An Open-labeled, Phase I Study to Evaluate the Safety and Tolerability of Apatinib with Nivolumab in Patients with Unresectable or Metastatic Cancer

Disclosures – Dr. Sant Chawla

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Background

- Apatinib (APA, rivoceranib and YN968D1) is an orally administered, highly selective tyrosine kinase inhibitor of VEGFR-2 with demonstrated efficacy and approval as ≥3rd-line treatment for advanced gastric cancer in China[1]
- Recently, clinical activities of anti-angiogenic tyrosine kinase inhibitors (TKIs) combined with immunotherapies have been demonstrated in multiple tumor types.
- Monotherapy of nivolumab (NIV), a PD-1 monoclonal antibody, has not shown a notable tumor response for sarcoma.[2,3]
- The potential benefit of APA + NIV combination therapy has been demonstrated in preclinical murine lung carcinoma syngeneic models, in which the combination increased anti-tumor activities of individual therapies.[4]
- Results of a Phase I study of RIV + NIV in subjects with unresectable / metastatic cancer is presented here.

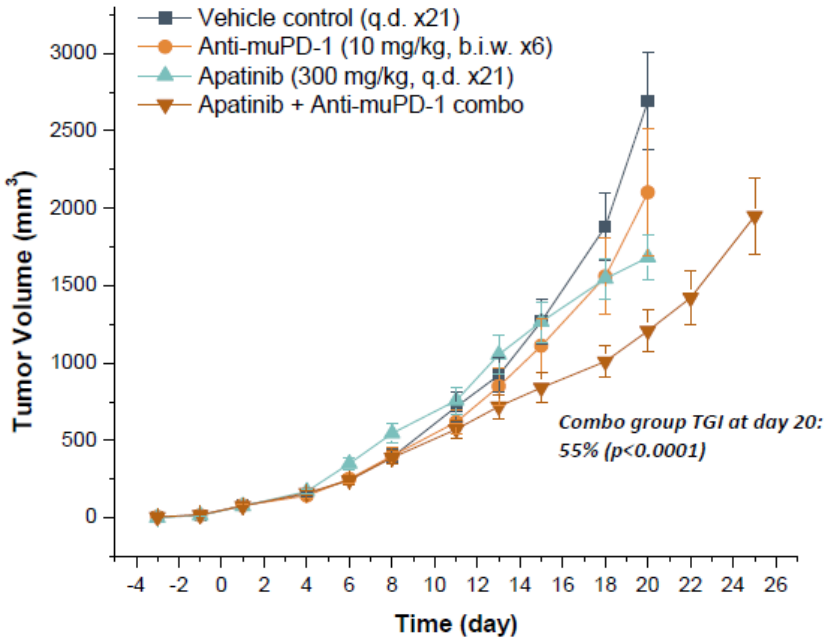
1. Li J, et al. J Clin Oncol 2016;34:1448–54
2. L. Pouluzzi, et al. ASCO 2016. Abstract #11047.
3. E. Ben-Ami, et al. Cancer. 123(17):3285-90, 2017.
4. B. Kim, et al. *AACR 2018*. Abstract #2756.

Synergistic tumor-suppressive effect of apatinib (rivovernib) in combination with immunotherapy

Preclinical studies demonstrated that apatinib synergistically suppressed tumor growth when combined with anti-PD-1 in mouse model of lung carcinoma.

Tumor growth inhibition

Figure 1. Tumor growth curve.



%TGI (tumor growth inhibition) = (([mean day 20 control] - [mean day 0 control]) - ([mean day 20 combo group] - [mean day 0 combo group])) / ([mean day 20 control] - [mean day 0 control]) * 100%

