# An open-label, Phase 1b/2 study of surufatinib in combination with tislelizumab in patients with advanced neuroendocrine tumors

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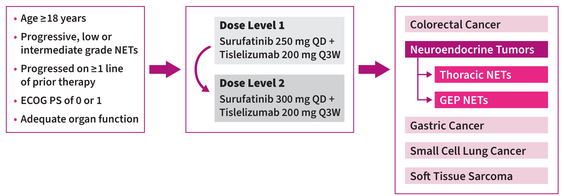
## INTRODUCTION

- The incidence and prevalence of neuroendocrine tumors (NETs) is increasing globally[1,2]
- Immune checkpoint inhibitors (ICIs) have demonstrated limited anti-tumor activity in patients with well differentiated NETs as monotherapy[3,4]
- Combining vascular endothelial growth factor receptor (VEGFR) inhibitors with ICIs may potentiate efficacy and suppress tumor growth and reduce metastasis[5,6] by:
  - Normalizing vascular immune crosstalk
  - Improving immune effector cell infiltration
- Surufatinib, an oral small molecule tyrosine kinase inhibitor, selectively inhibits VEGFR 1, 2, and 3; fibroblast growth factor receptor 1; and colony-stimulating factor 1 receptor
  - In 2 Phase 3 randomized trials (SANET-ep, NCT02588170 and SANET-p, NCT02589821), surufatinib, as a monotherapy, demonstrated a manageable safety profile and statistically significant efficacy in patients with NETs[7,8]
- Tislelizumab is a humanized immunoglobulin G4-variant anti-programmed cell death protein-1 monoclonal antibody
- Combining surufatinib and tislelizumab may have synergistic effects, where inhibition of angiogenesis and stimulation of an immune response may enhance overall anti-tumor activity

## METHODS

- This is an open-label, Phase 1b/2 dose escalation (ESC)/expansion (EXP) study (NCT04579757) to determine the recommended Phase 2 dose (RP2D) and/or the maximum tolerated dose for the combination of surufatinib and tislelizumab in patients with advanced or metastatic solid tumors and to explore the preliminary anti tumor activity of the combination
- ESC used a 3+3 design at 2 surufatinib dose levels 250 mg and 300 mg once daily (QD). The RP2D was determined to be surufatinib 300 mg orally, QD in combination with tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W) in 3 week cycles.
- In EXP, patients received surufatinib 300 mg orally QD (RP2D) in combination with tislelizumab 200 mg IV in 3-week cycles and tumor imaging was performed every 6 weeks
- Cohorts with NETs, colorectal cancer, gastric cancer, small cell lung cancer, and soft tissue sarcoma were included in EXP
- Inclusion criteria for the NET cohorts included progressive, low, or intermediate grade NETs of thoracic or gastroenteropancreatic (GEP) origin
- Findings from the 2 EXP cohorts of thoracic NETs and GEP NETs are reported here

### Figure 1. Study Design




ECOG=Eastern Cooperative Oncology Group; GEP=gastroenteropancreatic; NET=neuroendocrine tumors; PS=performance status; Q3W=every 3 weeks; QD=once daily

## RESULTS

- The surufatinib RP2D established in ESC was 300 mg QD
- Twenty-nine patients with NETs were enrolled in EXP (9 thoracic NET, 20 GEP NET [GEP primary tumor location: 10 bowel, 8 pancreas, and 2 unknown]). All patients had received prior anticancer treatment: 25 (86.2%) somatostatin analogs, 14 (48.3%) radionuclide therapy, 10 (34.5%) everolimus, and 2 (6.9%) sunitinib.
- No patient demonstrated a complete response. Five (17.2%) patients (including 1 unconfirmed) had a partial response (PR; 2 small bowel and 1 each pancreas, lung, and unknown), and 10 (34.5%) patients had stable disease. Of the confirmed PRs, one was in a patient with a pancreatic NET patient and the other 3 were patients with non-pancreatic NET.

### Table 1. Baseline Demographics

| | Thoracic NETs (N=9) | GEP NETs (N=20) |
|---|---|---|
| **Age, n (%)** | | |
| <65 years | 6 (66.7) | 9 (45.0) |
| ≥65 years | 3 (33.3) | 11 (55.0) |
| **Gender, n (%)** | | |
| Male | 6 (66.7) | 10 (50.0) |
| **Race, n (%)** | | |
| Asian | 1 (11.1) | 0 |
| Black or African American | 0 | 3 (15.0) |
| White | 8 (88.9) | 17 (85.0) |
| **Ethnicity, n (%)** | | |
| Hispanic or Latino | 0 | 2 (10.0) |
| Not Hispanic or Latino | 8 (88.9) | 18 (90.0) |
| Not reported | 1 (11.1) | 0 |
| **ECOG PS, n (%)** | | |
| 0 | 1 (11.1) | 9 (45.0) |
| 1 | 8 (88.9) | 11 (55.0) |
| **Prior lines of therapy, median (range)** | 1 (1 - 6) | 3 (1 - 5) |
| **Prior anticancer treatment, n (%)** | 9 (100.0) | 20 (100.0) |
| Somatostatin analog | 5 (55.6) | 20 (100.0) |
| Radionuclide therapy | 2 (22.2) | 12 (60.0) |
| Everolimus | 2 (22.2) | 8 (40.0) |
| Sunitinib | 2 (22.2) | 0 |
| **Functional status, n (%)** | | |
| Functional | 2 (22.2) | 10 (50.0) |
| Non-functional | 6 (66.7) | 6 (30.0) |
| Unknown | 1 (11.1) | 4 (20.0) |
| **Primary tumor location** | | |
| Colon | - | 2 (10.0) |
| Pancreas | - | 8 (40.0) |
| Small bowel | - | 8 (40.0) |
| Unknown | - | 2 (10.0) |

