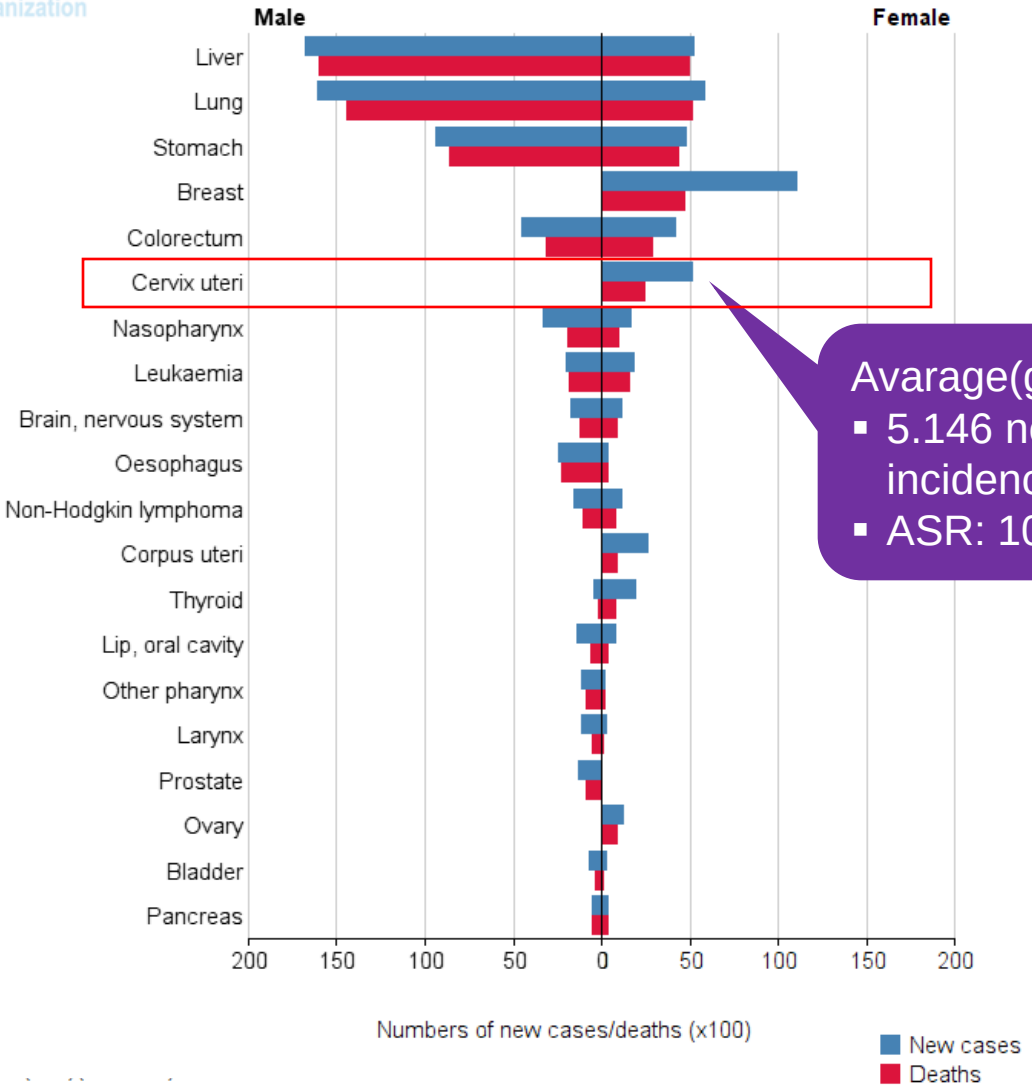
EFFECTS OF AVASTIN IN THE TREATMENT OF ADVANCED CERVICAL CANCER

Content

1. Epidemy
2. VEGF and the mechanism of Avastin
3. Indications
4. Reasearch on GOG 0240
5. Treatment instructions through NCCN
6. Dosage and method

Content

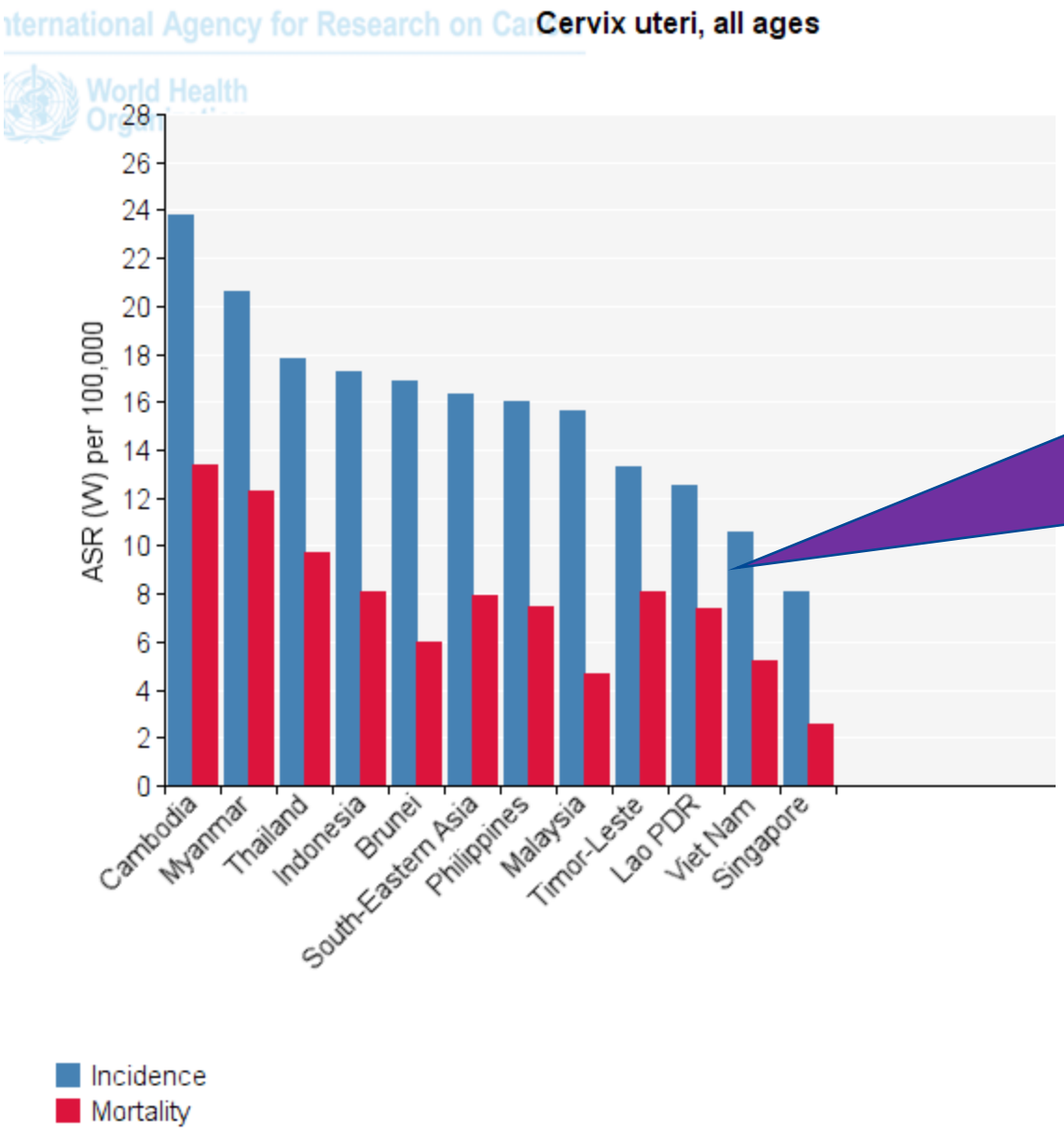
Cervical cancer is the 6th most common type of cancer



Avarage(group 5):

- 5.146 new incidences
- ASR: 10,6

GLOBOCAN 2012 (IARC)

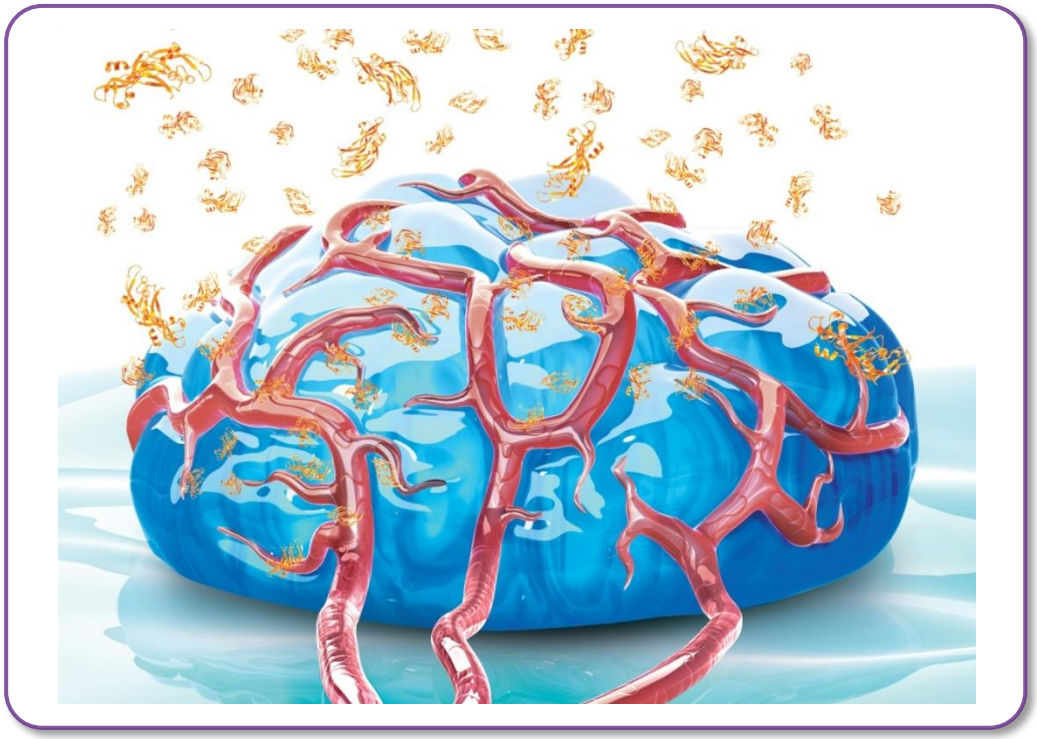


Incidence of Cervical Cancer in Vietnam is 10.6

GLOBOCAN 2012 (IARC)

