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TC ± AMG 386 as first-line therapy of Stage III-IV ovarian cancer

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Growing Tumors Require a Dedicated Blood Supply

- Tumors require development of blood supply to grow beyond a limiting size
- Solid tumors are angiogenesis dependent
  - Cells need to be within 100 µm of a capillary to obtain oxygen and nutrients
- The ability to induce and sustain angiogenesis is acquired via an "angiogenic switch" from vascular quiescence
  - A shift in the balance between angiogenesis inducers and inhibitors

Hanahan D, Weinberg RA. Cell. 2000;100:57–70.

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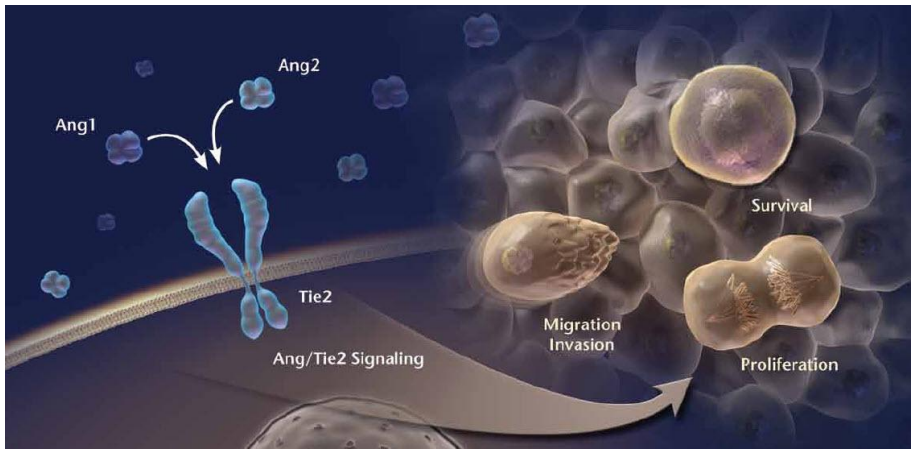
Angiopoietin Targeting

Hypoxic tumors produce a variety of pro-angiogenic factors to initiate new blood vessel sprouting VEGF, MMP, PDGF and bFGF

Under this stimulus, angiopoietin-1 and -2 are released from existing vessels to propagate new vessel formation

AMG 386 selectively targets the interaction of Ang1 and Ang2 with the Tie2 receptor

Eklund L, Exp Cell Res. 2006;312:630–641.
Thomas M, Angiogenesis. 2009;12:125–137.



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AMG 386

- In preclinical tumor models
  - AMG 386 decreased endothelial proliferation, increased tumor necrosis, and decreased tumor growth[1]
  - The combination of AMG 386 with irinotecan, 5-fluorouracil, or docetaxel showed no evidence of increased toxicity or antagonism of single-agent efficacy[2]
  - The combination of AMG 386 with the VEGF antagonist, bevacizumab, showed enhanced antitumor activity compared with either antiangiogenic agent alone[3,4]

1. *Schliemann C, Leukemia. 2007;21:1901-1906.*
2. *Sfiligoi C, Int J Cancer. 2003;103:466-474.*
3. *Giuliani N, Leuk Lymphoma. 2005;46:29-33.*
4. *Hong ESMO 2008*

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AMG386 – PK interactions

- The PK of AMG 386 in combination with FOLFOX-4, wkly paclitaxel, PLD, carboplatin/paclitaxel, and docetaxel chemotherapy has been evaluated in phase 1b and did not show interaction.

- Phase Ib (AMG386 15mg/kg iv wkly) in combination with Paclitaxel and Carboplatin in first line ovarian cancer is currently ongoing.

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AMG386 – Side effects

- The side effects have been limited and different from other VEGF directed angiogenesis inhibitors: no significant increase in bowel perforation, hypertension or thrombosis.

- No significant increase in bone marrow toxicity when combined with chemotherapy

- Linked with peripheral edema.

