Leboulleux <i>et al.</i> 2019	Dabrafenib + trametinib/8 weeks	1 BRAF K601E	1	0	Thyrotoxicosis

PD, progressive disease; PR, partial response; SD, stable disease.

In another pilot trial, vemurafenib (a BRAF inhibitor) was evaluated in 12 patients with *BRAF*-mutated advanced RAI-R DTC, with a methodology similar to the previous initial study (Dunn *et al.* 2019). Four of the ten evaluable patients reached the dosimetry threshold on <sup>124</sup>I PET/CT and were treated with <sup>131</sup>I; 6 months after radioiodine therapy, two achieved a partial response and two patients had stable disease. Of the four <sup>131</sup>I-treated patients, two required subsequent thyroid cancer treatment at 9 and 18 months, and the other two patients have not required further therapy at 22 and 33 months, respectively, suggesting prolonged benefits. Molecular tumor biopsy analysis performed before and during vemurafenib treatment in three patients revealed a decrease in MAPK pathway transcriptional output and induction of thyroid-specific gene expression, suggesting that these two modifications are related.

The BRAF inhibitor dabrafenib was evaluated in ten patients with *BRAF V600E*-mutated advanced RAI-R thyroid cancer (Rothenberg *et al.* 2015). These patients had no radioiodine uptake on a baseline WBS, and five of them had documented progression during the 14 months prior to enrolment. After 6 weeks of dabrafenib treatment, radioiodine uptake after rhTSH stimulation was detectable on diagnostic WBS in six patients who were treated with a standard activity of 150 mCi <sup>131</sup>I. At 3 months after radioiodine therapy, two patients showed partial response and four stable disease.

The retrospective analysis of patients with RAI-R DTC treated with MAPK inhibitors (BRAF and/or MEK inhibitors) confirmed these data (Jaber *et al.* 2018, Iravani

*et al.* 2019). In a study of 13 patients treated with a BRAF or a MEK inhibitor for 1 to 76.4 months and who had RAI uptake on a diagnostic WBS performed on TKI treatment, nine were treated with a therapeutic activity of 150–250 mCi of <sup>131</sup>I. An increase in serum Tg or Tg Ab levels was observed in seven of nine responders while on TKI treatment. All nine patients had durable disease control, and *RAS*-mutated tumors were the best responders compared to *BRAF*-mutated tumors (Jaber *et al.* 2018). In another study, six patients were treated with a MEK inhibitor (*NRAS* mutated) or with a combination of a BRAF inhibitor and a MEK inhibitor (*BRAF* mutated) for 4 weeks, and four were considered suitable for radioiodine therapy based on the results of <sup>124</sup>I PET/CT (Iravani *et al.* 2019). All three *BRAF*-mutated patients responded to the redifferentiation strategy, while only one of the three *NRAS*-mutated patients did. Of these four patients, three achieved partial tumor response and one had stable disease with a median follow-up of 16.6 months.

Additional case reports demonstrated the potential redifferentiating effect of pharmacological MAPK inhibition in thyroid cancer patients with extended disease. In one patient with a *BRAF V600E*-mutated papillary thyroid cancer, both vemurafenib and dabrafenib sequentially induced tumor uptake and <sup>131</sup>I treatments induced partial response (Huillard *et al.* 2017). In another case report, clinical thyrotoxicosis developed in a patient with a *BRAF K601*-mutated advanced papillary carcinoma treated with dabrafenib and trametinib (Leboulleux *et al.* 2019). In both cases, this redifferentiation effect was transitory and RAI uptake disappeared shortly after

discontinuation of the redifferentiation drugs as well as thyrotoxicosis in the second case. FDG uptake on PET/CT decreased during redifferentiation treatment. The observed rise in serum thyroglobulin levels during redifferentiation treatment might indicate redifferentiation rather than disease progression, and no increase in serum Tg level was observed in patients who had no restoration of iodine uptake (Ho *et al.* 2013, Rothenberg *et al.* 2015, Huillard *et al.* 2017, Jaber *et al.* 2018, Dunn *et al.* 2019, Leboulleux *et al.* 2019). Serum Tg level rapidly decreased following discontinuation of redifferentiation therapy.

This redifferentiation concept might apply to refractory thyroid cancers with other mutations using a specific inhibitor, as shown by the redifferentiation observed in a patient with *TRK* fusion following treatment with larotrectinib, a NTRK inhibitor (Groussin *et al.* 2020).

