E2100

Bevacizumab Combined With Weekly Paclitaxel

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E2100

Trial Design

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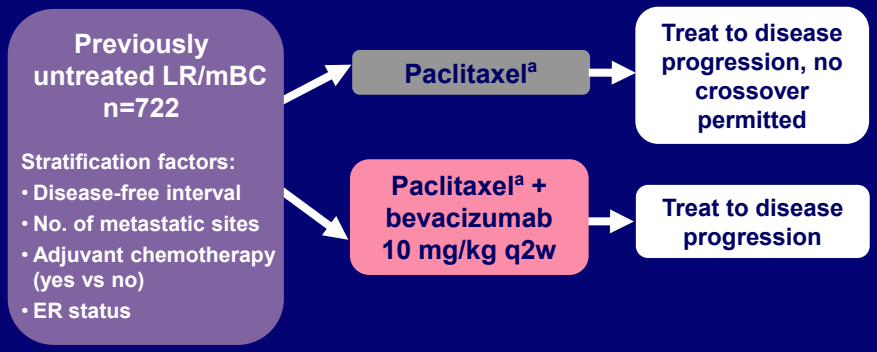
E2100: Pivotal Trial of Paclitaxel ± Bevacizumab Leading to Regulatory Approval



- Primary endpoint: PFS
  - Other endpoints: ORR, OS, quality of life, safety

[a]90 mg/m^2 weekly for 3 weeks of a 4-week cycle
Miller et al. NEJM 2007

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E2100: Baseline Characteristics Well Balanced

Characteristic	Paclitaxel (n=354)	Bevacizumab + paclitaxel (n=368)
Median age, years (range)	55 (27–85)	56 (29–84)
ER positive, %	63	61
PgR positive, %	45	45
HER2 positive, %	1.7	2.4
Disease-free interval, %		
≤24 months	41	41
>24 months	59	59
Number of metastatic sites, %		
<3	52	57
≥3	48	43
Prior taxane therapy, %	19	20
Prior anthracycline therapy, %	51	50

Gray et al. JCO 2009

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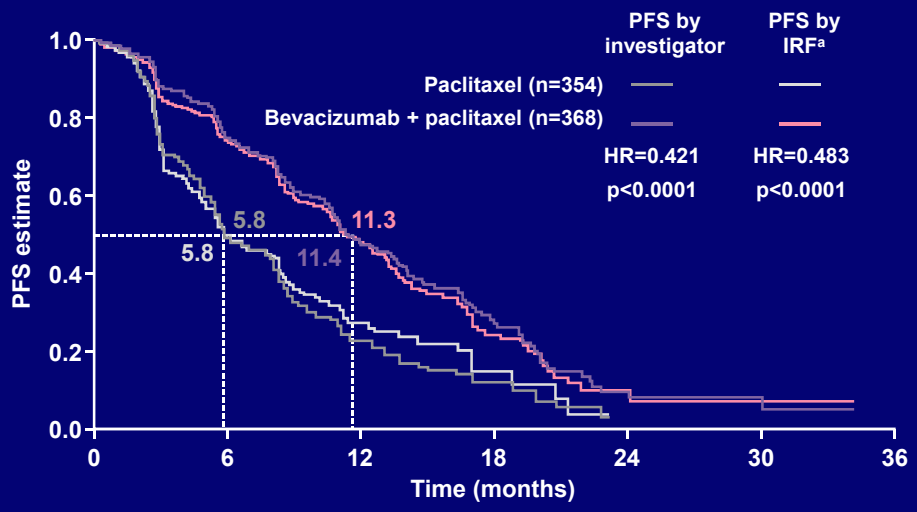
E2100: Significantly Improved PFS With Bevacizumab + Paclitaxel, Confirmed by Independent Review