Content

Angiogenesis is essential for tumour growth and survival[1]



Tumours >2mm in diameter require an independent blood supply to survive and grow[1–4]

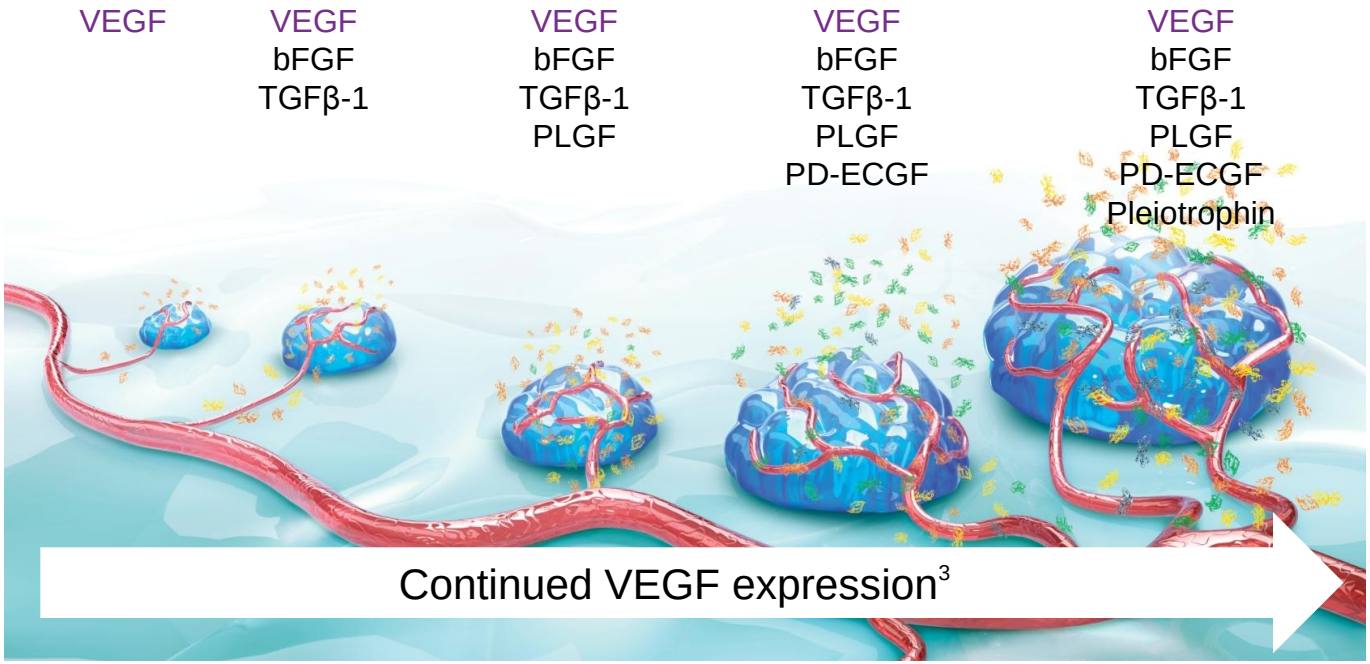
1. Folkman. In: Kufe, Pollock, Weichselbaum, eds. Cancer Medicine (Holland). 6th ed. Hamilton, Ontario: BC Decker; 2000; 2. Bergers, Benjamin. Nat Rev Cancer 2003; 3. Folkman. NEJM 1971; 4. Folkman. J Natl Cancer Inst 1990

VEGF, the key mediator of tumour angiogenesis

- Key mediator of angiogenesis
- Stimulates growth of endothelial cells
- Also known as VEGF-A
- Related molecules are VEGF-B, C and D, placental growth factor (PlGF)
- Homodimeric glycoprotein
- Molecular weight: 45,000Da
- Binds VEGF receptor-2 and heparin
- Four molecular species
  - $VEGF_{121}$
  - $VEGF_{165*}$
  - $VEGF_{189}$
  - $VEGF_{206}$

*Predominant molecular species
Ferrara, et al. Endocr Rev 1997

VEGF is an early and persistent promoter of tumour angiogenesis[1–4]



Tumours continually require VEGF to recruit new vasculature[5]

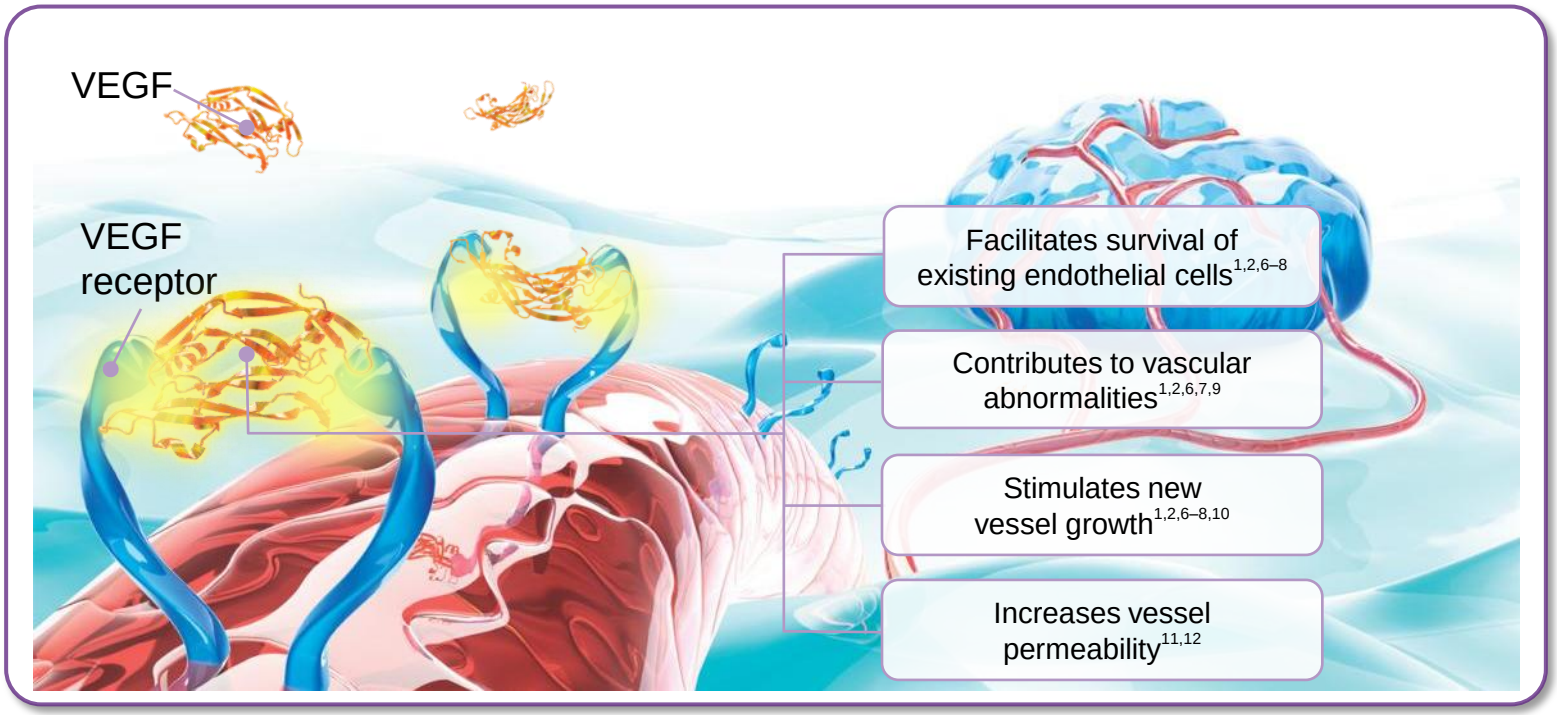
VEGF continues to be expressed throughout tumour progression, even as secondary pathways emerge[2,3,6,7]

IGF = insulin-like growth factor; PDGF = platelet-derived growth factor; EGF = epidermal growth factor

1. Bergers, Benjamin. Nat Rev Cancer 2003; 2. Kim, et al. Nature 1993; 3. Folkman. In: DeVita, Hellman, Rosenberg, eds. Cancer: Principles & Practice of Oncology. Vol 2. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2005; 4. Ferrara, et al. Nat Med 2003; 5. Inoue, et al. Cancer Cell 2002; 6. Mesiano, et al. Am J Pathol 1998; 7. Melnyk, et al. J Urol 1999

