ONLINE SUPPLEMENTARY MATERIAL

A Phase 1, First-in-Human Study of AMG 900, an Orally Administered Pan-Aurora Kinase Inhibitor, in Adult Patients With Advanced Solid Tumors

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Supplementary Methods

Eligibility Criteria

Inclusion Criteria

- Men or women ≥18 years old
- Part 1 – Dose escalation only: pathologically documented, definitively diagnosed advanced solid tumor that is refractory to standard treatment, for which no standard therapy is available or the subject refuses standard therapy
- Part 1 – Dose escalation only: measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines
- Part 2 – Dose expansion only: must have one of the following diagnoses:
    - Epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) that is platinum resistant (defined as having progressed during or within 6 months of last platinum-containing regimen) and taxane resistant (defined as refractory to or progressing within 6 months of discontinuing paclitaxel or docetaxel if stopped for a reason other than progression)
    - Triple-negative breast cancer (estrogen receptor/progesterone receptor–negative and HER2-negative); must have received at least one prior regimen for metastatic disease
    - Castration-resistant and taxane- or cisplatin-etoposide–resistant stage IV prostate cancer (CRPC) with at least one of the following:
        - Anaplastic features as defined by at least one of the following:
            - Histologic evidence of small cell (pure/mixed), at least 30% neuroendocrine differentiation, locally advanced or metastatic, or

- Any of the following: exclusive visceral metastases, predominant lytic bone metastases, bulky (≥5 cm) lymphadenopathy, or bulky (≥5 cm) high-grade (Gleason ≥8) tumor mass in the prostate/pelvis, or
- Low (<3 ng/mL) and stable prostate-specific antigen with metastatic progressive disease

▪ Neuroendocrine markers in histology (2+ chromogranin A and/or synaptophysin) or serum (high-serum chromogranin A × 10, or neuron specific enolase × 3) at diagnosis or at progression plus any of the following:

- Elevated serum carcinoembryonic antigen (>5 × upper limit of normal [ULN]) in the absence of other etiologies, or
- Short interval (<6 months) to progression after initiation of hormonal therapy, or
- Malignant hypercalcemia (>ULN), or
- Elevated serum lactate dehydrogenase (>2 × ULN)

o Subjects with small-cell carcinoma on histology are not required to have received prior androgen deprivation therapy. All other subjects must have evidence of disease progression while on androgen deprivation therapy or an unsatisfactory response after ≥1 month of castration, as defined by lack of symptom control and/or serum tumor marker response <20% (confirmed by a second value drawn on a different day).

- Part 2 – Dose expansion only:
  - o Ovarian cancer cohort: measurable disease per RECIST or CA 125 evaluable per Rustin criteria (2011) if nonmeasurable but evaluable by RECIST
  - o Breast cancer cohort: measurable disease per RECIST

    - Prostate cancer cohort: measurable disease per RECIST
- Eastern Cooperative Oncology Group performance status ≤2
- Life expectancy >3 months, in the opinion of the investigator
- Reproductive criteria as follows:
    - Female subjects who are postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterilized. Female subjects of childbearing potential must remain abstinent or use double-barrier birth control method during therapy and be willing to use contraception for 2 months following the last study drug administration, and have a negative serum pregnancy test on study entry
    - Male subject is willing to remain abstinent or use contraception on enrollment, during the course of the study, and for 2 months following the last study drug administration
    - All study subjects must be willing to ensure that corresponding sexual partners practice these same methods of highly effective birth control for the same duration
- Willing to provide existing and/or future paraffin-embedded tumor samples
- Ability to take oral medications
- Competent to sign and date the latest institutional review board–approved informed consent form
- Fridericia's QT formula corrected for heart rate (QTcF) ≤470 ms (based on average of screening triplicates)
- Hematologic function, as follows:
    - Absolute neutrophil count ≥1.5 x 10^9/L
    - Platelet count ≥100 × 10^9/L
    - Hemoglobin >9 g/dL

    - Prothrombin time and partial thromboplastin time <1.5 × ULN
- Renal function, as follows:
    - Serum creatinine <2.0 mg/dL
    - Calculated creatinine clearance ≥50 mL/min
    - Urinary protein quantitative value <30 mg/dL in urinalysis or ≤1+ on dipstick, unless quantitative protein is <500 mg in a 24-hour urine sample
- Hepatic function, as follows:
    - Aspartate aminotransferase <2.5 × ULN (if liver or bone metastases are present, ≤5 × ULN)
    - Alanine aminotransferase <2.5 × ULN (if liver or bone metastases are present, ≤5 × ULN)
    - Alkaline phosphatase <2.0 × ULN (if liver or bone metastases are present, ≤5 × ULN)
    - Total bilirubin <1.5 × ULN

