CHEMO

MATERIAL # / PRODUCT : ******

VERSION : ** DATE: ****** SUBSTITUTE/HALT # : ******

PANTONES Only a max. of 4 printing colors / Please, indicate below the colours to be used

LINE 1: FRONT SIDE PRINTING COLOUR: C M Y K

LINE 2: BACK SIDE PRINTING COLOUR: C M Y K

LINE 3: TECH. COLOUR NO PRINTING COLOUR: DIE CUT

Please, indicate if there are any special requirements in the adhesive area: PMU FOLDED / GLUE POINT

Customer shall be responsible for the contents of the approved artwork, text and colours of the printed material, reflected in this drawing. Therefore, Customer shall bear any and all post and/or expense, and it shall keep General Parts harmless from any claim, cost and/or expenses, related to the correctness and accuracy of such information.

DRAWING: U403

UNIVERSAL FRAME PATRIAL TYPE : LEAFLET

SCALE : DIMENSIONS: 100 % 975 x 495 (16x45) ± 1 mm

PURPOSE: LAUNCH / CUSTOMER CHANGE / INTERNAL CHANGE

LAETUS : ******

FOLDED: NO / YES ONLY FOR POSITION

FOLDED DIMENSIONS: fold to 66 x 45 mm

PLEASE, DONT DELETE ANY LAYERS FOR THE CORRECT REVISION. PLEASE, MAKE SURE THE IMAGES HAVE A RESOLUTION AT LEAST 300 PP

DREWED BY: (CHEPO ARTWORK TECNICIAN)

APPROVED BY CUSTOMER : (REGULATORY AFAIR OR QUALITY ASURANCE) / SIGNATURE & DATE

With the signed proof of the file you commit to have had reviewed and signed with the following points as part of your revision:
- Keyline (.red) / Free vectoR (.eps) / Colors / Text.
- Professionally for exceptions of the vector is changed you commence clearly comunicate this change to Chemo's artworks department, otherwise Chemo will not be responsible.
- Any other info included in the file.

FRONT SIDE / PLEASE, INCLUDE YOUR DESIGN ON THIS KEYLINE

AVAMAB
Bevacizumab
Solution For Infusion
KALBE

AVAMAB

AVAMAB is a biosimilar to AVASTIN.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section **Undesirable Effects** for how to report adverse reactions.

Composition
Each mL of concentrate contains 25 mg of bevacizumab*.
Each 4 mL vial contains 100 mg of bevacizumab.
Each 16 mL vial contains 400 mg of bevacizumab.
For dilution and other handling recommendations, see section
Special precautions for disposal and other handling.

*Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.

List of excipients:
Trehalose dihydrate
Monobasic sodium phosphate monohydrate
Disodium phosphate
Polysorbate 20
Water for injections

Pharmaceutical Form
Concentrate for solution for infusion (sterile concentrate). Colourless to yellowish or brownish liquid with opalescence.

Pharmacological Properties
Pharmacodynamic
Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FG01

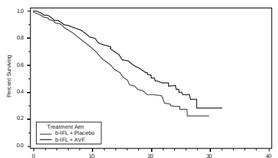
I. Mechanism of Action
Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with the complementarity-determining regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese Hamster ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.
Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, there by inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

II. Clinical efficacy
Metastatic carcinoma of the colon or rectum (mCRC)
The safety and efficacy of the recommended dose of bevacizumab (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomized, active controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Bevacizumab was combined with two chemotherapy regimens.
- **AVF2107g:** A weekly schedule of irinotecan/bolus 5- fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6 week cycle (Roswell Park regimen).
- **AVF0780g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen).
- **AVF2192g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with Bevacizumab have been conducted in mCRC patients: first-line (NO16966), second-line with six previous Bevacizumab treatment (E3200), and second-line with previous Bevacizumab treatment following disease progression in first-line (ML18147). In these studies, Bevacizumab was administered at the following dosing regimens, in combination with FOLFOX-4 (5FU/LV/Oxaliplatin) and XELOX (Capecitabine/Oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin:
- NO16966: Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or Bevacizumab 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- E3200: Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in Bevacizumab naïve patients.
- ML18147: Bevacizumab 5.0 mg/kg of body weight every 2 weeks or Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with Bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

