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A review of drugs in development for the personalized treatment of head and neck squamous cell carcinoma

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Abstract

Introduction—Head and neck squamous cell carcinoma remains a highly morbid and fatal disease, with poor survival rates among patients with advanced and recurrent disease. Recent advances in next generation sequencing, targeted therapeutics, and precision medicine trials are expanding treatment options for head and neck cancers; thus greater awareness of this rapidly evolving field is important.

Areas Covered—Recent next-generation sequencing studies in head and neck squamous cell carcinoma, targeted therapy clinical trials involving head and neck squamous cell carcinoma.

Expert Commentary—This review discusses the current state of head and neck cancer treatment, and considerations and implications for the incorporation of personalized medicine and targeted therapy for head and neck cancers in a dynamic clinical landscape.

Keywords

head and neck cancer; HNSCC; targeted therapy; precision medicine; personalized medicine

I. Background

Squamous cell carcinoma of the upper aerodigestive tract is the 6th most common cancer worldwide, with over 600,000 cases diagnosed annually [1]. It remains a highly morbid and fatal disease, particularly in advanced and recurrent cases. Historically, tobacco and alcohol have been the etiologic factors associated with this aggressive disease. More recently, high-risk serotypes of human papillomavirus (HPV) have emerged as the proximate cause of head and neck cancers, frequently involving the oropharynx, and altered demographic patterns as well as oncologic outcomes [2]. For decades, the same treatment modalities (surgery,

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radiation and non-targeted cytotoxic chemotherapy) have been used for head and neck cancer in varying combinations and algorithms. Despite decades spent attempting to optimize these protocols [3–5], survival has not improved significantly, particularly in high risk, advanced and recurrent disease [6,7]. Moreover, these traditional therapies can be highly toxic and morbid for patients [8].

There has long been interest in treatment stratification and optimization of specific therapies for individuals in order to "personalize" treatment approaches. For instance, head and neck cancer treatment stratification designs have been developed to evaluate clinical response to induction cytotoxic chemotherapy [9,10], and clinical and pathologic staging are used to stratify treatment intensity [11]. Other than HPV status, however, few predictive biomarkers have been validated.

There exists a massive effort and fund of data exploring novel therapeutics for head and neck cancer. Despite this interest and decades of research, however, only one FDA-approved targeted therapeutic agent has been introduced for head and neck cancer (cetuximab/ Erbitux®, a monoclonal anti-EGFR antibody) [13,14]. While many other agents are undergoing scrutiny in ongoing clinical trials, development and implementation of targeted therapy in head and neck cancers certainly lags behind other cancers, where FDA-approved targeted agents have been integrated into standard of care [15–18].

Recent next-generation sequencing studies have identified numerous mutated genes and dysregulated pathways in head and neck cancers [31–33]. Unlike many other cancers with a known etiologic driver mutation (e.g. *BCR/ABL* fusions in chronic myelogenous leukemia), there is not a universal driver mutation across head and neck cancer, which is genetically complex and heterogeneous. Importantly, however, many of these altered pathways are targetable with new agents in development or being used in other cancers. Indeed, as the National Cancer Institute (NCI) and American Society of Clinical Oncology (ASCO) push for the expansion of precision targeted medicine paradigms [34,35], incorporating available targeted drugs in personalized medicine applications will become a key facet in the management of head and neck cancer.

Additionally, immune escape is thought to play a pivotal step in carcinogenesis [19]. This has been elucidated in head and squamous cell carcinoma where an immunosuppressive environment, including increased PD-1/PD-L1 expression [20–22], promotes immune escape and tumor proliferation [23–25]. Based upon the recognition of this pattern of immune dysregulation, checkpoint inhibitors targeting CTLA-4 (ipilimumab) and PD-1 (pembrolizumab, nivolumab) have been approved for use in numerous other malignancies, including melanoma, lung cancer, and renal cell carcinoma. As these drugs have demonstrated impressive and, in some cases durable, responses there has been much interest in evaluating their utility in head and neck squamous cell carcinoma [26–29].

As we enter the era of personalized medicine and targeted therapeutics, there is potential for dramatic breakthroughs in the treatment of head and neck cancers. In this nascent and rapidly evolving era of targeted therapeutics and personalized medicine in head and neck cancer, there are no established guidelines or protocols for the employment of personalized

medicine. Nevertheless, ongoing discussion and consideration of optimizing protocols in real-time are obligatory. Thus, there is a great deal of anticipation and excitement as precision medicine and targeted therapies herald the evolution of 21st century cancer treatment algorithms.

