Supplementary Materials

Anti-angiogenic therapy in head and neck squamous cell carcinoma current limitations and future directions

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Supplementary Table 1

Target of anti-angiogenic therapy	**Ligand-directed antibodies**
Treatment modality	Bevacizumab, and chemotherapy or radiotherapy
Clinical results in other tumors	**Clinical trial:** phase II in patients with recurrent glioblastoma or anaplastic glioma (NCT01743950). **Results:** pending trial. **Clinical trial:** locoregionally advanced nasopharyngeal carcinoma patients (NCT00408694). **Results:** the 5- and 7-year rates were 79.5% (95% CI, 67.6%-91.5%) and 69.7% (95% CI, 55.9%-83.5%) for OS, 61.2% (95% CI, 46.8%-75.6%) and 56.3% (95% CI, 41.5%-71.1%) for PFS, 74.9% (95% CI, 61.4%-86.6%) and 72.3% (95% CI, 58.4%-84.7%) for LRPF interval, and 79.5% (95% CI,66.4%-90.0%) for both times for DMF interval, and low rate of distant metastasis (73).
Target of anti-angiogenic therapy	**Ligand-directed antibodies combined with receptor-directed antibodies**
Treatment modality	Bevacizumab and erlotinib, with or without chemotherapy
Clinical results in other tumors	**Meta-analysis:** randomized controlled trials erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-small-cell lung cancer. **Results:** combination significantly prolonged PFS but not OS (74). **Clinical trial:** phase II trial of combined therapy with standard chemotherapy in NSCLC. **Results:** treatment regimen is feasible in patients with advanced NSCLC (83). **Meta-analysis:** efficacy in advanced hepatocellular carcinoma. **Results:** significant and favorable PFS of combined treatment (84).
Target of anti-angiogenic therapy	**Receptor-directed antibodies combined with immune checkpoint inhibitors**

Treatment modality	Ramucirumab, a monoclonal antibody targeting VEGFR2 and pembrolizumab, a monoclonal antibody, FDA-approved for treatment of HNSCC, against programmed cell death protein 1 (PD-1)	Apatinib, VEGFR2 inhibitor, and camrelizumab, anti-PD-1 moncloonal antibody	Bevacizumab and atezolizumab, anti-PD-1 monoclonal antibody
Clinical results in other tumors	Ramucirumab gained regulatory approval in NSCLC, gastric cancer, colorectal cancer, and hepatocellular carcinoma (16). **Results:** in patients with previously treated advanced NSCLC, gastro-oesophageal cancer or urothelial carcinomas combined therapy favorable antitumor activity (51).	**Clinical trial: p**hase II clinical trial in platinum-resistant nasopharyngeal carcinoma (NCT04547088). **Results:** combined treatment effectiveness was associated with high expression of PD-L1, VEGFR2, and B-cell related genes signatures, with a measurable safety profile. **Clinical trial:** phase Ib/II (NCT03092895) in patients with liver cancer (NCT03092895). **Results:** promising antitumor activity with median PFS and OS 3,7 months and 13,2 months, respectively.	FDA approved combined therapy in unresectable hepatocellular carcinoma. **Clinical trial:** in patients with untreated locally advanced or metastatic hepatocellular carcinoma (NCT03434379). **Results:** OS at 12 months was 67.2% for combined treatment in compared to 54.6 % for sorafenib. Median PFS was 6.8 months and 4.3 months in the respective groups. **Clinical trial:** phase III combined therapy and chemotherapy for metastatic, persistent, or recurrent cervical cancer (NCT03556839). **Results:** significantly improves PFS (13,7 months with atezolizumab vs. 10,4 months with standard therapy bevacizumab and chemotherapy) and OS (32,1 months vs. 22.8 months, respectively).
Target of anti-angiogenic therapy	**Tyrosine kinase inhibitors**		
Treatment modality	Sorafenib and/or sunitinib, targeting multiple receptors involved in angiogenesis, including VEGFR		
Clinical results in other tumors	**Meta analysis: c**omparative efficiency of sorafenib vs. sunitinib as a first-line therapy in renal cell carcinoma. **Results:** significantly better OS and ORR for sunitinib then sorafenib but higher toxicity (75).		

	Clinical trial: comparing the efficacy of sunitinib and sorafenib, sunitinib followed by sorafenib (SU/SO) or sorafenib followed by sunitinib (SO/SU), as first-line treatment of metastatic clear cell renal cell carcinoma (NCT01481870). **Results:** no statistically significant differences were found in first-line PFS, total PFS, or OS between the 2 treatment arms. **Clinical trial:** sorafenib and sunitinib efficiency in the treatment of RAI-refractory metastatic differentiated thyroid cancer (DTC) first-line treatment with sorafenib subsequently switched to sunitinib, most due to disease progression. **Results:** PFS was 10.8 months with sorafenib and 6 months with sunitinib as a second-line treatment. Best overall response was partial remission (PR) with either agent – PR rate of 30.7% with sorafenib and 37.5% with second-line sunitinib (76).		
Target of anti-angiogenic therapy	**Histone deacetylase inhibitors (HDACi)**		
Treatment modality	Romidepsin - Zn-dependent histone deacetylase inhibitor	Vorinostat combined with chemotherapy and/or radiation therapy	Vorinostat combined with pembrolizumab
Clinical results in other tumors	**Clinical trial:** phase I/II in patients with recurrent glioblastomas (NCT00085540). **Results:** ineffective (79) **Clinical trial:** phase I in patients with solid tumors for which no standard therapy exists (NCT00053963) **Results:** 1 patient obtained a partial response. The recommended Phase II dose is 17.8 mg/m(2) (80).	**Clinical trial:** phase 1 in patients with gastrointestinal carcinoma (NCT00455351). **Results:** HDAC inhibitors have shown radiosensitising activity in preclinical tumour models (81). **Clinical trial:** phase II in resistant refractory solid tumors (NCT00404508). **Results**: a clinical benefit was observed in 12 (80%) patients: four PR, and eight SD (78).	**Clinical trial:** phase I in patients with relapsed/refractory (RR) classical Hodgkin lymphoma (cHL), diffuse large B-cell lymphoma, and follicular lymphoma. (NCT03150329). **Results**: the overall response rate (ORR) was 72 % and complete response (CR) rate was 34 % (82).