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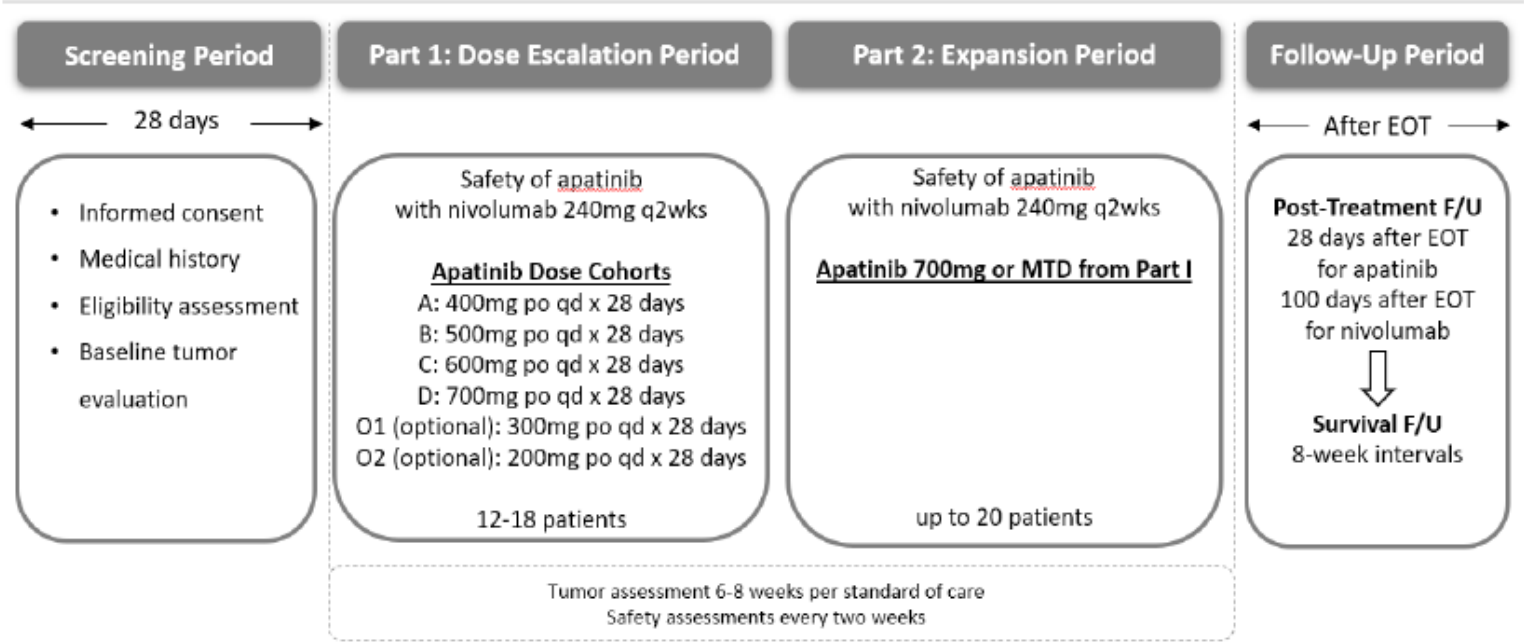
1) **<u>Part 1</u>: Dose Escalation Period** – A classic 3+3 design to evaluate the safety of apatinib in combination with nivolumab.

The MTD was defined as the dose level below that where 2 DLTs are experienced in 6 subjects or 700 mg, if no DLTs occur in 3 subjects or only 1 DLT occurs in the 700-mg cohort.

2) **<u>Part 2</u>: Expansion Period –** Open-label administration of apatinib at a dose up to 700 mg qd or at the maximum tolerated dose (MTD) obtained from Part I of this study. Some patients received a reduced dose of nivolumab (200 mg) in later treatments.



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Endpoints and main enrollment criteria

Primary outcome measures:

Incidence and severity of drug-related adverse events and serious adverse events:

- During the first two 28-day cycles (approximately 8 weeks for each subject)
- From the beginning of the third 28-day cycle until end of treatment (including 4 weeks post apatinib treatment and 100 days post nivolumab treatment, whichever is longest for each subject)

Efficacy measures:

- Objective response rate (ORR), best overall response rate (BOR), time to response (TTR), and duration of response (DoR) per RECIST v1.1 and/or iRECIST
- Disease control rate (DCR), and duration of disease control (DDC) by RECIST v1.1 and/or iRECIST

Secondary outcome measures:

- Overall Survival (OS)
- Event Free Survival (EFS)
- Progression Free Survival (PFS)

Exploratory outcome measures:

Exploratory objectives in this study are to evaluate the correlation between response to treatment and genomic tumor profile, serum cytokines, changes in PBMC subsets and MDSC population. They are measured by:

- Tumor mutational burden and mutations at baseline and at the time of progression
- Changes in serum cytokines pursuant to treatment response

Main eligibility criteria include patients with primary diagnosis of histologic- or cytologic-confirmed solid tumor cancer.