Bevacizumab in Combination with Irinotecan, 5-Fluorouracil and Leucovorin (IFL) for First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF2107g):
This was a phase III randomized, double-blind, active-controlled clinical trial evaluating Bevacizumab in combination with IFL as first line treatment for metastatic carcinoma of the colon or rectum. Eight hundred-thirteen patients were randomized to receive IFL + placebo (Arm 1) or IFL + Bevacizumab (5 mg/kg every 2 weeks, Arm 2) (see Table 1). A third group of 110 patients received bolus 5-FU/LV + Bevacizumab (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, once safety of Bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0.43% had a value of 1 and 0.4% had a value of 2; 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

Figure 1 Plot of Kaplan Meier Estimates for Survival in Study AVF2107g



IFL = Irinotecan, 5-FU, Leucovorin
AVF=Bevacizumab

Figure 2 Duration of Survival by Baseline Risk Factor in Study AVF2107g

CI = interval. IFL = irinotecan/5-fluorouracil/leucovorin.
Hazard ratio < 1 indicates a lower hazard of death in the IFL + Bevacizumab arm compared with the IFL + placebo arm. Size of circle is proportional to the number of patients in the subgroup.
Confidence interval is indicated by the horizontal line.

Bevacizumab in Combination with 5-FU/LV Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum in patients who were not optimal candidates for first-line irinotecan treatment (AVF2192g):
This was a phase II randomized, double-blind, active-controlled clinical trial investigating Bevacizumab in combination with 5-FU/Leucovorin as first line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin< 3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomized to 5-FU/LV + placebo arm and 104 patients randomized to 5-FU/LV + Bevacizumab (5 mg/kg every 2 weeks). All treatments were continued until disease progression. The overall age was 71 years; 28.2% of patients had an ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of Bevacizumab 5 mg/kg every two weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, compared with 5-FU/LV chemotherapy alone (see Table 4). This efficacy data is consistent with the results from study AVF2107g. The efficacy data from studies AVF0780g and AVF2192g investigating Bevacizumab in combination with 5-FU/FA chemotherapy are summarized in Table 4.

Table 1 Treatment Regimens in Study AVF2107g

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan	125 mg/m² i.v	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m² i.v	
	Leucovorin	20 mg/m² i.v	
	Placebo	i.v	Every 2 weeks
Arm 2	Irinotecan	125 mg/m² i.v	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m² i.v	
	Leucovorin	20 mg/m² i.v	
	Bevacizumab	5 mg/kg i.v	Every 2 weeks
Arm 3	5-Fluorouracil	500 mg/m² i.v	Given once weekly for 6 weeks every 8 weeks
	Leucovorin	500 mg/m² i.v	
	Bevacizumab	5 mg/kg i.v	Every 2 weeks

5-Fluorouracil: i.v. bolus injection immediately after leucovorin
Leucovorin: i.v. bolus injection (over 1 – 2 minutes) immediately after each irinotecan dose

The primary efficacy parameter of the trial was duration of survival.
The addition of Bevacizumab to IFL resulted in a statistically significant increase in overall survival (see Table 2 and Figure 1 for details). The clinical benefit of Bevacizumab, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease (see Figure 2). The efficacy results of Bevacizumab in combination with IFL chemotherapy are displayed in Table 2 and Figure 1 (Kaplan Meier plot for duration of survival).

Table 2 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 (IFL + Placebo)	Arm 2 (IFL + Bevacizumab[a])
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]		0.660
p-value[c]		0.00004
Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio		0.54
p-value		< 0.00001
Overall Response Rate		
Rate (percent)	34.8	44.8
95% confidence interval	30.2-39.6	39.9 - 49.8
p-value		0.0036
Duration of Response		
Median (months)	7.1	10.4
25–75 percentile (months)	4.7 – 11.8	6.7 – 15.0

[a] 5 mg/kg every 2 weeks
[b] Relative to control arm

Among the 110 patients randomized to Arm 3 (5-FU/LV + Bevacizumab), the median overall survival was 18.3 months, median progression free survival was 8.8 months, overall response rate was 39% and median duration of response was 8.5 months.

