**Investigational New Drugs**

# Phase 2 study of TAS-117 in advanced solid tumors harboring phosphatidylinositol 3-kinase/v-akt murine thymoma viral oncogene homolog gene aberrations

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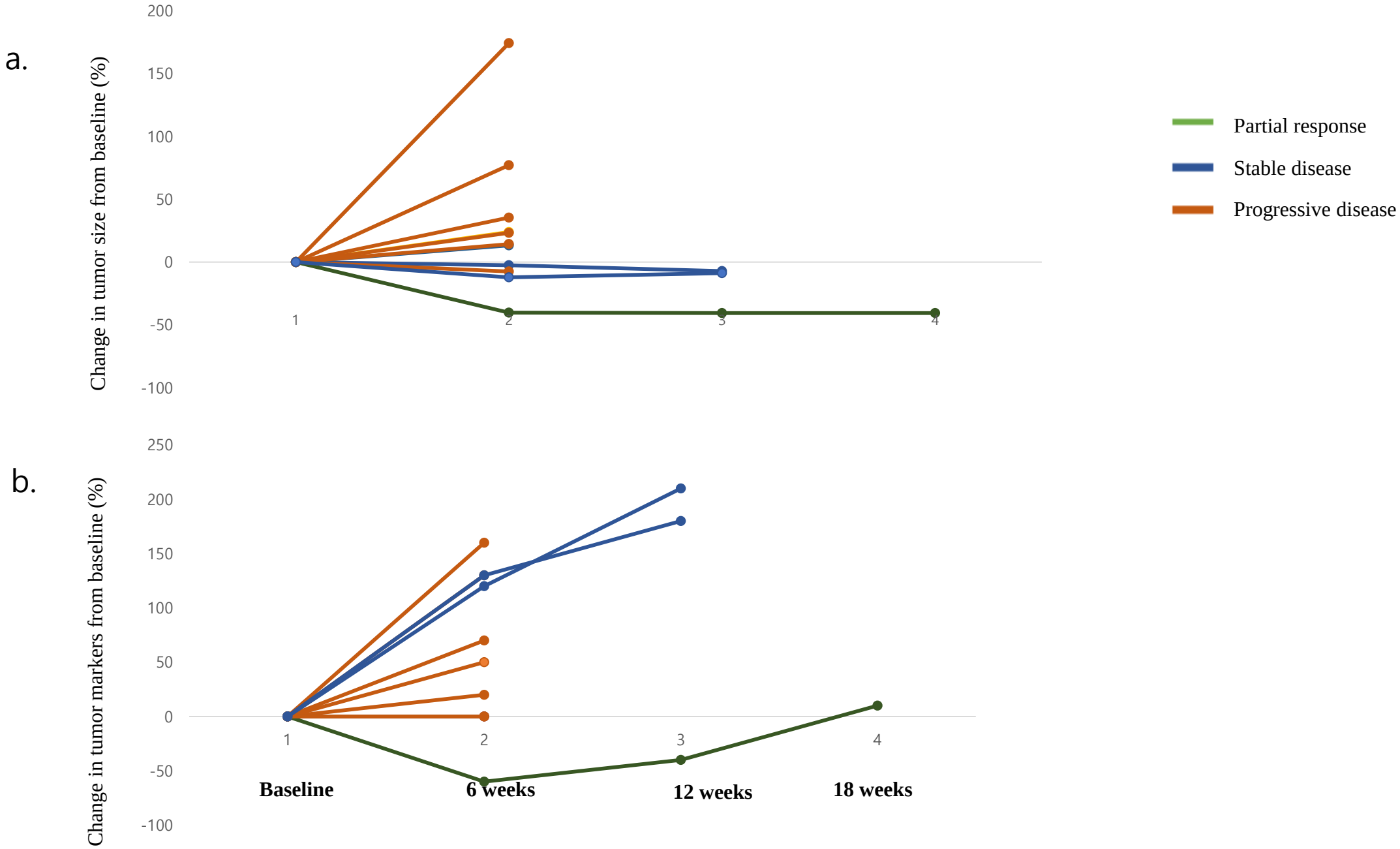
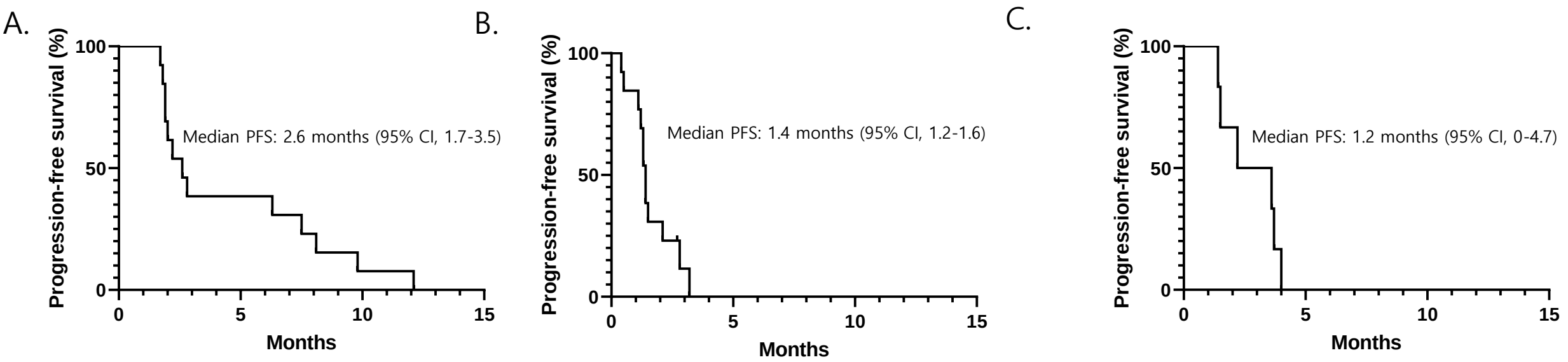



