New Strategies in Esophageal Carcinoma: Translational Insights from Signaling Pathways and Immune Checkpoints

Victoria E. Wang1, Jennifer R. Grandis2, and Andrew H. Ko1

1 Division of Hematology and Oncology, University of California San Francisco, San Francisco, California
2 Department of Otolaryngology-Head and Neck Surgery, University of California San Francisco, San Francisco, California

Corresponding Author: Andrew H. Ko, Division of Hematology and Oncology, University of California San Francisco, 550 16th Street, Box 3211, San Francisco, CA 94158. Phone: 415-353-7286; Fax: 415-353-7779; E-mail: Andrew.Ko@ucsf.edu

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ABSTRACT

Esophageal cancer remains a highly lethal malignancy in which relatively modest therapeutic advances have been made over the past several decades. Cytotoxic therapy remains the mainstay of treatment for both advanced esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC), with incremental benefit conferred by antibodies targeting human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor receptor (VEGFR) in select patients. However, intrinsic or acquired resistance in this disease almost invariably occurs and remains a major challenge. Moreover, while large-scale exome and whole genome sequencing efforts have identified a variety of somatic mutations and copy number variations, particularly amplifications, in esophageal cancer, the ability to translate these findings successfully into actionable therapeutic approaches has been elusive. More recently, immunotherapeutic strategies, most notably immune checkpoint inhibitors, have demonstrated benefit to a subset of patients with both EAC and SCC, and represent an area of active clinical investigation. In this article, we discuss some of the insights derived from past trials of esophageal cancer, highlight ongoing research efforts in this arena, and emphasize the need to refine our approach to treating patients based on distinct anatomic, histologic, and molecular features.
BACKGROUND

Esophageal cancer represents a heterogeneous disease entity associated with high morbidity and mortality. It is currently the eighth most common cancer worldwide, with approximately 450,000 new cases annually and 17,000 cases in the US alone (1,2). Because of its poor prognosis, with more than 80% of diagnosed patients ultimately succumbing to their disease (3), it also ranks as the sixth most common cause of cancer-related death worldwide and seventh in the US, with approximately 400,000 and 15,000 deaths every year, respectively (4,5). Soberingly, the five-year survival for patients with esophageal cancer has improved only modestly over the past 50 years, from 4% in the 1950s to 17% in 2010 (6), highlighting ongoing challenges in early detection, the high propensity for relapse even in patients with resectable early stage disease, and the relatively small incremental advances in effective therapies during this period of time.

The histologic and anatomic distribution for esophageal cancer has changed radically over the past thirty years (1). Squamous cell carcinomas (SCC), which originate from the squamous epithelial cells lining the esophagus, still account for approximately 90% of cases worldwide (7), with specific risk factors including alcohol and tobacco consumption, poor nutrition, achalasia, and caustic injury to the esophagus, as well as infection with human papilloma virus (HPV) in certain geographic regions. The so-called “Asian Esophageal Cancer Belt” extending from Northern Iran through the central Asian republics to Mongolia and North-Central China represents a particular high-risk area for SCC, with China alone accounting for more than half of global cases (8).
Conversely, in the US and parts of Western Europe, adenocarcinomas (EAC), arising from columnar metaplastic changes developing in the lower third of the esophagus (in particular from patients with longstanding gastroesophageal reflux disease and Barrett’s esophagus), have now surpassed SCC in incidence, with a striking increase of 600% since the mid-1970s (9). Temporal trends in Western countries show that this rise in EAC incidence, while common amongst all racial groups, is steepest amongst Caucasian individuals (10). During this same time period, there has been a significant decline in SCC, with the most prominent drop amongst blacks (10).

For patients diagnosed with localized or locoregional esophageal and gastroesophageal junction cancers who are suitable operative candidates, preoperative therapy consisting of either chemotherapy or concurrent chemoradiation is often recommended, based on phase III data indicating the superiority of combined-modality therapy compared to surgery alone (11,12). In select circumstances, patients may be spared the need for a major cancer operation, including those with very early stage tumors, in whom local endoscopic resection may be appropriate; as well as individuals with cancers located in the cervical esophagus, in whom definitive chemoradiation (without surgery) is typically administered. The intriguing possibility of moving in the direction of non-operative management more frequently in select patients was raised in one large French trial (13), in which patients with operable esophageal cancer (primarily SCC) were randomized to receive chemoradiation alone or chemoradiation followed by surgery.
Survival rates were similar in both arms, although patients assigned to the non-surgical approach had a higher incidence of locoregional relapse.