Table 5 Treatment Regimens in Study N016966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Bevacizumab	Oxaliplatin	85 mg/m² IV 2 h	Oxaliplatin on Day 1
	Leucovorin	200 mg/m² IV 2 h	Leucovorin on Day 1 and 2
	5-Fluorouracil	400 mg/m² IV bolus, 600 mg/ m² IV 22 h	5-fluorouracil IV bolus infusion, each on Days 1 and 2
	Placebo or Bevacizumab	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX	Oxaliplatin	130 mg/m² IV 2 h	Oxaliplatin on Day 1
or XELOX+ Bevacizumab	Capecitabine	1000 mg/m² oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Bevacizumab	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks

5-Fluorouracil, IV bolus injection immediately after leucovorin

The primary efficacy parameter of the trial was the duration of progression-free survival. In this study, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that Bevacizumab in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met:
i.) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.
ii.) Superiority of the Bevacizumab-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 6).

Secondary PFS analyses, based on 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Bevacizumab (analyses shown in Table 6), consistent with the statistically significant benefit observed in the primary analysis.

Table 6 Key efficacy results for the superiority analysis (ITT population, Study N016966)

Endpoint (months)	FOLFOX or XELOX = Placebo (n=701)	FOLFOX or XELOX + Bevacizumab (n=699)	P Value
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[c]	0.83 (0.72–0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Overall response rate (Investr. Assessment)**	49.2%.	46.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007
** Primary analysis at clinical cut-off 31 January 2006
[c] relative to control arm

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab treated patients, HR = 0.89, 97.5% CI = (0.73 , 1.08); p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63 , 0.94]; p-value = 0.0028. The median overall survival was 20.3 months in placebo and 21.8 months in bevacizumab treated patients, HR = 0.94, 97.5% CI = [0.75 , 1.14]; p- value = 0.4937, in the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68 , 1.04]; p-value = 0.0698.

ECOG E3200
This was a phase III randomised, active-controlled, open-label study investigating Bevacizumab 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 5 for Study NO16966. The primary efficacy parameter of the trial was overall survival, defined as the time from randomization to death from any cause. Eight hundred and twenty-nine patients were randomized (292 FOLFOX-4 , 293 Bevacizumab + FOLFOX-4 and 244 Bevacizumab monotherapy). The addition of Bevacizumab to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 7).

Table 7 Efficacy Results for Study E3200

	E3200		
	9.8	FOLFOX-4 + Bevacizumab[a]	
Number of Patients	292	293	
Overall Survival			
Median (months)	10.8	13.0	
95% confidence interval	10.12 – 11.86	12.09 – 14.03	
Hazard ratio[b]	0.751 (p-value = 0.0012)		
Progression-Free Survival			
Median (months)	4.5	7.5	
Hazard ratio	0.518 (p-value < 0.0001)		
Objective Response Rate			
Rate	8.0%	22.2%	
	(p-value < 0.0001)		

* 10 mg/kg every 2 weeks
[a] Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received Bevacizumab monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the Bevacizumab monotherapy arm when compared to the FOLFOX-4 arm. The benefit of Bevacizumab re-treatment in metastatic colorectal cancer patients who were exposed to Bevacizumab in previous therapies has not been addressed in randomized clinical trials.

ML18147
This was a Phase III randomized, controlled, open-label trial investigating Bevacizumab 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin chemotherapy alone in patients with mCRC who have progressed on a first-line Bevacizumab-containing regimen.
Patients with histologically confirmed mCRC and disease progression were randomized 1:1 within 3 months after discontinuation of Bevacizumab-containing first-line therapy to receive fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without Bevacizumab. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival defined as the time from randomization until death from any cause. A total of 820 patients were randomized. The addition of Bevacizumab to fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin chemotherapy resulted in a statistically significant prolongation of survival in patients with mCRC who have progressed on a first-line Bevacizumab-containing regimen (ITT = 819) (see Table 8).

