# Pelvic Malignancies in Older Patients: New drugs in the elderly?

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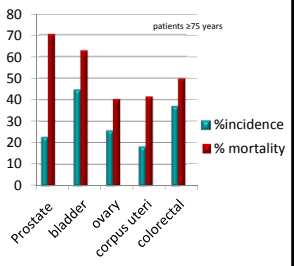
## Disclosures

- Travel grants from: Pfizer, Roche, Sanofi, Jansen Cilag, Novartis
- Lecture fees: Sanofi, Jansen Cilag

## Epidemiology

- Pelvic tumours are frequent in the elderly

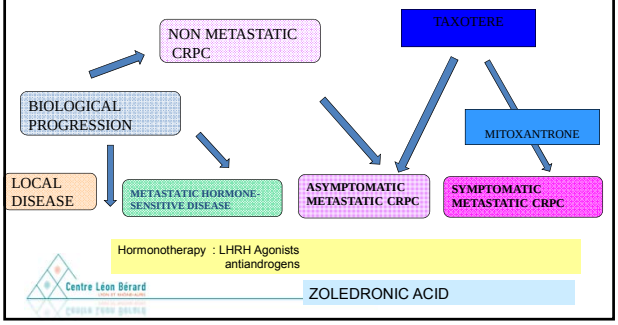
| | Median age at diagnosis | Median age at death |
|---|---|---|
| Prostate cancer | 67 years | 80 years |
| Bladder cancer | 73 years | 79 years |
| Colorectal cancer | 69 years | 74 years |
| Ovarian cancer | 63 years | 71 years |
| Endometrial cancer | 61 years | 71 years |



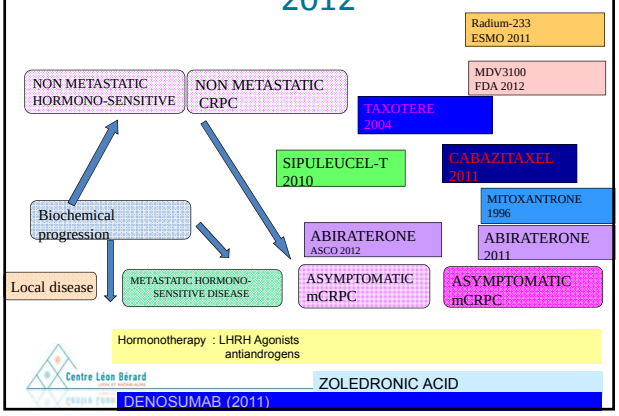

SEER database 2005-2009

## NEW DRUGS IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

## Until 2010

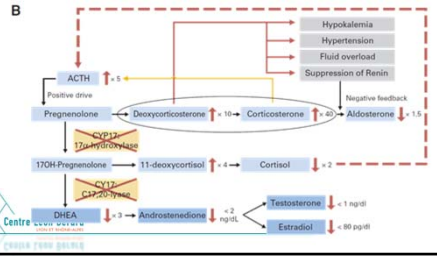



## 2012

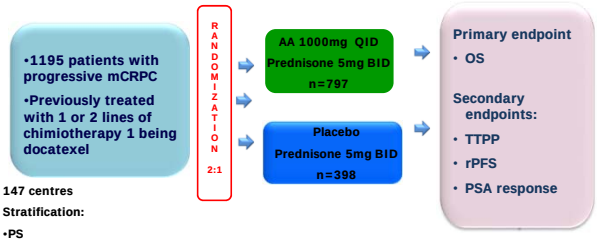


## mCRPC: new hormonal therapies: abiraterone acetate

- CYP 17, 21 lyase inhibitor
  - ↘ Adrenal, testicular and intratumoral testosterone synthesis




## Abiraterone acetate: COUGAR AA-301 trial




147 centres

Stratification:

