St Paul de Vence 2012

Ovarian cancer

Targeted therapies

J. Alexandre, F. Joly, C. Lhommé, F. Selle, E. Pujade – Lauraine, H. Curé

Bevacizumab as initial treatment: which patients?

Expert opinion

- A- Situations in which bevacizumab **is not recommended** (absence of prospective data).
  - **FIGO stages I to IIIA** inclusive (no marketing authorisation in this indication)**.**
  - **In combination with neoadjuvant chemotherapy** before cytoreductive surgery**.**
  - In combination with intra-peritoneal chemotherapy.

Bevacizumab as initial treatment: which patients?

Grade A

B- Situations in which bevacizumab is recommended.

- **Macroscopic residual disease** after initial cytoreductive surgery for FIGO stages IIIB to IV**.**
- **Stage IIIC-IV disease in which complete cytoreduction is definitively not possible.**
  - The absolutely non-resectable nature of the lesions must be assessed in the MSM with an experienced surgical team.

Bevacizumab as initial treatment: which patients?

- C- Situations in which the indication for bevacizumab must be **assessed in the MSM and discussed with the patient according to the risk/benefit ratio***

Grade B

- **Stages IIIB or IIIC with macroscopically complete cytoreduction** during initial surgery**.**

- **After interval debulking surgery** following 3 or 4 courses of neoadjuvant chemotherapy**.**

Expert opinion

*in particular, taking into account any nephro-cardiovascular history and gastrointestinal anastomosis during initial surgery or any risk of fistulas.

Bevacizumab as initial treatment

Grade A

- **When to start bevacizumab?**
  - Bevacizumab should be introduced during the 1st cycle of postoperative chemotherapy if started not less than 28 days after surgery.
  - If not, or if the patient has a gastrointestinal anastomosis or unresolved post-operative complications, bevacizumab should be started at the 2nd cycle.

Bevacizumab as initial treatment

- **With what kind of chemotherapy?**
  - Grade A — Carboplatin-paclitaxel IV every 3 weeks.
  - Grade C — Option: Weekly regimen of paclitaxel combined with carboplatin (every 3 weeks)
- **For how long?**
  - Grade A — Total duration of beva: 15 months, total of 22 courses.
- **What dose?**
  - Grade A — The dosage of marketing authorization is 15 mg/kg every 3 weeks.
  - Grade A — Option: 7.5 mg/kg every 3 weeks.

Bevacizumab as initial treatment

Expert opinion

- **Blood pressure monitoring**
  - Before treatment
  - Once a week for the first month
  - During the week preceding treatment thereafter
  - By the GP: normal < 140/90
  - Or self-measurement (3 consecutive measurements in a seating position, for 3 days, during a period of normal activity): normal < 135/85

Halimi JM, Azizi M, Bobrie G, Bouche O, Deray G, Des Guetz G, et al. Effets vasculaires et rénaux des médicaments anti-angiogéniques : recommandations françaises pour la pratique. Sang Thromb Vaiss 2009;21:151-66

Bevacizumab as initial treatment

Expert opinion

What to do if the patient presents with proteinuria?

- Dip stick test for urinary protein before each injection.
- If dip stick ≥ ++ : urinary protein checked in a 24 hour urine collection before the next cycle.

Protéinuria	Approach to be taken
If urinary protein is **< 1** g/24h	• **Antiangiogenic treatment to be pursued.** • **Dipstick test on monthly basis or before each course.**
If urinary protein is between **1 and 3** g/24 h	• **Treatment pursued and nephrological advice sought rapidly.** • **Monthly quantitative measurement of urinary protein.** • **Start treatment with ACE or AA2 for anti-proteinuria purposes.** • **Optimisation of anti-hypertensive treatment for target BP < 130/80.**
If urinary protein is **>3** g/24 h	• **The antiangiogenic treatment may be pursued if the patient does not have hypertension or renal failure, but this treatment must be discussed with the nephrologist.** • **If the urinary protein levels remain stable and without severe nephrotic syndrome, the antiangiogenic treatment may be pursued if the patient is a responder.**

Halimi JM, et al. Sang Thromb Vaiss 2009;21:151-66

Bevacizumab treatment of relapse

Grade B

- **Indications for recurrence?**
  - No MA has been granted for this indication.
  - The indication for bevacizumab must be assessed in the MSM and discussed with the patient.
  - Bevacizumab must not be administered to patients with partial ileus or lesions involving hollow organs.
  - The risks related to bevacizumab increase with the number of previous lines of chemotherapy.