Table 8 Efficacy Results for Study ML18147

	ML18147		
	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy		fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + Bevacizumab[a]
Number of Patients	410		409
Overall Survival			
Median (months)	9.8		11.2
95% confidence interval	9-11		10-12
Hazard ratio	0.81 (p-value = 0.0062)		
Progression-Free Survival			
Median (months)	4.1		5.7
Hazard ratio	0.68 (p-value < 0.0001)		
Objective Response Rate (ORR)			
Rate	3.9 %		5.4 %
	(p-value = 0.3113)		

[a] 5 mg/kg/week
Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and did not meet statistical significance.

Metastatic breast cancer (mBC)
Study E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating Bevacizumab in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomized to paclitaxel alone (90 mg/m² IV over 1 hour once weekly for three out of four weeks) or in combination with Bevacizumab (10mg/kg IV infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Of the 722 patients in the study, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastasis, including previously treated or resected brain lesions, were excluded. In Study E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with Bevacizumab as a single agent continued until disease progression. The patient characteristics were similar across the study arms. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted. The results of this study are presented in Table 9.

Table 9 Study E2100 Efficacy Results: Eligible Patients

Progression-free survival				
	Investigator Assessment[a]		IRF Assessment	
	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)
Median P F S (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	<0.0001		<0.0001	
Response rates	(for patients with measurable disease)			
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n=273)	Paclitaxel/Bevacizumab (n=252)	Paclitaxel (n=243)	Paclitaxel/Bevacizumab (n=229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	<0.0001		<0.0001	
primary analysis				
Overall Survival				
	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)		
Median OS (months)	24.8	26.5		
HR (95% CI)	0.869 (0.722; 1.046)			
p-value	0.1374			

AVF3694g
Study AVF3694g was a Phase III, multicentre, randomised, placebo controlled trial designed to evaluate the efficacy and safety of Bevacizumab in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment in patients with HER2-negative metastatic breast cancer or locally recurrent breast cancer. Chemotherapy was chosen at the investigator's discretion prior to randomization in a 2:1 ratio to receive either chemotherapy plus Bevacizumab or chemotherapy plus placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/cyclophosphamide, 5-fluorouracil/ doxorubicin/cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) given every three weeks (q3w). Bevacizumab or placebo was administered at a dose of 15 mg/kg q3w.
This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Bevacizumab or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death. On documented disease progression, patients who entered the optional open-label phase could receive open-label Bevacizumab together with a wide range of second line therapies.
Statistical analyses were performed independently for 1) patients who received capecitabine in combination with Bevacizumab or placebo; 2) patients who received taxane-based or anthracycline based chemotherapy in combination with Bevacizumab or placebo. The primary endpoint of the study was PFS by investigator assessment. In addition, the primary endpoint was also assessed by an independent review committee (IRC).
The results of this study from the final protocol defined analyses for progression free survival and response rates in the independently monitored post capecitabine cohort of Study AVF3694g are presented in Table 10. Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 45% of patients had died) are also presented. The percentage of patients who received Bevacizumab in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + Bevacizumab arm.

Table 10 Efficacy results for study AVF3694g: + Capecitabine[a] and Bevacizumab/Placebo (Cap + Bevacizumab/Pl)

Progression-free survival[b]				
	Investigator Assessment		IRC Assessment	
	Cap + Pl (n= 206)	Cap + Bevacizumab (n=409)	Cap + Pl (n= 206)	Cap + Bevacizumab (n=409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio vs placebo arm (95% CI)	0.69 (0.56; 0.84)		0.68 (0.54; 0.86)	
p-value	0.0002		0.0011	
Response rate (for patients with measurable disease)[b]				
	Cap + Pl (n= 161)	Cap + Bevacizumab (n=325)		
% pts with objective response	23.6	35.4		
p-value	0.0097			
Overall survival[b]				
HR (95% CI)	0.88 (0.69; 1.13)			
p-value (exploratory)	0.33			

* 1000 mg/m² oral twice daily for 14 days administered every 3 weeks
+ Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumor assessment prior to starting NPT.

An unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

Non-small cell lung cancer (NSCLC)
The safety and efficacy of Bevacizumab, in addition to platinum based chemotherapy, in the first- line treatment of patients with non squamous non-small cell lung cancer (NSCLC), was investigated in studies E4599 and BO17704. An overall survival benefit has been demonstrated in study E4599 with a 15 mg/kg/3wk dose of bevacizumab. Study BO17704 has demonstrated that both 7.5 mg/kg/3wk and 15 mg/kg/3wk bevacizumab doses increase progression free survival and response rate. Due to the short duration of follow-up in study BO17704 no conclusions can be drawn regarding a benefit in overall survival. E4599 was an open-label, randomized, active-controlled, multicenter clinical trial evaluating Bevacizumab as first-line treatment of patients with locally advanced (stage IIIb with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.
Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC + Bevacizumab. Bevacizumab at a dose of 15 mg/kg IV infusion day 1 of every 3- week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the Bevacizumab + carboplatin-paclitaxel arm continued to receive Bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.
During the study, of the patients who received trial treatment, 32.2% (138/422) of patients received 7-12 administrations of Bevacizumab and 21.1% (89/422) of patients received 13 or more administrations of Bevacizumab. The primary endpoint was duration of survival. Results are presented in Table 11.

Table 11 Efficacy results for study E4599

	Arm 1 Carboplatin/ Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + Bevacizumab 15 mg/kg 3 weeks
Number of Patients	444	434
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	10.3	12.3
Hazard ratio	0.81 (p-value = 0.0062)	0.80 (p=0.003) 95% CI (0.69, 0.93)
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio	0.64	0.65 (p<0.0001) 95% CI (0.58, 0.76)
Overall Response Rate		
Rate (percent)	12.9	29.0 (p<0.0001)

In an exploratory analysis, the extent of Bevacizumab benefit on overall survival was less pronounced in the subgroup of patients who did not have adenocarcinoma histology.

Study BO17704 was a randomised, double-blind phase III study of Bevacizumab in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival (PFS); secondary endpoints for the study included the duration of overall survival. Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m² i.v. infusion on day 1 and gemcitabine 1250 mg/m² i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Bevacizumab at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the Bevacizumab-containing arms, patients could receive Bevacizumab as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Study results show that 94% (277 / 296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti cancer therapies, which may have impacted the analysis of overall survival. The efficacy results are presented in Table 12.

Table 12 Efficacy results for study BO17704

	Cisplatin /Gemcitabine	Cisplatin/ Gemcitabine + Bevacizumab 7.5 mg/kg q 3 weeks	Cisplatin/ Gemcitabine + Bevacizumab 15 mg/kg q 3 weeks
Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62;0.91]	0.82 [0.68;0.98]
Overall Response Rate *	20.1%	30.4% (p=0.0023)	
* patients with measurable disease at baseline			
Overall Survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86; 1.23]

JO25567
Study JO25567 was a randomized, open-label, multi-center Phase II study conducted in Japan to evaluate the efficacy and safety of bevacizumab in combination with erlotinib in patients with non squamous NSCLC with EGFR activating mutations who had not received prior systemic therapy for Stage IIIB/IV or recurrent disease.
The primary endpoint was progression-free survival (PFS) based on independent review assessment. Secondary endpoints included overall survival, response rate, disease control rate, duration of response, safety and Health Related Quality of Life based on the FACT-L (Functional Assessment of Cancer Therapy for Patients with Lung Cancer) questionnaire.
EGFR mutation status was determined for each patient prior to patient screening and 154 patients were randomised to receive either erlotinib + bevacizumab (erlotinib 150 mg oral daily + bevacizumab (15 mg/kg IV every 3 weeks)] or erlotinib monotherapy (150 mg oral daily until disease progression (PD) or unacceptable toxicity. In the absence of PD, discontinuation of one component of study treatment in the erlotinib + bevacizumab arm did not lead to discontinuation of the other component of study treatment as specified in the study protocol. The efficacy results of the study are presented in table 13.