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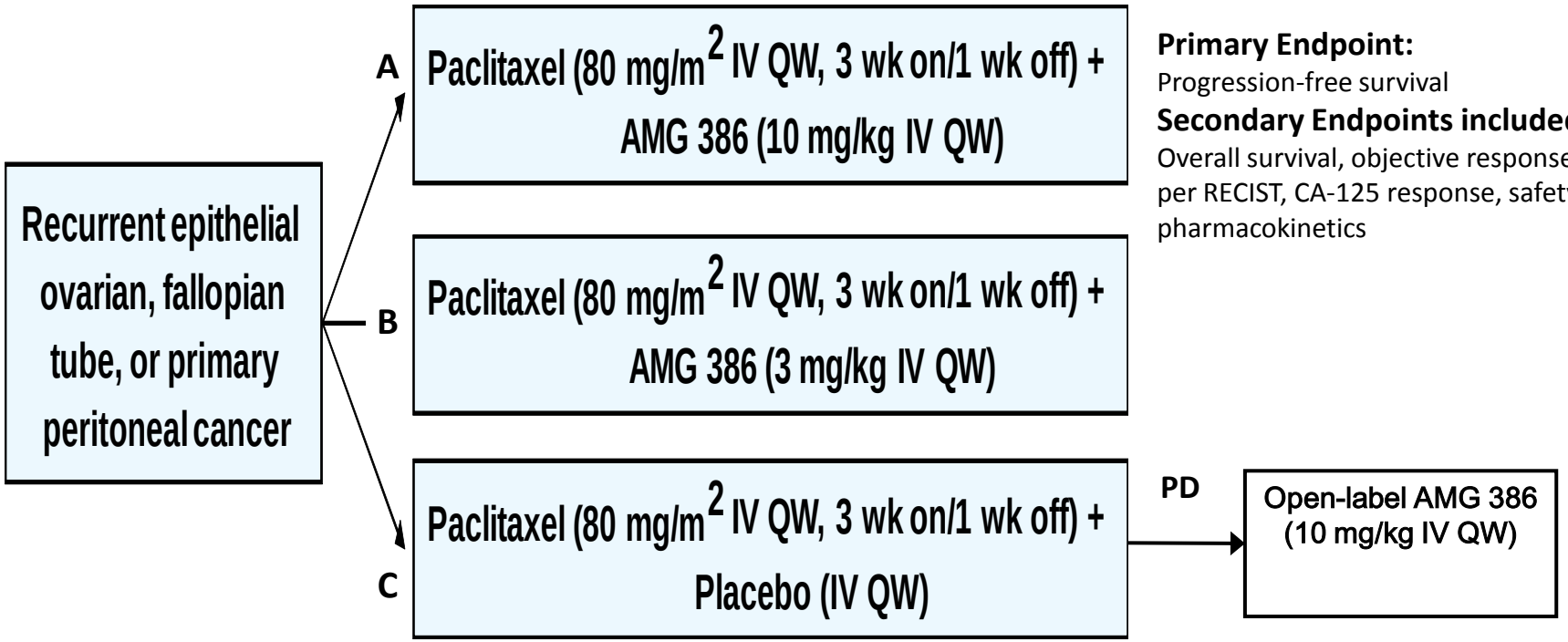
ESMO 2010

A randomized, double-blind, placebo-controlled phase 2 study of AMG 386 plus weekly paclitaxel in patients with advanced ovarian cancer

Ignace B. Vergote, Amit M. Oza, Vincent L. Hansen, Gary E. Richardson, Diane Provencher, Prafull Ghatage, Marjan Tassoudji, Yu-Nien Sun, Daniel E. Stepan, Beth Y. Karlan



Primary Endpoint:
Progression-free survival

Secondary Endpoints included:
Overall survival, objective response per RECIST, CA-125 response, safety, pharmacokinetics

