2018 ASCO Rivoceranib (Apatinib) abstracts (8)

1. Phase II trial of apatinib in patients with recurrent and/or metastatic adenoid cystic carcinoma of the head and neck: Updated analysis.
Presented Saturday, June 2, 2018

Authors:
Guopei Zhu, Lin Zhang, Rongrong Li, Shengjin Dou, Wenjun Yang, Chenping Zhang; Department of Oral and Maxillofacial Head & Neck Oncology, Shanghai Ninth People’s Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

Background:
There is no specific therapy, including targeted agents, has consistently improved clinical outcomes in recurrent/metastatic adenoid cystic carcinoma of the head and neck (ACCHN). Recently, anti-angiogenic targeted therapy represents a potential effective strategy. We conducted a single-arm, phase II trial to evaluate apatinib, a small-molecule inhibitor of VEGFR-2, in ACCHN, and promising response was observed (2018 Multidisciplinary Head and Neck Cancers Symposium Abstract: 20160). Here we report the updated efficacy and safety data.

Methods:
Pathologically confirmed recurrent and/or metastatic ACCHN patients (pts) who had evidence of disease progression within 3 months or had failed at least 1 line of systemic chemotherapy were eligible. All pts received continuous apatinib 500 mg qd until disease progression, death, or intolerable toxicity.

Results:
Between Apr 2016 and Dec 2017, 59 pts were recruited, including 22 (37.3%) males and 37 (62.7%) females. The median age was 47.5 years. 61.0% cases had metastases, and the main metastatic site was lung. All pts were evaluable for efficacy and safety analyses. At the cutoff date of 12/31/2017, 9 progression-free survival (PFS) events and 2 deaths after progression occurred. The median PFS and overall survival (OS) had not been reached; however, the median time of apatinib treatment was already 6.4 (IQR, 3.8–9.9) months. The 6-month PFS rate was 87.9% (95%CI, 76.6%–99.1%), and the 12-month PFS rate was 50.7% (95%CI 21.8%–79.7%). The 12-month OS rate was 96.3% (95%CI, 91.3%–101.3%). Moreover, the objective response rate and disease control rate was 47.1% and 98.1%, respectively. 34 (57.6%) pts experienced dose reduction. The incidence of drug-related adverse events (AEs) was 88.1% (52/59). 22.0% (13/59) pts developed AEs of Grade ≥3. Main AEs were hypertension (54.2%), hand-foot syndrome (33.9%), and proteinuria (23.7%).
Conclusions:
This updated analysis further confirmed that apatinib appears to be effective and safe for recurrent/metastatic ACCHN. It did achieve the best reported response rate and long duration of disease control with a good safety profile. Further investigation is warranted. Clinical trial information: NCT02775370

2. Efficacy and safety of apatinib in advanced soft tissue sarcoma: A multi-center, open-label phase II clinical trial.
Presented Saturday, June 2, 2018

Authors:
Wenxi Yu, Zhengfu Fan, Jing Chen, Hong-Mei Zhang, Xing Zhang, Guofan Qu, Yong Chen, Gang Huang, Yang Yao; Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China; Beijing Cancer Hospital, Beijing, China; Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; Xiking Hospital, The Fourth Military Medical...

Background:
Soft tissue sarcomas (STSs) are a heterogeneous group of mesenchymal tumors, accounting for < 1% of all adult malignancies. Although surgery combined with radiation results in high local control rates in localized STSs, high-risk patients (pts) have only 50% 5-year survival. Moreover, chemotherapy has been shown to be lack of consistent overall survival benefit in clinical trials. The vascular endothelial growth factor (VEGF) signaling mediated tumor growth plays an important role in the pathogenesis of several STSs subgroups. This study aimed to explore the efficacy and safety of apatinib, an oral tyrosine kinase inhibitor targeting VEGFR-2, in pts with advanced STS after failure of prior chemotherapy preliminarily.

Methods:
This is a prospective, open-label, single-arm, multi-center phase II study, with planned sample size of 53. All pts with histologically confirmed STSs experienced failure of prior chemotherapy in the last 6 months. Oral apatinib (500 mg) was given to pts daily in cycles of 28 days until disease progression, death or unacceptable toxicity. The primary outcome was 6-month progression-free survival (PFS) rate. Results:35 pts were enrolled as of January 16, 2018. The top 3 subtypes of STSs were alveolar soft tissue sarcoma (20%), leiomyosarcoma (17%) and liposarcoma (12%). The 6-month PFS rate was not reached. Of 35 pts, 23 were available for response evaluation: 6 achieved partial response, 15 had stable disease, and 2 had progressive disease, resulting in an overall response rate of 26.1% and a disease control rate of 91.3%, at primary response. 33 pts were eligible for safety evaluation. The incidence of adverse events (AEs) was 93.9%. The most common AEs were hypertension (63.6%), proteinuria (60.6%), and hand-foot syndrome...
The incidence of Grade 3-4 AEs was 42.2%, and hypertension (30.0%) was the most common Grade 3-4 AEs.