- PS
- pain
- Number of previous chemotherapy
- Progression type

de Bono JS et al N Engl J Med. 2011 May 26;364(21):1995-2005

## COUGAR AA-301

- Key inclusion criteria:
  - mCRPC
  - Progression after docetaxel
  - PS=0-2
  - Albumin>30g/L
- Key exclusion criteria:
  - Abnormal LFT
  - Créatinine < 1.5 xULN or calculated creatinine clearance ≥ 60 ml/mn
  - chronic liver disease
  - Uncontrolled hypertension
  - Clinically significant heart disease
  - Use of aldactone, spironolactone and drugs metabolized by the CYP2D6 and 1A2

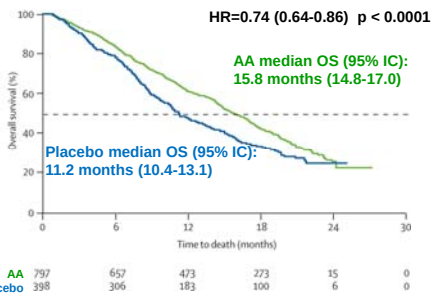
de Bono JS et al N Engl J Med. 2011 May 26;364(21):1995-2005

## COUGAR AA-301

| | Abiraterone +Prednisone (n=797) | Placebo + Prednisone (n=398) |
|---|---|---|
| Median age | 69 (42-95) | 69 (39-90) |
| ≥75 years | 28% | 28% |
| PS:<br>0-1<br>2 | <br>90%<br>10% | <br>89%<br>11% |
| Nb previous chemotherapy<br>1<br>2 | <br>70%<br>30% | <br>69%<br>31% |

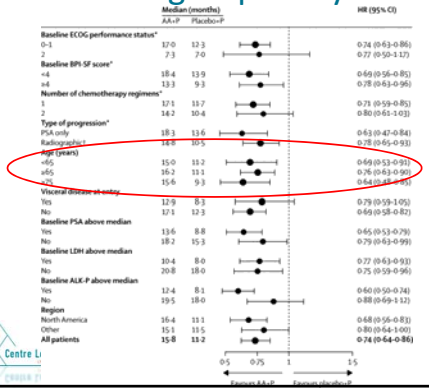
de Bono JS et al N Engl J Med. 2011 May 26;364(21):1995-2005

## Results: overall survival




Fizazi K et al Lancet Oncol. 2012 Oct;13(10):983-992

## Subgroup analysis



## Results(2)

| | ABIRATERONE | PLACEBO | p |
|---|---|---|---|
| **Response rates** | | | |
| **•PSA≥50%** | 29.5% | 5.5% | <0.0001 |
| **•radiological** | 14.8% | 3.3% | <0.0001 |
| **bTTP (months)** | 8.5 (8.3-11.1) | 6.6 (5.6-8.3) | <0.0001 |
| **rPFS (months)** | 5.6 (5.6-6.5) | 3.6 (2.5-5.5) | <0.0001 |

## Toxicity

| | Abiraterone + Prednisone (n=791) | | Placebo + Prednisone (n=394) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3/4 (%) | All grades (%) | Grade 3/4 (%) |
| Oedema | 33 | 2,5 | 24 | 1,0 |
| Hypokalemia | 18 | 4.4 | 9 | 0,8 |
| Abnormal LFTs | 11 | 3,5 | 9 | 3,5 |
| Hypertension | 11 | 1 | 8 | 0,3 |
| Cardiac disorders | 16 | 5 | 12 | 2,3 |

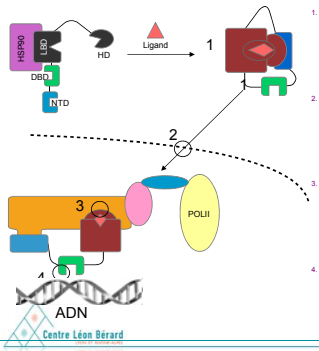
Fizazi K et al Lancet Oncol. 2012 Oct;13(10):983-992

## Conclusions

- Approved in post-docetaxel
- Benefit in every age group
- More than a ¼ of the patients were over 75
- Selected patients
- Preliminary data from a retrospective monocentric experience suggest that patients with cardiac disorders can receive abiraterone (n=34/46)
  - but this needs to be evaluated in larger populations
  - Close monitoring
- Approval in Pre-chemotherapy space?

