Case study: 64-year-old woman presenting with abdominal bloating, PS = 0

July 8, 2011: underwent debulking of ovarian cancer

- Bilateral salpingo-oophorectomy
- Hysterectomy
- Stripping of pelvic peritoneum, retrocavital peritoneum of the omentum and Morrison's pouch peritoneum
- Infra and gastrocolic omentectomy
- Dissection of right paracolic gutter and diaphragm, with partial resection of the right diaphragm
- Drainage of ascites
- Anterior resection of the sigmoid colon and rectum (end anastomosis)
- Ileocaecal resection (ileocolic anastomosis)

Case study: surgical outcome

Optimal debulking with < 5mm residual disease

Diagnosis: high-grade, stage IIIC serous tubal adenocarcinoma

Blood and urine chemistry normal, blood pressure normal (110/60mmHg)

3 days after surgery (July 11, 2011):

- Active bleeding at anastomotic site following resection of the sigmoid colon and rectum
- Colonoscopy: small, actively bleeding artery at level of colorectal anastomosis
- 4 metal clips used to stop the bleeding

Question: would you use iv chemotherapy or ip chemotherapy?

1. IV
2. IP

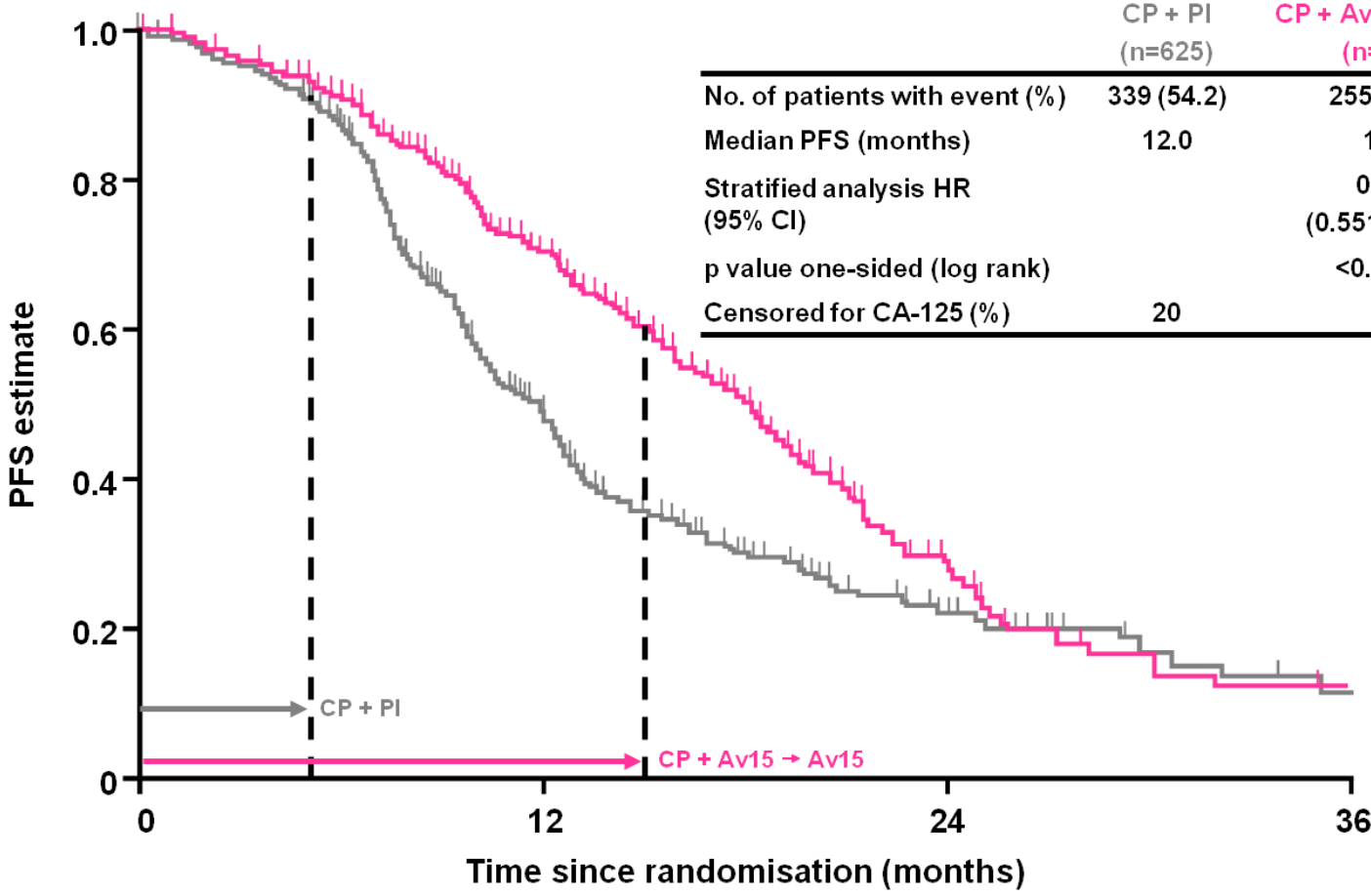
Question: Would you use dose dense chemotherapy or 3-weekly chemotherapy ?