Bevacizumab treatment of relapce

Grade B

- ***What protocols?***
  - **Platinum-sensitive recurrence** (free interval ≥ 6 ms)
    - Bevacizumab in combination with a platinum-based chemotherapy (especially carbo-gemcitabine).
  - **Platinum-resistant recurrence** (free interval < 6 ms)
    - Bevacizumab administered alone.
    - In combination with single-agent chemotherapy (especially weekly paclitaxel and oral cyclophosphamide).

Other targeted therapies

- **No recommendations in the absence of data**
  - Other antiangiogenic agents
  - Trastuzumab (Herceptin™)
  - EGF-R inhibitors

Expert opinion

- **Hormone therapy**
  - Marginal effect. May be used for recurrence.

Grade C

No proof to support selection of patients based on well differentiated grade or presence of hormonal receptors

- **Catumaxomab (Removab™)**

Grade B

  - Has MA for intraperitoneal treatment in the event of refractory ascites.

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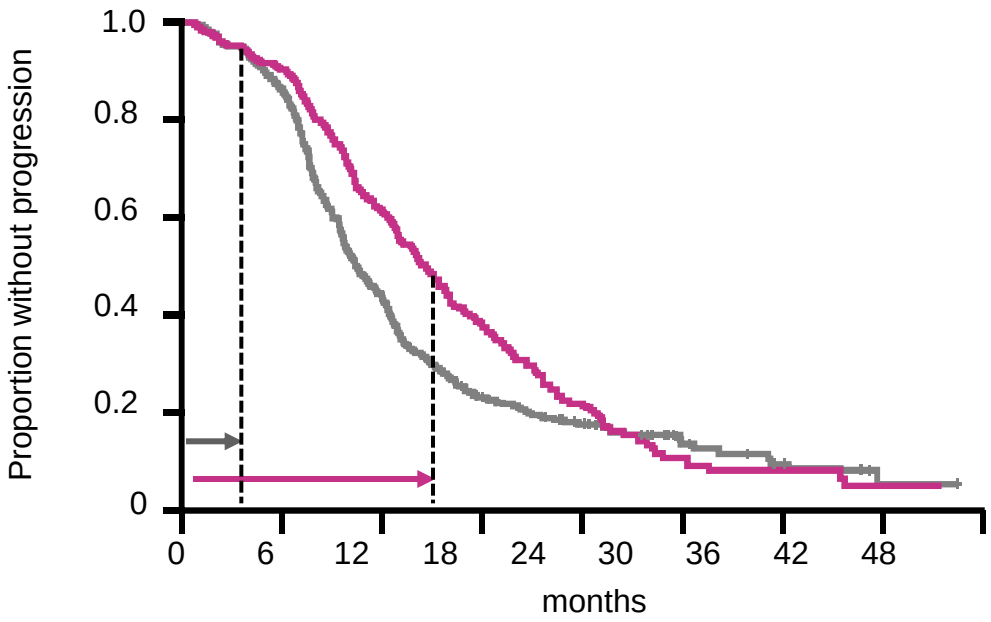
Ovarian cancer

Additional slides

GOG-218
Progression Free Survival

	CP + placebo → placebo (n=625)	CP + Beva 15 → Beva 15 (n=623)
Median PFS (months)	10.6	**14.7**
HR (95% CI)	0.70 (0.61–0.81)	
p	<0.0001	