II. Targetable and commonly dysregulated pathways in head and neck cancer

Prior to the widespread adoption of next generation sequencing techniques, early investigations into potential targetable pathways and prognostic biomarkers in head and neck cancers identified a few candidate gene products, including *EGFR* [36,37], *BCL2* [38], and *CCND1* [39], among others. While valuable, these initial studies were limited by available technology to validate findings in larger cohorts, and to perform large-scale screens to identify additional dysregulated pathways.

Subsequent whole exome and whole genome sequencing studies [31–33] have identified commonly mutated pathways in head and neck cancer (Table I). Some of these verified the results of previous studies (e.g. *EGFR*, *CCND1* amplifications), while other findings were novel or unexpected in head and neck cancer (e.g. loss of function mutations in *NOTCH1*) [40–42]. Importantly, the overall mutational burden in head and neck cancers is quite high, with an average of over 140 mutations per tumor. As a result, numerous targetable mutations are potentially present in each individual tumor. Notably, HPV+ tumors have been found to have different frequencies and patterns of mutations; however, the same core pathways and genes are affected in both HPV+ and HPV- cancers [31].

Currently, cetuximab is the only FDA-approved targeted therapy in head and neck cancer; its benefit was validated through two landmark randomized controlled trials demonstrating improved survival in conjunction with platinum or radiation [13,14]. Nevertheless, an ever-increasing number of agents are under evaluation in clinical trials. Additionally, many agents currently approved for other tumors may have applicability in head and neck cancer. Indeed, both the ongoing NCI-MATCH and TAPUR trials leverage the use of targeted therapies personalized to a patient's mutation status, regardless of tumor type. This provides study subjects access to FDA-approved drugs used in other cancers if the mutational profile matches (e.g. patients with breast and head and neck cancer carrying the same *ERBB2* amplification would both be treated with trastuzumab). Indeed, we and others have shown that up to 3% of HNSCC patients harbor *ERBB2* amplifications suggesting that although rare, these agents may have an important role in personalized medicine trials [43,44]. Investigational agents in early clinical trials can be broadly grouped into specific classes based on key targeted pathways, included those for cell growth and proliferation, cell differentiation, cell cycling, anti-apoptosis, and immune modulation (Table I).

Immunotherapy research has been reinvigorated in head and neck cancer, particularly in the HPV era. Preliminary results of the Phase 1b Keynote-012 evaluating pembrolizumab in unresectable recurrent/metastatic head and neck cancer demonstrated response or disease stability in almost half of enrolled subjects [45]. Of particular excitement was its apparent durability, with 86% of patients who achieved a response demonstrating no progression by

the time of publication. Treatment with pembrolizumab was well tolerated with only 14% of patients experiencing high-grade adverse events [45]. Similarly, preliminary results from Checkmate-141, a randomized, open-label, phase 3 trial evaluating the role of nivolumab versus investigators' choice in platinum-refractory recurrent/metastatic head and neck cancer, demonstrated an improvement in median overall survival with the use of nivolumab (7.5 vs. 5.1 months). Similar to Keynote-012, treatment was well tolerated with high-grade adverse events in 13.5% of patients treated with Nivolumab vs. 35.1% treated with investigators' choice [46]. In addition, a plethora of trials incorporating checkpoint inhibitors into the first line treatment of recurrent/metastatic head and neck cancer (NCT02358031, NCT02658214), combining with anti-CTLA4 agents (NCT02551159) or radiation (NCT02609503, NCT02289209), and addition in the adjuvant setting (NCT02296684, NCT02641093) are ongoing and will be critical in defining their incorporation into current treatment algorithms.

III. Expert Commentary: Considerations for tumor sequencing and biomarkers in targeted therapy

One principal concept to address for patients with head and neck cancer is whether targeted agents should be truly personalized based directly or in part upon their tumor genetic or expression signature. As an example, cetuximab has a similar effect across head and neck cancer patients, with no definitive biomarkers (specifically EGFR expression status) that reliably predict response [47]. Unlike colorectal cancer in which *KRAS* and *NRAS* mutational status assist in identifying patients who respond to anti-EGFR therapy [48], there remains a lack of a biomarker to predict response to cetuximab in head and neck cancer. Indeed, currently the only reliable (but still suboptimal) marker of response to cetuximab in head and neck cancer is development of an acneiform skin rash [49]. Similarly, investigations into exceptional responders to other agents in head and neck cancers have failed to yield a direct correlation between genotype and phenotype [50].