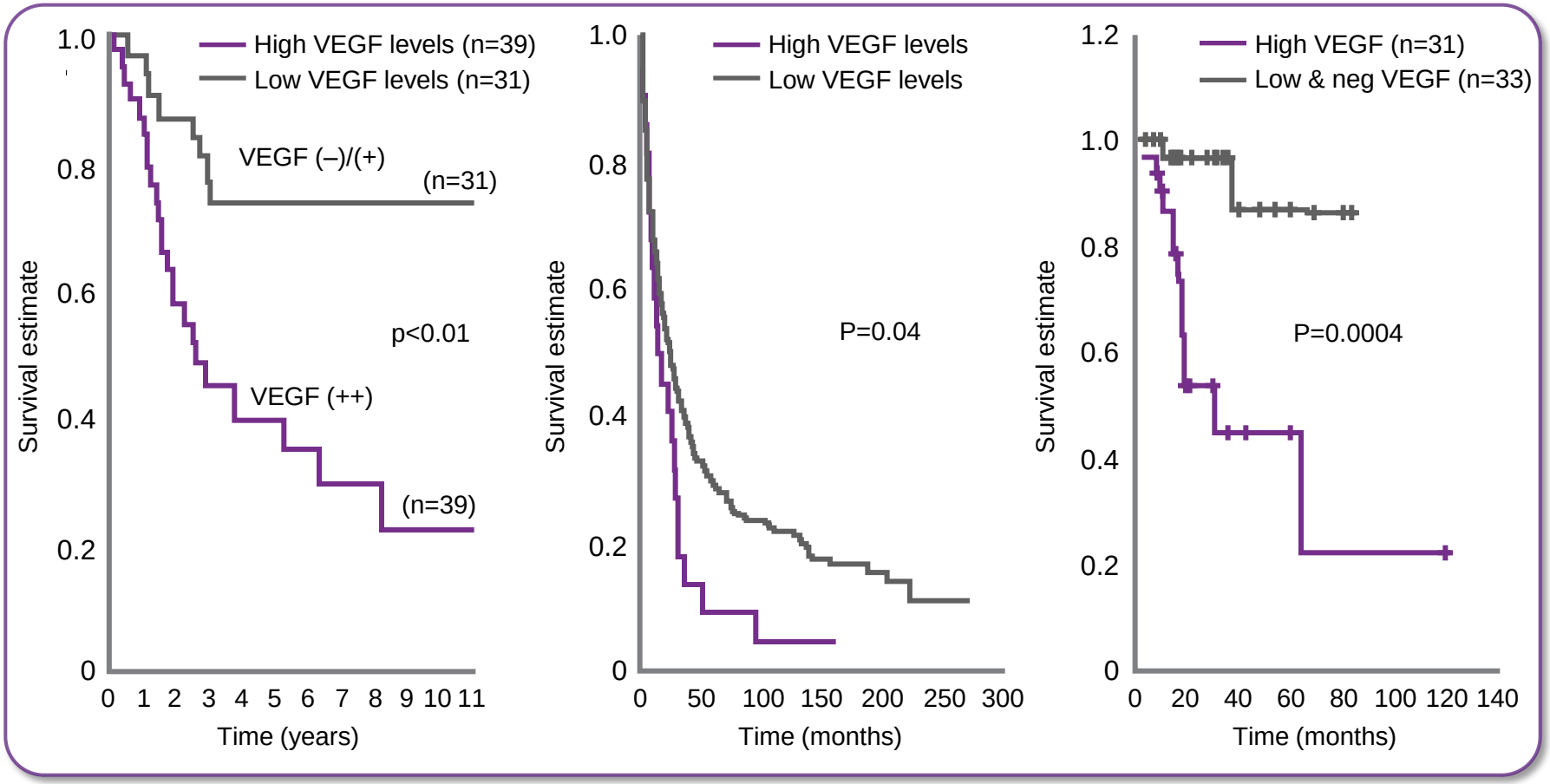
Tumour VEGF contributes to the functional abnormalities of tumour vasculature[1–5]

Interaction of VEGF with VEGF receptors is a key mediator of tumour angiogenesis



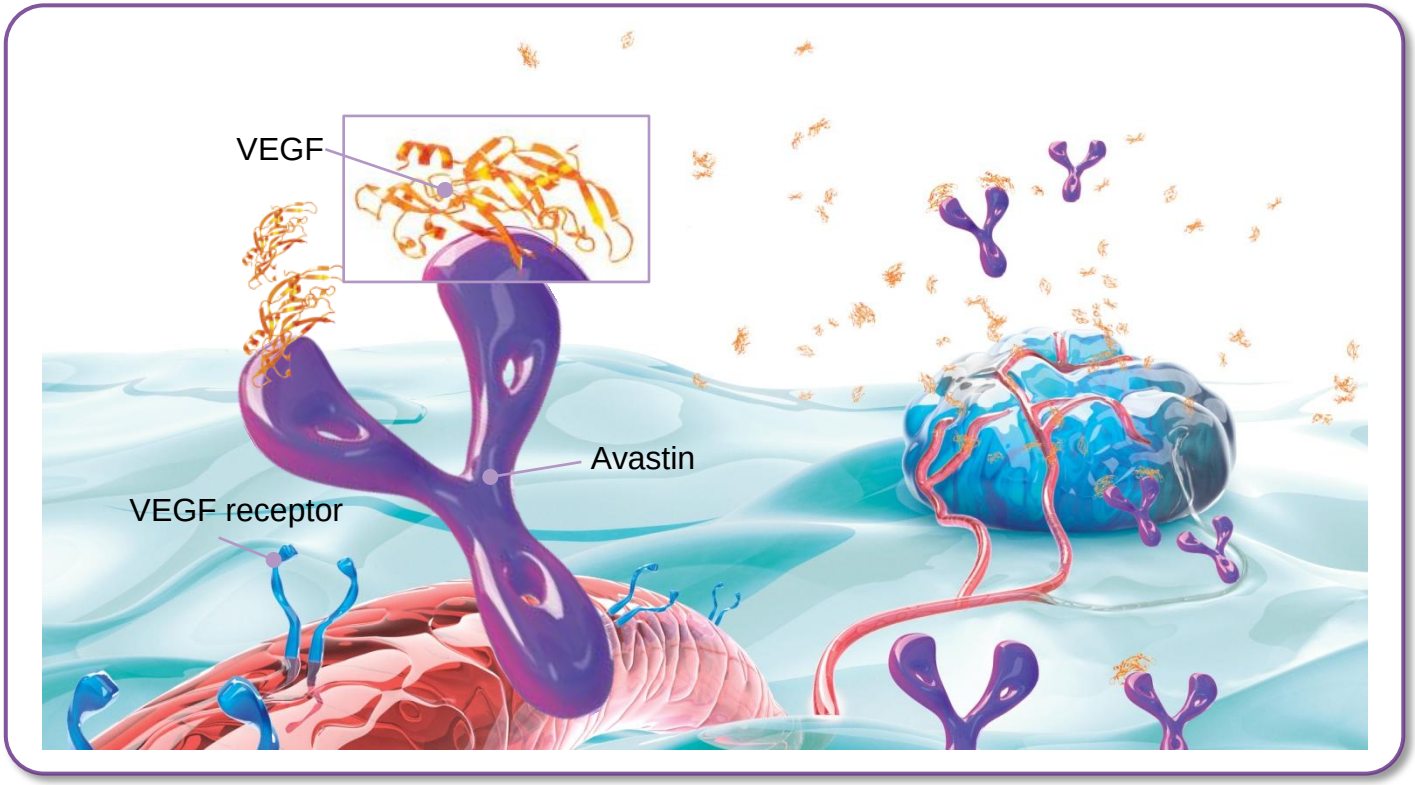
1. Ferrara. Endocr Rev 2004; 2. Hicklin, Ellis. JCO 2005; 3. Baka, et al. Expert Opin Ther Targets 2006;
4. Morabito, et al. Oncologist 2006; 5. de Vries, et al. Science 1992; 6. Bergers, Benjamin. Nat Rev Cancer 2003;
7. Jain. Science 2005; 8. Gerber, Ferrara. Cancer Res 2005; 9. Jain. Nat Med 2001; 10. Inoue, et al. Cancer Cell 2002;
11. Margolin. Curr Oncol Rep 2002; 12. Hu, et al. Am J Pathol 2002

Association of VEGF expression with poor survival supports rationale for inhibition



Yamamoto, et al. BJC 1997; Duncan, et al. Clin Cancer Res 2008
Shen, et al. BJC 2000

