

Mitogen-Activated Protein Kinase Inhibitor Selumetinib Fails to Increase the Complete Response Rate of Radioactive Iodine Alone in High-Risk Differentiated Thyroid Cancer: Lessons From the Phase III ASTRA Study

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Radioactive iodine (RAI) remains the standard adjuvant therapy for patients with high-risk persistent or recurrent thyroid cancer after surgery. In the majority of cases, the combination of surgery and radioiodine will result in a cure, but for approximately 10% of patients, disease will persist. This may be due to reduced RAI avidity, innate resistance, or dedifferentiation and consequent loss of ability to actively transport iodide ions into the thyroid cancer cells. Given the success of radioiodine as an effective and highly targeted therapy in the majority of thyroid cancers, there has been great interest in developing methods to enhance or reinstate RAI uptake in refractory disease to maximize the usefulness of this targeted therapy. Constitutive activation of the RAS-RAF-mitogen-activated protein kinase (MAPK) pathway in many thyroid cancers inhibits the expression of the sodium-iodide symporter and thyroid peroxidase, which facilitates iodine uptake and organification, respectively. MEK inhibition has been shown in preclinical studies to increase the uptake of RAI through blockade of the RAS-RAF-MAPK pathway.¹

In the accompanying article to this editorial, Ho et al² aim to use the addition of the MAPK inhibitor selumetinib to improve the complete response (CR) rate in high-risk patients after their initial surgery and treatment with RAI. Unfortunately, the study was negative and, therefore, should not change current practice: RAI alone in the adjuvant setting for high-risk patients remains the standard of care. The authors are to be commended, however, as this is the first time that a phase III study has been conducted to assess the efficacy of the addition of a kinase inhibitor to improve the efficacy of RAI in any setting. In this instance, they aim to determine if selumetinib can improve the CR rate in patients at high risk for recurrence when treated with adjuvant RAI after surgery. Simply the execution of such a large study affords many learning opportunities to inform further research into these challenging clinical dilemmas. In a disease widely considered to have a

favorable prognosis, the field has been predominantly focused on the risk of overtreatment. Thus, the identification and prospective confirmation of a subset of high-risk patients, < 50% of whom are free of disease 18 months after curative-intent therapy, is important as such patients are at risk of undertreatment.

The concept and design of the ASTRA phase III study was based on years of innovative preclinical discovery^{1,3} followed by a pilot study in patients with RAI-refractory thyroid cancer in whom the role of selumetinib in reinducing RAI uptake was investigated.⁴ These data provide a compelling putative (and druggable) mechanism for the loss of RAI avidity in patients with RAI-refractory advanced disease⁴⁻⁷ and are continued to be actively studied by multiple groups globally.⁸ However, it is unclear whether the same mechanism is the primary (or even an important) driver of the high recurrence rate in the population with early disease studied here. Given that mutations are common between high-risk patients and those with advanced disease, hypothesizing an adjuvant benefit of selumetinib was reasonable.

However, the protocol design faced several challenges. The first challenge was in estimating the likely CR rate to RAI alone in this patient population using available data. A figure of 30% was used on the basis of a retrospective analysis of historical data (before 2012) and thus was at risk of being lower than in contemporary practice. Indeed, the CR in the placebo arm of this study was higher than that predicted at 38%, which is almost certainly an underestimate given that 23% of those who received placebo had missing 18-month assessments and were all designated as treatment failures, a fraction of whom undoubtedly would have CRs. Therefore, with the true CR rate in this population with radioiodine alone likely to be higher than that estimated, it likely made it more difficult to identify a benefit of the addition of selumetinib. Second, the choice of primary end point of an absolute improvement in the CR of 20% was ambitious as it would represent a relative 67% increase over the predicted control CR rate used in the study design.

ASSOCIATED CONTENT

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THE TAKEAWAY

In the accompanying article to this editorial, Ho et al² aim to use the addition of the mitogen-activated protein kinase inhibitor selumetinib to improve the complete response rate in high-risk patients after their initial surgery and treatment with radioactive iodine. Although this is the first phase III study in this setting and provides important lessons for future studies, the study was negative and, therefore, should not change current practice: radioactive iodine alone in the adjuvant setting for high-risk patients remains the standard of care.

Third, excluding patients with thyroglobulin (Tg) levels performed on the wrong day along with those who did not have Tg levels done at all likely decreased the number of evaluable patients further although this is unlikely to have changed the outcome of the study.

Having shown no improvement in CR rates, the authors suggest that this is the study design that should be used for registration trials going forward. This remains to be seen given the magnitude of the challenges that the study faced. For example, a very high screen failure rate (160 of 400) is problematic and adds burdens to study sites and to patients. The supplemental data discloses that anti-Tg antibodies were the most common reason for screen failure, but understanding other causes would be important for future study designs. For example, if the increased scrutiny during screening uncovered more patients with gross residual or metastatic disease than that would be detected by standard clinical care, the remaining patients presumably would have a better-than-expected CR rate on that basis alone. Thus, the information gleaned from the screen failures is valuable, may be helpful in planning future studies, and should be reported.