**Fig. S1** Spider plot depicting percentage changes in both target tumor burden and tumor markers. Two patients with clinical progression were excluded. Tumor volumes (a) are depicted in same colors as best response of tumor markers (b). Although tumor burden decreased in subjects who achieved partial response (green), tumor marker (CA 125) increased by >30%.




| Cancer | Prior to TAS-117 (n=13) | TAS-117 (n=13) | Subsequent line of treatment (n=6) |
|---|---|---|---|
| Breast cancer | 3 | 4 | 5 |
| Breast cancer | 5 | 6 | none |
| Breast cancer | 3 | 4 | none |
| Breast cancer | 4 | 5 | 6 |
| Ovarian cancer | 3 | 4 | 5 |
| Ovarian cancer | 2 | 3 | 4 |
| Endometrial cancer | 3 | 4 | none (expired) |
| Colon cancer | 3 | 4 | none (expired) |
| Colon cancer | 2 | 3 | none (expired) |
| Rectal cancer | 4 | 5 | 6 |
| Gastric cancer | 8 | 9 | none (expired) |
| Gallbladder cancer | 1 | 2 | 3 |
| Non-small cell lung cancer | 3 | 4 | none (expired) |

**Figure S2.** Analysis of progression-free survival by A) PFS 1 (prior to TAS 117), B) PFS 2 (TAS 117), and C) PFS 3 (after TAS 117)
Table depicts the line of treatments received.
Abbreviations: PFS, progression-free survival; CI, confidence interval.