These preliminary data clearly demonstrate that redifferentiating drugs induce a re-expression of NIS that is responsible for increased iodine uptake and also of other thyroid functional proteins that are needed for its retention inside thyroid tumor cells. Available data also suggest that these redifferentiation treatments might decrease the heterogeneity of radioiodine uptake among metastases and also in a given metastasis, thereby increasing the efficacy of <sup>131</sup>I treatment (Ho *et al.* 2013).

Additionally, the efficacy of RAI therapy depends not only on sufficient absorbed doses to metastatic lesions but also on the radiosensitivity of the tumor cells, and MEK inhibitor has been reported to radiosensitize tumors to external beam radiation therapy (Fig. 1). Thyroid cancer cell lines carrying the *BRAF V600E* mutation were associated with resistance to ionizing radiation, and the BRAF inhibitor, vemurafenib, selectively radiosensitized *BRAF V600*-mutated tumor cells by inhibiting DNA double-strand break repair. Vemurafenib in combination with radiation therapy resulted in marked and sustained regression of thyroid tumor xenografts carrying the *BRAF V600E* mutation (Robb *et al.* 2019). Thus, BRAF/MEK inhibitors probably not only enhance RAI delivery but also increase RAI radiosensitivity.

Future prospects to improve tumor redifferentiation, especially of *BRAF V600E*-mutated thyroid cancers, might come from a profound inhibition of the MAPK pathway. An ongoing multicentric clinical trial performed by the French RAI-R thyroid cancer TUTHYREF network is testing the treatment of metastatic RAI-R DTC with either a MEK inhibitor (trametinib) alone (for *RAS*-mutated tumors) or in combination with a BRAF inhibitor (dabrafenib) (for *BRAF V600E*-mutated tumors) followed by a standard therapeutic activity of 150 mCi of <sup>131</sup>I after rhTSH stimulation in case

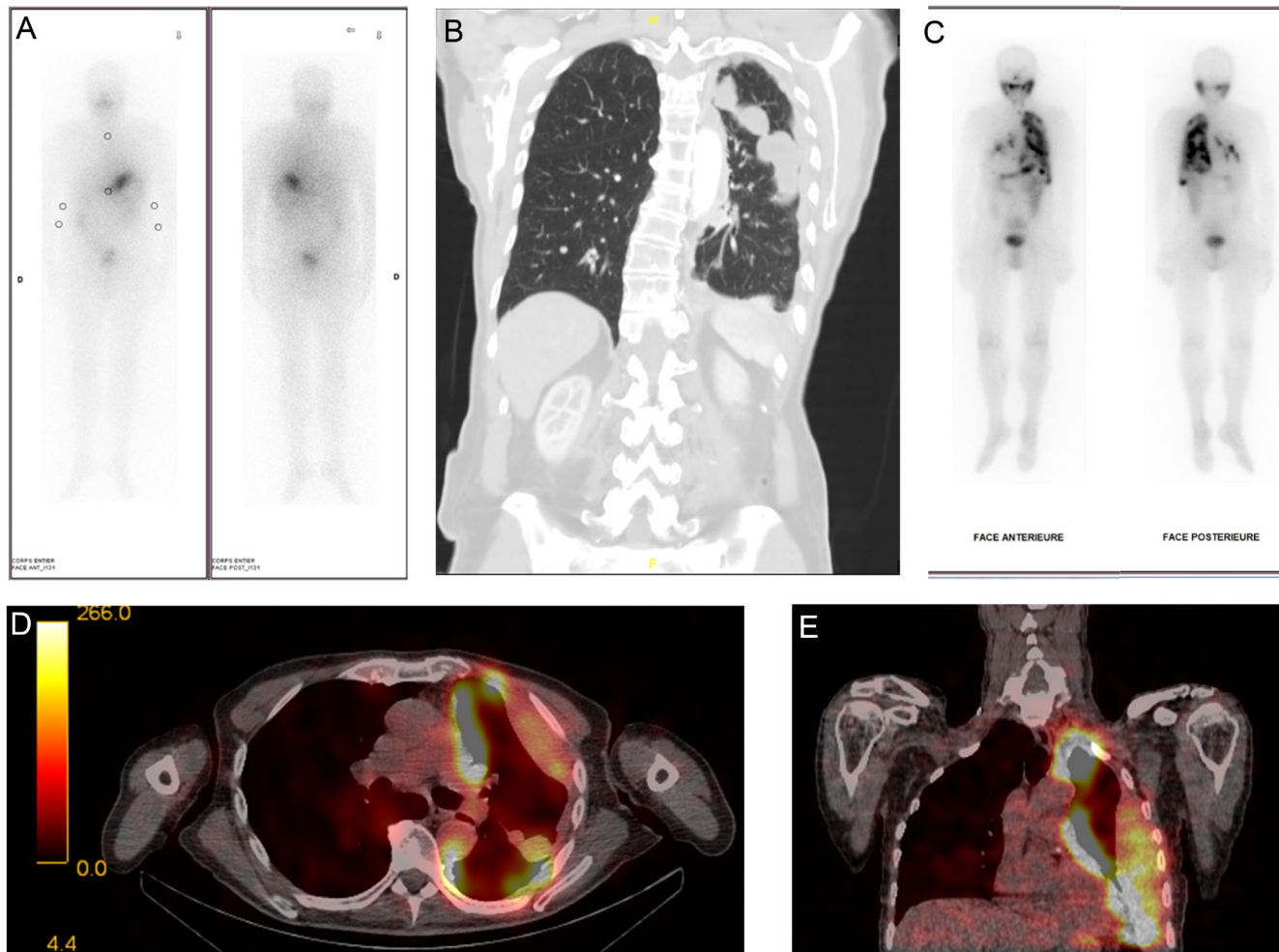
of restoration of radioiodine uptake (NCT03244956). The clinical merit of lesional dosimetry will be evaluated, as will the duration of response, and any potential benefit of a second course of redifferentiating treatment in cases of tumor response after some months per protocol or only at progression. This trial includes selected patients with a relatively small metastatic burden and with a slow progression rate that are the best candidates for response to <sup>131</sup>I treatment (Durante *et al.* 2006). Whether the findings of this trial could be applied to metastatic patients with other characteristics, such as larger metastases or higher progression rates, will need further studies.