[a]Scans available for 90% of patients

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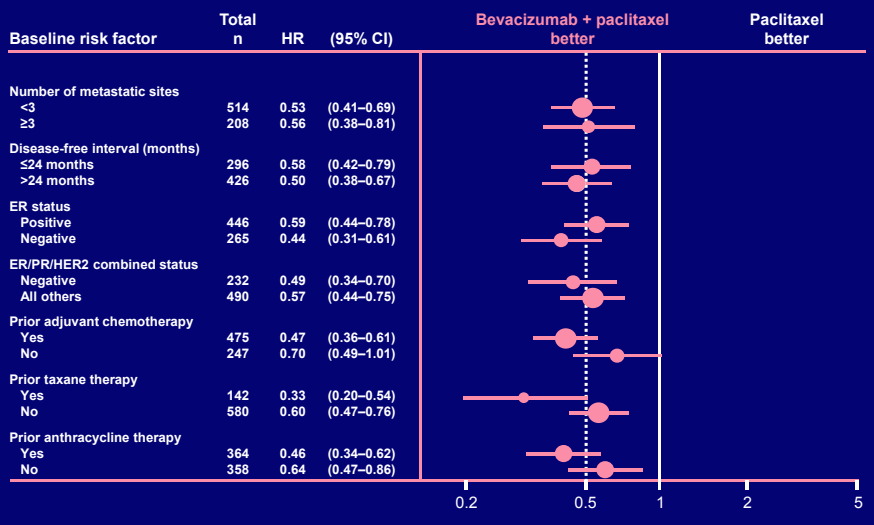
E2100: Consistent PFS Benefit of Bevacizumab + Paclitaxel in All Subgroups Analysed[a]



[a]IRF assessment

Gray et al. JCO 2009

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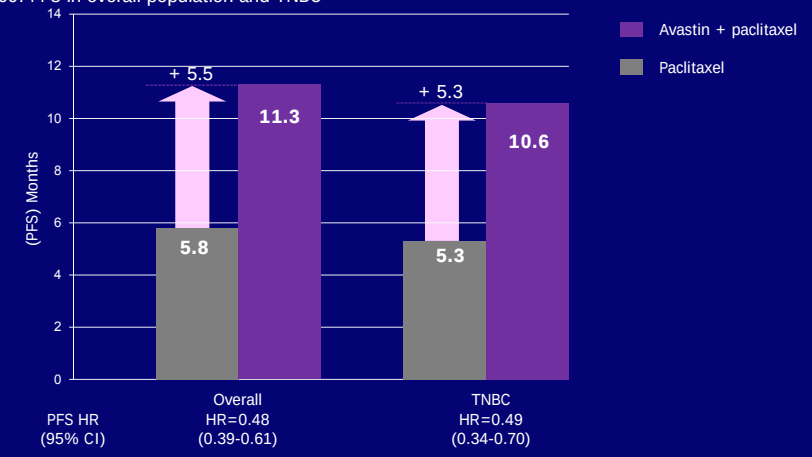
E2100: Avastin Doubles PFS to More Than 10 Months in Combination with Paclitaxel in First-Line mTNBC

Avastin PFS Benefit in Overall Population Confirmed in TNBC Subgroup[1,2]

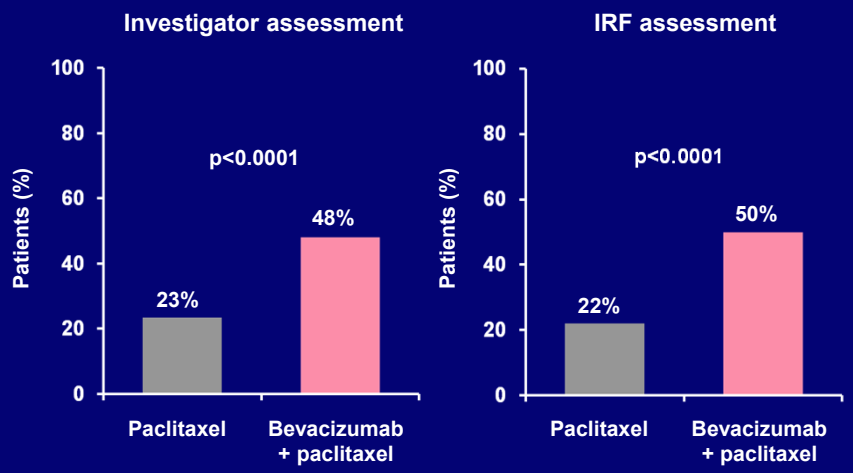
E2100: PFS in overall population and TNBC[1,2*]