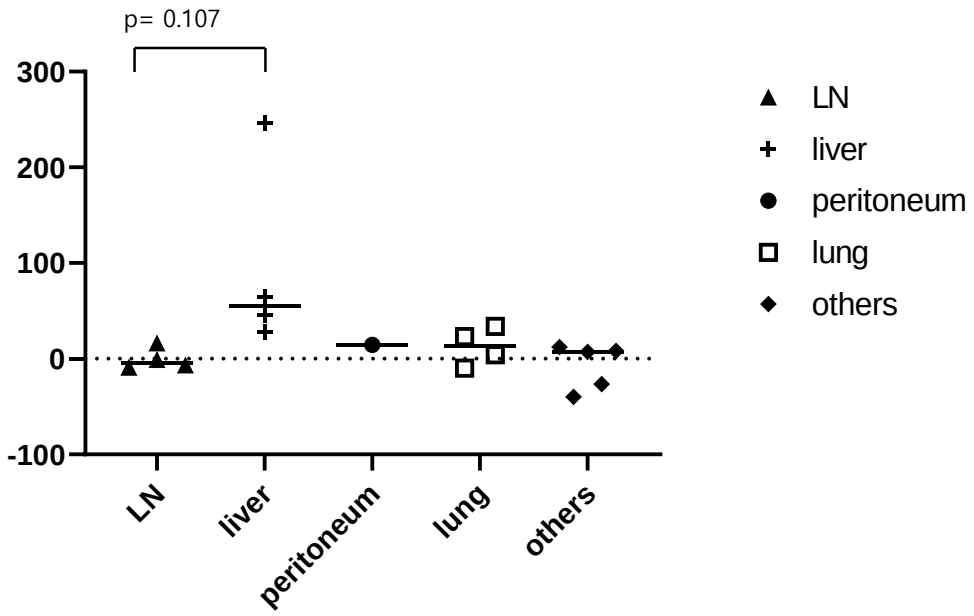



**Figure S3.** Analysis of responses per metastatic organs by using one-way analysis of variance (ANOVA)
There was no significant difference in progression in all organs (p = 0.076) and the lymph nodes and liver (p = 0.107). Other metastatic organs included: 1) soft tissue around the peri-aortic area, 2) inguinal mass, 3) pelvic cavity mass, 4) seeding nodule in the anterior renal fascia, and 5) spleen.

Abbreviations: LN, lymph nodes.