Exclusion Criteria

- Active parenchymal brain metastases. Subjects who have had brain metastases resected or have received radiation therapy ending at least 4 weeks before study day 1 are eligible if they meet all of the following criteria: (a) residual neurologic symptoms grade ≤1; (b) no dexamethasone requirement; and (c) follow-up magnetic resonance imaging shows no new lesions appearing
- Prior bone marrow transplant (autologous or allogeneic)
- History or presence of hematologic malignancies
- History of bleeding diathesis

- Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or unstable cardiac arrhythmia requiring medication
- Active peptic ulcer disease
- Gastrointestinal (GI) tract disease causing the inability to take oral medication, malabsorption syndrome, requirement for intravenous (IV) alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (eg, Crohn disease, ulcerative colitis)
- Active infection requiring IV antibiotics within 2 weeks of study enrollment (day 1)
- Known positive test for HIV
- Active or chronic hepatitis B or C infection, determined by serologic tests
- Unresolved toxicities from prior antitumor therapy, defined as not having resolved to CTCAE grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (grade 2 or 3 toxicities from prior antitumor therapy that are considered irreversible [defined as having been present and stable for >6 months], such as ifosfamide-related proteinuria, may be allowed if they are not otherwise described in the exclusion criteria and there is agreement to allow by both the investigator and sponsor)
- Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy, or investigational agent) within 14 days or 5 half-lives of study day 1 (whichever is longer); concurrent use of hormone deprivation therapy for hormone-refractory prostate cancer or breast cancer is permitted
- Treatment with immune modulators including but not limited to corticosteroids, cyclosporine, and tacrolimus within 2 weeks before enrollment. Prednisone will be allowed for prostate cancer subjects (up to 10 mg/day or equivalent)
- Therapeutic or palliative radiation therapy within 2 weeks of study day 1

- Treatment with known substrates or inhibitors of the CYP2C family including but not limited to sulphaphenazole, tolbutamide, phenytoin, warfarin, gemfibrozil, montelukast, or omeprazole within 2 weeks before study day 1 (other CYP2C inhibitors may be allowed if there is agreement between the sponsor and investigator)
- Treatment with known inhibitors of CYP3A4 including but not limited to amiodarone, azithromycin, clarithromycin, delavirdine, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, mibefradil, miconazole, saquinavir, telithromycin, or troleandomycin within 2 weeks before study day 1 (other CYP3A4 inhibitors may be allowed if there is agreement between the sponsor and investigator)
- Treatment with known inducers of CYP3A4 including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, or glitazones (thiazolidinediones) within 2 weeks before study day 1 (other CYP3A4 inducers may be allowed if there is agreement between the sponsor and investigator)
- Treatment with medications known to cause QTc interval prolongation within 7 days of study day 1
- Systemic anticoagulation therapy, including warfarin, within 2 weeks of day 1
- Prior treatment with Aurora inhibitors
- Prior participation in an investigational study (drug or device) within 28 days of study day 1
- Major surgery within 28 days of study day 1
- Any comorbid medical disorder that may increase the risk of toxicity in the opinion of the investigator or sponsor
- Any disorder that compromises the ability of the subject to give written informed consent and/or to comply with the study procedures
- Reproductive criteria as follows:

    - Women who are lactating/breastfeeding
    - Women with a positive pregnancy test
    - Women planning to become pregnant during the study
- Subject has known sensitivity to any products to be administered during dosing
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge

Definition of Dose-Limiting Toxicity

- A dose-limiting toxicity (DLT) was defined as any adverse event (AE) meeting the criteria listed below occurring during the first two treatment cycles of AMG 900 (day 1 through day 28) in each dose-escalation cohort where relationship to AMG 900 could not be ruled out
    - Hematologic toxicity
    - Febrile neutropenia
    - Neutropenic infection
    - Grade 4 neutropenia >7 days in duration
    - Grade ≥3 thrombocytopenia >7 days in duration
    - Grade 4 thrombocytopenia
- Nonhematologic toxicity
    - Grade ≥3 nausea, vomiting, or diarrhea despite optimal medical support
    - Grade 3 fatigue persisting >7 days or grade 4 fatigue
    - Any other grade ≥3 AE (except alopecia)
- Failure to recover from toxicities related to AMG 900 to grade ≤1 or baseline severity (or grade ≤2 at the discretion of the investigator and sponsor) after delaying next cycle up to 7 days
- Failure to complete the first two treatment courses (≤75% of planned dose)

- If grade 4 neutropenia, grade 3 or higher thrombocytopenia, and/or grade 3 or higher nonhematologic toxicity occurred during treatment days, AMG 900 administration was to be stopped immediately for the remainder of that cycle