Avastin, a humanised monoclonal antibody, precisely targets VEGF

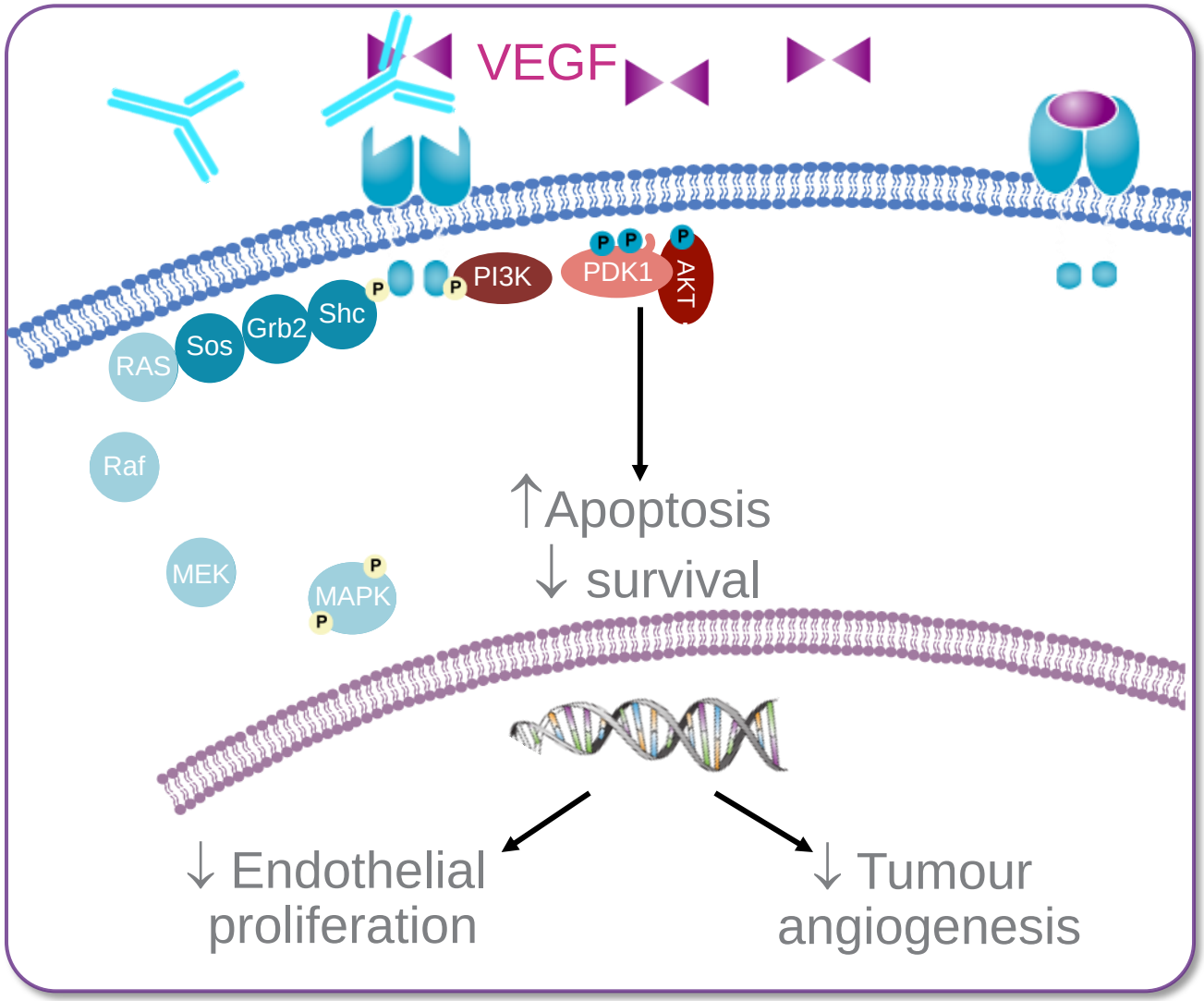


Avastin prevents binding of VEGF to receptors[1,2]

Avastin has a long elimination half life (approximately 20 days) which may contribute to continuous tumour control[3]

1. Avastin Summary of Product Characteristics; 2. Presta, et al. Cancer Res 1997;
3. Avastin prescribing information

Avastin inhibits tumour angiogenesis



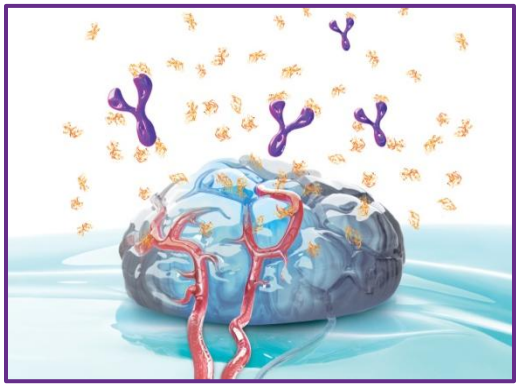
Avastin binding to VEGF prevents binding to the VEGF receptor

VEGF receptor signalling pathways are not stimulated

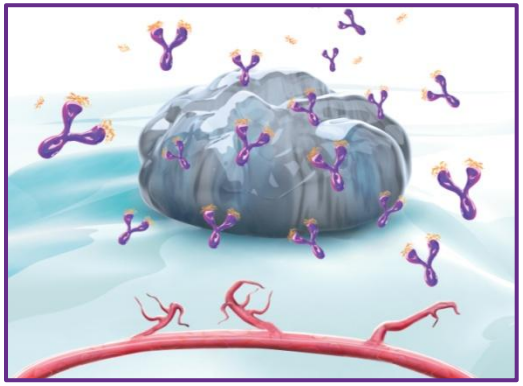
Apoptosis is increased and cell survival is decreased due to inhibition of VEGF receptor signalling

Endothelial cell proliferation and tumour angiogenesis are thus decreased

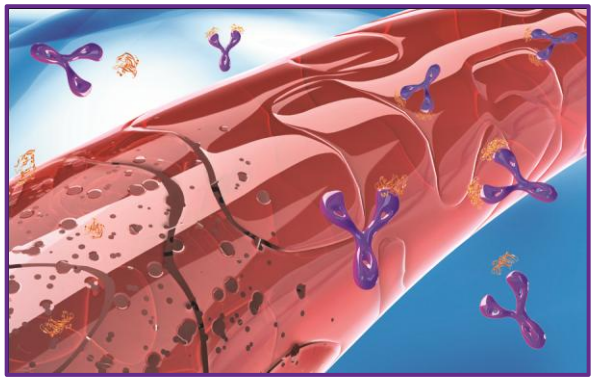
Avastin exerts multiple effects that contribute to increased treatment efficacy[1–20]



Regression
of existing tumour vasculature[1–3]



Inhibition
of new vessel growth[1–3,8]



Anti-permeability
of surviving vasculature[11–13]

Consistently increased response rates[4–7]
Continuous control of tumour growth[8–10]
Reduction of ascites and effusions[2,3,11,14–20]

1. Baluk, et al. Curr Opin Genet Dev 2005; 2. Willett, et al. Nat Med 2004; 3. O'Connor, et al. Clin Cancer Res 2009; 4. Hurwitz, et al. NEJM 2004; 5. Sandler, et al. NEJM 2006; 6. Escudier, et al. Lancet 2007; 7. Miller, et al. NEJM 2007; 8. Mabuchi, et al. Clin Cancer Res 2008; 9. Wild, et al. Int J Cancer 2004; 10. Gerber, Ferrara. Cancer Res 2005; 11. Prager, et al. Mol Oncol 2010; 12. Yanagisawa, et al. Anti-Cancer Drugs 2010; 13. Dickson, et al. Clin Cancer Res 2007; 14. Hu, et al. Am J Pathol 2002; 15. Ribeiro, et al. Respirology 2009; 16. Watanabe, et al. Hum Gene Ther 2009; 17. Mesiano, et al. Am J Pathol 1998; 18. Bellati, et al. Invest New Drugs 2010; 19. Huynh, et al. J Hepatol 2008; 20. Ninomiya, et al. J Surg Res 2009

Content

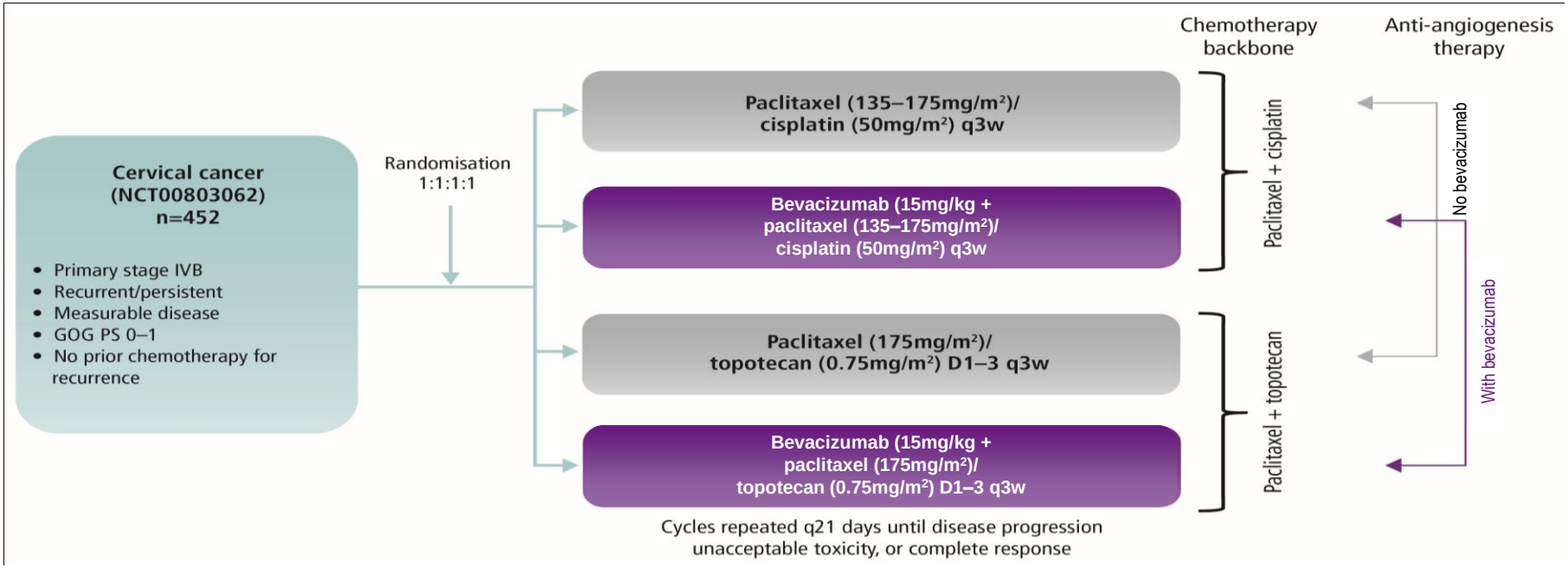
Indications of Avastin in Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is approved to treat persistent, recurrent, or metastatic cancer of the cervix.