For patients with advanced and metastatic disease, systemic therapy constitutes the primary treatment modality, with combination chemotherapy representing the most rigorously evaluated treatment approach. Of note, most studies of novel agents and regimens have enrolled patients with both gastric and esophageal (plus GE junction) cancers, for reasons of practicality and accrual; very few have been limited exclusively to esophageal cancer, let alone to one specific esophageal histologic subtype. Acknowledging the genetic differences between gastric and esophageal cancers, as discussed in further detail below, the discussion that follows in this and the following section reflects clinical data from studies that included gastric cancer, unless noted otherwise.

While there remains some debate regarding whether two- vs. three-drug chemotherapy combinations should be used in the advanced disease setting, typically the most widely accepted first line of therapy consists of the combination of a platinum agent together with a fluoropyrimidine (14,15). Other cytotoxic agents, including taxanes and irinotecan, have also demonstrated activity in this disease, including proven survival benefit over best supportive care in the second-line setting (16,17). Unfortunately, median survival associated with all of these regimens is less than one year from the time of initial diagnosis.

Beyond traditional cytotoxic agents, the first targeted therapy to gain approval in gastroesophageal cancer was the anti-HER-2 monoclonal antibody trastuzumab (Herceptin) into frontline chemotherapy for patients with
ERBB2/HER-2 positive disease. The basis of its approval in this disease context was positive results from the ToGA trial (18), an international phase III study that randomized patients with advanced HER-2 positive gastroesophageal adenocarcinoma (3+ expression by immunohistochemistry or positive by fluorescence in situ hybridization) to either standard platinum and fluoropyrimidine-based chemotherapy alone or in combination with trastuzumab. Median overall survival (OS) was significantly higher in the trastuzumab arm (13.8 versus 11.1 months; HR 0.74; 95% CI 0.6 to 0.91; p = 0.0048), as was objective response rate (RR) (47 versus 35%), without substantial increases in toxicity.

More recently, ramucirumab (Cyramza), a recombinant monoclonal antibody which binds to vascular endothelial growth factor receptor (VEGFR) -2, has been approved for use in the second-line setting both as monotherapy and in combination with paclitaxel based on results from two separate randomized phase III trials. In the REGARD study, patients receiving ramucirumab demonstrated improved survival compared to placebo (median OS 5.2 vs. 3.8 months; HR 0.78; p = 0.047), albeit with higher rates of hypertension (19). In the RAINBOW trial, the addition of ramucirumab to paclitaxel also improved survival (median OS 9.6 vs 7.4 months; HR 0.81, p = 0.017), again, with higher incidence of specific adverse events including hypertension, neutropenia, and fatigue.

A schema showing HER2, VEGFR, and other known and potential therapeutic targets for esophageal cancer is depicted in Figure 1.
ON THE HORIZON

Beyond HER-2: Potential new biomarkers, microRNAs, and molecular subtyping

The lack of prognostic or predictive biomarkers has been a clear impediment to developing a more “precision medicine” approach to treating patients with gastroesophageal cancer. Currently, the only validated therapeutic target for this disease is HER2, which is overexpressed in approximately 7-22% of gastroesophageal cancers, depending on the case series (18,20), and informs use of trastuzumab. Meanwhile, discovery of blood- or tumor-based biomarkers that predict sensitivity to inhibitors of VEGF/VEGFR signaling remains elusive. Exploratory candidate biomarker analysis of tumor biopsies and serum from patients enrolled on the REGARD trial, for example, did not identify any significant markers that were predictive of sensitivity to ramucirumab (21).

While still in its infancy, preclinical models have shown that microRNAs (miRNAs) may represent promising prognostic biomarkers in esophageal SCCs (22,23), especially as they have the added potential benefit of being measurable via liquid biopsy (peripheral blood collection). High levels of miRNA-375 are correlated with increased lymphatic invasion in this disease (24), while miRNA-9 represses E-cadherin (whose downregulation is a hallmark of epithelial-to-mesenchymal transition) to promote metastasis in SCC xenografts (25). In one large genomic profiling effort, miRNA-548K was characterized as a novel oncogene, with functional assays demonstrating its ability to enhance malignant phenotypes of SCC cells (26). Future work in this area consists of multiplexing several miRNAs to increase its
robustness as biomarkers and to validate the utility of such a panel in prospective clinical studies (27).