N = 161

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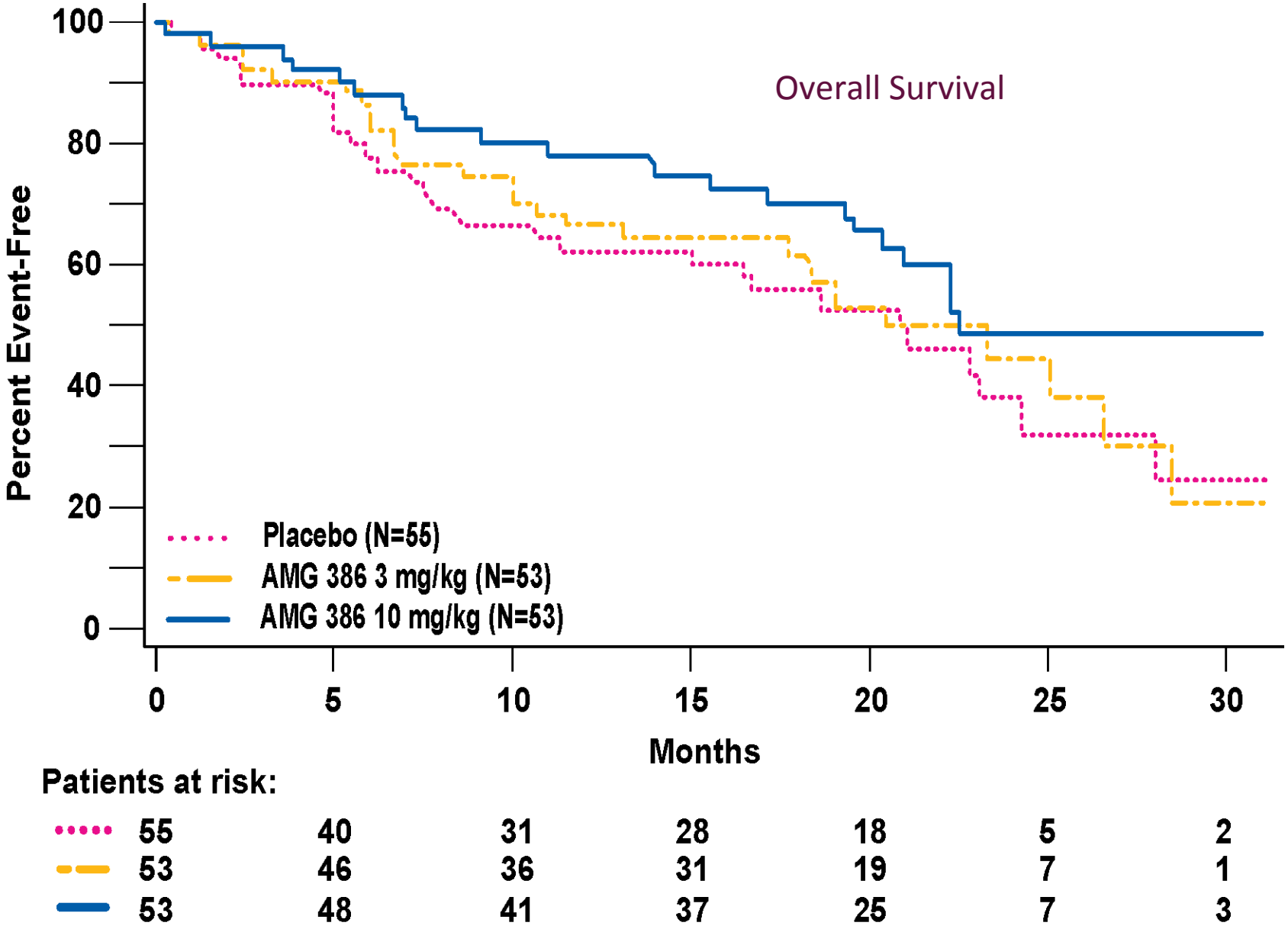
ESMO 2010



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Adverse Events Occurring in ≥ 25% of Patients