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Subject Baseline Characteristics

A total of 30 patients were recruited where 10 patients participated in part I and 20
patients in part II.

Subject Baseline Characteristics

Parameter	RIV + NIV Part 1 (n=10)	RIV + NIV Part 2 (n=20)	RIV + NIV Overall (n=30)
Sex, n (%)			
Female	6 (60.0)	9 (45.0)	15 (50.0)
Male	4 (40.0)	11 (55.0)	15 (50.0)
Median age, years (range)			53 (25-76)
ECOG, n (%)			
1	10 (100.0)	20 (100.0)	30 (100.0)
Race, n (%)			
Asian	2 (20.0)	0 (0.0)	2 (6.7)
Black or African American	0 (0.0)	1 (5.0)	1 (3.3)
White	8 (80.0)	19 (95.0)	27 (90.0)
Tumor type, n (%)			
Angiosarcoma	0 (0.0)	3 (15.0)	3 (10.0)
Cervical cancer (squamous cell carcinoma)	1 (10.0)	1 (5.0)	2 (6.7)
Cholangiocarcinoma	1 (10.0)	0 (0.0)	1 (3.3)
Chondrosarcoma	1 (10.0)	2 (10.0)	3 (10.0)
Fibrous histiocytoma	1 (10.0)	0 (0.0)	1 (3.3)
Gastric cancer	1 (10.0)	2 (10.0)	3 (10.0)
Leiomyosarcoma	2 (20.0)	7 (35.0)	9 (30.0)
Liposarcoma	1 (10.0)	0 (0.0)	1 (3.3)
Malignant spindled and epithelioid sarcoma	1 (10.0)	0 (0.0)	1 (3.3)
Osteosarcoma	0 (0.0)	2 (10.0)	2 (6.7)
Synovial sarcoma	1 (10.0)	3 (15.0)	4 (13.3)
Prior lines of therapy, n (%)			
≤ 1	1 (11.1)	5 (31.3)	6 (24.0)
2	3 (33.3)	1 (6.3)	4 (16.0)
3	3 (33.3)	5 (31.3)	8 (32.0)
≥ 4	2 (22.2)	5 (31.3)	7 (28.0)

ECOG, Eastern Cooperative Oncology Group; NIV, nivolumab; RIV, rivoceranib

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Diagnosis and Dosing

Tumor Type	Part I (n=10)			Part II (n=20)	Total (n=30)
	400mg (n=3)	300mg (n=7)	Combined 400mg and 300mg (n=10)		
Angiosarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (15.0%)	3 (10.0%)
Cervical cancer (squamous cell carcinoma)	0 (0.0%)	1 (14.3%)	1 (10.0%)	1 (5.0%)	2 (6.7%)
Cholangiocarcinoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Chondrosarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	2 (10.0%)	3 (10.0%)
Fibrous histiocytoma	1 (33.3%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Gastric cancer	0 (0.0%)	1 (14.3%)	1 (10.0%)	2 (10.0%)	3 (10.0%)
Leiomyosarcoma	1 (33.3%)	1 (14.3%)	2 (20.0%)	7 (35.0%)	9 (30.0%)
Liposarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Malignant spindled and epithelioid sarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Osteosarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (6.7%)
Synovial sarcoma	1 (33.3%)	0 (0.0%)	1 (10.0%)	3 (15.0%)	4 (13.3%)

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Summary of Tumor Response

ORR: 13.3% (95% CI: 3.8 % to 30.7 %)

DCR: 76.7% (95% CI: 57.7 % to 90.1 %)

PFS: 7.2 months (95% CI: 5.3 to 9.0 months)

There were no CRs and PRs were observed in 4

patients (13.3%).