Esophageal SCC and EAC – along with gastroesophageal and gastric adenocarcinoma, the latter of which is further subdivided histologically into diffuse and intestinal subtypes – represent distinct entities, each with their own unique molecular features. However, trials of novel therapies in esophageal cancer have, out of practical necessity, often included within their eligibility parameters any and all of the above cancers, making it more challenging to tease out the treatment effects unique to one particular anatomic or histologic subtype. A number of comprehensive genomic analysis efforts have elucidated key molecular differences underlying SCC and EAC that suggest these entities should indeed be considered separately in future clinical trials of novel targeted therapies. In one early study, Agrawal and colleagues performed whole exome sequencing (WES) on 23 esophageal cancers from the U.S. (11 EAC, 12 SCC) and found a substantial disparity in the spectrum of mutations, including identification of inactivating mutations in NOTCH1 in 21% of SCCs compared to none in adenocarcinomas (28). Interestingly, when these investigators then analyzed the complete coding sequence of NOTCH1 in SCCs from Chinese patients, they found a mutation in only 1 of 48 samples (2%), providing an additional important reminder regarding the ethnic and racial variations in disease prognosis and tumor biology that may influence trial results. While much attention has been paid to these differences for gastric cancer (especially the “East vs West” debate), comparatively less emphasis has been placed specific on esophageal cancer.
Another, more recently published genomic profiling study of SCC and EAC by Wang et al (29), in which next-generation sequencing (NGS) was performed on coding exons from 315 cancer-related genes plus selected introns of 28 genes frequently rearranged in cancer, suggested similar rates of “clinically relevant” genomic alterations between the two, but with differing profiles. SCC more frequently harbored PIK3CA and PTEN mutations, in addition to NOTCH1, whereas EAC showed higher rates of KRAS mutations and HER2 amplification. Other mutations in SCC described by Hu and colleagues in their WGS analysis include JAK3, BRCA2, FGF2, FBXW7, MSH3, PTCH, NF1, ERBB2 and CHEK2 (30), many of which represent additional potentially actionable targets. Pathway assessment from a comprehensive genomic analysis performed by Song et al on 158 SCC cases from China revealed that somatic aberrations are mainly involved in the Notch, Wnt, and cell cycle pathways (26).

Specific to EAC, Dulak and colleagues (31) analyzed 149 samples via WES and/or WGS and reported mutations or amplifications in “actionable genes” (those with a known associated targeted agent) in 48% of tumors in their cohort, with the most common ones including PIK3CA, HER2, EGFR, and MET (see following discussion regarding therapeutic agents targeting a number of these proteins). Furthermore, 24% of samples harbored mutations in members of the SWI/SNF family of chromatin-remodeling factors, including ARID1A, SMARCA4, and ARID2, which suggest potential new targets worth exploring. ARID1A mutations, for example, have been shown to be synthetic lethal with EZH2 inhibition (32) and the EZH2 inhibitor tazemetostat is currently in clinical trials.
Intriguingly, efforts by The Cancer Genome Atlas (TCGA) project have recently identified four major genomic subtypes of gastric adenocarcinomas (33). Although only a small subset (less than 20%) of the analyzed specimens originated from the GE junction, this approach may be relevant in refining our treatment approach to EACs in the future. The identified molecular subtypes include: 1) tumors positive for the Epstein-Barr virus (9%) which display recurrent PIK3CA mutations as well as amplifications of JAK2, PD-L1 and PD-L2, 2) tumors with high levels of microsatellite instability (MSI) (22%), 3) tumors with chromosomal instability (50%), and 4) a genomically stable subtype (30%) comprised of mostly a diffuse histological variant that harbor mutations in either RHOA or the RHO-family GTPase. Although these findings have yet to be fully incorporated into clinical practice and are specific to gastric rather than esophageal cancer, they provide a unique therapeutic opportunity and selection strategy for future clinical trial design based on molecular, rather than histological, markers that may prove to be similarly relevant in EAC. The first two categories, for instance, offer the possibility of readily testable tumor biomarkers (PD-L1, MSI-high/hypermutated phenotype) that, if validated, may serve as useful predictors of sensitivity to immunotherapies, as discussed in further detail below.