Table 13 Efficacy results for study JO25567

	Erlotinib N = 77*	Erlotinib + Bevacizumab N = 75*
PFS* (months)	9.7	16.0
Median		
HR (95% CI)	0.54 (0.36; 0.79)	
p-value	0.0013	
Overall Response Rate		
Rate	63.6%	69.3%
p-value	0.4951	
Duration of Response (months)		
Median	9.3	13.3
HR (95% CI)	0.68 (0.43; 1.10)	
p-value	0.118	
Disease Control Rate		
Rate	88.3%	98.7%
p-value	0.0177	
Overall Survival* (months)		
Median	NR	NR
HR (95% CI)	1.04 (0.61- 1.77)	
p-value	0.8926	

* A total of 154 patients were randomized. However two of the randomized patients discontinued the study before receiving any study treatment
[1] blinded independent review (protocol-defined primary analysis)
[2]exploratory analysis, OS updated analysis at clinical cut-off on Nov 2014, approx. 35% patient had died and OS is therefore considered immature.
CI, confidence interval, HR, Hazard ratio from unstratified Cox regression analysis; NR, not reached;

In the open label study JO25567, Health Related Quality of life (HRQoL) was assessed by the FACT-L total and trial outcome index (TOI) scores and lung cancer symptoms, as assessed by the FACT-L lung cancer symptom subscale (LCS). During the progression-free time, mean baseline FACT-L scores were maintained in both treatment arms. There were no clinically meaningful differences in the FACT-L HRQoL observed between the two treatment arms. Of note, patients in the erlotinib + bevacizumab arm were treated for a longer duration and received intravenous administration of bevacizumab as opposed to oral erlotinib monotherapy in the control arm.

YO25404 (BEYOND)
Study YO25404 was a randomized, double-blind, placebo controlled, multicenter Phase III study of bevacizumab used in addition to carboplatin and paclitaxel (CP) chemotherapy in Chinese patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy for advanced disease. The primary endpoint was progression free survival, secondary endpoints for the study included overall survival and objective response.
Patients were randomized to CP (carboplatin AUC = 6.0 and paclitaxel 175 mg/m², both by IV infusion) on day 1 of every 3-week cycle for up to 6 cycles or CP in combination with bevacizumab at a dose of 15 mg/kg IV infusion on day 1 of every 3-week cycle. After completion of six cycles of CP chemotherapy or upon premature discontinuation of chemotherapy, patients were to continue to receive bevacizumab or placebo as a single agent every 3 weeks until disease progression or unacceptable toxicity.
Study results show that 78% (107/138) of patients in the bevacizumab-containing treatment arm went on to receive single agent bevacizumab at cycle 7, and 57% (78/138) of patients in the placebo-containing arm went on to receive single agent placebo at cycle 7. The efficacy results are presented in Table 14.

Table 14 Efficacy Results for study YO25404

	Arm 1 Carboplatin/ Paclitaxel + placebo	Arm 2 Carboplatin/ Paclitaxel + Bevacizumab 15 mg/kg q 3 weeks
Number of Patients	138	138
Progression-Free Survival Median (months)	6.5	9.2
Hazard ratio	0.4 (p<0.0001) 95% CI (0.29, 0.54)	
Overall Response Rate*	26.3	54.4
Rate (percent)	(p<0.0001)	
Overall Survival Median (months)	17.7	24.3
Hazard ratio	0.68 (p=0.0154) 95%CI (0.50, 0.93)	

*Only patients with measurable disease at baseline were analysed.

Advanced and/or metastatic Renal Cell Cancer (mRCC)
BO7705 was a multicenter, randomized, double-blind phase III trial conducted to evaluate the efficacy and saf