Content

GOG-0240: study design

- A randomised phase III trial investigating cisplatin/paclitaxel ± bevacizumab or topotecan/paclitaxel ± bevacizumab in women with stage IVB (metastatic), recurrent or persistent cervical cancer[1]



- Primary endpoints: OS and tolerability of the four regimens
- Secondary endpoints: PFS and ORR

1. Tewari K, et al. N Eng J Med 2014

GOG-0240: key inclusion criteria[1]

- Primary stage IVB, recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy
- Measurable disease. Patients must have at least one “target lesion” to assess response (by RECIST)
- Patients must have adequate haematological function, renal function, hepatic function, blood coagulation parameters and have a urine protein-creatinine ratio (UPC ratio) <1.0mg/dL
- GOG performance status (PS) of 0 or 1
- Free of active infection requiring antibiotics
- Recovered from the effects of surgery/radiation therapy/chemoradiotherapy
  - At least six weeks since last chemoradiotherapy
  - At least three weeks since last radiation therapy alone
  - At least six weeks since any major surgical procedure

GOG = Gynecologic Oncology Group;
RECIST = Response Evaluation Criteria In Solid Tumors

1. Tewari K, et al. N Engl J Med 2014
(GOG-0240 study protocol available as supplementary material)

GOG-0240: key exclusion criteria[1]

- GOG PS of 2, 3 or 4
- Patients with bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage
- Prior chemotherapy (except concurrent with radiation therapy) or anti-VEGF
  - Patients who have received concurrent paclitaxel and/or concurrent topotecan with radiation therapy are ineligible
- Craniospinal soft tissue metastases
- Concomitant or prior invasive malignancy (except non-melanoma skin cancer)
- History or evidence upon physical examination of CNS disease
- Clinically significant cardiovascular disease

CNS = central nervous system;
VEGF = vascular endothelial growth factor

1. Tewari K, et al. N Engl J Med 2014
(GOG-0240 study protocol available as supplementary material)

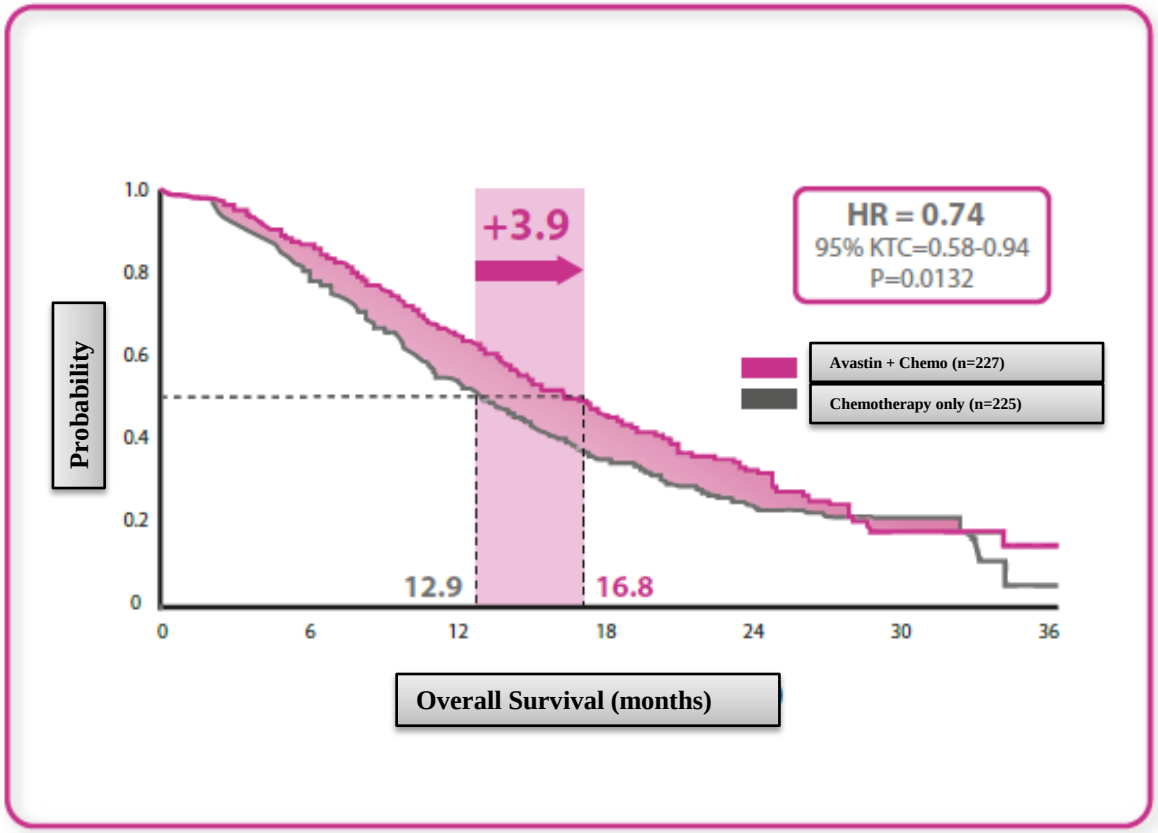
GOG-0240: key exclusion criteria (continued)[1]

- Serious non-healing wound, ulcer, or bone fracture (if history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess, 3 to 6 months must pass before study entry and patient must have undergone correction or spontaneous healing of the perforation/fistula and/or the underlying process causing the fistula/perforation)
- Active bleeding or pathologic conditions that carry high risk of bleeding
- Major surgical procedure within 28 days prior to the first date of bevacizumab therapy or anticipated during the course of the study
- Pregnancy or nursing
- Clinical symptoms or signs of gastrointestinal obstruction and parenteral hydration and/or nutrition required
- Significant peripheral vascular disease
- Pre-existing grade ≥2 peripheral neuropathy

1. Tewari K, et al. N Engl J Med 2014
(GOG-0240 study protocol available as supplementary material)

GOG-0240: Study results

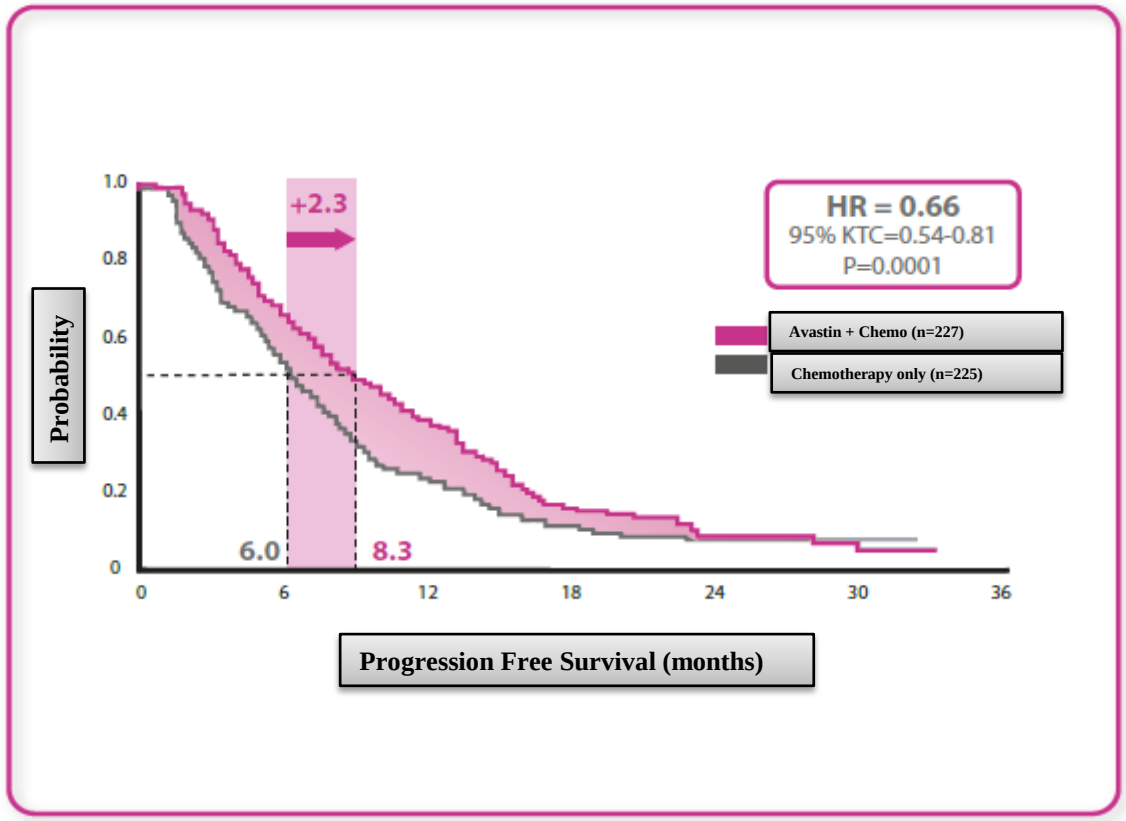
Avastin prolonged Overall Survival up to 3.9 months vs Chemotherapy only