Procopio et al, ESMO, 2012, P926

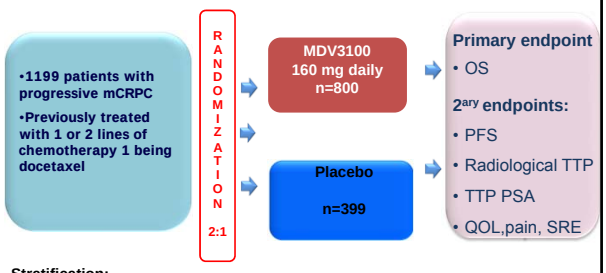
## MDV 3100: enzalutamide




1. Affinity
   - DHT ~5nM
   - Bicalutamide ~160 nM
   - MDV3100 ~35 Nm
2. Nuclear translocation
   - DHT ++++
   - Bicalutamide ++++
   - MDV3100 ++
3. DNA binding
   - DHT ++++
   - Bicalutamide ++
   - MDV3100 -
4. Coactivators recruitment
   - DHT ++++
   - Bicalutamide ++
   - MDV3100 -

*ASCO 2009 adapted from SCHER., abstract 5011 actualisé*

## MDV3100: AFFIRM trial




**Stratification:**
**•PS**
**•pain**

Scher HI et al N Engl J Med. 2012 Sep 27;367(13):1187-97

## AFFIRM trial

- Key inclusion criteria:
  - mCRPC
  - Progression after docetaxel
  - PS=0-2
  - Albumin>30g/L
- Key exclusion criteria:
  - **Severe** concurrent disease, infection, or **co-morbidity**
  - Abnormal LFT
  - Serum Creatinine >177µmol/L
  - Clinically **significant cardiac disease**
    - Uncontrolled hypertension
    - Angina, myocardial infaction
    - Pulmonary embolism
  - History **of Seizures** or any condition that could favour seizures
  - Transient cerebral attack in the past 12 months
  - medications **known to lower the seizure threshold or prolong the QT interval** insulin, Class IA and III antiarrhythmics, Venlafaxine…
  - Gastrointestinal disorder affecting absorption

Scher HI et al N Engl J Med. 2012 Sep 27;367(13):1187-97

## AFFIRM trial

| | MDV 3100 (n= 800) | Placebo (n=399) |
|---|---|---|
| **Median age** | **69 (41-92)** | **69 (49-89)** |
| **≥75 years** | **24,9%** | **26,1%** |
| **PS:** | | |
| 0-1 | **91,3%** | **92%** |
| 2 | **8,8%** | **8%** |
| **Nb previous chemotherapy** | | |
| 1 | **72,4%** | **74,2%** |
| ≥2 | **27,6%** | **25,8%** |

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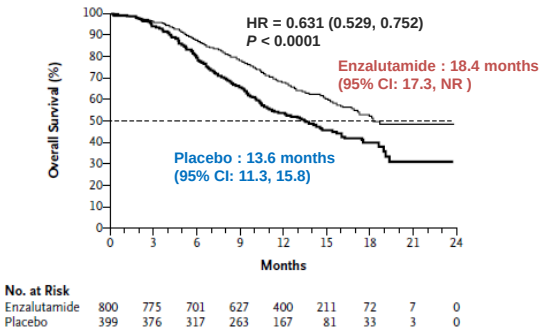
Scher HI et al N Engl J Med. 2012 Sep 27;367(13):1187-97