ECOG=Eastern Cooperative Oncology Group; GEP=gastroenteropancreatic; NET=neuroendocrine tumors; PS=performance status

### Table 2. Anti-tumor Activity

| | Thoracic NETs (N=9) | GEP NETs (N=20) |
|---|---|---|
| **Best overall response, n (%)** | | |
| Complete response | 0 | 0 |
| Partial response | 1 (11.1) | 4 (20.0)* |
| Stable disease | 3 (33.3) | 7 (35.0) |
| Progressive disease | 1 (11.1) | 4 (20.0) |
| Not evaluable | 1 (11.1) | 2 (10.0) |
| Missing | 3 (33.3) | 3 (15.0) |
| **Objective response rate, n (%)** | **1 (11.1)** | **4 (20.0)*** |
| (95% CI) | (0.3, 48.2) | (5.7, 43.7) |
| **Disease control rate, n (%)** | **4 (44.4)** | **11 (55.0)** |
| (95% CI) | (13.7, 78.8) | (31.5, 76.9) |

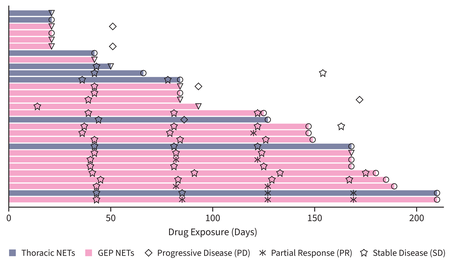
*Includes 1 unconfirmed PR at data cutoff
CI=confidence interval; GEP=gastroenteropancreatic; NET=neuroendocrine tumor; PR=partial response

### Table 3. Duration of Exposure

| | Surufatinib | | Tislelizumab | |
|---|---|---|---|---|
| | Thoracic NETs (N=9) | GEP NETs (N=20) | Thoracic NETs (N=9) | GEP NETs (N=20) |
| Duration of exposure, days, median (min, max) | 71.5 (14, 189) | 109.5 (8, 197) | 50.0 (21, 210) | 84.0 (21, 210) |
| Number of cycles received, median (min, max) | 3.0 (1, 8) | 5.0 (1, 10) | 2.0 (1, 9) | 4.0 (1, 9) |
| Dose interruption, n (%) | 4 (44.4) | 10 (50.0) | 0 | 2 (10.0) |
| Dose reduction, n (%) | 2 (22.2) | 6 (30.0) | N/A | N/A |
| Treatment discontinuation, n (%) | 1 (11.1) | 3 (15.0) | 0 | 0 |

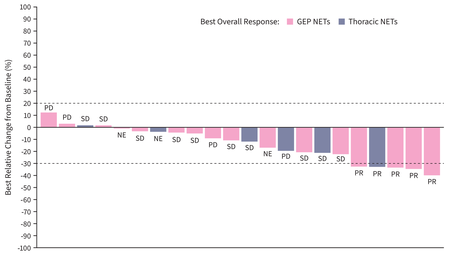
GEP=gastroenteropancreatic; max-maximum; min=minimum; NET=neuroendocrine

### Figure 2. Duration of Treatment




GEP=gastroenteropancreatic; NET=neuroendocrine tumor

### Figure 3. Best Percent Change in Target Lesion Diameter




GEP=gastroenteropancreatic; NET=neuroendocrine tumor; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease
Partial responses include patients with primary tumor locations of: small bowel (2), pancreas, lung, and unknown (1 each).

### Safety

- All 29 (100.0%) patients reported at least 1 treatment-emergent adverse event (TEAE); 20 (69.0%) patients reported TEAEs grade ≥3
- The most common TEAEs of any grade were increased aspartate aminotransferase (AST) (51.7%), nausea and hypertension (44.8% each), decreased appetite and fatigue (41.4% each), diarrhea (37.9%), and increased alanine aminotransferase (ALT) (34.5%)
- The most common grade ≥3 TEAEs were increased AST in 6 (20.7%) patients and increased ALT in 5 (17.2%) patients
- The most common TEAEs leading to surufatinib dose reduction were increased AST and ALT in 2 (10%) patients each in the GEP NET cohort