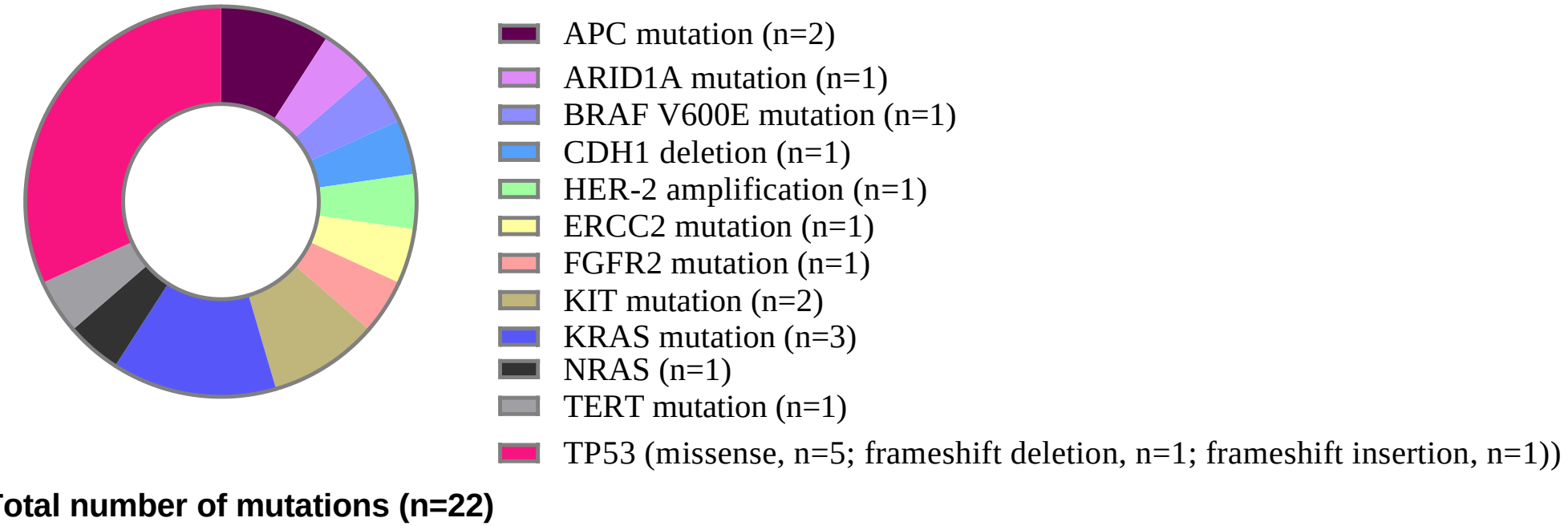



**Figure S4.** Co-existing mutations identified in patients treated with TAS-117
A total of 22 mutations were identified in 13 patients. TP53 mutations (n = 7) were the most common.

**Abbreviations:** TP-53, tumor protein 53; APC, adenomatous polyposis coli; KRAS, Kirsten rat sarcoma viral oncogene homolog; ERBB2, Erb-B2 receptor tyrosine kinase 2; CDH1, Cadherin 1; BRAF, B-Raf proto-oncogene; FGFR, fibroblast growth factor receptors; TERT, telomerase reverse transcriptase; ARID-1A, AT-rich interactive domain-containing protein 1A; NRAS, neuroblastoma RAS viral oncogene homolog.