1. Tewari KS et al. NEJM 2014

GOG-0240: Study results

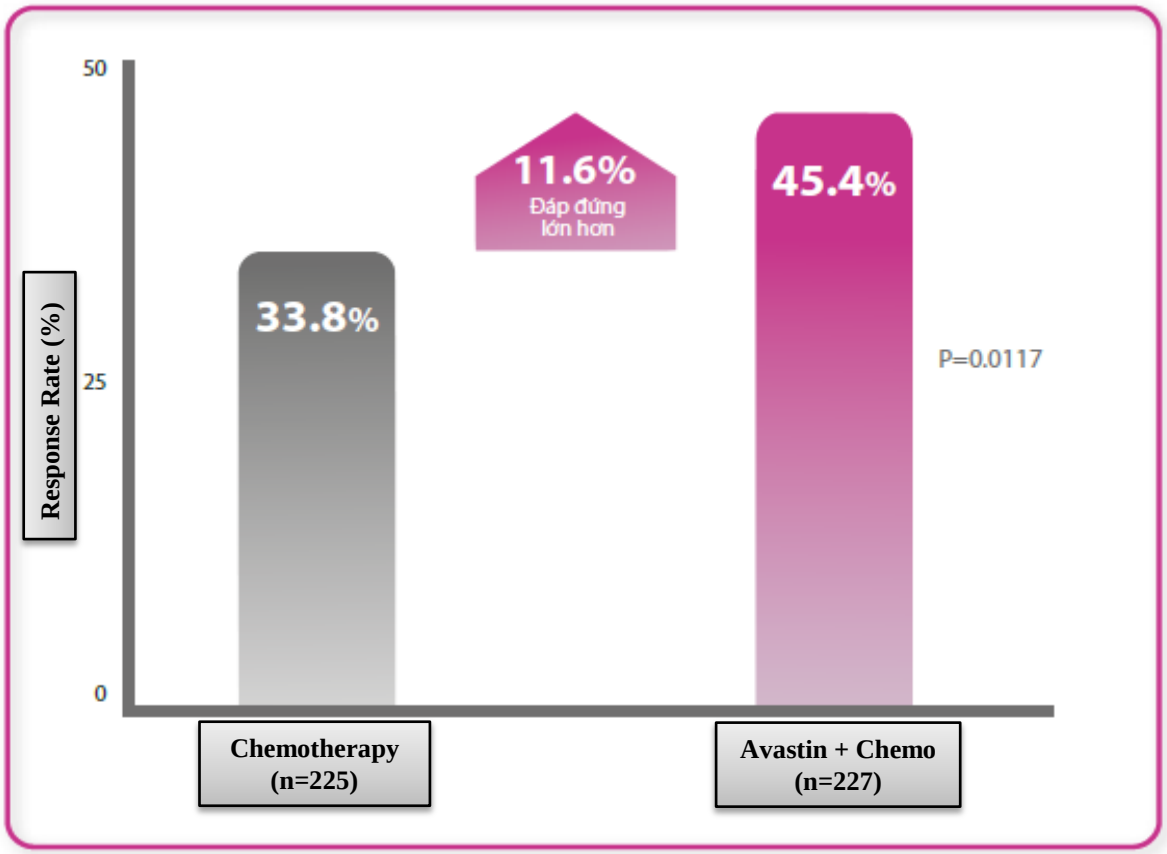
Avastin prolonged Progression Free Survial up to 2.3 months vs Chemotherapy only



1. Tewari KS et al. NEJM 2014

GOG-0240: Study results

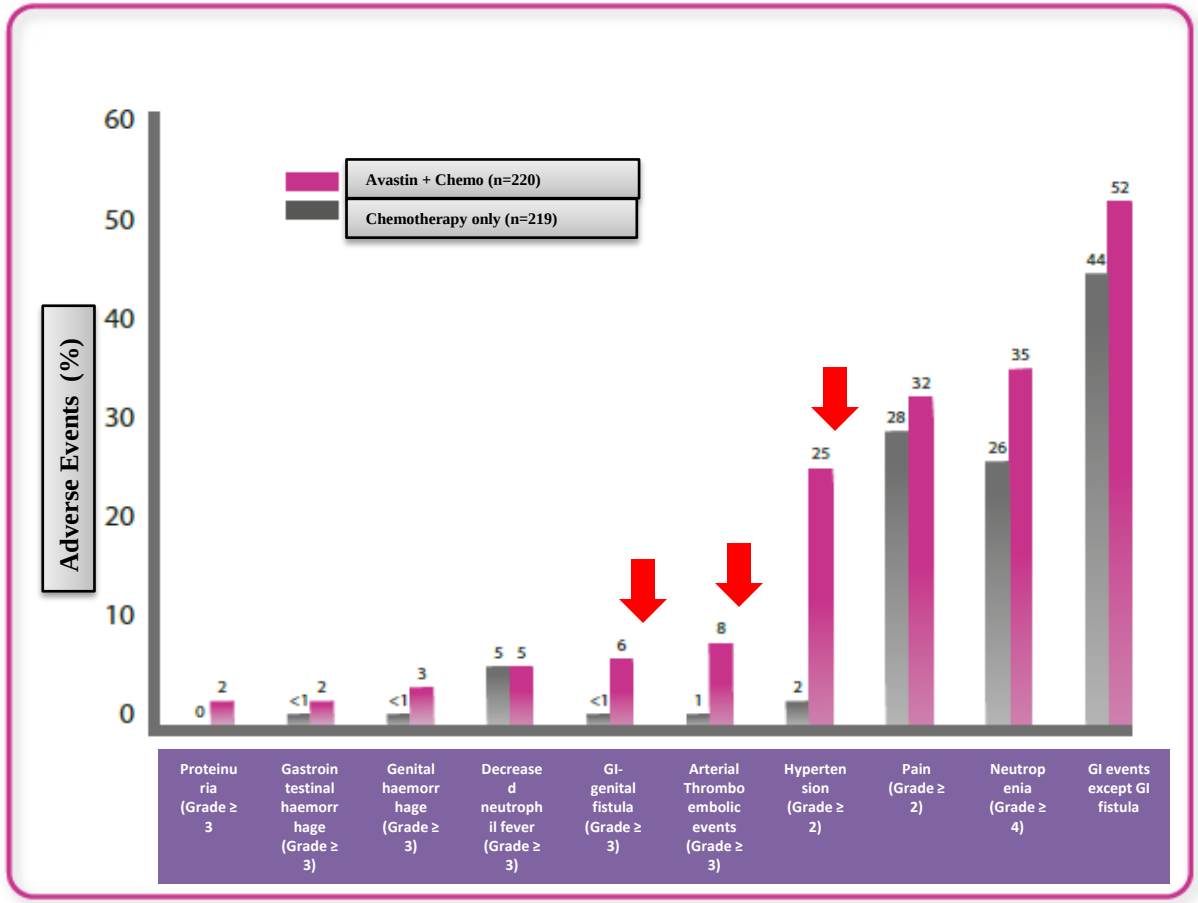
Avastin improved Response Rate in patients with Cervical Cancer



1. PI Avastin.
2. Tewari KS et al. NEJM 2014

GOG-0240: Study results

Demonstrated safety of Avastin.



1. Tewari KS et al. NEJM 2014

GOG-240: dữ liệu về tính an toàn

- Dữ liệu về tính an toàn trong các nhãn quy định được dựa trên những phân tích của Roche theo hướng dẫn của pháp luật và phù hợp với phương pháp luận của các thử nghiệm với Avastin

Dữ liệu chính về tính an toàn

- Ở những bệnh nhân được điều trị ung thư cổ tử cung dai dẳng, tái phát hoặc di căn với Avastin
  - — Việc xạ trị trước đó là một yếu tố nguy cơ gây thủng dạ dày-ruột[1–3]
  - — Việc xạ trị trước đó là một yếu tố nguy cơ chính gây rò dạ dày-ruột-âm đạo[1–3]
  - — Nguy cơ thuyên tắc huyết khối tĩnh mạch (VTE) có thể tăng[1–3]

Tác dụng phụ	Hóa trị (n=219)	Avastin + Hóa trị (n=220)
Thủng đường tiêu hóa	0,0%	3,2%
Rò đường tiêu hóa-âm đạo	0,9%	8,3%
Lỗ rò không thuộc GI	1,4%	1,8%
VTE Cấp độ ≥3	5,4%	10,6%

GI, đường tiêu hóa; VTE, thuyên tắc huyết khối tĩnh mạch

1. EU SmPC; 2. US prescribing information; 3. Swissmedic prescribing information

GOG-240: kết luận

– Avastin phối hợp hóa trị giúp cải thiện đáng kể OS trong ung thư biểu mô cổ tử cung tái phát hoặc dai dẳng, giai đoạn IVB[1]

- Cải thiện OS gần 4 tháng và PFS lên 2.3 tháng.
- Tăng đáng kể ORR.
- Nhánh cisplatin + paclitaxel (điều trị chuẩn hiện hành) không kém hiệu quả hơn, và do đó không thể giải thích cho sự khác biệt về OS.
- Lợi ích nhận thấy ngay cả khi bệnh tái phát nằm ở khung xương chậu được chiếu xạ trước đây.