In contrast to this is the paradigm of ongoing personalized medicine trials (NCI-MATCH, TAPUR), where targeted therapies are proposed to be given only to those patients who carry mutations in the pathway of the potential agent. As an example, these trial designs suggest the same treatment be applied to *ERBB2*-amplified breast, renal and head and neck cancers under the presumption that aberrant genetic processes factor more importantly than tumor site of origin. Notably for head and neck cancers, specific tumor subsite distinctly guides treatment (e.g. early stage larynx cancers often receive radiation alone, whereas early stage oral cavity cancers are surgically resected). Further investigation into the implications of tumor subsite and responsiveness to targeted agents needs to be performed.

Another key consideration in interpreting sequencing results for personalized therapy application is how to stratify and select among the many identified mutations for targeted agents in genetically complex tumors (such as head and neck cancer with over 140 mutations per tumor). For instance, should we pick an EGFR inhibitor or a PIK3CA inhibitor in a head and neck cancer harboring both *EGFR*- and *PIK3CA*-amplifications? Currently, simplified monotherapy algorithms do not account for the potential for

complicated gene-gene interactions. As mutations do not arise individually and may be fundamentally impacted by other aberrant genes, additional considerations must be made into factoring combinations of mutations and dysregulated gene networks for targeted therapy. Thus, we will need to design algorithms into prioritizing which mutations are most "actionable", and in what combinations to employ targeted agents [42]. Further research into the potential synergistic effects of combination strategies will need to be performed.

For immunotherapeutics, although the promise of improved outcomes exists for a subset of patients, it is obligatory to better predict who may achieve clinical benefit. Hence, there is great urgency to develop valid and robust biomarkers. Given the mechanism of action, there has been interest in predicting response based on tissue PD-1/PD-L1 staining. However, in both the Keynote-012 and CheckMate-141 trials, patients with negative staining still had responses to therapy, highlighting the inadequacy of this biomarker. Additional candidate biomarkers are under study, including interferon-gamma expression, which in an exploratory analysis of patients enrolled in Keynote-012, demonstrated a 95% negative predictive value and 40% positive predictive value for response [45]. To date, there are no prospective data exploring how to combine immunotherapy and non-immune targeted therapies. Whether patients may be more suited for one type of adjuvant over the other is unknown, particularly without any biomarkers or genomic signatures reliably predictive of response.

IV. Considerations for inclusion criteria and paradigms for application

A fundamental but challenging question involves when and whom to enroll in clinical trials of precision head and neck cancer treatment (Figure 1, Table II). Should every newly diagnosed patient be sequenced and offered a targeted agent if available (e.g. Do we sequence a T1N0 oral tongue cancer that is highly curable with surgery alone)? These vexing decisions are based upon myriad factors including tumor factors, patient factors, shared decision-making, and institutional resources/goals. Tied in to this decision-making are cost and feasibility. For instance, whole exome sequencing still can take a matter of weeks and costs thousands of dollars. If we enroll every patient with a cancer into personalized medicine protocols, this would be an enormous burden on our healthcare system. Additionally, we may run the risk of delaying care for patients while waiting for sequencing and data analysis to be performed on their tumors. Thus, a crucial component in advancing personalized medicine will be to make reasoned decisions regarding which patients may optimally benefit from such protocols, and how the healthcare system as a whole can support this paradigm in a transparent, fair and sustainable manner.

Currently, most personalized medicine trials involving head and neck cancers are targeting patients who are refractory to all other current treatments (e.g. unresectable recurrent or metastatic disease refractory to first line treatment). While some isolated successes with targeted therapy have been documented from this group [51], there is the potential for biased poor outcomes in these patients given their inherent advanced or recurrent disease state and biologic resistance to other treatments. Additionally, many unexplored targeted therapy algorithms remain. Paradigms to consider include precancerous lesions, the neoadjuvant setting, adjuvant treatments, or treatment for previously untreated advanced or metastatic disease; Figure 1, Table II).