*By independent review facility

1. O'Shaughnessy, et al. Cancer Res 2009; 2. Gray, et al. J Clin Oncol 2009

E2100: Response Rate Doubled in the Bevacizumab + Paclitaxel Arm[a]



[a]Patients with measurable disease at baseline

Klencke et al. ASCO 2008

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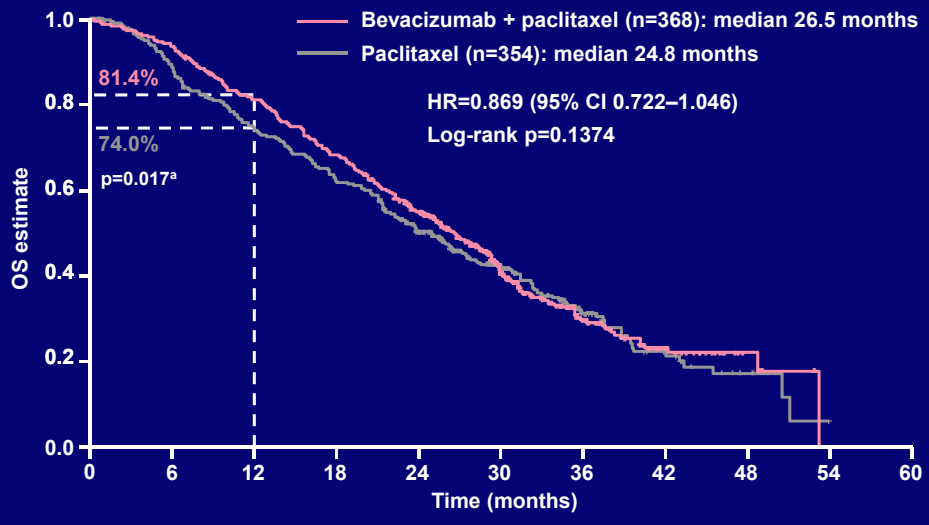
E2100: Overall Survival



[a]Post-hoc

Avastin SmPC 2009; Cameron Eur J Cancer Suppl 2008; Roche data on file 2007

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E2100: Summary

- E2100 results demonstrate the statistically meaningful benefit of combining bevacizumab with weekly paclitaxel
  - Increase median PFS form 5.8 to 11.3 months
    (Hazard ratio 0.48, p<0.0001)
  - Increase ORR from 22% to 50% (p<0.0001)
- Subpopulation analysis of patients with TNBC treated in the E2100 phase III trial of first-line bevacizumab in combination with paclitaxel demonstrated a significant improvement in PFS
  - Median PFS from 5.3 to 10.6 months
    (Hazard ratio 0.49 [95% CI 0.34–0.70])
- The addition of bevacizumab to paclitaxel resulted in an improvement in PFS with no significant improvement in OS.
  - Median OS: bevacizumab+paclitaxel vs. paclitaxel
    = 26.5 vs. 24.8 months (p=0.14)

Safety and Patient Management

Review of Data, Biology and Practical Recommendations

Practical recommendations are based on the available literature and the current Avastin SmPC

Contents

Overview of Safety Data

E2100

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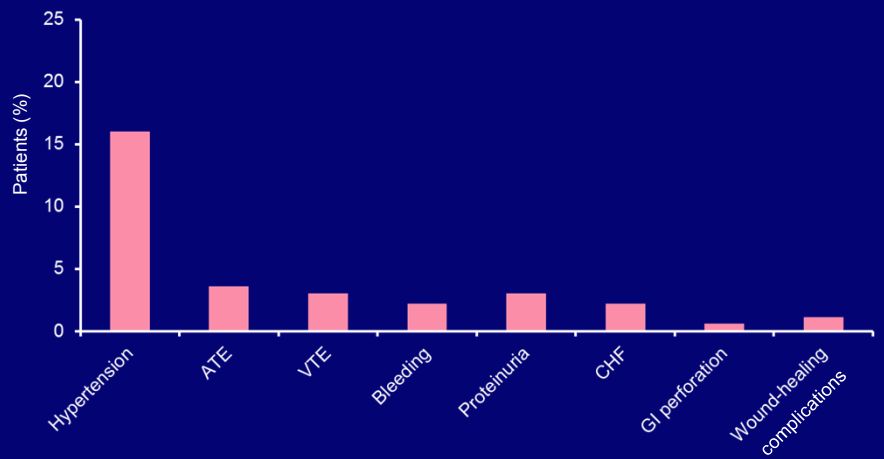
Overview of Grade ≥3 Adverse Events in E2100