Finally, in these studies it is difficult to distinguish between tumor response resulting from a cytotoxic effect of the pharmacological inhibitor and the effect of <sup>131</sup>I therapy after the restoration of radioiodine uptake or a combination of both effects. However, a treatment given for 4 to 6 weeks is unlikely to produce long-term tumor responses; in one study (Jaber *et al.* 2018) in nine patients who had either stable disease (in eight) or progressive disease (in one) during long-term kinase inhibitor treatment, <sup>131</sup>I treatment induced a partial response in three, including in the one with progressive disease and stable disease in the other six patients, with some tumor regression in three of them. This short-term treatment will induce low toxicity, if any, that will then be much lower than toxicities observed during long-term TKI treatments and will probably reduce the global cost of treatment.

### Redifferentiation: potential advances

Several strategies based on current knowledge of the biology of refractory thyroid cancer might improve the efficacy and tolerance of redifferentiation.

To date, it remains unknown why some RAI-R DTC patients do not have restoration or enhanced RAI uptake after BRAF/MEK inhibitor therapy. The comparison of genomic characteristics of responsive and non-responsive patients and their relationships with changes in thyroid functional gene expression, both at baseline and during the redifferentiation treatment, might be informative. Furthermore, a standard protocol is applied in these trials, but probably some optimization might be warranted in the length of treatment or in the protocol used for TSH stimulation. This optimization might be guided during treatment by the trend in serum Tg level and the decrease of FDG uptake on PET/CT, and by lesion dosimetry assessed following rhTSH stimulation with a diagnostic activity of radioiodine. The risk of radiation-induced

**Figure 1**

Redifferentiation treatment in a 72 year old patient with metastatic radioiodine refractory tall cell papillary thyroid cancer with BRAF V600E mutation. The patient had a 8 cm tall cell variant papillary thyroid carcinoma with tracheal invasion, synchronous lung and pleural metastases: pT4a N1b M1, stage IV according to AJCC/UICC TNM 7th edition. He was initially treated with total thyroidectomy, tracheal resection and anastomosis, central and lateral neck dissection. The post-therapeutic whole body scan after the first radioiodine treatment with an activity of 100 mCi (3700 MBq), following a prolonged thyroid hormone withdrawal showed no uptake in the distant metastases. Three years later the patient was treated with lenvatinib for progressive disease; this treatment was maintained for 4 years and was withdrawn for progressive disease. A BRAF V600E mutation was found in the primary tumor tissue. A whole body scan with 5 mCi (185 MBq)  $^{131}\text{I}$  was performed following thyroid hormone withdrawal and did not show any uptake (panel A) in bulky pulmonary and pleural metastatic disease (panel B). The patient received a treatment with dabrafenib and trametinib for 6 weeks and then an activity of 150 mCi (5550 MBq) of  $^{131}\text{I}$  was administered after recombinant human TSH stimulation. The post therapeutic whole body scan (panel C) and SPECT/CT (panel D and E) on the redifferentiation treatment showed a high radioiodine uptake in the multiple pulmonary and pleural lesions, that represented 9% of the administered activity at day 3 after  $^{131}\text{I}$  administration, corresponding to 275 MBq.

toxicity (Jaber *et al.* 2018), such as lung irradiation due to high RAI uptake in diffuse lung metastases as well as bone marrow toxicity should be minimized with the use of whole-body/blood clearance dosimetry.