	AMG 386					
	Arm A 10 mg/kg (N = 53)		Arm B 3 mg/kg (N = 52)		Arm C Placebo (N = 55)	
Adverse Event (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Peripheral edema	71	4	51	6	29	4
Fatigue	65	2	72	6	51	5
Nausea	52	2	58	2	40	2
Alopecia	50	0	38	2	36	0
Diarrhea	42	2	36	4	29	0
Peripheral neuropathy	38	10	26	2	31	4
Constipation	38	2	23	0	31	0
Cough	35	0	30	0	22	2
Abdominal pain	33	2	32	4	36	5
Pain in extremity	29	0	28	0	18	0
Headache	29	0	25	0	13	0
Vomiting	27	4	26	6	20	4
Dizziness	27	0	11	0	20	0

Includes adverse events occurring during treatment and within 30 days of the decision to end all study treatment.

Selected Adverse Events of Specific Interest

	AMG 386					
	Arm A 10 mg/kg (N = 53)		Arm B 3 mg/kg (N = 52)		Arm C Placebo (N = 55)	
Adverse Event (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Bowel perforation	0	0	0	0	2	2
Hypertension	8	0	8	0	5	0
Venous TE	8	6	8	6	11	9
Arterial TE	2	2	2	2	0	0
Proteinuria	8	0	6	0	5	0
Cardiac toxicity events	0	0	0	0	2	2
Hemorrhagic events	26	2	27	4	24	0
Impaired wound healing	2	0	2	0	0	0

TE, thrombo-embolic events. Includes adverse events occurring during treatment and within 30 days of the decision to end all study treatment. None of these events had a statistically significant incident rate ($P < 0.05$) when comparing the AMG 386 treatment arm with the placebo arm.

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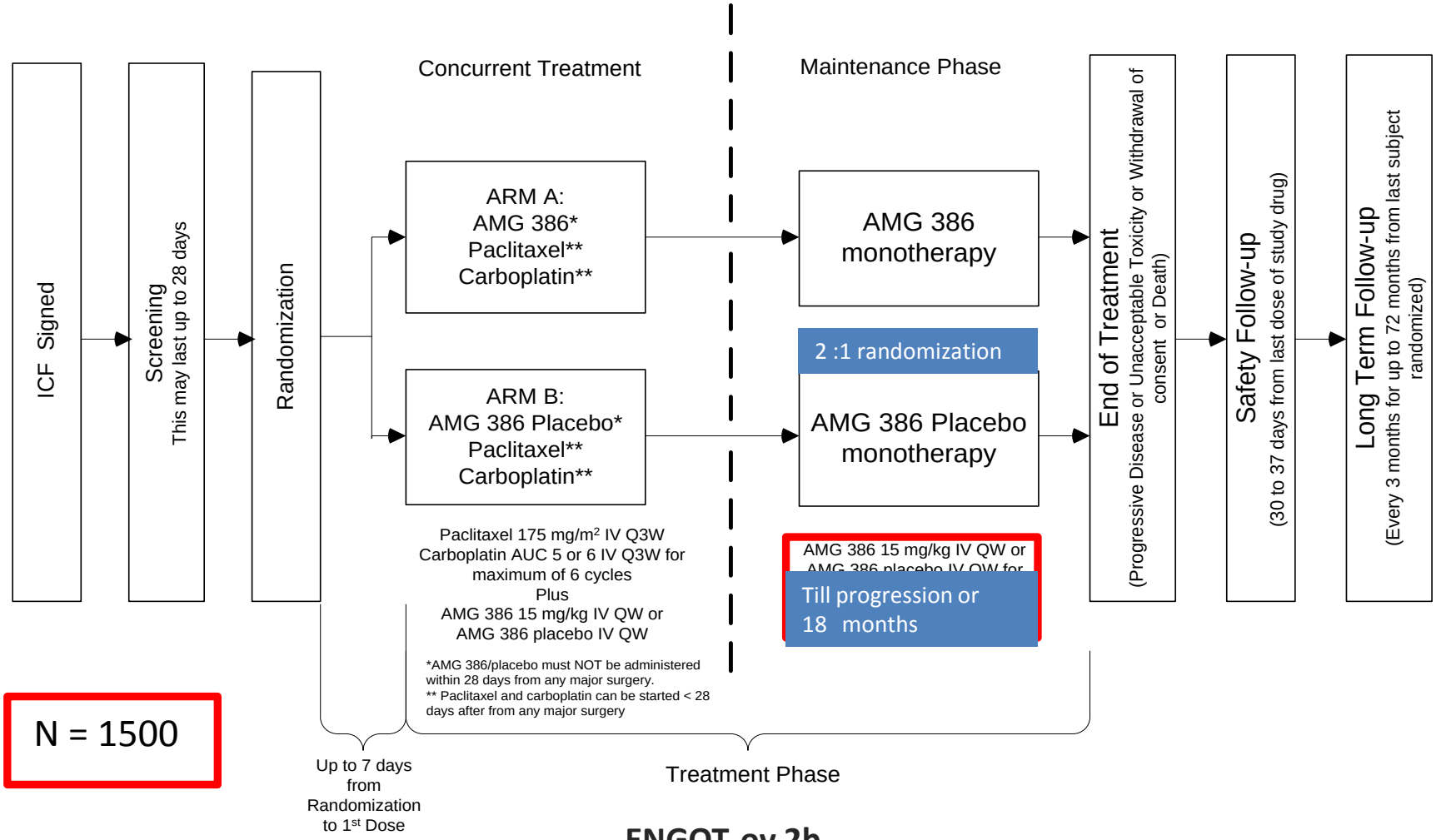