## AFFIRM trial: Overall survival

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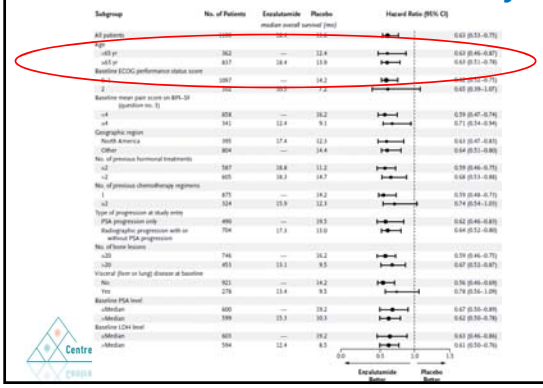
Scher HI et al N Engl J Med. 2012 Sep 27;367(13):1187-97

## AFFIRM trial:subgroup analysis



Centre

## AFFIRM trial: Results (2)

| | MDV 3100 | Placebo | |
|---|---|---|---|
| **Response rates** | | | |
| **•PSA≥50%** | **54%*** | **1,5%** | **p<0,001** |
| **•radiological** | **28,9%*** | **3,8%** | **p<0,001** |
| **bTTP (months)** | **8,3*** | **3** | **p<0,001** |
| **rPFS (months)** | **8,3*** | **2,9** | **p<0,001** |
| **Median OS (months)** | **18.4*** (17.3-NA) | **13.6** (11,3-15,8) | **p<0,001** |

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Scher HI et al N Engl J Med. 2012 Aug 15

## AFFIRM trial: toxicity

| | MDV3100 (n=800) | | Placebo (n=399) | |
|---|---|---|---|---|
| | All grades (%) | Grades 3/4 (%) | All grades (%) | Grades 3/4 (%) |
| Fatigue | 33,6 | 6,3 | 29 | 7,3 |
| Diarrhoea | 21,4 | 1,1 | 12,5 | 0,3 |
| Hepatic disorders | 1 | 0,4 | 1,5 | 0,8 |
| Cardiac disorders | 6,1 | 0,9 | 7,5 | 2 |
| Convulsion | 0,6 | 0,6 | 0 | 0 |

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Scher HI et al N Engl J Med. 2012 Sep 27;367(13):1187-97

## Conclusions

- A quarter of the patients were over 75
- Benefit in every age group
- Selected patients
- Acceptable toxicity

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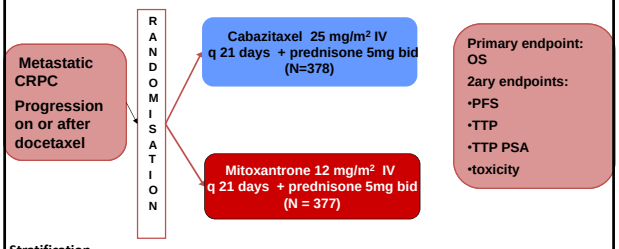
## Cabazitaxel: TROPIC trial




**Stratification**
**ECOG PS (0, 1 vs. 2)**
**mesurable disease *vs.* non mesurable**

de Bono JS et al Lancet. 2010 Oct 2;376(9747):1147-54

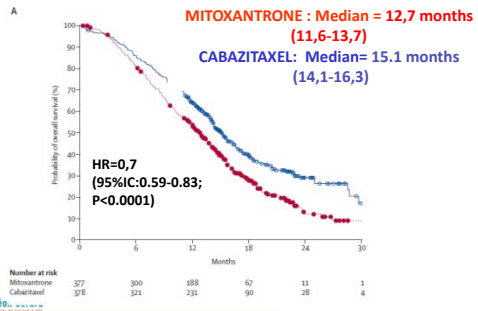
## Cabazitaxel: TROPIC trial

- Key inclusion criteria:
  - Adequate hematological, hepatic; renal and cardiac function (LVEF>50%)
- Key exclusion criteria:
  - Concurrent serious illness