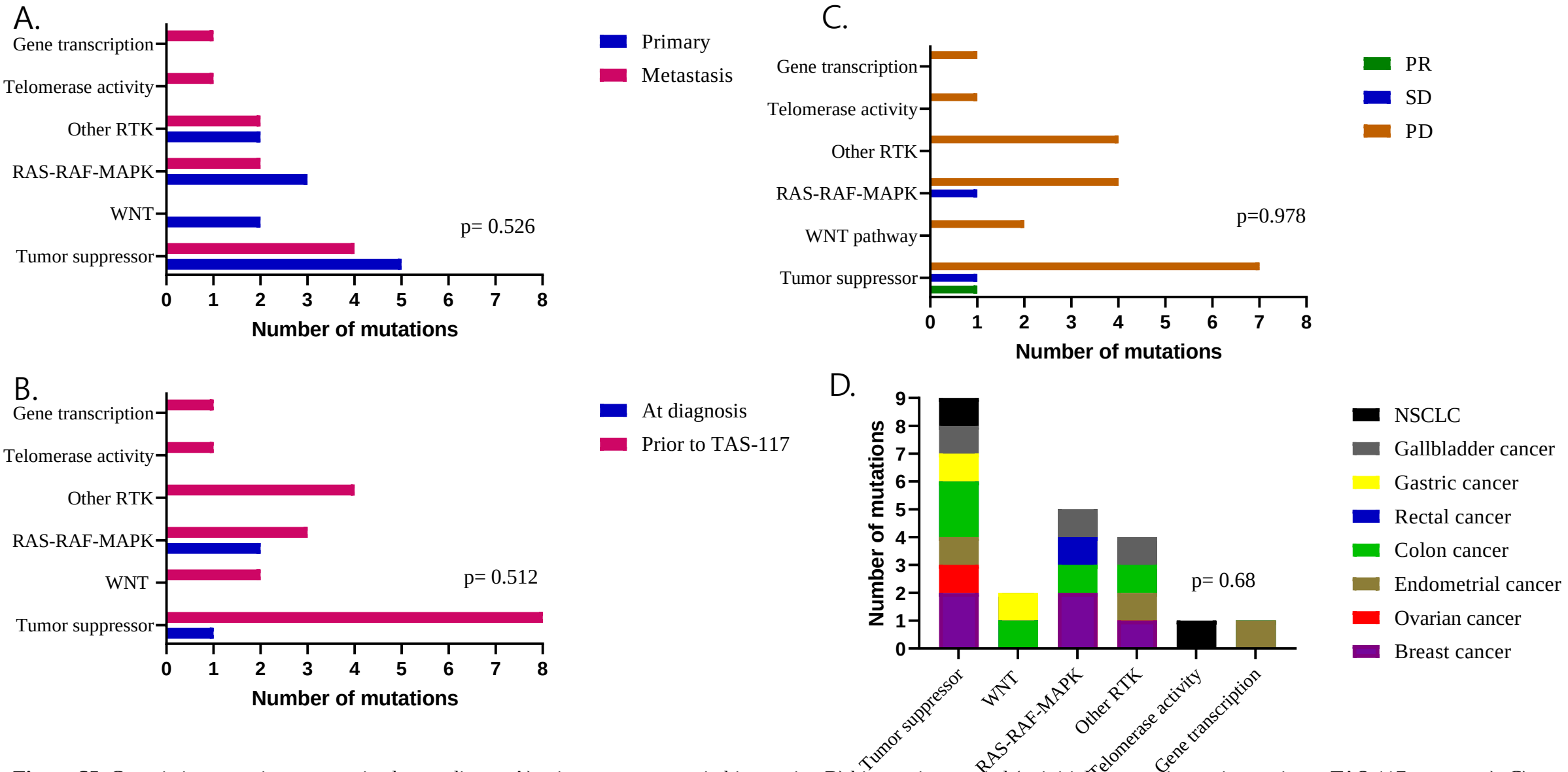



**Figure S5.** Co-existing mutations categorized according to A) primary or metastatic biopsy site, B) biopsy time period (at initial cancer diagnosis or prior to TAS-117 treatment), C) response evaluation by RECIST criteria (PR, SD, PD), and D) tumor types
There are no correlations between co-existing mutations.
Abbreviations: RTK, receptor tyrosine kinase; RAS-RAF-MAPK, Ras-Raf-Mitogen-activated protein kinase; PR, partial response; SD, stable disease; PD, progressive disease; RECIST, response evaluation criteria in solid tumors; NSCLC, non-small cell lung cancer