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Study Design

- 1500 subjects randomized in a 2:1 ratio to receive one of the following treatments:
  - Arm A: AMG 386 15 mg/kg IV QW, paclitaxel 175 mg/m^2 IV Q3W and carboplatin AUC 5 or 6 IV Q3W for 6 cycles followed by AMG 386 15 mg/kg IV QW maintenance for 18 months
  - Arm B: AMG 386 placebo IV QW, paclitaxel 175 mg/m^2 IV Q3W and carboplatin AUC 5 or 6 IV Q3W for 6 cycles followed by AMG 386 placebo IV QW maintenance for 18 months

Primary and Secondary Endpoints:

- **Primary Endpoint:** PFS
- **Key Secondary Endpoint:** OS
- **Other Secondary Endpoints:**
  - Incidence of adverse events and significant laboratory abnormalities
  - Pharmacokinetics of AMG 386 (C_{max} and C_{min})
  - Incidence of anti-AMG 386 antibody formation
  - Patient reported ovarian cancer-specific symptoms and health related quality of life (HRQoL) as measured by FACT-O
  - Patient reported status as measured by the EQ-5D
- **Exploratory endpoints**
  - AMG 386 exposure-response relationships for PFS and OS
  - Correlation of serum biomarkers with measures of response (PFS, OS,)

Statistical plan:

- PFS primary analysis .
  - 858 PFS events
  - significance level of 0.025 for a one-sided test.
  - 96% overall power to detect a 30% improvement in median PFS time - from 16.0 months to 20.8 months.
- OS 633 events
  - 80% overall power at the 0.025 overall significance level for one-sided tests to detect a 25% improvement in OS median time from 39.0 months in the control arm (≈10months).