Conclusions:
Current results demonstrated encouraging signs of anti-tumor activity, and well-tolerated toxicity of apatinib in previously treated advanced STSs. Clinical trial information: NCT03064243

3. Apatinib as a salvage treatment for refractory metastatic colorectal cancer.
Presented Sunday, June 3, 2018

Authors:
Xiaofeng Chen, Ping Li, Jing Sun, Biao Wang, Peinan Lin, Xiaomin Cai, Xiao Han, Yanhong Gu; The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background:
Apatinib, an oral VEGFR2 inhibitor, has been approved as third line treatment for metastatic gastric cancer in China. The aim of this study was to evaluate the efficacy and safety of apatinib, in the treatment of refractory metastatic colorectal cancer patients who failed from two or more lines of chemotherapy.

Methods:
In this open-label, single-arm, phase II study, patients were treated with apatinib in daily dose of 500 mg, po, in the third - or more line setting. Capture sequencing was dynamically performed to identify somatic variants in circulating tumor DNA (ctDNA) with a panel of 1021 cancer related genes. The primary endpoint was progression-free-survival (PFS) and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Interim analyses was applied as predefined.

Results:
From June 01, 2016 to December 31, 2017, 26 patients were enrolled. The median PFS of the whole group was 3.9m (95% CI: 2.1-5.4). Patients with PS 0-1 had longer PFS than those with PS 2 (4.17m vs 1.93m, p = 0.0014). Patients without liver metastasis also had longer PFS than those who had live metastasis (5.87m vs 3.33m, p = 0.0274). Median overall survival was not reached. 10-month survival rate was 55%. The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria and diarrhea. The incidence for grade 3-4 hypertension, hand-foot syndrome, proteinuria and diarrhea were 76.92%, 11.54%, 73.08%, and 23.08%, respectively. All of the patients received dose reduction due to
adverse effect. Results of capture sequencing showed APC, TP53 and KRAS were most frequently mutant genes. Patients with high tumor mutation burden (TMB) in baseline blood had a trend of prolonged overall survival than those with low TMB (p = 0.077). The molecular tumor burden from ctDNA increased before the radiographic assessment in 10 patients.

Conclusions:
Apatinib monotherapy showed promising efficiency for refractory colorectal cancer patients, especially in patients with PS 0-1 or no liver metastasis. TMB is a potential prognostic biomarker. In addition, tumor molecular burden may be a predictor in serial monitoring of tumor load. Clinical trial information: NCT03190616

4. Apatinib, a novel VEGFR inhibitor, combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer: A single-arm, open-label, phase 2 study.
Presented Monday, June 4, 2018

Authors:
Chunyan Lan, Yin Wang, Ying Xiong, Judong Li, Yanfang Li, Yanna Zhang, Min Zheng, Yanling Feng, Huiqiang Huang, Xin Huang; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Centre, Guangzhou, China; Cancer Center, Sun Yat-sen University, Guangzhou, China; Sun Yat-Sen University Cancer Center, Guangzhou, China

Background:
Anti-angiogenic therapy combined with chemotherapy could improve the outcome of platinum-resistant ovarian cancer. Apatinib is an oral tyrosine kinase inhibitor which selectively inhibits VEGFR2. We assessed the efficacy and safety of combination of apatinib and oral etoposide, which has the advantage of home administration without an infusion pump and hospitalization, in patients with platinum-resistant or platinum-refractory ovarian cancer.