Miles. Eur J Cancer Suppl 2008

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Hypertension

Management

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Potential Risk Factors for Hypertension

- Age[1]
  - With bevacizumab, higher incidence in patients ≥65 vs <65 years (15.9% vs 13.2%, respectively)
- Race[1,2]
  - More grade 3/4 hypertension in blacks than whites or Hispanics (21.2% vs 16.5% vs 10.3%, respectively)
- Gender[1]
  - No apparent difference with bevacizumab
- Lifestyle (eg smoking, alcohol intake, obesity, salt intake, physical activity)[1,3,4]
- Family history[1,4,5]
- Diabetes mellitus[4]

[1]Shord et al. Am J Health Syst Pharm 2009; [2]Choi et al. ASCO 2007; [3]Primatesta et al. Hypertension 2001; [4]Mancia et al. Eur Heart J 2007; [5]Tozawa et al. Hypertens Res 2001

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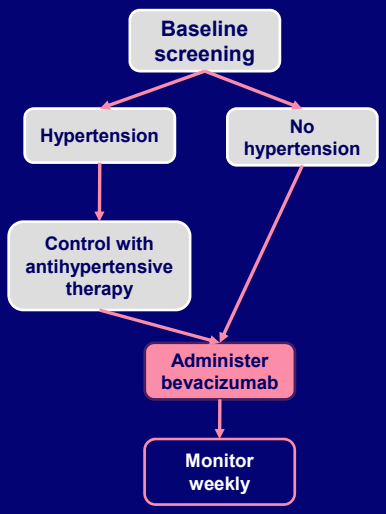
Hypertension and Eligibility for Bevacizumab

- Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment[1,2]
- Prophylactic antihypertensive therapy is not recommended[2]
- No information is available on the effect of bevacizumab in patients with uncontrolled hypertension at treatment start[1]
- Blood pressure monitoring is generally recommended during therapy[1]



[1]Avastin SmPC 2009; [2]Kappers et al. J Hypertens 2009

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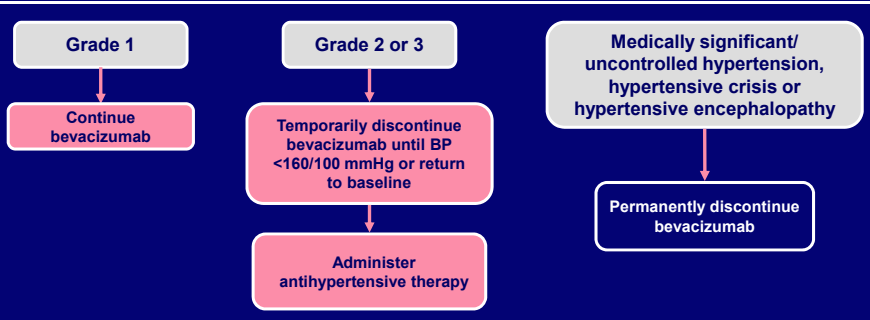
Managing Hypertension in Patients Treated With Bevacizumab



- Generally hypertension is adequately controlled with oral antihypertensives (eg ACE inhibitors, diuretics, calcium channel blockers)
  - ACE inhibitors preferred for patients with proteinuria
  - Non-dihydropyridine calcium channel blockers should be avoided in patients receiving cytochrome P450 inhibitors
  - Calcium channel blockers preferred in elderly and black patients
- The optimal antihypertensive agent for managing bevacizumab-induced hypertension has not been established