### Table 4. TEAEs in ≥20% in Either Cohort

| | Thoracic NETs (N=9) n (%) | | GEP NETs (N=20) n (%) | | NET Cohorts (N=29) n (%) | |
|---|---|---|---|---|---|---|
| Preferred term | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any TEAE | 9 (100.0) | 7 (77.8) | 20 (100.0) | 13 (65.0) | 29 (100.0) | 20 (69.0) |
| AST increase | 4 (44.4) | 2 (22.2) | 11 (55.0) | 4 (20.0) | 15 (51.7) | 6 (20.7) |
| Hypertension | 4 (44.4) | 1 (11.1) | 9 (45.0) | 2 (10.0) | 13 (44.8) | 3 (10.3) |
| Nausea | 4 (44.4) | 0 | 9 (45.0) | 0 | 13 (44.8) | 0 |
| Fatigue | 2 (22.2) | 0 | 10 (50.0) | 2 (10.0) | 12 (41.4) | 2 (6.9) |
| Decreased appetite | 4 (44.4) | 0 | 8 (40.0) | 0 | 12 (41.4) | 0 |
| Diarrhea | 3 (33.3) | 2 (22.2) | 8 (40.0) | 1 (5.0) | 11 (37.9) | 3 (10.3) |
| ALT increase | 3 (33.3) | 2 (22.2) | 7 (35.0) | 3 (15.0) | 10 (34.5) | 5 (17.2) |
| Proteinuria | 3 (33.3) | 1 (11.1) | 6 (30.0) | 0 | 9 (31.0) | 1 (3.4) |
| Hyponatremia | 2 (22.2) | 0 | 6 (30.0) | 2 (10.0) | 8 (27.6) | 2 (6.9) |
| Platelet count decrease | 4 (44.4) | 0 | 4 (20.0) | 1 (5.0) | 8 (27.6) | 1 (3.4) |
| Blood LD increase | 3 (33.3) | 0 | 5 (25.0) | 0 | 8 (27.6) | 0 |
| Arthralgia | 3 (33.3) | 0 | 5 (25.0) | 0 | 8 (27.6) | 0 |
| Blood bilirubin increase | 2 (22.2) | 1 (11.1) | 5 (25.0) | 1 (5.0) | 7 (24.1) | 2 (6.9) |
| Lipase increase | 2 (22.2) | 1 (11.1) | 5 (25.0) | 1 (5.0) | 7 (24.1) | 2 (6.9) |
| Hypokalemia | 2 (22.2) | 0 | 5 (25.0) | 1 (5.0) | 7 (24.1) | 1 (3.4) |
| Hyperglycemia | 2 (22.2) | 0 | 5 (25.0) | 1 (5.0) | 7 (24.1) | 1 (3.4) |
| Headache | 2 (22.2) | 0 | 5 (25.0) | 0 | 7 (24.1) | 0 |
| Blood creatinine increase | 1 (11.1) | 0 | 6 (30.0) | 0 | 7 (24.1) | 0 |
| Vomiting | 3 (33.3) | 0 | 4 (20.0) | 0 | 7 (24.1) | 0 |
| Abdominal pain | 1 (11.1) | 1 (11.1) | 5 (25.0) | 1 (5.0) | 6 (20.7) | 2 (6.9) |
| Anemia | 3 (33.3) | 0 | 3 (15.0) | 1 (5.0) | 6 (20.7) | 1 (3.4) |
| Amylase increase | 2 (22.2) | 1 (11.1) | 3 (15.0) | 1 (5.0) | 5 (17.2) | 2 (6.9) |
| Cough | 2 (22.2) | 0 | 3 (15.0) | 0 | 5 (17.2) | 0 |
| Pyrexia | 1 (11.1) | 0 | 4 (20.0) | 0 | 5 (17.2) | 0 |
| Hyperuricemia | 2 (22.2) | 0 | 2 (10.0) | 0 | 4 (13.8) | 0 |
| Weight decrease | 2 (22.2) | 0 | 2 (10.0) | 0 | 4 (13.8) | 0 |
| Hematuria | 0 | 0 | 4 (20.0) | 0 | 4 (13.8) | 0 |
| aPTT prolonged | 2 (22.2) | 0 | 1 (5.0) | 0 | 3 (10.3) | 0 |
| Dry mouth | 2 (22.2) | 0 | 1 (5.0) | 0 | 3 (10.3) | 0 |
| Dry skin | 2 (22.2) | 0 | 0 | 0 | 2 (6.9) | 0 |

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; GEP=gastroenteropancreatic; LD=lactate dehydrogenase; NET=neuroendocrine tumor; TEAE=treatment-emergent adverse event

## CONCLUSIONS

- **Surufatinib 300 mg QD with tislelizumab 200 mg IV Q3W was established as the RP2D in ESC**
- **The combination of surufatinib and tislelizumab demonstrated encouraging anti-tumor activity in pretreated patients with thoracic and GEP NETs**
- **The combination of surufatinib and tislelizumab demonstrated a manageable safety profile in patients with NETs**
- **This combination study with surufatinib and tislelizumab is ongoing in patients with other advanced or metastatic solid tumors**

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