For BRAF V600E-mutated thyroid cancers, a strategy could be to combine inhibitors of the human EGF receptor (HER) with MAPK inhibitors. In thyroid cancer cells harboring the BRAF V600E mutation, inhibition of the MAPK pathway by a RAF or a MEK inhibitor might be transient due to the release of a transcriptional repressor

from the HER3 promoter and consequently induced HER3 gene overexpression (Montero-Conde *et al.* 2013). An autocrine secretion by thyroid cancer cells of a ligand able to bind to and activate by dimerization the tyrosine kinase receptors HER2/HER3 resulted in the reactivation of the MAPK and PI3K pathway. The HER kinase inhibitor lapatinib prevented MAPK rebound and overcame BRAF-mutated thyroid cancer cell resistance to MAPK inhibitors (Montero-Conde *et al.* 2013). In BRAF V600E-mutated human thyroid cancer derived cell lines, the combination



of lapatinib with dabrafenib or selumetinib increased radioiodine uptake (Cheng *et al.* 2017). A clinical trial (NCT02456701) which tests the ability of vemurafenib combined with an anti-HER3 monoclonal antibody to restore iodine incorporation in *BRAF* mutant RAI-R thyroid cancer patients is ongoing.

As PI3K inhibition seems to prolong radioiodine retention in thyroid cells in experimental models (Lakshmanan *et al.* 2015), the combination of MAPK and PI3K inhibitors might be an interesting strategy (ElMokh *et al.* 2017) but with the disadvantage of potential synergistic side effects.

As previously discussed, NOX4 is activated in *BRAF V600E*-mutated tumors and by producing ROS might be responsible for a decreased expression of thyroid functional genes, including NIS. These inhibitory effects might be achieved through epigenetic changes such as acetylation of histones of the *NIS* promoter gene or the hypermethylation of its promoter region. Therefore, drugs inhibiting NOX4, acetylation of histones (HDAC inhibitors) or hypermethylation of the NIS promoter might be used in these patients, probably in association with inhibitors of the MAPK pathway.

## Redifferentiation: applications for adjuvant treatment

When the benefits of redifferentiation are demonstrated in patients with advanced RAI-R DTC, this therapeutic strategy might also be used for post-operative RAI administration in selected patients with localized thyroid cancer. It is often recommended to perform an aggressive treatment that includes post-operative <sup>131</sup>I administration in patients with either an aggressive form or a papillary thyroid cancer with a *BRAF V600E* mutation. However, RAI may be ineffective in these patients due to a low or absent RAI uptake in the tumor tissue. The ASTRA phase III study (NCT01843062) in DTC patients at high risk of recurrence after total thyroidectomy (i.e. pT > 4 cm, pT4, N1 with ≥ 5 lymph nodes or with at least one lymph node ≥ 1 cm) was disappointing. Patients were randomized to receive placebo or selumetinib for 4 weeks prior to post-operative radioiodine ablation. The complete remission rate at 18 months was not improved by the addition of selumetinib to radioiodine (40% vs 38.5% in the placebo group) in this patient population, or in any subgroup of patients, even when genotype was taken into account (Ho *et al.* 2018). However, patients with a low probability of radioiodine uptake, such as patients with a *BRAF*-mutated

tumor, might benefit from a redifferentiation strategy before post-operative RAI administration after selection by genomic studies that might also be performed in patients with aggressive thyroid cancer even confined to the neck.

## Conclusion

Redifferentiation appears to be an alternative treatment for RAI-R thyroid cancers, but clinical data are still preliminary. It is feasible based on genomic studies of thyroid cancer tissue and has already provided significant clinical benefits in a limited number of patients, and will probably reduce the global cost of treatment. However, it needs to be optimized, its toxicity should be assessed and its role in treating these patients has to be delineated in future trials. Furthermore, this method might be also applied to patients with aggressive disease even confined to the neck and in the presence of a *BRAF V600E* mutation, when no uptake of radioiodine is highly probable. Finally, whether this strategy might afford benefits in patients with anaplastic thyroid cancer carrying a targetable mutation has to be tested in specific trials

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review

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