Laboratory Tests

Blood chemistry and coagulation (including blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase; and prothrombin time and partial thromboplastin time) were assessed at baseline; predose in cycles 1, 2, 3, and 5; on days 2 and 8 in cycle 1; on day 1 in cycle 4; at every subsequent cycle beginning with cycle 6; and at the end-of-study visit. Urinalysis was conducted at baseline; predose in cycles 1, 2, and 5; on days 2 and 8 in cycle 1; and at the end-of-study visit. Hematology (including white blood cells, hemoglobin, platelets, and neutrophils) was assessed at baseline; predose in treatment cycles 1, 2, 3, and 5; on days 2 and 8 in cycle 1; on day 8 in cycles 2 to 4; day 1 in cycle 4; at every subsequent cycle (beginning with cycle 6); and at the end-of-study visit.

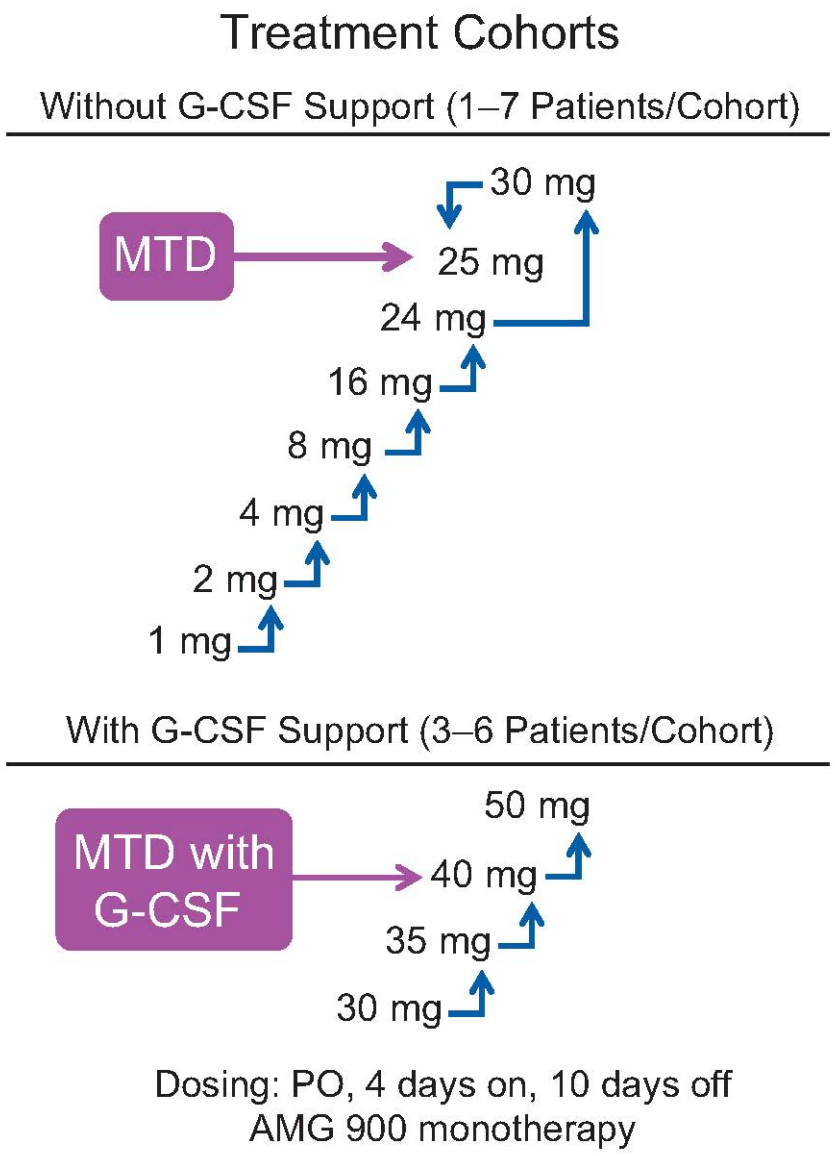
Supplementary Table 1. Patient Disposition