| | Cabazitaxel +prednisone | Mitoxantrone +prednisone |
|---|---|---|
| Median age | 67 (61-72) | 68 (62-73) |
| ≥75 years | 19% | 18% |
| PS: 0-1 | 91% | 93% |
| 2 | 9% | 7% |
| Nb previous chemo 1 | 71% | 69% |
| ≥2 | 29% | 31% |

de Bono JS et al Lancet. 2010 Oct 2;376(9747):1147-54

## TROPIC trial: overall survival

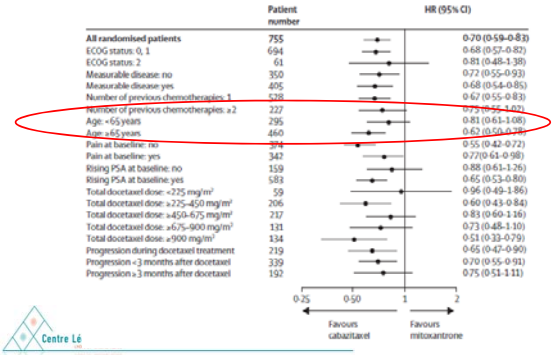



**MITOXANTRONE : Median = 12,7 months (11,6-13,7)**
**CABAZITAXEL: Median= 15.1 months (14,1-16,3)**

**HR=0,7 (95%IC:0.59-0.83; P<0.0001)**

de Bono JS et al Lancet. 2010 Oct 2;376(9747):1147-54

## TROPIC trial: subgroup analysis




de Bono JS et al Lancet. 2010 Oct 2;376(9747):1147-54

## TROPIC trial toxicity

| | Cabazitaxel +prednisone | | Mitoxantrone +prednisone | |
|---|---|---|---|---|
| | All | Grade≥ 3 | All | Grade≥ 3 |
| Neutropenia | 94% | 82% | 88% | 58% |
| Febrile neutropenia | | 8% | - | 5% |
| Anemia | 97% | 11% | 81% | 5% |
| Thrombocytopenia | 47% | 4% | 43% | 2% |
| Diarrhoea | 47% | 6% | 11% | <1% |
| Fatigue | 37% | 5% | 27% | 3% |
| Asthenia | 20% | 5% | 12% | 2% |
| Vomiting | 23% | 2% | 10% | 0% |

de Bono JS et al Lancet. 2010 Oct 2;376(9747):1147-54

## Cabazitaxel in the elderly: results from the EAP/CUP Europe

- 746 mCRPC patients:
  - 325 were aged ≥ 70 years (including 145 men aged ≥ 75 years)
  - 421 were aged < 70 years.

| | <70 years | ≥ 70 years |
|---|---|---|
| TEAE all grade | 88,1% | 89,5% |
| TEAE grade ≥ 3 | 47% | 52,9% |
| SAE | 28% | 29,2% |
| TEAE: treatment discontinuation | 13,3% | 19,1% |
| TEAE : toxic death related to cabazitaxel | 2,1% | 2,5% |

Heindenreich et al, ESMO, 2012, P932

| | <70 YEARS | | ≥ 70 YEARS | |
|---|---|---|---|---|
| | All grade | Grade≥ 3 | All grade | Grade≥ 3 |
| Neutropenia | 17,8% | 15% | 22,5% | 19,7% |
| Anemia | 20,9% | 5,8% | 22,5% | 4,3% |
| Use of G-CSF<br>•At 1st cycle<br>•At any cycle | | 47%<br>58% | | 58,5%<br>66,8% |
| Febrile neutropenia | 5,5% | 5,2% | 5,5% | 5,5% |
| Thrombocytopenia | 5% | 1,4% | 4,3% | 0,6% |
| Neutropenic sepsis | 1% | 1% | 1,8% | 1,8% |
| Diarrhea | 34,9% | 3,9% | 34,2% | 2,2% |
| Fatigue/asthenia | 24,5/13,5% | 4/1,4% | 26,2/21,2% | 4,3/4,2% |
| Hematuria | 6,2% | 0,5% | 9,2% | 2,2% |
| Peripheral neuropathy | 5,2% | 0% | 3,4% | 0,3% |

Heindenreich et al, ESMO, 2012, P932

## CONCLUSIONS

- Cabazitaxel seems as effective in older patients
- Similar toxicity in the EAP/CUP but
  - more prophylactic use of G-CSF
- Measures to improve tolerability in the elderly should be taken:
  - Use of G-CSF
  - Pro-active management of side effects
  - Dose adaptation?