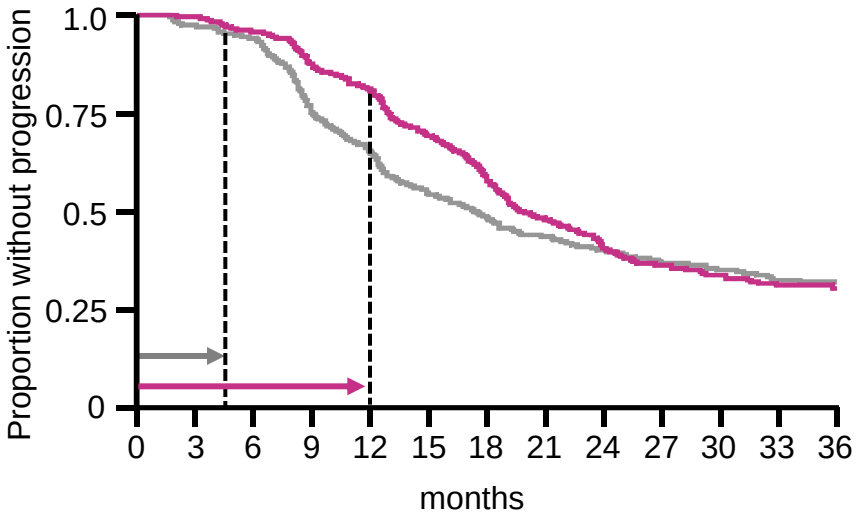


Burger RA et al. N Engl J Med 2011; 365:2473-83

ICON7
Progression Free Survival

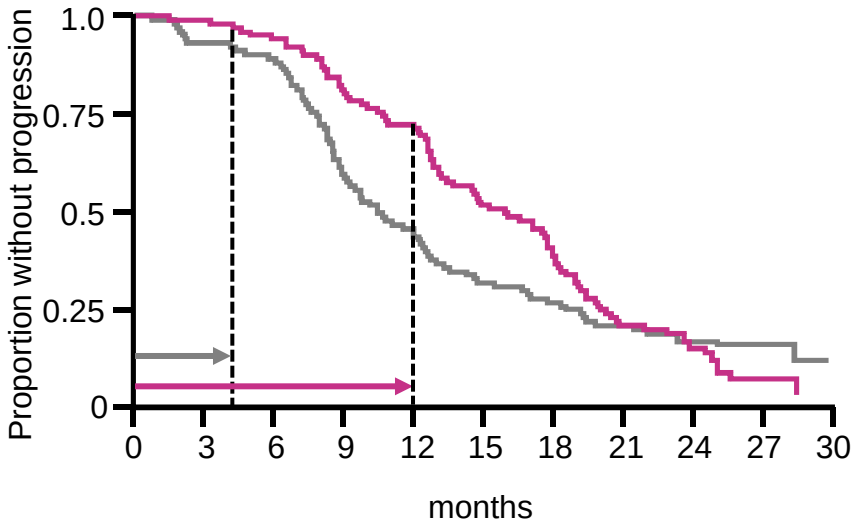
Total population

	CP (n=764)	CP + BEVA 7.5 BEVA 7.5 (n=761)
Median PFS (months)	17.4	19.8
HR (95% CI)	0.87 (0.77–0.99)	
p	0.04	



FIGO III (residual disease > 1cm) & FIGO IV

	CP (n=234)	CP + BEVA 7.5 BEVA 7.5 (n=231)
Median PFS (months)	10.5	15.9
HR (95% CI)	0.68 (0.55–0.85)	
p	<0.001	