Neoadjuvant and adjuvant treatment algorithms for primary and early head and neck cancers could enhance quality of life and functional outcomes, and potentially improve survival. However, caution is necessary when considering neoadjuvant and adjuvant targeted therapy as it has yet to demonstrate a definitive benefit. Recent studies evaluating EGFR targeted therapy in premalignant head and neck lesions demonstrated conflicting results [52,53]. Lung cancers have not shown a survival benefit with adjuvant targeted agents [54–56], although phase III studies in *EGFR* mutated patients are being planned.

Given the design of current trials, there is a risk of overlooking potentially efficacious agents for earlier stage and/or previously untreated patients. As recurrent and metastatic tumors proliferate, inherent genetic instability causes increased mutagenesis with the generation of potentially treatment-resistant subclones. Additionally, tumor subpopulations that survive initial chemotherapy and radiation may be selected for mutations that drive resistance to treatment. As a result, many of these tumors have developed alternative molecular escape pathways, potentially making targeted blockade of a single pathway less efficacious [57–60]. Similarly, there is a risk of missing the potential benefit of double-targeted therapy compared to standard of care (i.e. BRAF inhibitor and MEK inhibitor doublet). Such doublets have been demonstrated to have greater efficacy in metastatic melanoma compared to either alone [61].

Currently, clinical trials often employ targeted agents to escalate existing therapeutic paradigms (e.g. cetuximab as an adjuvant therapy in addition to radiation or cisplatin). However, given the identification of a subset of patients with better prognoses related to HPV, there has been increased interest in de-escalating treatment regimens to mitigate toxicity. Currently, RTOG and ECOG have ongoing clinical trials assessing treatment reduction stratified after initial surgery (RTOG 1221, ECOG 3311). In a similar fashion, careful consideration of the potential for targeted agents in de-escalation protocols to mitigate toxicities of traditional therapies currently remains an underexplored avenue.

Finally, merging personalized medicine and targeted therapy paradigms with conventional clinical trials employing traditional cytotoxic chemotherapy, radiation and surgery remains underexplored. As discussed above, while early studies in cetuximab validated a beneficial role as an additive agent to cisplatin and radiation, [13,14], few personalized medicine and targeted therapy trials are investigating potential combinations in head and neck cancer. In part this is due to the early investigational phase of many agents specifically in head and neck cancer. Nevertheless, concerted efforts should be made to bridge conventional trials with novel treatment paradigms (for instance including genetic biomarkers for treatment response and stratification or employing investigator choice targeted agents in addition to conventional therapies as an arm for clinical trials).

V. Ethical considerations

As patients with head and neck cancer are increasingly enrolled in clinical trials, we must proactively address fundamental ethical issues. Chief among these include disclosure of incidental findings in genomic testing, and mitigating the therapeutic misconception [62]. It will be important to explicitly state to patients that the primary purpose of early phase

clinical trials is to document appropriate drug dose and toxicity, and not to achieve cure. Additionally, we should consider framing early precision medicine trials as clinical research trials, not clinical care trials given the investigational and proof-of-concept nature of these studies. Involvement of genetic counselors will be invaluable in relaying and interpreting findings (primary, incidental and secondary) and managing expectations. Indeed, inclusion of genetic counselors is becoming an equally important part of the oncology team and Precision Medicine Tumor Board in centers implementing genomically based personalized oncology paradigms [63].

VI. Five Year View: Considerations in determining efficacy

Despite fundamental scientific advances in identifying genetic targets and developing novel agents, no studies have demonstrated improved survival with personalized medicine paradigms. Only one randomized phase II multicenter clinical trial has been performed evaluating the role of molecularly targeted therapy, the SHIVA trial. This large study screened 741 patients with metastatic solid tumors (including head and neck cancers) refractory to standard of care, of which 40% had actionable mutations. Patients with actionable mutations were randomized to either a molecularly targeted agent or standard treatment. No difference in toxicity profile, progression free survival, or overall survival was noted between the two groups [64]. Notably, numerous issues complicate the interpretation of these results as well as ongoing clinical trials, namely the inclusion of heavily pretreated patients, presence of numerous mutations in single patients, and use of targeted therapies as single agents despite complex mutational landscapes.