## NEW DRUGS IN OVARIAN CARCINOMA

## Ovarian carcinoma role of bevacizumab

Phase III trials

- 1st line treatment
  - ICON-7
  - GOG
- 2nd line treatment:
  - OCEANS: Carbo-gemcitabine+/-bevacizumab (15 mg/kg q 3 wks)

Perren TJ et al . N Engl J Med. 2011 Dec 29;365(26):2484-96.
Burger RA et al N Engl J Med. 2011 Dec 29;365(26):2473-83
Aghajanian C, et al J Clin Oncol. 2012 Jun 10;30(17):2039-45

## Primary treatment: ICON-7 and GOG

- ICON-7
  - Carbo (AUC5-6)-paclitaxel (175mg/m²)+/-bevacizumab( 7.5 mg/ kg, q 3wks; 5-6+ 12 cycles)
  - High risk early cancers or stage III-IV
  - Post-operative
  - Adequate coagulation values and bone marrow, liver, and renal function
  - PS=0-2
- GOG
  - Carbo (AUC=6)-paclitaxel (175mg/m²)+/-bevacizumab (15 mg/kg q 3 wks)
    - Initiation: C2-C7
    - Throughout: C2-C22
  - newly diagnosed
  - stage III (incompletely resectable)
  - stage IV
  - undergone debulking surgery
  - No thromboembolic events
  - No intestinal occlusion

Perren TJ et al . N Engl J Med. 2011 Dec 29;365(26):2484-96.
Burger RA et al N Engl J Med. 2011 Dec 29;365(26):2473-83

## Patient characteristics

| | ICON-7 | |
|---|---|---|
| | CT N=764 | CT+BEVA N=764 |
| Age ≥70 | 57 (18-81) 10% | 57 (18-81) 9.5% |
| PS=0-1 | 94% | 94% |
| Stage III-IV | 81% | 82% |
| Debulking surgery | 98% | 98% |
| Completed CT | 91% | 94% |
| Completed beva | NA | 62% |

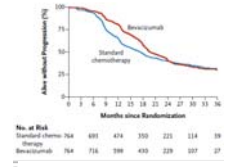
| | GOG | | |
|---|---|---|---|
| | Beva Initiation N=625 | Beva Throughout N=625 | Control N=623 |
| Age | 60 (24-88) | 60 (22-89) | 60 (25-86) |
| PS=0-1 | 93,6% | 91,9% | 93,3 |
| Stade III-IV | 100% | 100% | 100% |
| % completed treatment | 16% | 17% | 24% |

Perren TJ et al . N Engl J Med. 2011 Dec 29;365(26):2484-96.
Burger RA et al N Engl J Med. 2011 Dec 29;365(26):2473-83

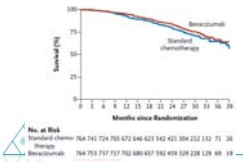
## Results (1)