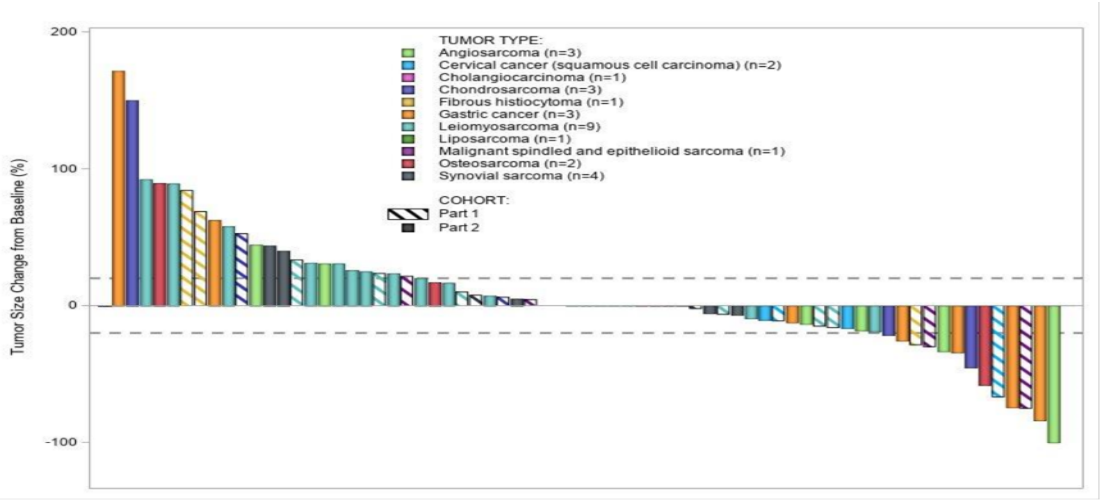
Table 4. Summary of Tumor Response

	RIV + NIV		
Parameter	Part 1 (n=10)	Part 2 (n=20)	Overall (n=30)
BOR, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	1 (10.0)	3 (15.0)	4 (13.3)
SD	6 (60.0)	13 (65.0)	19 (63.3)
PD	1 (10.0)	1 (5.0)	2 (6.7)
ORR, n (%)	1 (10.0)	3 (15.0)	4 (13.3)
DCR, n (%)	7 (70.0)	16 (80.0)	23 (76.7)

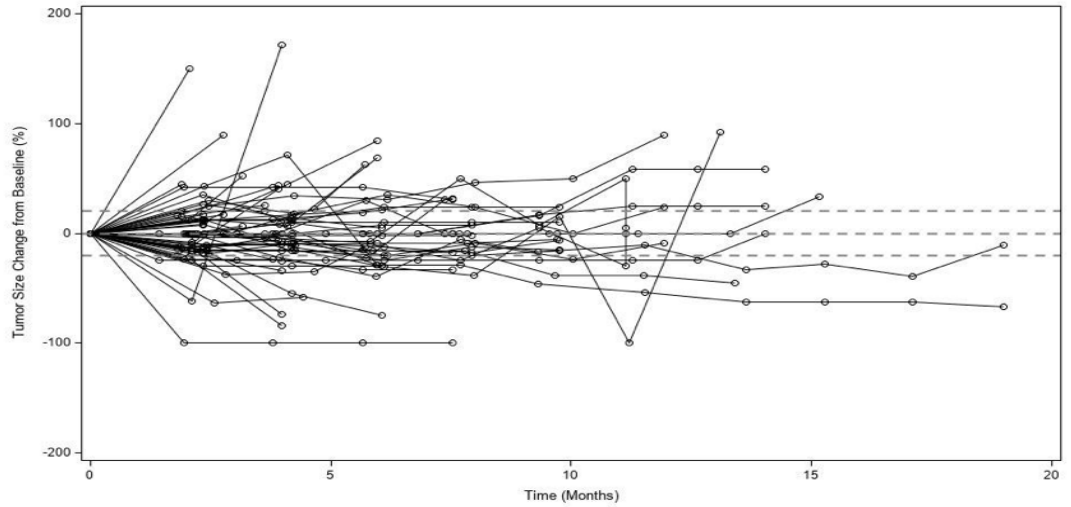
BOR, best overall response; CR, complete response; DCR, disease control rate; NIV, nivolumab; ORR, overall response rate; PD, progressive disease; PR, partial response; RIV, rivoceranib; SD, stable disease