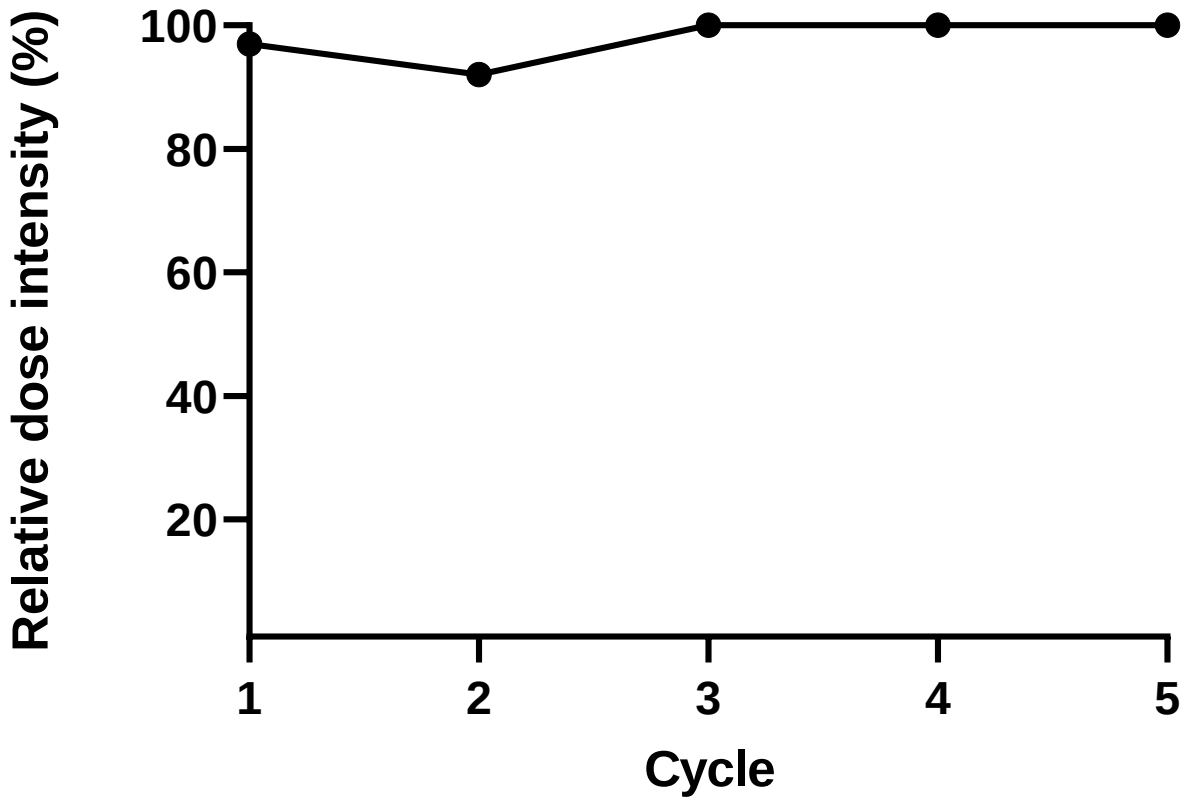



**Figure S6.** Relative dose intensity of TAS-117

**Supplementary Appendix**

**Investigational New Drugs**

# Phase 2 study of TAS-117, an allosteric Akt inhibitor in advanced solid tumors harboring phosphatidylinositol 3-kinase/v-akt murine thymoma viral oncogene homolog gene mutations

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**Table S1.** Phosphatidylinositol 3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (Akt) pathway aberrations of patients

| Cancer type | Line of treatment | NGS time point* | Biopsy site | PIK3CA/AKT aberration | Amino acid change | Other mutations |
|---|---|---|---|---|---|---|
| Breast cancer | 4 | 1 | Lymph node | PIK3CA | H1047R | KRAS mutation |
| Breast cancer | 6 | 2 | Liver | PIK3CA | H1047R | HER-2 amplification |
| Breast cancer | 4 | 1 | Chest wall | PIK3CA | H1047R | TP53 mutation, KRAS mutation |
| Breast cancer | 5 | 2 | Orbit | AKT1 | E17K | CDH1 deletion |
| Ovarian cancer | 4 | 2 | Ovary | PIK3CA | E545K | ARID1A mutation |
| Ovarian cancer | 3 | 2 | Ovary | PIK3CA | E545K | TP53 mutation |
| Endometrial cancer | 4 | 2 | Ovary | PIK3CA | H1047R | TP53 mutation, KIT mutation, ERCC2 mutation |
| Colon cancer | 4 | 2 | Colon | PIK3CA | Q546K | APC mutation, TP53 mutation, TP53 deletion |
| Colon cancer | 3 | 2 | Colon | PIK3CA | E545A | BRAF mutation, KIT mutation |
| Rectal cancer | 5 | 2 | Rectum | PIK3CA | E545K | NRAS mutation |
| Gastric cancer | 9 | 2 | Stomach | PIK3CA | E545K | TP53 insertion, APC mutation |
| Gallbladder cancer | 2 | 2 | Gallbladder | PIK3CA | E542K | KRAS mutation, FGFR2 mutation |
| NSCLC | 4 | 2 | Lymph node | PIK3CA | E542K | TP53 mutation, TERT mutation |

Abbreviations: PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; NSCLC, non-small cell lung cancer, TP-53, tumor protein 53; APC, adenomatous polyposis coli; KRAS, Kirsten rat sarcoma viral oncogene homolog; ERBB2, Erb-B2 receptor tyrosine kinase 2; CDH1, Cadherin 1; ERCC, excision repair cross-complementing; BRAF, B-Raf proto-oncogene; FGFR, fibroblast growth factor receptor; TERT, telomerase reverse transcriptase; ARID-1A, AT-rich interactive domain-containing protein 1A; NRAS, neuroblastoma RAS viral oncogene homolog.