Additional considerations in determining targeted therapy efficacy should be made in regards to evaluating a specific drug and gene target separately. For instance, although cetuximab has shown efficacy in head and neck cancer, gefitinib (a tyrosine kinase inhibitor also targeting EGFR) has not shown any survival benefits [65]. Thus, we should not necessarily be so quick to dismiss genes with no responsiveness to a targeted agent, but rather consider additional related agents with effects along the same pathway.

For head and neck cancer, we are far from demonstrating the benefit of the use of targeted therapies as monotherapies. Cetuximab as a monotherapy has proven only minimal benefit [66]. Furthermore given inherent tumor heterogeneity and clonal evolution [67,68], there is risk of selection of resistant tumor subpopulations that will subsequently proliferate, necessitating novel targeted options or permutations thereof.

Ultimately, interrogating the efficacy of personalized medicine regimens will be necessary. However, this will be more complex than with traditional randomized controlled trials for a specific intervention, as any of a number of drugs will be matched to a single patient or tumor. Thus, we must account for potential variability in efficacy of individual drugs as part of a larger study. For example, perhaps trastuzumab will work well for head and neck cancer patients with *ERBB2* amplifications, but bevacizumab may not be effective for patients with *VEGF* aberrations. The difficulty will be in figuring out means to combine these potential results to determine the success of personalized medicine trials, which are essentially composed of repeated n = 1 observations.

VII. Conclusion

Personalized medicine and targeted therapy represent the horizon of contemporary head and neck cancer care. While proof of efficacy and implementation of these therapies has lagged behind other solid tumors, their importance and potential are just being unearthed. Challenges in study design and applicability of results to real-world treatment paradigms represent the current challenges faced by translational scientists and clinicians. Results of ongoing clinical trials regarding molecularly targeted therapy are eagerly awaited and will be pivotal in identifying how we might best "personalize" the modern management of head and neck cancer. Despite these formidable challenges, personalized medicine involving targeted therapies, integration of genomic data, and immunotherapeutics along with established treatment modalities will fundamentally reshape the approach to head and neck cancer management.

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Key Issues

- Head and neck squamous cell carcinoma remains a highly morbid and fatal disease, with poor survival rates among patients with advanced and recurrent disease.

- Recent advances in next generation sequencing, targeted therapeutics, and precision medicine trials are expanding treatment options for head and neck cancers.

- Challenges in study design and applicability of results to real-world treatment paradigms represent the current challenges faced by translational scientists and clinicians.

- Results of ongoing clinical trials regarding molecularly targeted therapy are eagerly awaited and will be pivotal in identifying how we might best "personalize" the modern management of head and neck cancer.