Tumor Responses

Percent change from baseline to Nadir in Sums of Diameters of target lesions



Percent change from baseline in sums of diameters of target lesions over time



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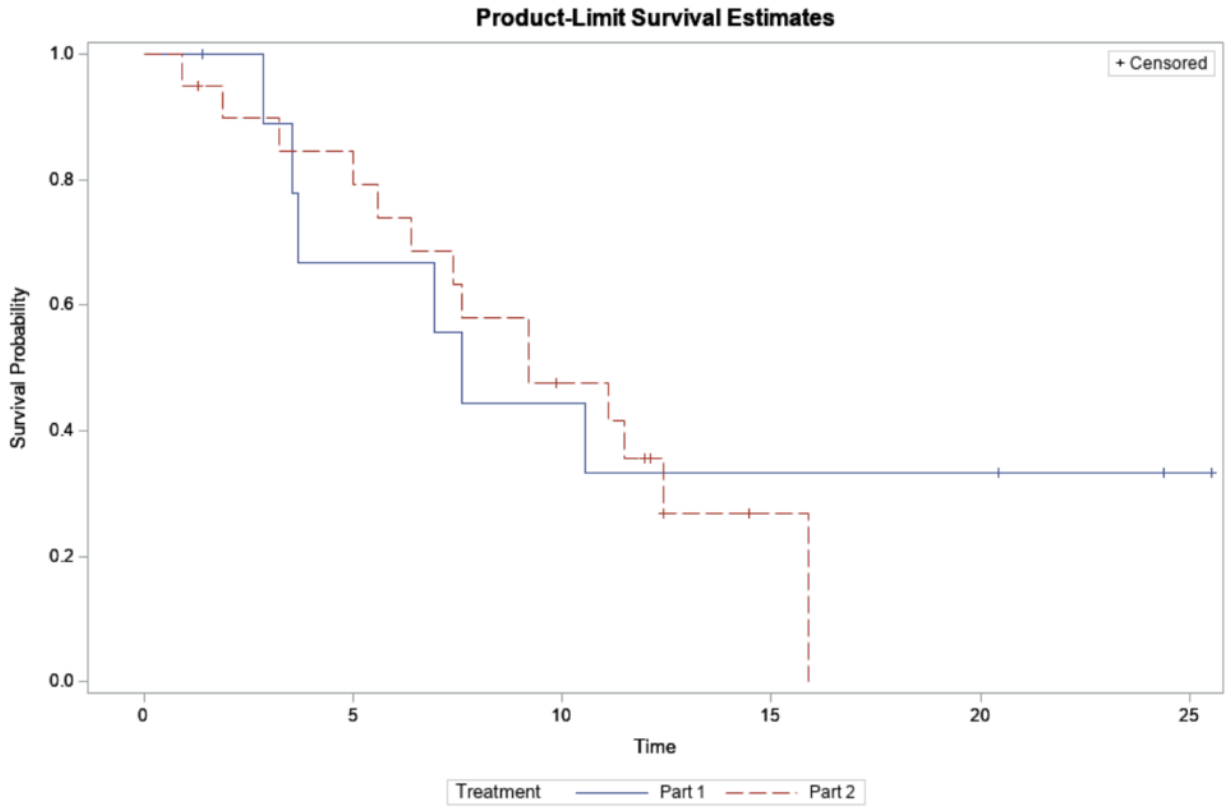
Probability of Survival