ACE = angiotensin-converting enzyme

Shord et al. Am J Health Syst Pharm 2009; Izzedine et al. Ann Oncol 2009; Avastin SmPC 2009

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Recovery From Hypertension

- Data vary on hypertension outcomes after discontinuing bevacizumab:
  - Decreased blood pressure after discontinuation[1]
  - Persistent hypertension for up to 6 months after discontinuation[2,3]
- Recommendations[3]:
  - Monitor blood pressure at least monthly for 4–6 months after discontinuing bevacizumab until decreased to baseline levels
  - Stop antihypertensive therapy once blood pressure is normal in patients with no history of hypertension

[1]Yang et al. NEJM 2003; [2]Mourad et al. Ann Oncol 2008; [3]Shord et al. Am J Health Syst Pharm 2009

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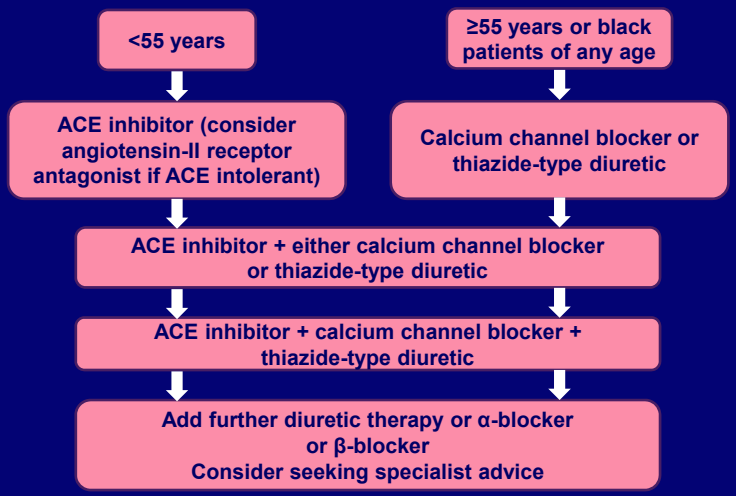
NICE Guidelines for the Management of Newly Diagnosed Hypertension



NICE Clinical Guideline 34, June 2006

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Proteinuria

Management

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Risk Factors for Proteinuria

- Underlying renal disease
- Nephrectomy
- Uncontrolled hypertension
- Diabetes mellitus
- Immunosuppression
- Bevacizumab treatment

Shord et al. Am J Health Syst Pharm 2009; Wu et al. J Am Soc Nephrol 2010

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Definition and Measurement of Proteinuria

- Definition of proteinuria:
  - Urinary protein excretion of >300 mg/day
- Urinalysis dipstick
  - Detects glomerular proteinuria
  - Insensitive to presence of non-albumin protein (tubular proteinuria)
- 24-hour urine sample
  - Enables detection of tubular proteinuria

Izzedine et al. Eur J Cancer 2010

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Grading of Proteinuria

	NCI CTCAE, version 3.0			
	Grade 1	Grade 2	Grade 3	Grade 4
Urine dipstick	1+	2+/3+	4+	Nephrotic syndrome
Protein (g/L)	0.3	1–3	>3	Nephrotic syndrome
24-hour urine collection (g/24h)	0.15–1.0	>1.0–3.5	>3.5	Nephrotic syndrome