1. Dose dense
2. 3-weekly

Question: Would you add bevacizumab to chemotherapy ?

1. Yes
2. No

GOG-0218 demonstrates a 6-month median PFS benefit - Investigator assessed

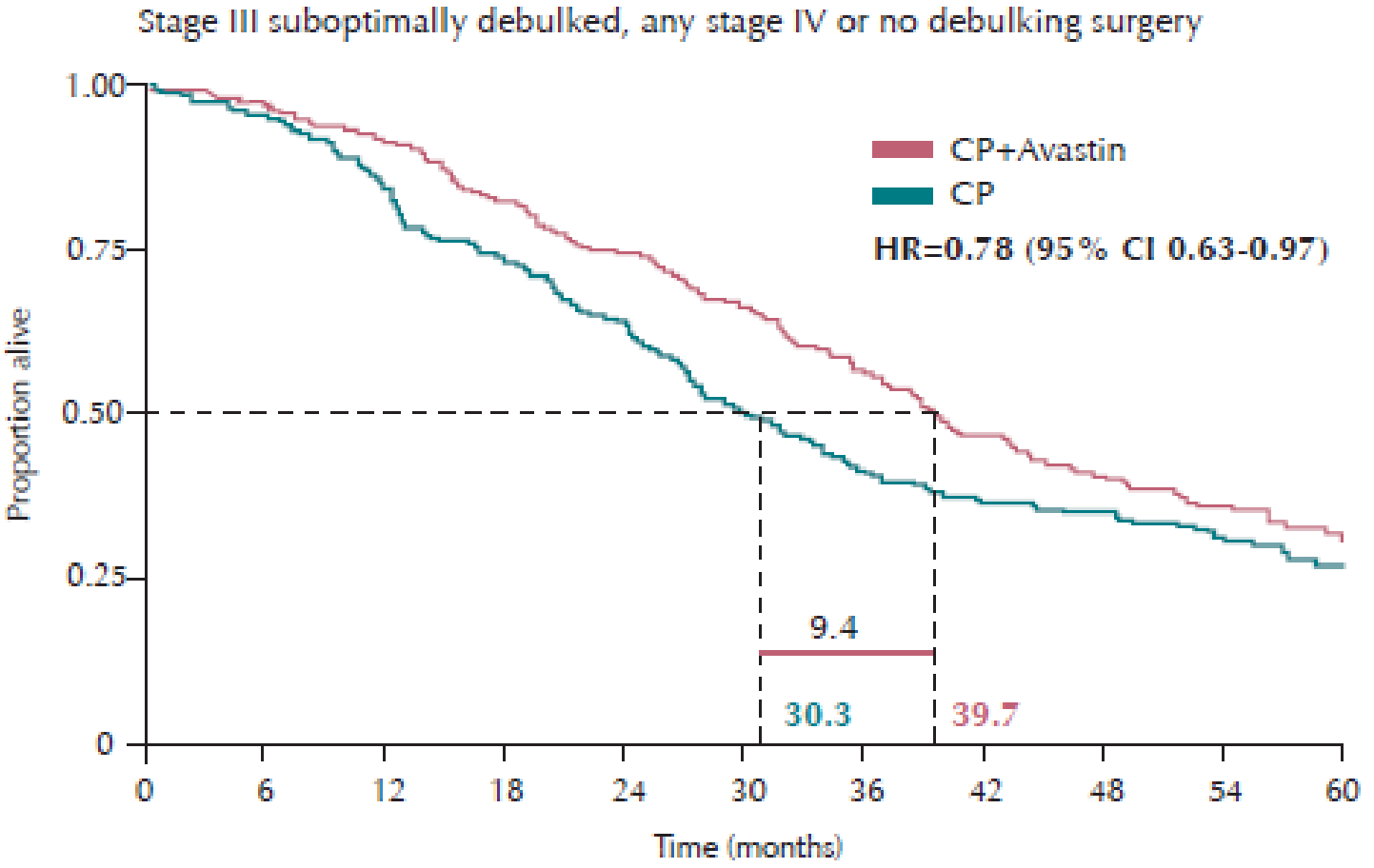


	I CP + PI (n=625)	III CP + Av15 → Av15 (n=623)
No. of patients with event (%)	339 (54.2)	255 (40.9)
Median PFS (months)	12.0	18.0
Stratified analysis HR (95% CI)		0.645 (0.551–0.756)
p value one-sided (log rank)		<0.0001*
Censored for CA-125 (%)	20	29

GOG 218: PFS as determined by the IRC and the investigators

	IRC-assessed PFS[a]		Investigator-assessed PFS[b]	
	Arm I CP (n=625)	Arm III CP + BEV → BEV (n=623)[c]	Arm I CP (n=625)	Arm III CP + BEV → BEV (n=623)[c]
Patients with events	203	177	277	248
Median, mos[d]	13.1	19.1	12	18.2
Hazard ratio, stratified[e]		0.630		0.644
95% CI		0.513, 0.773		0.541, 0.766
Improvement in PFS , mos		6		6.2