Summary of TEAEs

Table 2. Summary of TEAEs

Parameter, n (%)	RIV + NIV		
	Part 1 (n=10)	Part 2 (n=20)	Overall (n=30)
TEAEs	10 (100.0)	20 (100.0)	30 (100.0)
Treatment-related TEAEs	10 (100.0)	19 (95.0)	29 (96.7)
TEAEs ≥ grade 3	7 (70.0)	16 (80.0)	23 (76.7)
Serious AEs	4 (40.0)	9 (45.0)	13 (43.3)
Fatal AEs	1 (10.0)	1 (5.0)	2 (6.7)
Dose modifications			
RIV or NIV dose interruptions due to AEs	6 (60.0)	15 (75.0)	21 (70.0)
RIV dose reductions due to AEs	3 (30.0)	6 (30.0)	9 (30.0)
Discontinuation of RIV or NIV due to AEs	4 (40.0)	5 (25.0)	9 (30.0)

AE, adverse event; NIV, nivolumab; RIV, rivoceranib; TEAE, treatment-emergent adverse event

≥ Grade 3 TEAEs: 23 (76.7%) patients (7 patients from Part 1 and 16 patients from Part 2)

Two patients (6.7%) experienced fatal AEs.

There were no unexpected side effects, no additive side effects
of the combined treatment (nivolumab and apatinib), and no drug related deaths noted.

Reasons of discontinuation were toxicity in 9 patients (30.0%; 4
from Part 1 and 5 from Part 2) and dose reduction was applied in 9 patients due to AEs (30.0%; 3 from Part 1 and 6 from Part 2).

Three patients experienced 4 dose-limiting toxicities, including
grade 3 non-hematology toxicity (DL4 and DL5) and
uncontrollable hypertension defined as stage 2 hypertension

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Most common TEAEs by preferred term and grade

≥ Grade 3 TEAEs
(occurring in ≥10% of patients)

- Fatigue (10.0%)
- Hypertension (10.0%),
- Nausea (10.0%),
- Anaemia (16.7%)
- Asthenia (10.0%)

Table 3. Most Common TEAEs by Preferred Term and Grade*

	RIV + NIV (n=30)	
Preferred term, n (%)	Any grade	Grade ≥ 3
Fatigue	19 (63.3)	3 (10.0)
Hypertension	18 (60.0)	3 (10.0)
Palmar-plantar erythrodysaesthesia syndrome	12 (40.0)	0 (0.0)
Nausea	11 (36.7)	3 (10.0)
Headache	9 (30.0)	2 (6.7)
Vomiting	9 (30.0)	2 (6.7)
Diarrhoea	8 (26.7)	0 (0.0)
Abdominal pain	7 (23.3)	2 (6.7)
Back pain	7 (23.3)	1 (3.3)
Blood thyroid stimulating hormone increased	7 (23.3)	0 (0.0)
Decreased appetite	7 (23.3)	0 (0.0)
Hypokalaemia	7 (23.3)	2 (6.7)
Tachycardia	7 (23.3)	0 (0.0)
Anaemia	6 (20.0)	5 (16.7)
Hypophosphataemia	6 (20.0)	2 (6.7)
Pyrexia	6 (20.0)	0 (0.0)
Rash	6 (20.0)	0 (0.0)
Urinary tract infection	6 (20.0)	2 (6.7)
Constipation	5 (16.7)	0 (0.0)
Hypomagnesaemia	5 (16.7)	0 (0.0)
Hyponatraemia	5 (16.7)	2 (6.7)
Aspartate aminotransferase increased	4 (13.3)	1 (3.3)
Asthenia	4 (13.3)	3 (10.0)
Chills	4 (13.3)	0 (0.0)
Dehydration	4 (13.3)	1 (3.3)
Pruritus	4 (13.3)	0 (0.0)

*Occurring in ≥4 subjects with an any-grade TEAE in the overall subject population.
NIV, nivolumab; RIV, rivoceranib; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone

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Conclusion

The results indicate the potential clinical benefit of apatinib combination with nivolumab in unresectable/metastatic solid tumors with a tolerable
safety profile.

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