Methods:
In this phase 2, single-arm, open-label study, we included patients aged 18-70 years with platinum-resistant or platinum-refractory ovarian cancer. Patients received oral etoposide 50 mg on days 1 to 14 in a 21-day cycle for a maximum of six cycles. In addition to the chemotherapy, apatinib 500 mg was administered orally once daily. The primary endpoint was objective response rate by RECIST version 1.1. A Simon two-stage design was employed. This study was registered with ClinicalTrials.gov, number
Results:
Between Aug 10, 2016 and Nov 9, 2017, 35 patients were enrolled. At data cutoff (Dec 31, 2017), 20 (57.1%) of 35 patients had discontinued study, and 15 (42.9%) patients remained on treatment. The reasons for treatment discontinuation included disease progression (n = 10), adverse events (n = 4), consent withdrawal (n = 2), lost of follow-up (n = 2), and others (n = 2). Objective responses were achieved in 19 (54.3%; 95% CI: 36.6–71.2) of 35 patients and disease control was obtained in 30 (85.7%; 95% CI: 69.7–95.2) patients. The median progression-free survival was 8.1 months (95% CI: 2.8–13.4). The most common grade 3 or 4 adverse events were neutropenia (41.2%), fatigue (32.4%), anaemia (29.4%), and mucositis (23.5%). No treatment-related death was recorded. All of the adverse events were manageable. Dose reductions occurred in 82.4% of the patients for apatinib and 76.5% of the patients for oral etoposide.

Conclusions:
The combination of apatinib with oral etoposide shows promising activities and manageable toxicities in patients with platinum resistant or refractory recurrent ovarian cancer, and warrants further study in phase 3 trials. Clinical trial information: NCT02867956

5. Development of non-hematological adverse events in apatinib-treated gastric cancer and their association with clinical outcome: Results from a phase IV study.
Presented Sunday, June 3, 2018

Authors:
Yi Ba, Jin Li, Shukui Qin, Lu Wen, Wenying Deng, Guifang Zhang, Tongfu Jia, Haijun Zhong, Jianwei Yang, Xiaoyan Lin, Yu-Xian Bai, Yifu He, Zhong Xie, Tienan Yi, Xiangyuan Wu, Feng Ye, Likun Liu, Yong Huang, Mei Wang, Junsheng Wang; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Tongji University Shanghai East Hospital, Shanghai, China; Cancer Center of PLA, 81 Hospital.

Background:
Ahead-G201, a multicenter Phase IV study, is conducting to evaluate apatinib as third-line or beyond therapy in a routine practice setting of gastric cancer patients (pts).

Methods:
This analysis was undertaken to evaluate the non-hematological adverse events (AEs), and to explore their potential associations with survival.
Results:
This analysis was based on 1468 pts as of 12/21/2017. The most common non-hematological AEs were hypertension (HTN; 22.8%), proteinuria (PTN; 18.1%), fatigue (16.7%), diarrhea (11.9%) and hand-foot-skin reaction (HFSR; 9.7%), irrespective of the relationship with medication. They were not correlated with progression free survival (PFS); however, pts with diarrhea or HFSR had a statistically longer overall survival (OS) (8.41 vs. 6.14 mos, p = 0.0048; 8.31 vs. 5.98 mos, p < 0.0001) (Table). After adjusting for baseline characteristics and treatment dose, presence of HFSR was an independent predictor for prolonged OS (HR: 0.62 [95%CI, 0.44–0.88]). Besides, we assessed hepatotoxicity and cardiotoxicity in pts. 269 (18.3%) pts who developed hepatotoxicity had a statistically longer PFS (4.70 vs. 3.38 mos; p = 0.0458). A low incidence of cardiotoxicity (2.1%) was detected, and it was not related to survival.

Conclusions:
Occurrence of HFSR could be an effective prognostic factor for OS in apatinib-treated gastric cancer pts, whereas hepatotoxicity might predict PFS. Clinical trial information: NCT02426034