– Avastin là thuốc được nhắm đích đầu tiên để cải thiện OS trong bệnh ung thư phụ khoa

– Sự cải thiện OS khi điều trị với Avastin không kèm theo sự suy giảm chất lượng cuộc sống liên quan đến sức khỏe[1]

– Rò tiêu hóa-sinh dục đã được xác định là một tác dụng phụ mới cho Avastin trong ung thư cổ tử cung và tỷ lệ huyết khối tĩnh mạch cao hơn so với ghi nhận trước đây trong các thử nghiệm lâm sàng của Avastin[2–4]

ORR, tỷ lệ đáp ứng; OS, thời gian sống còn toàn bộ; PFS, thời gian sống còn không bệnh tiến triển;

1. Tewari KS et al. NEJM 2014; 2. EU SmPC; 3. US prescribing information; 4. Swissmedic prescribing information

Content

FDA và EMA đã chấp thuận Avastin trong điều trị ung thư cổ tử cung

FDA News Release

FDA approves Avastin to treat patients with aggressive and late-stage cervical cancer

For Immediate Release August 14, 2014

Release

Español

The U.S. Food and Drug Administration today approved a new use for Avastin (bevacizumab) to treat patients with persistent, recurrent or late-stage (metastatic) cervical cancer.

Cervical cancer grows in the tissues of the lower part of the uterus known as the cervix. It commonly occurs when human papillomaviruses (HPV), a virus that spreads through sexual contact, cause cells to become cancerous. Although there are two licensed vaccines available to prevent many types of HPV that can cause cervical cancer, the National Cancer Institute estimates that 12,360 American women will be diagnosed with cervical cancer and 4,020 will die from the disease in 2014.

Avastin works by interfering with the blood vessels that fuel the development of cancerous cells. The new indication for cervical cancer is approved for use in combination with chemotherapy drugs paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

Inquiries

Media

Tara Goodin
240-402-3157

Consumers

888-INFO-FDA

Related Information

- Office of Hematology and Oncology Products (OHOP)
- Approved Drugs: Questions and Answers
- NCI: Cervical Cancer

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EMA/175824/2015
EMEA/H/C/000582

EPAR summary for the public

Avastin
bevacizumab

This is a summary of the European public assessment report (EPAR) for Avastin. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Avastin.

What is Avastin?

Avastin is a cancer medicine that contains the active substance bevacizumab. It is available as a concentrate that is made up into a solution for infusion (drip) into a vein.

What is Avastin used for?

Avastin is used to treat adults with the following types of cancer in combination with other cancer medicines:

- cancer of the colon or rectum (large intestine) that is metastatic (has spread to other parts of the body), in combination with chemotherapy medicines that include a 'fluoropyrimidine';
- metastatic breast cancer, in combination with paclitaxel or capecitabine;
- non-small cell lung cancer that is advanced (has started to spread), metastatic or recurrent (has come back after initial treatment) and cannot be removed by surgery. Avastin is given in combination with chemotherapy medicines that includes a 'platinum-based' medicine;
- advanced or metastatic kidney cancer, in combination with interferon alfa-2a;
- epithelial cancer of the ovary, cancer of the fallopian tube (part of the female reproductive system that connect the ovaries to the uterus) or the peritoneum (the membrane lining the abdomen). Avastin is used when the cancer is advanced or recurrent, in combination with certain chemotherapy medicines;
- cancer of the cervix (the neck of the womb) that is persistent, recurrent or metastatic. Avastin is given in combination with paclitaxel and either the platinum-based medicine cisplatin or, if this cannot be used, another chemotherapy medicine, topotecan.

See the summary of product characteristics (also part of the EPAR) for more information.

The medicine can only be obtained with a prescription.

How is Avastin used?

Avastin treatment should be supervised by a doctor who has experience in the use of cancer treatments.

The first infusion of Avastin should last 90 minutes, but subsequent infusions may be given over a shorter period if the first infusion is tolerated well. The dose is between 5 and 15 mg per kilogram body weight every two or three weeks, depending on the type of cancer being treated. The treatment is continued until the patient no longer benefits from it. The doctor may decide to interrupt or stop treatment if the patient develops certain side effects.

How does Avastin work?

The active substance in Avastin, bevacizumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and attach to a specific structure (called an antigen) in the body. Bevacizumab has been designed to attach to vascular endothelial growth factor (VEGF), a protein that circulates in the blood and makes blood vessels grow. By attaching to VEGF, Avastin stops it having an effect. As a result, the cancer cells cannot develop their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumours.

How has Avastin been studied?

In metastatic cancer of the colon or rectum, the effects of adding Avastin to chemotherapy including a fluoropyrimidine have been studied in three main studies. The first two studies involved patients whose metastatic disease was being treated for the first time ('first-line' treatment): the first study (in 923 patients) and the second study (in 1,401 patients) compared Avastin with placebo (a dummy treatment) when given in combination with chemotherapy. The third study involved 829 patients who had failed previous treatment including a fluoropyrimidine and irinotecan (other chemotherapy medicines).

In metastatic breast cancer, Avastin has been studied in two main studies. The first study compared the effects of Avastin with paclitaxel to paclitaxel alone in 722 patients. The second study compared the effects of adding either Avastin or placebo to various chemotherapy treatments, including capecitabine, in 1,237 patients.

In advanced, metastatic or recurrent lung cancer, Avastin has been studied in 878 patients. The study compared the effects of Avastin with platinum-based chemotherapy to chemotherapy alone.

In advanced or metastatic kidney cancer, Avastin has been studied in 649 patients with advanced or metastatic disease. The study compared Avastin with placebo when given in combination with interferon alfa-2a.

In ovarian, fallopian tube and peritoneal cancer, two main studies were performed involving 3,401 patients with newly diagnosed cancer including advanced cancer. In these studies, Avastin, in combination with carboplatin and paclitaxel, was compared with carboplatin and paclitaxel alone.

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Summary of clinical treatment steps for cervical cancer

<table>
<tr><th>Stages</th><th colspan="2">NCCN v2.2015[1]</th><th colspan="2">ESMO 2012[2]</th></tr>
<tr><th></th><th>First treatment</th><th>Recurrence</th><th>First treatment</th><th>Recurrence</th></tr>
<tr><td>IA1</td><td>Surgery</td><td rowspan="3">Surgery or
RT ± chemo or
Cisplatin, carboplatin or paclitaxel singular</td><td>surgery</td><td rowspan="3">First time patient with Platin cisplatin/paclitaxel</td></tr>
<tr><td>IA2</td><td>Surgery or RT</td><td>surgery</td></tr>
<tr><td>IB1, IIA1</td><td>Surgery or
RT ± cisplatin</td><td>surgery± support or
RT+ cisplatin</td></tr>
<tr><td>IB2–IVa</td><td>RT + cisplatin</td><td></td><td>RT + cisplatin</td><td></td></tr>
<tr><td>IVb</td><td>Chemo± Avastin</td><td>Surgery or
RT ± chemo or
Or Chemo± Avastin
Or best service</td><td>(Cisplatin or carboplatin) + paclitaxel
or
cisplatin + topotecan</td><td>Reduced chemo with cisplatin</td></tr>
</table>

ESMO, Hội ung thư châu Âu; NCCN, Mạng lưới Ung thư Toàn quốc; RT, xạ trị

1. Điều chỉnh theo hướng dẫn của NCCN 2015; 2. Điều chỉnh theo Colombo N et al. Ann Oncol 2012.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER†
(Strongly consider clinical trial)

First-line combination therapy††
- Cisplatin/paclitaxel/bevacizumab[1] (category 1)
- Cisplatin/paclitaxel (category 1)[2,3]
- Topotecan/paclitaxel/bevacizumab[1] (category 1)
- Carboplatin/paclitaxel[4,5] (Category 1 for patients who have received prior cisplatin therapy)
- Carboplatin/paclitaxel/bevacizumab
- Cisplatin/topotecan[6]
- Topotecan/paclitaxel
- Cisplatin/gemcitabine (category 3)[7]

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)[3]
- Carboplatin[8]
- Paclitaxel[9]

Second-line therapy†††
(Agents listed are category 2B unless otherwise noted)
- Bevacizumab
- Albumin-bound paclitaxel
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Pemetrexed
- Topotecan
- Vinorelbine

†Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C]).
††Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
†††References for second-line therapy are provided in the Discussion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

short courses of RT may provide symptomatic relief to patients with bone metastases, painful para-aortic nodes, or supraclavicular adenopathy.[172,216,217]

Chemotherapy is often recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients whose disease responds to chemotherapy may have relief from pain and other symptoms. If cisplatin was previously used as a radiosensitizer, combination platinum-based regimens are preferred over single agents in the metastatic disease setting based on several randomized phase III trials (see next paragraph).[218,219] However, responses to chemotherapy are often of short duration and survival is rarely increased.