**Targeted therapies**

**The ERBB family**

The ERBB or HER (human epidermal growth factor) family of receptor tyrosine kinases, most notably HER-1 (EGFR) and HER-2 (ERBB2), are amenable to pharmacologic inhibition via either small molecules that disrupt tyrosine kinase
signaling, or monoclonal antibodies (either naked or linked to a cytotoxic or radioactive payload) that bind to extracellular domain sites. The (relative) success of trastuzumab in the treatment of HER-2-expressing gastroesophageal cancers has led to evaluation of other HER-2 targeting agents (Table 1), although these trials only included a small minority of patients with esophageal or GE junction adenocarcinomas. Overall, these studies have produced disappointing results to date. The dual EGFR/HER-2 oral small molecule inhibitor lapatinib, for instance, was studied in combination with chemotherapy in both the first-line (LOGiC) and second-line settings (TyTAN), with no survival benefit observed in the intent-to-treat populations (34,35). More recently, the phase III GATSBY trial (NCT01641939), comparing the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1) to taxane monotherapy in the second-line setting, also failed to meet its primary endpoint of improved overall survival (36).

Nevertheless, several other randomized studies exploring alternative approaches to HER-2 inhibition are currently ongoing. The phase III JACOB trial (NCT01774786) adds a second monoclonal antibody, pertuzumab (which binds to a different epitope on the HER-2 extracellular dimerization domain independent of the trastuzumab binding site), to chemotherapy plus trastuzumab. The HELOISE trial (NCT01450696), which recently completed accrual, is testing the hypothesis that dose-intensification of trastuzumab (10 mg/kg versus 6 mg/kg of trastuzumab every three weeks) may improve OS when added to standard chemotherapy.

A second member of the ERBB family, ERBB1 or EGFR, is overexpressed in approximately 27-64% of gastroesophageal carcinomas (37-39) and has been
associated with an aggressive histology and poor prognosis. However, multiple large randomized clinical trials in advanced gastroesophageal carcinoma have failed to demonstrate any benefit of adding anti-EGFR antibodies (cetuximab or panitumumab) to chemotherapy (40,41), while a placebo-controlled phase III study of the oral tyrosine kinase inhibitor gefitinib showed no survival advantage in patients with advanced GE junction and esophageal cancers who had progressed after one prior chemotherapy (42).

It is interesting to speculate why EGFR inhibition has not demonstrated any benefit in gastroesophageal cancer to date. One potential issue is that none of the aforementioned trials were performed in appropriately selected patient populations. The phase III ENRICH study (NCT01813253), currently enrolling in Japan and Korea, is evaluating the EGFR antibody nimotuzumab in combination with irinotecan in the second-line setting, and is enriched specifically for patients whose tumors show high levels of EGFR expression. Another possibility may be that gastroesophageal cancers utilize feedback activation of alternate survival pathways in the presence of EGFR inhibition, similar to BRAF mutant colon cancers (43), suggesting the necessity of exploring rational combination therapies using functional genomic means to overcome such positive feedback mechanisms.

**VEGF and antiangiogenic therapy**

VEGF and its receptors are overexpressed in ~ 30-40% of all gastroesophageal carcinomas (44,45). As noted previously, the therapeutic benefits of VEGF blockade in this disease, either alone or in concert with chemotherapy, have been demonstrated with ramucirumab, an anti-VEGFR2 antibody now approved for
use in patients with previously treated advanced gastric and esophageal cancers.

Furthermore, small molecule inhibitors targeting VEGF receptor tyrosine kinase (TK) activity have demonstrated moderate evidence of efficacy in this chemorefractory setting; for example, apatinib, a VEGFR2 TKI, was recently shown in a randomized phase III trial in China to significantly improve clinical outcomes for patients who had previously received two or more lines of prior chemotherapy (median OS vs. placebo, 6.5 vs. 4.8 months, HR 0.71, p=.015; median PFS vs. placebo, 2.6 vs. 1.8 months, HR 0.44, p<0.001) (46).