<table>
<thead>
<tr>
<th>Relationship between non-hematological AEs and survival.</th>
<th>PFS, 95%CI (mos)</th>
<th>OS, 95%CI (mos)</th>
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<tbody>
<tr>
<td>HTN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>3.25, 2.89–4.63</td>
<td>6.57, 5.49–7.59</td>
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<tr>
<td>-</td>
<td>4.40, 3.32–4.70</td>
<td>6.51, 5.72–7.29</td>
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<tr>
<td>p</td>
<td>0.1797</td>
<td>0.7761</td>
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<tr>
<td>PTN</td>
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<td></td>
</tr>
<tr>
<td>+</td>
<td>4.27, 3.02–4.73</td>
<td>7.23, 6.21–7.85</td>
</tr>
<tr>
<td>-</td>
<td>3.91, 3.09–4.63</td>
<td>6.05, 5.29–6.93</td>
</tr>
<tr>
<td>p</td>
<td>0.9407</td>
<td>0.0849</td>
</tr>
<tr>
<td>Fatigue</td>
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<td></td>
</tr>
<tr>
<td>+</td>
<td>4.07, 3.06–4.73</td>
<td>5.78, 4.93–7.23</td>
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<tr>
<td>-</td>
<td>4.21, 3.09–4.67</td>
<td>6.67, 5.98–7.69</td>
</tr>
<tr>
<td>p</td>
<td>0.8237</td>
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</tr>
<tr>
<td>Diarrhea</td>
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</tr>
<tr>
<td>+</td>
<td>4.70, 3.55–5.29</td>
<td>8.41, 7.03–9.36</td>
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<td>3.71, 2.99–4.60</td>
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<tr>
<td>p</td>
<td>0.0713</td>
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<tr>
<td>HFSR</td>
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<td>+</td>
<td>4.70, 4.27–5.52</td>
<td>8.31, 6.93–12.75</td>
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<td>3.55, 2.99–4.60</td>
<td>5.98, 5.45–6.80</td>
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<tr>
<td>p</td>
<td>0.1264</td>
<td>&lt; 0.0001</td>
</tr>
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</table>
6. Anti-programmed death-1 antibody SHR-1210 (S) combined with apatinib (A) for advanced hepatocellular carcinoma (HCC), gastric cancer (GC) or esophagogastric junction (EGJ) cancer refractory to standard therapy: A phase 1 trial.
Presented Sunday, June 3, 2018

Authors:
Jian-Ming Xu, Yun Zhang, Ru Jia, Yan Wang, Rongrui Liu, Gairong Zhang, Chuanhua Zhao, Yaoyue Zhang, Jianjun Zou, Quanren Wang; Cancer Center, 307 Hospital, Academy of Military Medical Sciences, Beijing, China; The 307th Hospital of Chinese People’s Liberation Army, Beijing, China; Jiangsu Hengrui Medicine Co., Ltd., Shanghai, China

Background:
A phase 1 (P1) study to assess the safety and efficacy of combination of S, a fully human IgG4 monoclonal antibody against PD-1 with PD-L1/PD-L2 plus Apatinib (A), a VEGFR2 inhibitor in patients (pts) with advanced HCC, GC, EGJ cancer.

Methods:
In P 1a dose escalation, pts received A (125, 250, 500mg, QD, 5 pts per cohort) and S (200 mg, Q2W) until unacceptable toxicity, disease progression. In phase 1b cohort expansion, pts received A at recommended P2 dose (RP2D) + S (200 mg, Q2W). Response was evaluated by RECIST v1.1.
Results:
At the cut-off data (Feb. 2, 2018), 42 pts (P 1a, n = 15; P 1b, n = 27) were enrolled. Median prior lines of therapy in HCC and GC were 1 and 2, respectively. In P1a stage, 3 DLTs (all grade 3 pneumonia) were observed in A 500mg cohort. The RP2D was A 250mg + S. In P 1b stage, the median treatment duration was 19 wks (range, 2-57 wks). 19 pts (58%) had ≥ grade 3 treatment-related adverse events (TRAEs). The ≥10% grade 3 TRAEs were hypertension (18%), increased AST (15%) and ALT (12%). These AEs were manageable, only 1 pt discontinued treatment due to TR grade 3 hyperbilirubinemia. There were no TR-deaths. The ORR and DCR in 36 evaluable pts in all 3 cohorts were 30.6% (n = 11) and 83.3% (n = 30), respectively. All 11 responses occurred in A 125mg (n = 1) and 250mg (n = 10) cohorts. Among 18 HCC pts (14 evaluable: A 125mg cohort, n = 4; A 250mg cohort, n = 9, A 500mg cohort, n = 1), all infected with HBV. The ORR and DCR were 50.0% and 85.7%, respectively. Notably, 2 pts in A 125mg cohort had initial SD at best response, and achieved PR after escalating A dose to 250 mg, therefore the ORR at A 250 mg dose level was 54.5% (6/11). The median progression-free survival (PFS) was not reached. All 7 pts with PR were still on treatment, 5 lasted for 47 weeks+. Of 24 GC or EGJ cancer pts (22 evaluable: A cohort, 250mg n = 20; 500mg, n = 2), the ORR in A 250mg cohort was 20.0% and DCR was 80.0%. The median PFS was 3.0 months.