First-Line Combination Chemotherapy

Cisplatin has been considered the most effective agent for metastatic cervical cancer.[220] However, most patients who develop metastatic disease have received concurrent cisplatin/RT as primary treatment and may no longer be sensitive to single-agent platinum therapy.[218,219] Cisplatin-based combination chemotherapy regimens, such as cisplatin/paclitaxel/bevacizumab (category 1), cisplatin/paclitaxel (category 1), and cisplatin/topotecan (category 2A), have been extensively investigated in clinical studies.[218,219,221-224] A randomized phase III study (GOG 169) in 264 patients compared cisplatin/paclitaxel versus cisplatin alone for metastatic, recurrent, or persistent cervical cancer. Patients receiving the 2-drug combination had a higher response rate (36% vs. 19%) and improved PFS (4.8 months vs. 2.8 months; $P > .001$) compared to single-agent cisplatin, although no improvement was seen in median survival.[218] Patients who responded to cisplatin/paclitaxel had a significant improvement in quality of life.

Another randomized phase III study (GOG 179) in 294 patients investigated cisplatin/topotecan versus cisplatin alone for recurrent or persistent cervical cancer. The topotecan combination regimen was shown to be superior to single-agent cisplatin with respect to overall response rate (27% vs. 13%, $P = .004$), PFS (4.6 months vs. 2.9 months; $P = .014$), and median survival (9.4 months vs. 6.5 months; $P = .017$).[219] The FDA (Food and Drug Administration) has approved cisplatin/topotecan for advanced cervical cancer. However, the cisplatin/paclitaxel or carboplatin/paclitaxel regimens are less toxic and easier to administer than cisplatin/topotecan.[225]

A phase III trial (GOG 204) compared 4 cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine) in 513 patients with advanced metastatic or recurrent cancer.[223] The trial was closed early based on futility analysis, because it was apparent that the cisplatin/topotecan, cisplatin/gemcitabine (category 3), and cisplatin/vinorelbine regimens were not superior to the control arm of cisplatin/paclitaxel. No significant differences in overall survival were seen; however, the trends for response rate, PFS, and overall survival (12.9 months vs. 10 months) suggest that cisplatin/paclitaxel is superior to the other regimens. Cisplatin/paclitaxel was associated with less thrombocytopenia and anemia (but with more nausea, vomiting, infection, and alopecia) than the other regimens.

A recent randomized phase III trial (GOG 240) studied the addition of bevacizumab to combination chemotherapy regimens (cisplatin/paclitaxel/bevacizumab or topotecan/paclitaxel/bevacizumab) in 452 patients in the first-line setting of metastatic, persistent, or recurrent cervical cancer. An analysis of pooled data from the two chemotherapy regimens revealed significant improvements in overall survival among patients receiving bevacizumab (17.0 months vs. 13.3

months; *P* = .004). While topotecan/paclitaxel (category 2A) was not shown to be superior to cisplatin/paclitaxel, it may be considered as an alternative in patients who are not candidates for cisplatin.[224] While bevacizumab led to higher toxicity (eg, hypertension, thromboembolic events, and gastrointestinal fistula), it was not associated with a statistically significant decrease in patient-reported quality of life (*P* = .27).[226] Based on these data, the FDA approved bevacizumab as part of combination therapy with paclitaxel and either cisplatin or topotecan for treating persistent, recurrent, or metastatic cervical cancer.[227] The panel has accepted both bevacizumab-containing regimens as category 1 options for treatment of persistent, recurrent, or metastatic cervical cancer.

Recently published data from a phase III randomized trial (JCOG0505) suggested that carboplatin/paclitaxel is non-inferior to cisplatin/paclitaxel in 253 women with metastatic or recurrent cervical cancer.[228] Many physicians use carboplatin/paclitaxel because of ease of administration and tolerability.[229] Results from JCOG0505 showed that the carboplatin/paclitaxel (TC) regimen was non-inferior to cisplatin/paclitaxel (TP) in terms of median overall survival (18.3 months for TP vs. 17.5 months for TC; HR=0.994 (90% CI, 0.79 to 1.25); *P* = .032) and non-hospitalization periods were significantly longer for patients receiving TC.[228] However, among patients who had not received prior cisplatin, OS for TC and TP was 13.0 and 23.2 months, respectively (HR=1.571; 95% CI, 1.06 to 2.32).[228] Based on these data, the panel recommends carboplatin/paclitaxel as a category 1 option for patients who have received prior cisplatin therapy. Carboplatin/paclitaxel is a category 2A recommendation for other indications (ie, for patients who have not received prior platinum-based therapy).

A recent systematic review of the data on cisplatin/paclitaxel and carboplatin/paclitaxel regimens also suggested that lower toxicity carboplatin-based regimens appear to be an equally effective alternative to cisplatin-based regimens for treating recurrent or metastatic cervical cancer.[230] Based on the collective findings from GOG 240 and JGOG0505, the panel has opted to include carboplatin/paclitaxel/bevacizumab as an additional treatment option for recurrent or metastatic cervical cancer (category 2A).Based on the previous studies, cisplatin/paclitaxel and carboplatin/paclitaxel have become the most widely used systemic regimens for metastatic or recurrent cervical cancer. However, for patients who may not be candidates for taxanes, cisplatin/topotecan and cisplatin/gemcitabine remain reasonable alternative regimens.[168,219] Nonplatinum regimens are also being studied and may be considered in patients who cannot tolerate platinum-based chemotherapy.[231]

Single Agents

Cisplatin is generally regarded as the most active agent and is recommended as a first-line single-agent chemotherapy option for recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[218,220,232,233] Overall survival with cisplatin is approximately 6 to 9 months. Both carboplatin and paclitaxel have each been reported to be tolerable and efficacious and are also possible first-line single-agent chemotherapy.[234-237] Therefore, palliation with single agents—cisplatin, carboplatin, or paclitaxel—is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches.

Other agents (that are category 2B unless otherwise indicated) that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[238] docetaxel,[239] 5-FU,[240]

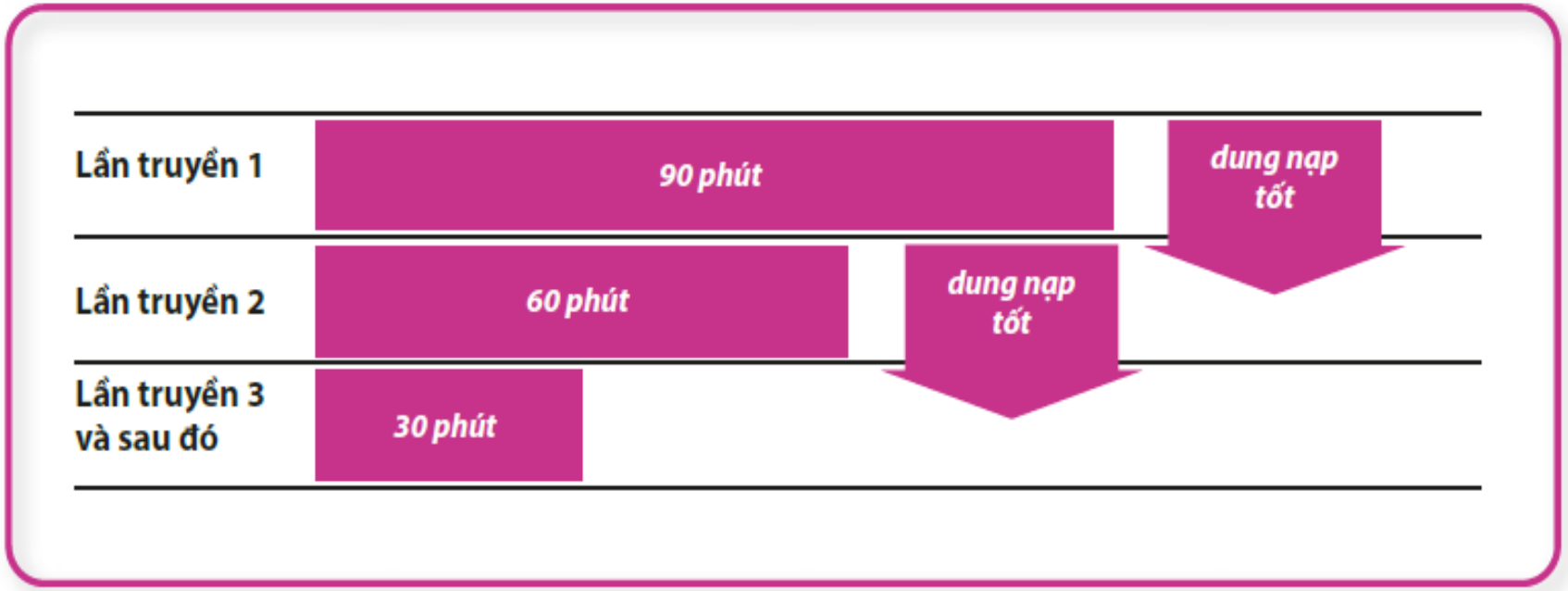
Content

dosage

- **Avastin is used with one or several of the these medicine in regimen chemo: paclitaxel and cisplatin or paclitaxel and topotecan.**
- **Recommended dosage of Avastin is 15 mg/kg once per 3 week through intravenous**
- **Recommend the usage of Avastin until the advancement of cancer or until the medicine does not work anymore**

1. Tài liệu thông tin kê toa Avastin.

Duration of intravenous



1. Tài liệu thông tin kê toa Avastin.

Thank you for your attention