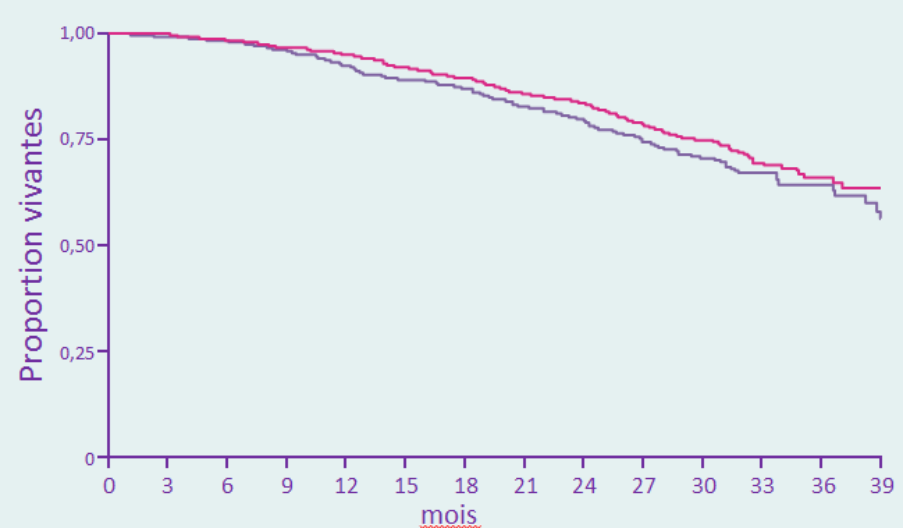


Perren TJ et al. N Engl J Med 2011; 365:2484-249

ICON7
Overall Survival

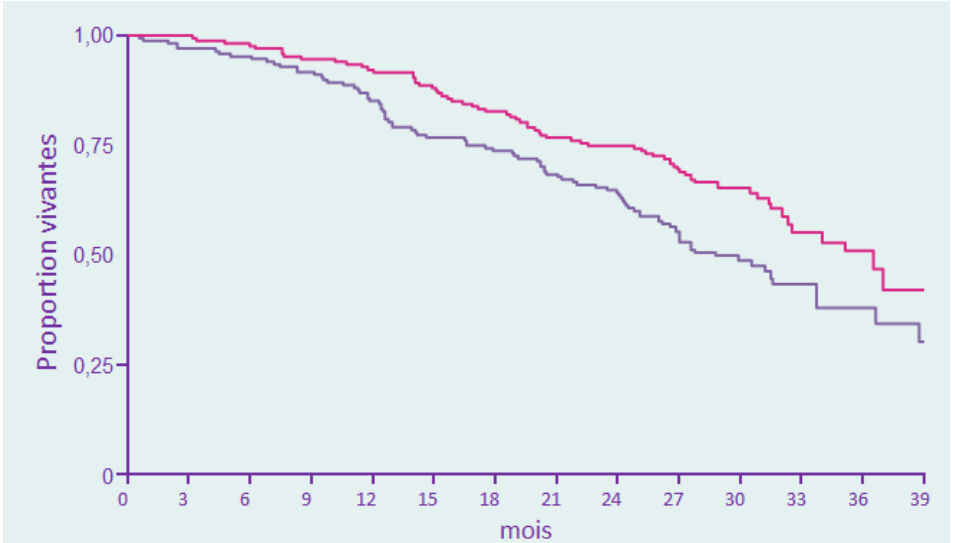
Total population

	CP (n=764)	CP + BEVA 7.5 BEVA 7.5 (n=761)
Median OS (months)	Not reached	
HR (95% CI)	0,85 (0,70–1,04)	
p	0,1167	