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Inclusion criteria:

- FIGO Stages III-IV epithelial ovarian, primary peritoneal or fallopian tube
  - pseudomyxoma, mesothelioma, adenocarcinoma with unknown primary tumor, carcinosarcoma, sarcoma, mucinous or neuroendocrine histology are excluded
- Subjects with FIGO Stage IIIA or IIIB disease must have undergone PDS for ovarian, primary peritoneal or fallopian tube cancer within 12 weeks prior to randomization
- Subjects with biopsy-proven Stage IIIC or IV disease who have not had PDS must have planned IDS following 3 cycles of AMG 386 or placebo, paclitaxel and carboplatin (see Section 6.4.1). If biopsy is not available, fine needle aspiration (FNA) is acceptable, if
  - pelvic mass, AND
  - presence of metastases of ≥ 2 cm outside the pelvis (or proof of stage IV), AND
  - a CA125/CEA ratio > 25.
  - If CA125/CEA ratio ≤ 25 obligatory imaging/endoscopy to exclude other primary tumors of colon, stomach and breasts
- Subjects with FIGO Stage IIIC or IV disease must have undergone PDS for ovarian, primary peritoneal or fallopian tube cancer within 12 weeks prior to randomization

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Assessments

Appendix A. Schedule of Assessments

STUDY CYCLE		1			2			3			4			5			6			Maintenance Tx	S-FUP[m]	LTFU
Study weeks		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 +		
Study Cycle Days		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Study Drug Administration																						
AMG 386 15 mg/kg IV QW or matching placebo IV QW		X[q]	X	X	X	X	X	X	X[n]	X[n]	X[n]	X	X	X	X	X	X	X	X	X[l]		
Paclitaxel 175 mg/m² IV Q3W		X[q]			X			X			X[n]			X			X					
Carboplatin AUC 5 or 6 IV Q3W		X[q]			X			X			X[n]			X			X					
Procedures	**Scr**																					
Informed Consent	X																					
Medical History	X																					
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X	
Adverse Events Assessment[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X	
Physical Exam, Height[a]	X	X			X			X			X			X			X			X[l]	X	
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X	
ECOG Performance Status	X	X						X						X						X[l]	X	
PRO[o]		X								X					X				X	X[o]	X	
12-lead ECG[j]	X					X				X											X	
Tumor sample[j]	X																					
Survival Assessment																						X[p]
Laboratory Assessments																						
Hematology	X[a]				X			X			X			X			X			X[l]	X	
Blood Chemistry	X[a]				X			X			X			X			X			X[l]	X	
Serum potassium																				X[l]		
CA-125[g]		X						X						X						X[g]	X	
Urinalysis or urine dipstick	X[a]							X						X						X[l]	X	
Creatinine clearance	X																					
PTT or aPPT, INR	X[a]																				X	
Urine/serum Pregnancy	X[c]																			X[l]	X	
AMG 386 PK[f]		X						X			X									X[f]	X	
Immunogenicity[d]		X									X										X	
Biomarkers[e]		X[e]						X[e]														
Radiological Assessments																						
CT/MRI chest, abdomen, pelvis	X[b]									X[b]				X[b]					X[b]	X[b]		X[k]

Response evaluation

- After chemotherapy:
  - every 12 weeks for the next 18 months, then
  - every 24 weeks for the subsequent 18 months and
  - then yearly thereafter.

- Subjects with IDS will have one additional imaging scan post IDS and prior to re-initiation of chemotherapy (approximately week 13).

Response evaluation

- Disease progression is defined as radiologic disease progression per RECIST 1.1 (investigator assessment) with modifications.

- Disease progression, and discontinuation of study therapy, may not occur for elevations in CA-125 unless radiographic disease progression is also documented.

- New onset or worsening of existing pleural effusions and/or ascites should not be called disease progression in the absence of documented tumor progression.

AMG386 – Proposal to ENGOT
Randomized phase III of Paclitaxel/Carboplatin with or without AMG 386 as first-line therapy

- Agreement to run the study according to ENGOT guidelines (including contracts via cooperative groups, database option C, independent statistical analysis by BGOG statistician, payments via cooperative groups).
- Feasability via the groups is discussed.
- Selection of sites together with groups.
- Monitoring via Amgen
- Pharmacovigilance via Amgen., ..
- **Study can be run by ALL ENGOT groups.**
- **First patient in 2011 JULY 01**

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