	Part 1 Dose Escalation									Part 2 Dose Expansion			
Patient, n (%)	**1, 2, 4, 8 mg (n=4)**	**16 mg (n=3)**	**24 mg (n=6)**	**25 mg (n=7)**	**30 mg (n=6)**	**30 mg + G-CSF (n=6)**	**35 mg + G-CSF (n=3)**	**40 mg + G-CSF (n=11)**	**50 mg + G-CSF (n=4)**	**OC (n=29)**	**TNBC (n=14)**	**CRPC (n=12)**	**Total (N=105)**
AMG 900 accounting													
Patients who received AMG 900	4 (100)	3 (100)	6 (100)	7 (100)	6 (100)	6 (100)	3 (100)	11 (100)	4 (100)	29 (100)	14 (100)	12 (100)	105 (100)
Completed AMG 900	0	0	1 (17)	0	0	1 (17)	0	1 (9)	0	6 (21)	0	0	9 (9)
Discontinued AMG 900	4 (100)	3 (100)	5 (83)	7 (100)	6 (100)	5 (83)	3 (100)	10 (91)	4 (100)	23 (79)	14 (100)	12 (100)	96 (91)
AE	0	0	1 (17)	2 (29)	4 (67)	1 (17)	0	2 (18)	2 (50)	5 (17)	5 (36)	3 (25)	25 (24)
Full consent withdrawn	0	0	0	1 (14)	0	0	1 (33)	0	0	2 (7)	1 (7)	0	5 (5)
Disease progression	4 (100)	2 (67)	4 (67)	4 (57)	2 (33)	4 (67)	2 (67)	8 (73)	2 (50)	15 (52)	8 (57)	7 (58)	62 (59)
Other	0	1 (33)	0	0	0	0	0	0	0	1 (3)	0	2 (17)	4 (4)
Safety analysis set	4 (100)	3 (100)	6 (100)	7 (100)	6 (100)	6 (100)	3 (100)	11 (100)	4 (100)	29 (100)	14 (100)	12 (100)	105 (100)
Responder analysis set	4 (100)	2 (67)	6 (100)	5 (71)	5 (83)	6 (100)	3 (100)	9 (82)	2 (50)	28 (97)	11 (79)	10 (83)	91 (87)
PK analysis set	4 (100)	3 (100)	6 (100)	7 (100)	6 (100)	6 (100)	3 (100)	11 (100)	4 (100)	29 (100)	14 (100)	12 (100)	105 (100)

Abbreviations: AE=adverse event; CRPC=castration-resistant prostate cancer; G-CSF=granulocyte colony-stimulating factor; OC=ovarian cancer; PK=pharmacokinetics; TNBC=triple-negative breast cancer.

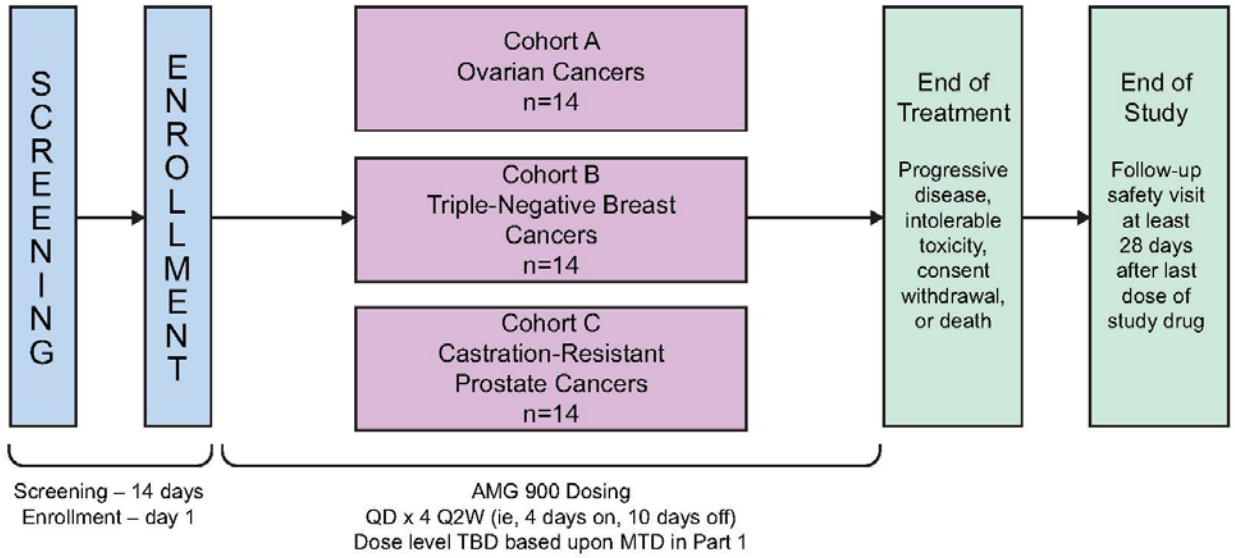
Fig. S1 Study schema

a Dose-escalation phase (part 1)



Abbreviations: G-CSF=granulocyte colony-stimulating factor; MTD=maximum tolerated dose; PO=by mouth.
The patients/cohort values represent planned number of patients in each cohort.

b Dose-expansion phase (part 2)



Abbreviations: MTD=maximum tolerated dose; n=planned number of patients in each cohort; TBD=to be determined; Q2W=every 2 weeks; QD=once daily.