ICON 7 Final OS: High-Risk Group

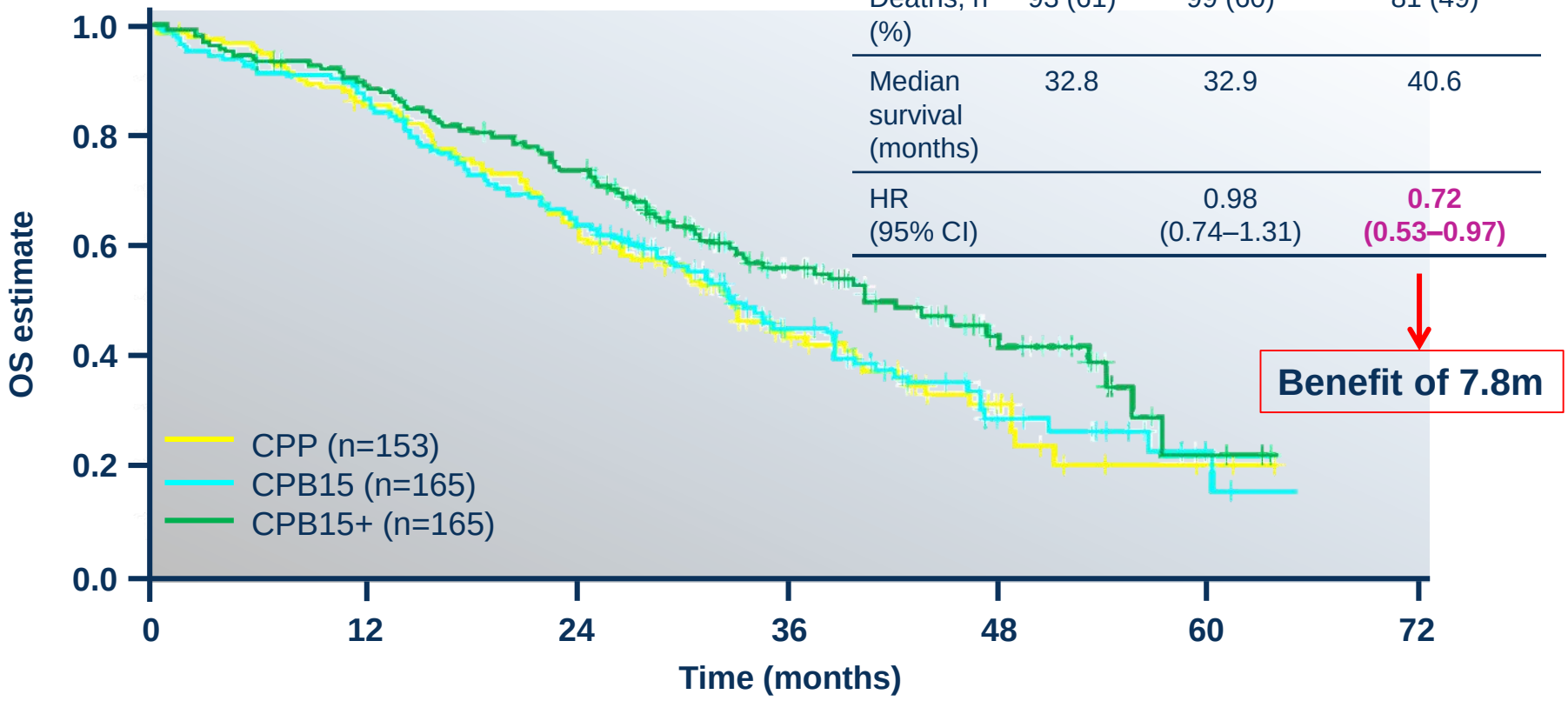


Non-proportionality test: p=0.0072. A benefit of 4.8 months in the restricted mean survival time

Oza AM, et al. European Cancer Congress 2013, abstract #6

GOG 218: OS benefit is suggested with chemotherapy + Bevacizuamb and continued single-agent Avastin in stage IV disease