- Despite these formidable challenges, personalized medicine involving targeted therapies, integration of genomic data, and immunotherapeutics along with established treatment modalities will fundamentally reshape the approach to head and neck cancer management.
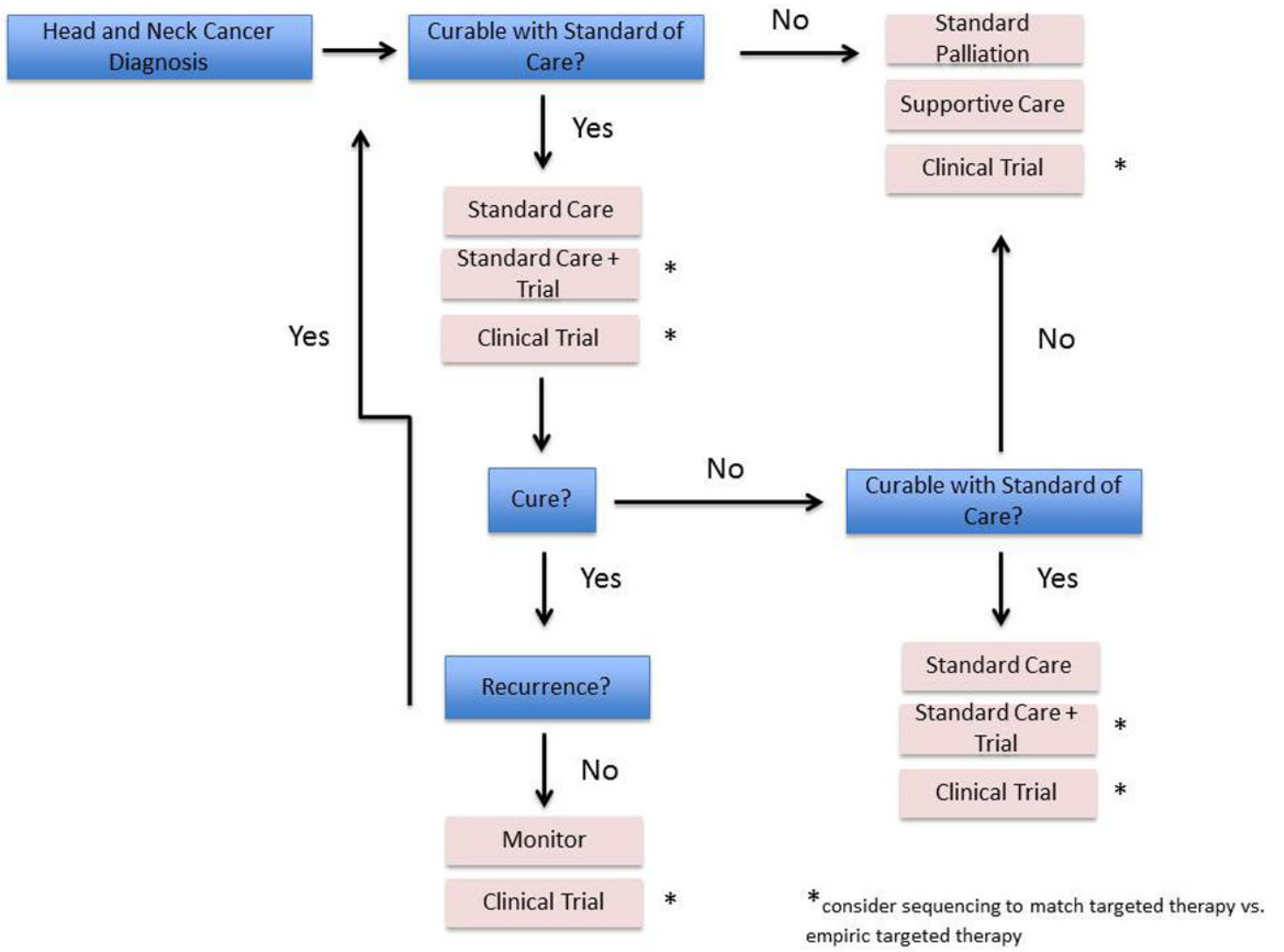
Figure 1.

Table I

Key Dysregulated Pathways in Head and Neck Cancer

Potential agents FDA-approved in other cancers that may be applicable to head and neck cancer. NSCLC = non-small cell lung cancer. RCC = renal cell carcinoma. CLL = chronic lymphocytic leukemia.

Common Dysregulated Genes	Pathway	Examples of FDA Approved Agents (for other cancers)
EGFR	Cell Growth/Proliferation	Osimertinib (NSCLC)
EGFR	Cell Growth/Proliferation	Afatinib (NSCLC)
ERBB2	Cell Growth/Proliferation	Trastuzumab (breast, gastric, gastroesophageal)
MTOR	Cell Growth/Proliferation	Everolimus (breast, RCC, neuroendocrine tumors)
VEGFR/PDGFR	Cell Growth/Proliferation	Pazopanib (sarcoma, RCC)
VEGFR/PDGFR	Cell Growth/Proliferation	Axinitib (RCC)
VEGFR2	Cell Growth/Proliferation	Ramicurimab (NSCLC, gastric, gastroesophageal)
CDK4/6	Cell Cycle Regulation	Palbociclib (breast)
BCL2	Anti-apoptosis	Venclexta (CLL)
PD1	Immune Modulation	Nivolumab (melanoma, NSCLC, RCC, Hodgkin lymphoma)
PD1	Immune Modulation	Pembrolizumab (melanoma, NSCLC)

Table II

Considerations for Designing Personalized Medicine Algorithms in HNSCC Patients

Considerations for Designing Personalized Medicine Trials/Algorithms
Which patients to sequence (stage criteria, site, etc.?)
HPV status and treatment stratification
Neoadjuvant vs. Adjuvant vs. Monotherapy
Targeted therapy vs. immunotherapy vs. both
Outcome measures
Ethical considerations