Izzedine et al. Eur J Cancer 2010; NCI CTCAE, v3.0, 2006

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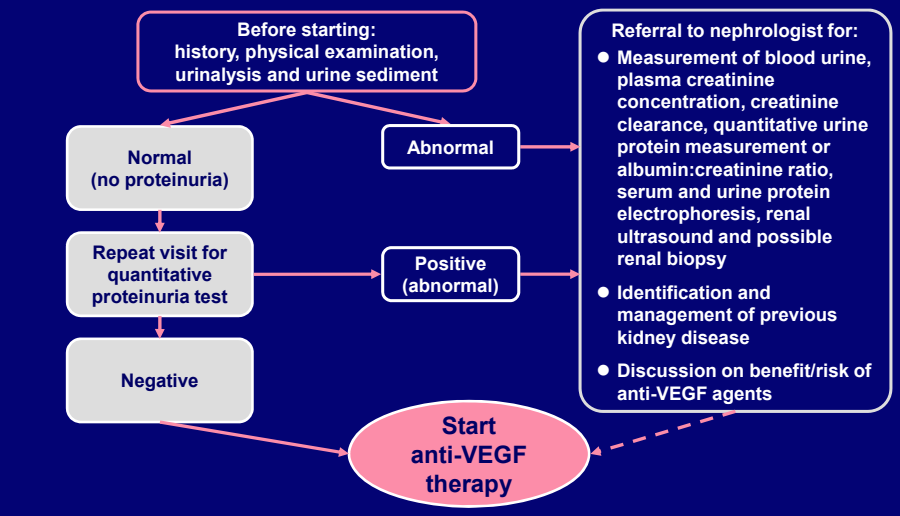
Monitoring and Detecting Proteinuria Before Starting Bevacizumab Therapy



Izzedine et al. Eur J Cancer 2010

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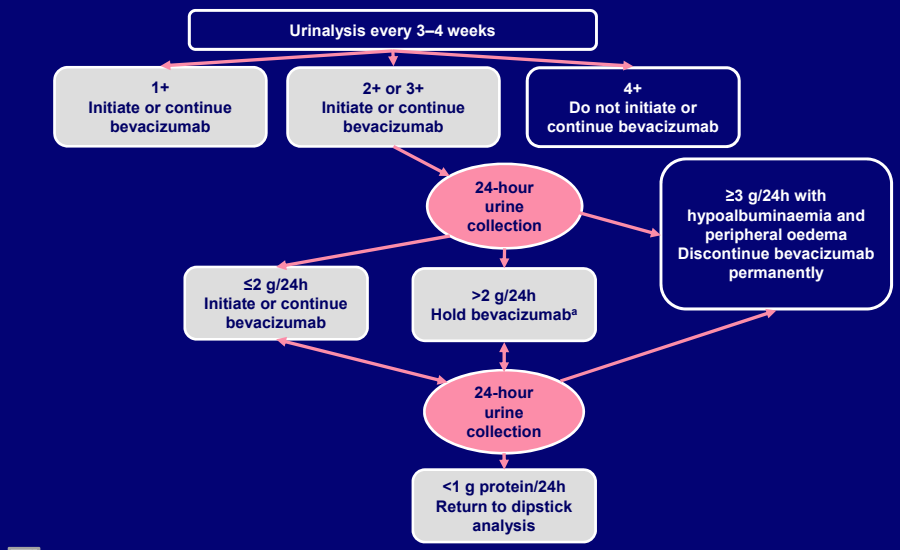
Monitoring and Managing Proteinuria During Bevacizumab Therapy



[a]If ≥ 2g for 3 months, discontinue bevacizumab
Shord et al. Am J Health Syst Pharm 2009

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Thromboembolic Events

Management

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Risk Factors for Thromboembolism

- Cancer, especially ovarian, pancreatic, bone or brain
- Major surgery
- Indwelling venous catheter
- Advanced age
- Prolonged immobility
- Prior ATE
- Bevacizumab
- Cardiac or respiratory failure
- Cytotoxic chemotherapy
- Oestrogen therapy
- Diabetes
- Hypercholesterolaemia
- Hypertension
- History of atherosclerosis (ATE)
- Myocardial infarction (ATE)

Nalluri et al. JAMA 2008; Shord et al. Am J Health Syst Pharm 2009; Zangari et al. J Clin Oncol 2009; Scappaticci et al. J Natl Cancer Inst 2007

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Grading of Thromboembolism

Grade 2	Grade 3	Grade 4
DVT or cardiac thrombosis; intervention not indicated	DVT or cardiac thrombosis; intervention (eg anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus

- Most common VTEs include DVT, pulmonary embolism, mesenteric venous thrombosis and axillary venous thrombosis
- Typical ATEs include cerebrovascular accident and myocardial infarction