An important weakness of the study intervention was that only 83 patients, one third of the patients on the selumetinib arm, were treatment-compliant, that is, able to tolerate the treatment as prescribed. Furthermore, critically missing is information on how frequently selumetinib-induced toxicity resulted in not receiving or delaying RAI, the standard therapy. Even in the 77% of patients who were compliant with selumetinib around the time of RAI, there was no significant improvement in CR rate. Thus, even if patients were able to tolerate treatment, there is still no evidence that this would improve outcome. These issues underscore the importance of selecting a tolerable agent that permits adequate dose intensity to test the putative goal of increased radioiodine avidity and efficacy, a point addressed by the authors in their discussion.

It is possible that the concept is solid, but selumetinib is the wrong agent. Selumetinib has significant toxicity, especially when compared with placebo. Keeping patients on the recommended dose throughout the study was a challenge. Other studies using agents that have more manageable side effect profiles may have more success in avoiding dose interruptions, reductions, and discontinuations. Several

pilot and phase II studies of other agents, some with more selective inhibitors, have been completed,⁴⁻⁷ and more are underway.⁸ However, it will be important to take into account how CR rates in the genetically altered subpopulations may differ from those seen in the general population to adequately power future trials.

A missed opportunity in this trial was the absence of any dosimetric data (that were highly informative in the pilot study of patients with advanced disease), which would have provided information on the impact of absorbed dose achieved with administered empirical RAI activity. Indeed, this study underscores the absence of significant toxicity from 100 mCi RAI therapy. RAI is an exquisitely targeted therapy in thyroid cancer, and one wonders if the RAI dose were escalated to the same level of toxicity accepted with selumetinib whether CR rate would improve. Certainly, this patient population has a high risk of additional cancer morbidity and so some treatment-induced morbidity might be acceptable. We lack data on the radiation sensitivity of thyroid cancer and the absorbed doses needed to achieve ablation of disease, particularly the higher-risk subtypes that lead to poorer prognosis. Dosimetry should be an integral part of future studies aimed at enhancing radioiodine uptake, acknowledging that clinically useful lesional dosimetry is difficult to perform and will require advanced imaging (eg, I-124 positron emission tomography/computed tomography) to achieve.

Differentiated thyroid cancer, even in this high-risk subset, is a relatively indolent disease leading to considerable clinical trial challenges. A surrogate end point like 18-month CR rate is desirable but will not necessarily predict long-term morbidity or mortality from disease. Furthermore, this end point is fraught with challenges as evidenced by the high rate of missing data. Not discussed is how often failure to achieve CR is due to residual normal thyroid tissue rather than recurrent/residual thyroid cancer. The inclusion of follow-up planar RAI whole-body scan in the CR rate is problematic given the limited sensitivity and specificity. It is difficult to interpret a positive scan in the absence of biochemical recurrence particularly if lack of RAI avidity is, as hypothesized, the primary cause for treatment failure.

Finally, this study emphasizes the importance of conducting large clinical trials to confirm earlier observations before adopting the use of an agent into clinical practice. The use of kinase inhibitors to treat patients with RAI-refractory disease outside of clinical trials has become

widespread, especially in the advanced setting, without large confirmatory studies showing that such interventions improve efficacy and are safe. Not only can this practice expose patients to futile treatments and delay other interventions that have shown activity in phase III studies, but also it runs the risk of exposing the patients to increased toxicity related to the agent, RAI, or the combination. In the pilot study with selumetinib in patients with advanced thyroid cancer,⁴ what is often overlooked is that one of the 20 patients treated subsequently developed acute myeloblastic leukemia, an outcome rarely seen in the era of kinase inhibitors. The significance of this event can only be understood in the context of a well-designed phase III study. Thus, the use of kinase inhibitors to induce redifferentiation should be limited to clinical trials until a prospective phase III study proves their safety and efficacy.

The authors should be congratulated on performing and completing this prospective phase III study investigating the

concept of enhancing radioiodine avidity and efficacy by blocking the inappropriately activated RAS/RAF/MEK/ERK (RAS-ERK) pathway in early thyroid cancers. Furthermore, the authors have highlighted a population of patients with differentiated thyroid cancer in whom standard curative-intent therapy fails early in the majority of patients. This represents a major unmet need and is, therefore, a field worthy of research and currently lacking in good clinical data. However, the ASTRA trial's disappointing failure to prove an advantage of the addition of selumetinib to adjuvant radioiodine highlights the importance of further examining the underlying biology to better define subpopulations that are likely to benefit. Thus, although the aim of improving the outcome of RAI in patients with high-risk differentiated thyroid cancer is a worthwhile goal, the ASTRA failed to demonstrate that this can be accomplished with the addition of the MEK inhibitor selumetinib, and RAI alone remains the current standard.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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