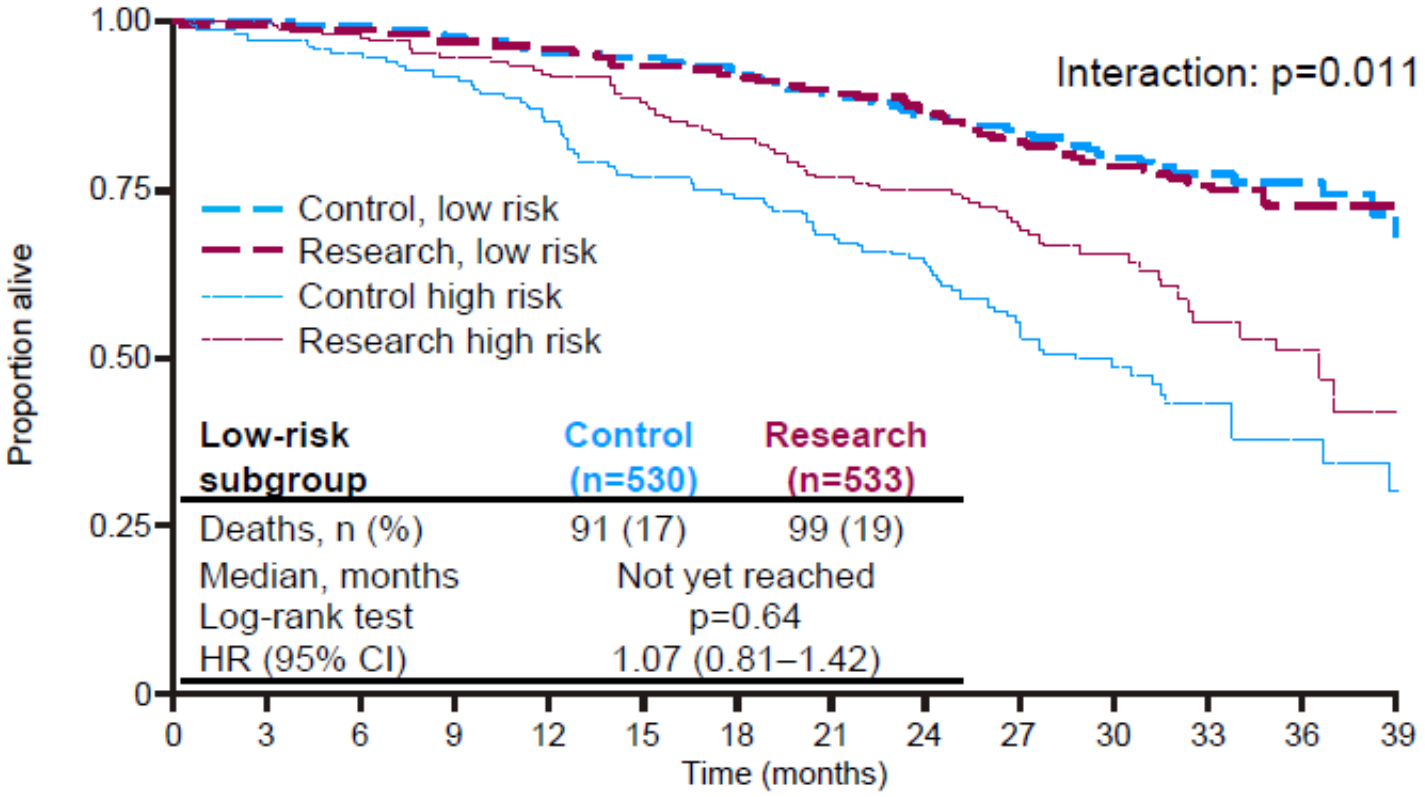
FIGO III (residual disease> 1cm) & FIGO IV

	CP (n=764)	CP + BEVA 7.5 BEVA 7.5 (n=761)
Median OS (months)	28,8	36,6
HR (95% CI)	0,64 (0,48–0,85)	
p	0,002	



Perren TJ et al. N Engl J Med 2011; 365:2484-249

ICON7
Survie globale



There is no clinical (e.g. age), biological or histological criteria allowing to identify a population of patients who would differently benefit from bevacizumab.

Bevacizumab as initial treatment

Expert opinion

Managing Hypertension

- Initiating antiangiogenic treatment for patients with uncontrolled HT is not recommended.
- De novo HT: ACE inhibitors or angiotensin 2 antagonists.
- Destabilisation of known HT: low dose calcium channel blockers from the dihydropyridine family.