Conclusions:
S + A at RP2D demonstrated manageable toxicity in HCC, GC or EGJ cancer pts. Particularly encouraging clinical activity (PR rate 54.5%) was observed in pts with pretreated, advanced HCC. Clinical trial information: NCT02942329

Presented Saturday, June 2, 2018

Authors:
Lu Xie, Jie Xu, Xin Sun, Xiaodong Tang, Taiqiang Yan, Rongli Yang, Wei Guo; Peking University People's Hospital, Beijing, China

Background:
Anti-angiogenesis Tyrosine kinase inhibitors (TKIs) have been proved to show promising effects on prolonging progression-free survival (PFS) for advanced osteosarcoma after failure of standard multimodal Therapy. Methylsulfonic apatinib is one of those TKIs which specifically inhibits VEGFR-2. We aimed to assess the activity of apatinib in patients with locally advanced or multiple metastatic high-grade osteosarcoma progressing after standard treatment.
Methods:
This non-randomised phase 2 trial was done in Peking University People's Hospital. We enrolled participants (≥16 years) with relapsed or unresectable osteosarcoma progressing after standard treatment (methotrexate, cisplatin, doxorubicin, and ifosfamide). Participants received 750 mg or 500mg apatinib according to body surface area (BSA) once daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (CR+PR at least 3 months according to RECIST 1.1) and PFS at 4 months. All analyses were intention-to-treat.

Results:
37 participants were enrolled between March 17th, 2016 and June 9th, 2017. Until final follow-up, the objective response rate (CR+PR at least 3 m) was 56.76% (21/37). And the 4-m PFS rate was 52% (95% CI 32%–68%). However 9/37 (24.32%) patients was progression free at 6 months. Median PFS and OS were 4.44 (95% CI 3.12–7.08) and 8.77 (95% CI 6.73–16.70) months, respectively. Toxic effects led to dose reductions, or interruptions in a total of 25/37 (67.57%) patients. The most common grade 3–4 adverse events were pneumothorax in 5 (13.51%) patients, wound dehiscence in 4 (10.81%), abdominal cramps in 3 (8.11%), hypokalemia in 2 (5.41%) and bilirubin increase, proteinuria, hypertriglyceridaemia, hand–foot skin reaction and anemia each in one (2.70%). No other serious adverse events were reported during the trial. There were no treatment-related deaths.

Conclusions:
Apatinib was a sensitive drug for advanced osteosarcoma with high response rate after failure of chemotherapy, with almost the same duration of response comparing to other TKIs. Clinical trial information: NCT02711007

Presented Sunday, June 3, 2018

Authors:
Hongyun Zhao, Zhonghan Zhang, Fan Luo, Yuxiang Ma, Wenfeng Fang, Yunpeng Yang, Yang Zhang, Yan Huang, Li Zhang; State Key Laboratory of Oncology in South China, Cancer Center, Sun Yat-sen University, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-Sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative...View More
**Background:**
Dual inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathway is becoming an encouraging strategy in the treatment of advanced NSCLC. Apatinib is a tyrosine kinase inhibitor that selectively inhibits the VEGF receptor-2. Our phase I study of Apatinib plus Gefitinib has shown a manageable tolerability profile and promising antitumor activity with an anticipated progressive-free survival (PFS) > 14 mos. This phase III study aims to evaluate the efficacy and safety of Apatinib or placebo plus Gefitinib as first-line treatment in patients (pts) with stage IIIb-IV NSCLC harboring an activating *EGFR* mutation.

**Methods:**
Treatment-naïve stage IIIb or IV NSCLC pts with *EGFR* 19 Del or 21 L858R mutation are enrolled. Other inclusion criteria include ECOG PS of 0 or 1, ≥1 measurable lesion according to RECIST v1.1 and adequate organ function. Eligible pts will be randomized in a 1:1 ratio to receive either Apatinib or Placebo 500 mg QD plus Gefitinib 250 mg QD until progressive disease or unacceptable toxicity. Stratified randomization is based on *EGFR* mutation status, gender and ECOG PS. The primary endpoint is PFS. Secondary endpoints include overall survival, objective response rate, disease control rate, time to progression, duration of response, quality of life and the safety profile. Independent Data Monitoring Committee and Independent Review Committee will be used in this study. According to previous report (erlotinib plus bevacizumab vs. erlotinib alone: 16.0 vs. 9.7 mos, HR 0.54, Lancet Oncol, 15(11):1236-1244), it was assumed that the estimated median PFS would be 15 mos in the Apatinib + Gefitinib group and 10 mos in the Placebo + Gefitinib group. To detect a 5-mos improvement of PFS in Apatinib + Gefitinib group at a two-sided significant level of 0.05 and a power of 0.8, allowing for a dropout rate of 20%, the sample size should be 155 patients per group. In total, 310 patients will be enrolled in this trial at 30 sites in China. From August 2017, 100 patients have been enrolled. Clinical trial information: NCT02824458