NCI CTCAE, v3.0, 2006; Shord et al. Am J Health Syst Pharm 2009

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Risk of ATE and Eligibility for Bevacizumab

- In patients at high risk of ATE, primary prevention with aspirin (<325 mg/day) is recommended
- There is no evidence of an increased risk of bleeding with concomitant aspirin and bevacizumab
  - However, patients should be monitored carefully because of the risk of haemorrhage with both agents

Shord et al. Am J Health Syst Pharm 2009; Hambleton et al. ASCO 2005

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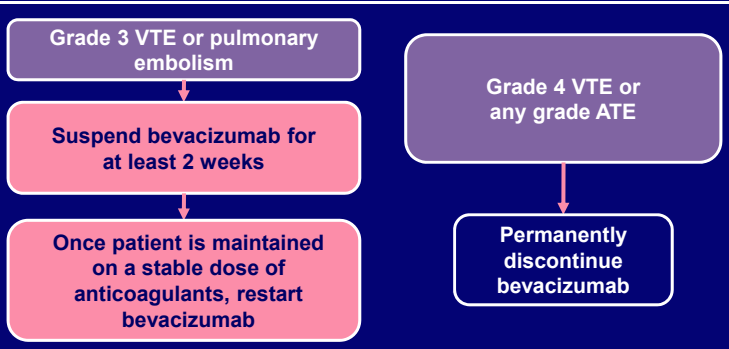
Managing Thromboembolism in Patients Treated With Bevacizumab



- Anticoagulation therapy: low molecular weight heparin or warfarin (with careful dose monitoring) according to anti-thrombotic therapy guidelines[1]
- Monitor patients carefully for bleeding and thrombosis[1,2]
  - No evidence of an increased risk of bleeding when anticoagulants are given concomitantly with bevacizumab[3,4]

[1]Shord et al. Am J Health Syst Pharm 2009; [2]Kabbinavar & Shah. Cancer Therapy 2008
[3]Wardley et al. SABCS 2008; [4]Hambleton et al. ASCO 2005

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Wound-Healing Complications

Management

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Angiogenesis and Wound Healing

- Angiogenesis is an essential process in wound healing[1]
  - New blood vessels deliver oxygen and nutrients (and drugs) to the damaged endothelium
  - VEGF-A regulates normal and pathological angiogenesis
  - Inhibition of VEGF-A inhibits normal as well as pathological angiogenesis, potentially impairing wound healing
- Impaired wound healing[1]
  - Presents as wound dehiscence, bruising or bleeding
  - Potential risk factors include: radiotherapy, anastomotic leaks, infection, tumour involvement at the surgery site, history of diabetes requiring medication and obesity[1,2]

[1]Shord et al. Am J Health Syst Pharm 2009; [2]Gresset & Shah. Ann Pharmacother 2009

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Reducing the Risk of Wound-Healing Complications in Patients Receiving Bevacizumab

- "Wound-healing complications induced by bevacizumab are very preventable"[1]

  Major surgery (any intervention requiring more than local anaesthesia and/or open cavity)[1–3]
  - Suspend bevacizumab therapy ≥28 days before elective surgery
    - As mandated in clinical trials of bevacizumab
  - Do not resume bevacizumab until at least 28 days after major surgery, and only after the surgical incision is fully healed[4]

  Minor surgery (any intervention under local anaesthesia)[1,2]
  - Recommended not to administer bevacizumab within 7 days before or after minor surgery (eg catheter placement)
    - No evidence that bevacizumab increases the risk of bleeding with these procedures
  - Permanently discontinue bevacizumab in patients with wound dehiscence requiring medical intervention

[1]Gresset & Shah. Ann Pharmacother 2009; [2]Shord et al. Am J Health Syst Pharm 2009; [3]Gordon et al. Ann Plast Surg 2009
[4]Blowers & Hall. Br J Nurs 2009