	CPP	CPB	CPB15
Deaths, n (%)	93 (61)	99 (60)	81 (49)
Median survival (months)	32.8	32.9	40.6
HR (95% CI)		0.98 (0.74–1.31)	**0.72 (0.53–0.97)**



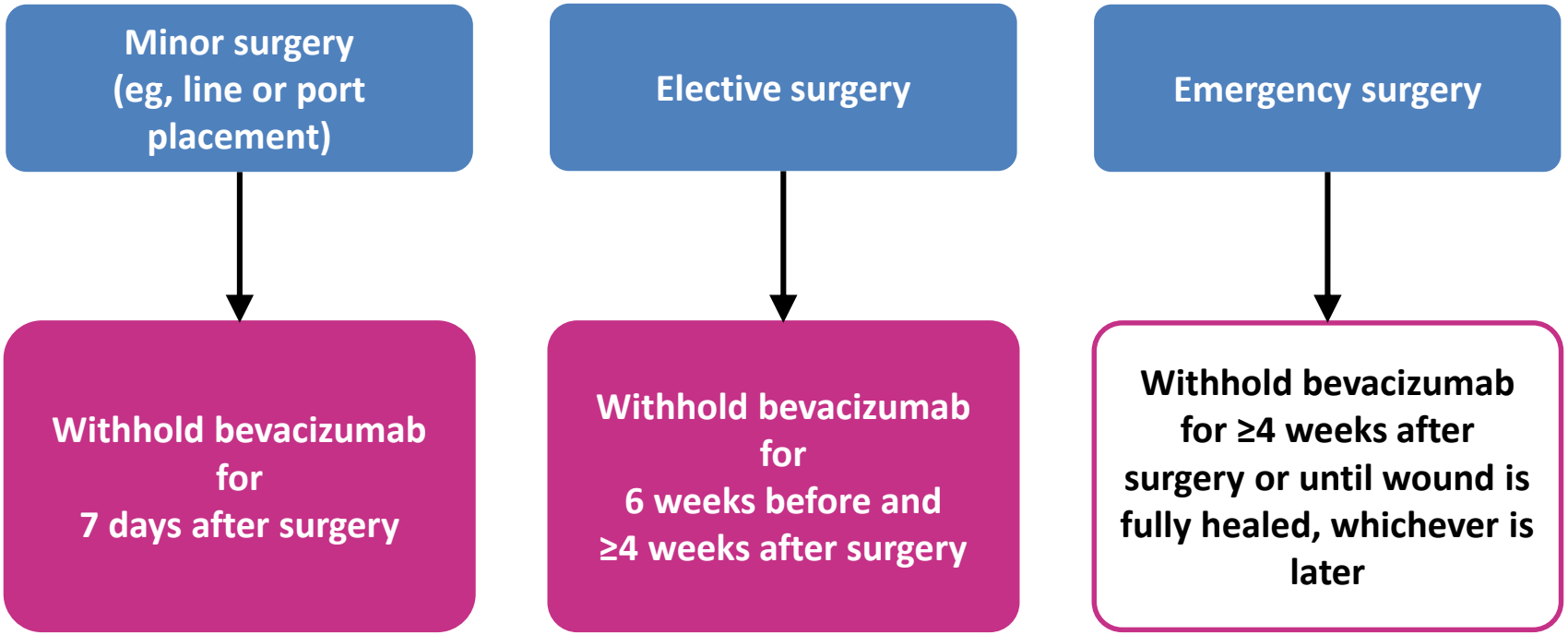
CPP	153	144	129	113	95	72	42	28	15	5	3	0	0
CPB	165	149	142	117	104	73	44	30	15	10	3	1	0
CPB15	165	154	144	130	117	83	57	37	21	10	3	0	0