Interestingly, incorporation of VEGF/VEGFR-directed therapies in the front-line disease setting has not proven similarly successful. The anti-VEGF antibody bevacizumab was evaluated as part of first-line therapy in two separate phase III trials (AVAGAST (47) and AVATAR (48)) in combination with cisplatin/fluoropyrimidine-based chemotherapy, neither of which met its primary endpoint of improved overall survival. A smaller, randomized phase II trial of ramucirumab in combination with chemotherapy likewise did not show any survival benefit in the first-line setting (49), although a larger, ongoing phase III study of this agent (NCT0231417) should answer this question more definitively. Future efforts in this anti-angiogenic arena should focus on refining how and to whom we offer this class of agents. These include (1) continuing to search for potential tumor- and blood-based biomarkers of sensitivity (47); (2) exploring possible ethnic and geographic differences in the benefit derived from VEGF-directed therapy; (3) studying novel combinations of these agents, for example together with immunotherapies given the potential for synergistic activity between these drug
classes (50); and (4) evaluating VEGF/VEGFR-directed therapies in other, possibly earlier clinical contexts. For example, ongoing randomized trials are evaluating the addition of bevacizumab to chemotherapy in the perioperative setting for patients with operable gastric, GE junction, and distal esophageal cancers (NCT00450203); while the oral multikinase (including VEGFR) inhibitor regorafenib is being tested in the adjuvant setting for patients with resected node-positive esophageal or GE junction cancer who completed preoperative therapy (NCT02234180).

**Other therapeutic targets**

Overexpression of MET, the receptor tyrosine kinase for the hepatocyte growth factor (HGF), confers a worse prognosis in gastroesophageal adenocarcinomas (51,52). Disappointingly, results from two recently completed phase III trials did not indicate any benefit with the addition of MET-directed antibodies to combination chemotherapy in the first-line setting for patients with MET-positive adenocarcinomas of the stomach or GE junction (53,54). On the bases of these negative trials, there appears to be limited justification for further testing of agents that inhibit the MET/HGF pathway in this disease.

Other targeted therapies to date have similarly produced underwhelming results in phase II and phase III trials of advanced gastroesophageal cancer, especially when evaluated as monotherapy following progression on standard chemotherapy. These include studies that have looked at agents both in molecularly enriched patient populations (for example AZD4547, a selective inhibitor of fibroblast growth factor receptors (FGFR) 1-3, which was tested in patients whose
tumors showed FGFR2 amplification or polysomy) (55), and in unselected patients (e.g. everolimus, an inhibitor of mammalian target of rapamycin (mTOR)) (6).

**Immunotherapy**

Given the disappointing results from a number of targeted agents in gastroesophageal cancer, there has been growing interest in novel therapeutic strategies that may be more target-agnostic and reliant instead on alternative tumor features, such as immunogenicity and overall mutational burden – thus the shift in focus of attention onto immunotherapies. This burgeoning field of immunotherapy has shown preliminary evidence of activity across a wide spectrum of solid tumors, including both esophageal SCC and EAC. Esophageal cancers fall on the higher end of the spectrum in terms of overall mutational burden for solid tumors (56), and this greater neoantigen load could potentially translate into greater sensitivity to immune-based therapies.

Programmed death-1 and -2 ligands (PD-L1 and PD-L2), which are involved in the negative regulatory pathway of T cell activation, are expressed in upwards of 40% of esophageal cancers and have been shown to be associated with poor prognosis (19). Clinical trials of PD-1 monoclonal antibodies have reported preliminary evidence of activity in a subset of patients with this disease. In the KEYNOTE-028 trial (NCT02054806), which was limited to subjects with PD-L1-positive tumors, the esophageal cancer cohort included 23 patients with both SCC and EAC. Objective responses were observed in both histologic subtypes, including 4 of 17 with SCC (29%) and 2 of 5 with EAC (40%). In total, 52% of patients showed at least some degree of tumor shrinkage (57). A separate phase II trial of nivolumab...
from Japan in a purely SCC cohort, not-preselected for PD-L1 status, reported objective response in 11 of 60 patients (17.2%), including one complete responder (58). Successor studies are now underway, including two trials evaluating pembrolizumab in the second- and third-line settings for advanced disease (NCT 02564263, NCT02559687) (Table 1).