*1, At initial cancer diagnosis; 2, prior to TAS-117

**Table S2.** Summary of treatment

| | |
|---|---|
| Median duration of treatment (range, months) | 1.4 (0.4–3.2) |
| Median cycle of treatment (range) | 2 (1–5) |
| Dose delays | 2 (15%) |
| Dose reduction | 0 (0%) |
| Dose intensity median (range) | 100% (56%–100%) |
| Subsequent treatment | |
| Yes | 6 (46%) |
| No | 7 (54%) |
| Subsequent regimen | |
| Cytotoxic chemotherapy [a)] | 3 (23%) |
| Immunotherapy [b)] | 2 (15%) |
| Targeted agent [c)] | 1 (8%) |

[a)] Patients were treated with 1) pegylated liposomal doxorubicin, 2) capecitabine, and 3) belotecan and cisplatin.

[b)] Patient was enrolled in clinical trial and was treated with PD-L1 and IDO inhibitor.

[c)] Patient was treated with regorafenib.

**TABLE S3.** Summary of best response to TAS-117

| | |
|---|---|
| CR | 0 (0%) |
| PR | 1 (8%) |
| SD | 2 (15%) |
| PD | 10 (77%) |
| Overall response rate (CR+PR) | 1 (8%) |
| Disease control rate (CR+PR+SD) | 3 (23%) |

Abbreviations: CR, complete response; PR, partial response;

SD, stable disease; PD, progressive disease

**Table S4.** Summary of best response according to cancer types

| **Cancer** | PR | SD | PD |
|---|---|---|---|
| Breast cancer (n=4) | 0 | 2 | 2 |
| Ovarian cancer (n=2) | 1 | 0 | 1 |
| Endometrial cancer (n=1) | 0 | 0 | 1 |
| Colon cancer (n=2) | 0 | 0 | 2 |
| Rectal cancer (n=1) | 0 | 0 | 1 |
| Gastric cancer (n=1) | 0 | 0 | 1 |
| Gallbladder cancer (n=1) | 0 | 0 | 1 |
| NSCLC (n=1) | 0 | 0 | 1 |

Abbreviations: n, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NSCLC, non-small cell lung cancer

**Table S5.** Summary of best response according to PI3K/Akt aberrations

| **PI3K/AKT aberrations** | PR | SD | PD |
|---|---|---|---|
| PIK3CA mutation | | | |
| E542K (n=2) | 0 | 0 | 2 |
| E545A (n=1) | 0 | 0 | 1 |
| E545K (n=4) | 1 | 0 | 3 |
| H1047R (n=4) | 0 | 1 | 3 |
| Q546K (n=1) | 0 | 0 | 1 |
| AKT1 mutation | | | |
| E17K (n=1) | 0 | 1 | 0 |

Abbreviations: n, number; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease;

Percentages may not sum to 100 because of rounding.

**Table S6.** Univariate analysis of progression-free survival and overall survival

| Variables | Total number of patients (%) | PFS (months) | p-value | OS (months) | p-value |
|---|---|---|---|---|---|
| Line of treatment for TAS-117 (<4 or ≥4) | 3 (23%) vs. 10 (77%) | 1.3 vs. 1.4 | 0.575 | 2.9 vs. 6.9 | 0.743 |
| Royal Marsden Score (0,1 vs. ≥2) | 6 (46%) vs. 7 (54%) | 1.3 vs. 2.1 | 0.219 | 4.3 vs. 9.2 | 0.139 |
| Grim-Score (0,1 vs. ≥2) | 6 (46%) vs. 7 (54%) | 1.3 vs. 2.1 | 0.219 | 4.3 vs. 9.2 | 0.139 |
| Number of metastatic (<2 vs. ≥2) | 1 (8%) vs. 12 (92%) | 1.3 vs. 2.1 | 0.594 | 4.8 vs. 10.1 | 0.391 |