Randall, et al. SGO 2013: Abstract 80

Case study: surgery and eligibility for bevacizumab

- Is it possible to treat patients with double bowel resection with bevacizumab?
  - Need to establish that the intestinal anastomoses have healed prior to bevacizumab therapy, potentially through assessment by colonoscopy
- Is previous bleeding at the anastomosis an exclusion criterion?
  - Potentially relevant exclusion criteria need to be checked carefully, ie
    - Active gastrointestinal bleeding
    - History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months of first dose of bevacizumab

Reducing the risk of wound-healing complications



Miles, et al. Br J Hosp Med 2010

Case study: front-line therapy

August 19, 2011

- Initial treatment with carboplatin 500 mg (AUC6)
  - + paclitaxel 234 mg (175 mg/m^2)
  - + bevacizumab 585 mg (15 mg/kg)
- Therapy initiated >5 weeks after surgery when wound had fully healed and the bleeding controlled

August 23, 2011

- Suspected partial intestinal obstruction → iv fluid
- Abdominal x-ray: constipation with no free air in abdomen
- Spontaneous resolution of bowel obstruction

Question: would you stop chemotherapy ?

1. Yes
2. No

Question: would you stop bevacizumab ?

1. Yes
2. No

Case study: front-line therapy

"Since this was a partial occlusion that resolved spontaneously with medical therapy alone, the patient can continue therapy"

August 19, 2011–January 18, 2012

- 6 cycles of therapy with carboplatin, paclitaxel and bevacizumab administered
- CT at cycles 3 and 6 showed no evidence of disease

January 18, 2012

- No evidence of disease progression based on imaging, symptoms and CA125 levels

Case study: continuation of therapy

January 18, 2012

- Continued therapy with single-agent bevacizumab

February 15, 2012

- Blood pressure: 150/100 mmHg (120/90 mmHg at baseline; all prior readings <140/90 mmHg)
- No other symptoms related to increased blood pressure
- Pressure returns to <140/90 mmHg in subsequent measurements

Question: how would you manage this patient's raised blood pressure?

1. Stop bevacizumab

2. Continue bevacizumab

Question: how would you manage this patient's raised blood pressure?

1. Initiate antihypertensive therapy with an ACE inhibitor, continue bevacizumab

2. No antihypertensive treatment, continue bevacizumab

Case study: continuation of therapy

January 18, 2012

- Continued therapy with single-agent bevacizumab

February 15, 2012

- Blood pressure: 150/100 mmHg (120/90 mmHg at baseline; all prior readings <140/90 mmHg)
- No other symptoms related to increased blood pressure
- Blood Pressure remains 150/100 mmHg in subsequent measurements

Question: how would you manage this patient's raised blood pressure?

1. Initiate antihypertensive therapy, continue bevacizumab

2. Discontinue bevacizumab and initiate antihypertensive therapy

What course of action would you take if a patient develops grade 3 hypertension during treatment with chemotherapy and Bevacizumab ?

1. Stop both chemotherapy and Bevacizumab immediately and treat hypertension

2. Continue chemotherapy, stop Bevacizumab and treat hypertension

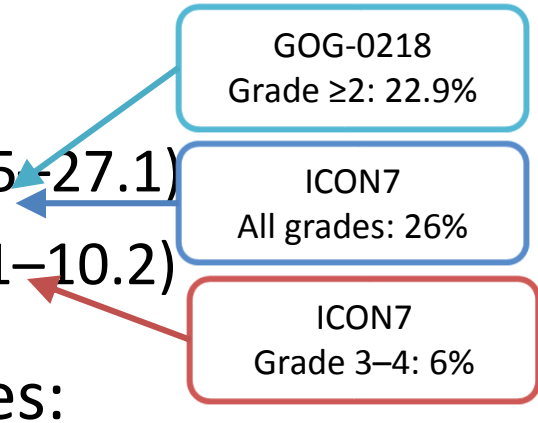
What course of action would you take if a patient develops grade 3 hypertension during treatment with chemotherapy and Bevacizumab?