While these immune checkpoint inhibitors certainly hold considerable promise, our understanding of their clinical applications to esophageal cancer is still in its nascent phase with a number of outstanding questions still remaining. First of all, it is apparent that only a subset of patients derive benefit from this class of agents, and predictive biomarkers specific to esophageal cancer need to be validated. For example, we do not yet know whether intratumoral levels of PD-L1, as either a dichotomous variable or at specific cutpoints of expression, predict for sensitivity to these agents. Other potential predictors of response, such as hypermutational status or an “Immunoscore” that quantifies the in situ immune infiltrate (59), warrant further investigation as well. Second, a therapeutic strategy of potentiating the effects of PD-1 antibodies by combining them with additional agents, in particular other immunotherapies, has already been demonstrated in certain solid tumors (60), but has not been looked at extensively in esophageal cancer. Preliminary results from a phase I/II study of patients with esophageal, gastric, and GE junction adenocarcinomas unselected for PD-L1 expression (CHECKMATE-032) treated with the combination of nivolumab and the anti-CTLA-4 antibody ipilimumab at prespecified dose levels showed a response rate of 26% (61); these results have prompted plans to test the combination for this same
patient population in phase III study design. Other novel agents, including OX40 and CD40 agonist antibodies, IDO (indoleamine 2,3-dioxygenase) inhibitors, and others that potentiate T-cell mediated immunity either alone or in combination, are worth exploring further but have yet to be tested specifically in esophageal cancers. Finally, there is the unanswered question regarding the potential role of these drugs in earlier stages of disease. A trial scheduled to open later in 2016 will be addressing this possibility, by comparing adjuvant nivolumab to placebo in patients who have undergone resection of their esophageal or GE junction cancer (NCT02743494).

CONCLUSION AND FUTURE DIRECTIONS

We propose the following in future studies of esophageal cancer: first, clinical trials should make clear distinctions according to histologic, anatomic, and even molecular subtypes in terms of trial enrollment criteria, or at least as stratification variables. Given the genetic and immunogenic differences between each of these entities, it is highly likely that their sensitivity to each of these novel therapies will differ. Acknowledging the practical challenges of such an approach, it would be ideal to develop protocols specific for esophageal cancer, rather than lumping these together with gastric cancer and assuming their biologic behavior will be similar. Second and on a related note, all trials should mandate tumor acquisition, whether in the form of archived samples or prospective tissue collection, to help us move esophageal cancer more squarely into the modern era of precision oncology. While our eventual goal is to tailor treatment for any given patient based on both host and tumor characteristics, we still lack prognostic and predictive biomarkers in this disease that are available for current clinical use beyond HER2. Such tests may come
in the form of a single tissue- or blood-based marker, or (in the case of immunotherapies) a broader measure of total mutational burden or pattern of intratumoral immune cell infiltrate. The key for future studies will be to identify such predictors of response that allow us to gradually refine selection criteria and move away from enrolling unselected patient populations just for expediency's sake. Third, the potential for some of these novel therapies to achieve long-term disease control (the “tail of the curve” on Kaplan-Meier survival curves) with manageable toxicity indicates that it may be essential in future trial design to formally study longitudinal quality-of-life measures as well as explore surrogate endpoints of survival. Lastly, the novel approaches discussed in this review, if ultimately approved, will likely be used in addition to, rather than entirely supplanting, standard cytotoxic therapies. Therefore, treatment paradigms for esophageal cancer will ultimately need to address issues of optimal timing and sequencing of these different therapeutic approaches, including sequential vs concurrent administration (prioritizing therapeutic combinations that are based on sound mechanistic rationale, rather than a purely empiric basis), as well as testing in earlier disease settings with the goal of increasing rates of cure.
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FIGURE LEGEND

Figure 1. Schematic of several of the most well-studied therapeutic targets in esophageal cancer. Agents in red boldface represent approved drugs for this indication; in regular font, agents currently undergoing evaluation/final study results not yet available; in italics, agents previously evaluated in clinical trials with negative results.
Figure 1:
New Strategies in Esophageal Carcinoma: Translational Insights from Signaling Pathways and Immune Checkpoints

Victoria E. Wang, Jennifer R. Grandis and Andrew H. Ko

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