Abbreviations: GRIm-Score, Gustave Roussy Immune Score; PFS, progression-free survival; OS, overall survival

**Table S7.** Organs showing disease progression

| Metastasis | Number (%) |
|---|---|
| **New site of metastasis** | **1 (9%)** |
| Liver¶ | 1 (9%) |
| **Progression of target lesions** | **9 (82%)** |
| Lung | 2 (18%) |
| Lymph node* | 1 (9%) |
| Peritoneum | 1 (9%) |
| Liver, peritoneum | 1 (9%) |
| Lung, liver, peritoneum | 2 (18%) |
| Lung, liver, bone | 1 (9%) |
| Large intestine, peritoneal carcinomatosis¶ | 1 (9%) |
| **New site of metastasis (A) with progression of target lesion (B)** | **1 (9%)** |
| Common bile duct and pancreas (A), lung and lymph node (B) | 1 (9%) |

Organs of progression are categorized as newly developed lesion or progression of previous metastatic lesions.

An ovarian cancer patient with partial response progressed with liver metastasis (new site of metastasis). Two breast cancer patients with stable disease progressed to lymph node (target lesion) and large intestine and peritoneal carcinomatosis, respectively.

*Ovarian cancer with partial response. ¶Breast cancer patients with stable disease

**Table S8.** Adverse events during treatment

| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | All grades |
|---|---|---|---|---|---|
| **Any event** | 8 (24%) | 22 (65%) | 3 (9%) | 1 (2%) | 34 (100%) |
| Anorexia | 1 (9%) | 2 (18%) | 1 (9%) | 0 (%) | 4 (36%) |
| Constipation | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |
| Diarrhea | 1 (9%) | 1 (9%) | 0 (%) | 0 (%) | 2 (18%) |
| Nausea | 2 (18%) | 1 (9%) | 0 (%) | 0 (%) | 3 (27%) |
| Mucositis | 1 (9%) | 0 (%) | 0 (%) | 0 (%) | 1 (9%) |
| Skin rash | 2 (18%) | 3 (27%) | 0 (%) | 0 (%) | 5 (45%) |
| Itching | 0 (%) | 2 (18%) | 0 (%) | 0 (%) | 2 (18%) |
| Fatigue | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |
| Headache | 0 (%) | 2 (18%) | 0 (%) | 0 (%) | 2 (18%) |
| Back pain | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |
| Shoulder pain | 0 (%) | 2 (18%) | 0 (%) | 0 (%) | 2 (18%) |
| Dyspnea | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |
| Pneumonia | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |
| Pulmonary thromboembolism | 0 (%) | 2 (18%) | 0 (%) | 0 (%) | 2 (18%) |
| Hyponatremia | 0 (%) | 0 (%) | 1 (9%) | 0 (%) | 1 (9%) |
| Hyperglycemia | 1 (9%) | 1 (9%) | 1 (9%) | 1(9%) | 4 (36%) |
| Neutropenia | 0 (%) | 1 (9%) | 0 (%) | 0 (%) | 1 (9%) |

Adverse events were those with onset after enrollment to last follow-up after disease progression.

**Table S9.** Incidence of adverse event of special interest*

| AESI | Grade 1 | Grade 2 | Grade 3 | Grade 4 | All grades |
|---|---|---|---|---|---|
| **Any event** | 4 (36%) | 5 (45%) | 1 (9%) | 1 (9%) | 11 (100%) |
| Mucositis | 1 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (9%) |
| Skin rash | 2 (18%) | 2 (18%) | 0 (0%) | 0 (0%) | 4 (36%) |
| Hyperglycemia | 1 (9%) | 2 (18%) | 1 (9%) | 1 (9%) | 5 (45%) |
| Neutropenia | 0 (0%) | 1 (9%) | 0 (0%) | 0 (0%) | 1 (9%) |

Abbreviations: AESI, adverse event of special interest

Adverse events were those with onset after enrollment to last follow-up after disease progression.

Percentages may not sum to 100 because of rounding.