1. Resume Bevacizumab when adequate control of hypertension is achieved

2. Stop permanently Bevacizumab.

Increased risk of high-grade hypertension with Bevacizumab in cancer patients: a meta-analysis

- 12,656 patients with a variety of tumours from 20 studies
- Incidence:
  - all-grade hypertension: **23.6%** (95% CI: 20.5–27.1)
  - high-grade (grade 3 or 4): **7.9%** (95% CI: 6.1–10.2)
- No significant differences between doses:
  - relative risk at 2.5mg/kg/week (RR=4.78, 95% CI: 3.59–6.36) as well as 5mg/kg/week (RR=5.39, 95% CI: 3.68–7.90)



Ranpura, et al. Am J Hypertens 2010

How to manage grade 3/4 hypertension?

(Requiring more than one drug or more intensive therapy than previously-Life-threatening)

- In patients with severe (grade 3) hypertension
  - temporary interruption of Bevacizumab is recommended until adequate control is achieved
  - if hypertension cannot be controlled, Bevacizumab should be permanently discontinued
- Bevacizumab should be discontinued in patients who develop grade 4 hypertension
  - hypertensive crisis, hypertensive encephalopathy or reversible posterior leucoencephalopathy syndrome (RPLS)
- Discontinuation of Bevacizumab is rarely required due to hypertension
  - only 2.4% in the GOG-0218 trial

Case study: current status

- The patient continues on single-agent bevacizumab therapy with no evidence of progression
- Hypertension continued to be controlled using an ACE inhibitor
- She is now NED, 19 months after stopping bevacizumab (35 months since diagnosis)

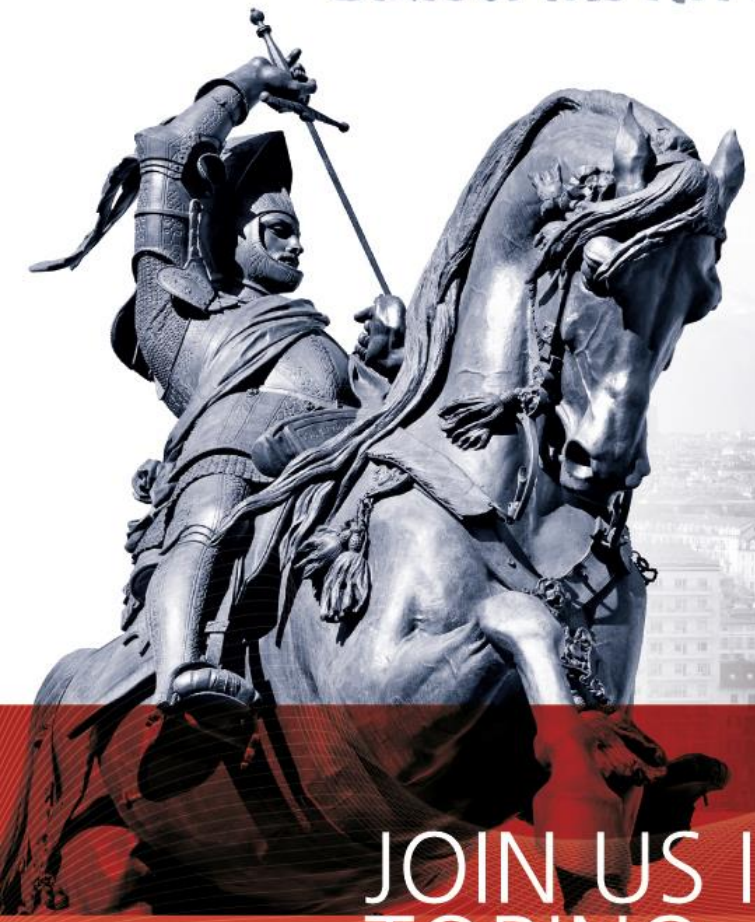
Conclusions

- Patients who have undergone extensive surgery, including bowel resection, can receive bevacizumab
- Bevacizumab-associated side effects in ovarian cancer are generally manageable and as expected
- Events can often be avoided with appropriate planning, eg wound-healing complications, or managed using standard medical therapy, eg hypertension and thrombosis

ESGO

FOLLOW UP IN
GYNAECOLOGICAL MALIGNANCIES
SEPTEMBER 11-13, 2014 | TORINO, ITALY

State of the Art Conference 2014



JOIN US IN
TORINO, ITALY 2014

www.esgo.org