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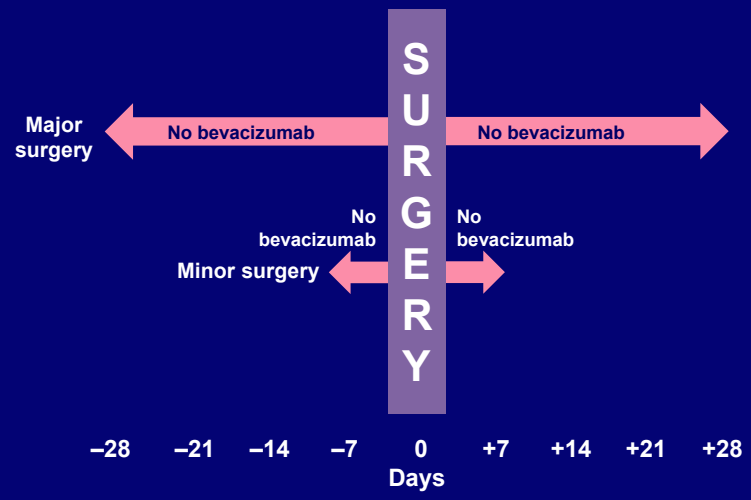
Recommended Bevacizumab-Free Interval in Patients Undergoing Surgery



Blowers & Hall. Br J Nurs 2009

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Bleeding

Management

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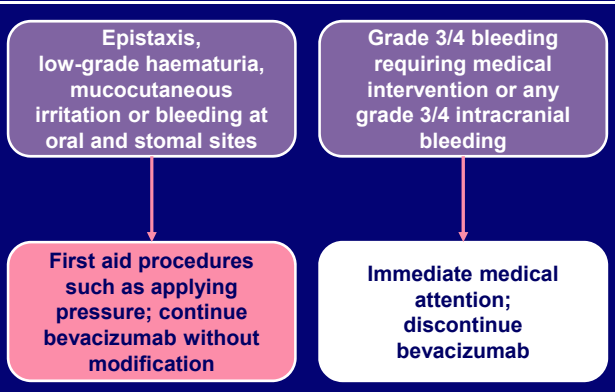
Managing Bleeding Events



- Exercise caution in patients with bleeding diathesis, acquired coagulopathy and in patients receiving full-dose anticoagulation before starting bevacizumab therapy

Shord et al. Am J Health Syst Pharm 2009; Blowers & Hall. Br J Nurs 2009; Kabbinavar & Shah. Cancer Ther 2008; Mars & Zubal. Clin J Oncol Nurs 2009

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Gastrointestinal Perforation

Management

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Recommendations for Monitoring and Managing GI Perforation in Patients Treated With Bevacizumab

Before initiating bevacizumab	• Control peptic ulcer disease with histamine H_2 receptor antagonists or proton-pump inhibitors before starting bevacizumab • Do not initiate bevacizumab within 3 months of an endoscopic GI procedure
Monitoring	• Closely monitor patients with risk factors for early signs and symptoms of bowel perforation (sudden and severe abdominal pain, constipation, nausea, vomiting, high temperature)
Management	• Discontinue bevacizumab permanently if patients experience bowel perforation • Manage surgically if indicated (non-surgical management may be possible if GI perforation is detected early)

Shord et al. Am J Health Syst Pharm 2009

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Cardiac Safety

Clinical Trial Data

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Bevacizumab and CHF

- The double-blind randomised phase III trials revealed no excess of CHF among patients receiving bevacizumab-containing therapy compared with chemotherapy alone[1,2]
- Caution should be exercised when administering bevacizumab in patients with clinically significant cardiovascular disease or pre-existing CHF[3]

[1]Miles et al. JCO 2010; [2]Miles et al. EBCC 2010; [3]Avastin SmPC 2009

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Summary

- The safety profile of bevacizumab is well defined
- The most common adverse effects are hypertension and proteinuria, which are generally manageable with proactive monitoring and treatment
- Most adverse effects associated with bevacizumab appear to relate to inhibition of VEGF and are a class effect of agents targeting VEGF ligands or receptors
- Experience of bevacizumab in >1 million patients worldwide has led to better understanding of the risk factors and management of adverse effects and to the development of recommendations and guidelines

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