ICON-7

Median PFS=17.3 vs19* months

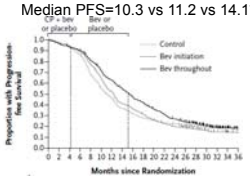


Median OS=NR

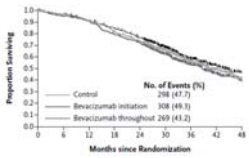


GOG

Median PFS=10.3 vs 11.2 vs 14.1* mo

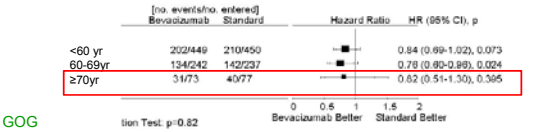


Median OS=39.3 vs 38.7 vs 39.7 mo

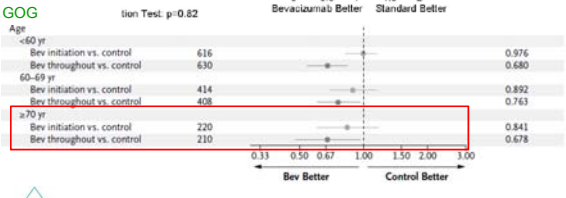


## Results (2)

ICON-7




GOG




Perren TJ et al . N Engl J Med. 2011 Dec 29;365(26):2484-96.
Burger RA et al N Engl J Med. 2011 Dec 29;365(26):2473-83

**TOXICITY**

| | ICON-7 | | GOG | | |
|---|---|---|---|---|---|
| | Carbo-Taxol | CT+beva | Control | Beva initiation | Beva throughout |
| GI events (Gr≥ 2) | 1% | 2% | 1.2% | 2.8% | 2.6% |
| HTA(Gr≥2) | 2% | 18% | 7.2% | 16.5% | 22.9% |
| Proteinuria (Gr≥3) | <1% | 1% | 0.7% | 1.6% | 0.7% |
| Neutropenia (Gr≥4) | 15%* | 17%* | 57.7% | 63.3% | 63.3% |
| Febrile neutropenia | 2% | 3% | 3.5% | 4.9% | 4.3% |
| VTE<br>ATE | 4%<br>1% | 7%<br>4% | 5.8%<br>0.8% | 5.3%<br>0.7% | 6.7%<br>0.7% |
| Wound disruption | 2% | 5% | 2.8% | 3.6% | 3% |
| Bleeding<br>CNS<br>Non CNS(Gr≥3) | <br>0<br><1% | <br><1%<br>1% | <br>0<br>0.8% | <br>0<br>1.3% | <br>0.3%<br>2.1% |
| Toxic death | n=1 | N=4 | 1% | 1.6% | 2.4% |

## OCEANS: Gemcitabine-Carboplatin+/- bevacizumab
## recurrent platinum sensitive ovarian carcinoma

- Exclusion criteria:
  - history of abdominal fistula, GIP, intra-abdominal abcess
  - GI obstruction
  - Nonhealing wound
  - Coagulopathy
  - Clinical significant cardiovascular disease

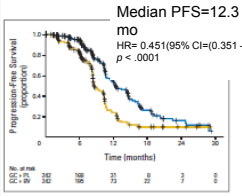
Median PFS

| | GCa+pl N=242 | GCa+BEVA N=242 |
|---|---|---|
| Age<br>≥65y | 61(28-86)<br>38.4% | 60 (38-87)<br>35.1% |
| PS=0-1 | 100% | 99.6% |
| Median nb cycles CT | 6<br>(1-10) | 6<br>(1-10) |
| Median nb pl/beva | 10 (1- 36) | 12 (1-43) |

Aghajanian C, et al J Clin Oncol. 2012 Jun 10;30(17):2039-45

Median PFS=12.3 vs 8.6 mo

HR= 0.451(95% CI=(0.351 - 0.580)) ; $p < .0001$




Median OS= 35.2 vs 33.3 mo

HR= 1.027 (95% 0.792- 1.331); p<0.001

## OCEANS: RESULTS

**TOXICITY**

| | GCa | GCa+beva |
|---|---|---|
| GI events | 0.4% | 1.6% |
| HTA(Gr≥3) | 0.4% | 17.4% |
| Proteinuria (Gr≥3) | 0.9% | 8.5% |
| Neutropenia (Gr≥4) | 21.9% | 20.6% |
| Febrile neutropenia | 1.7% | 1.6% |
| VTE(Gr≥3)<br>ATE | 2.6%<br>0.9% | 4%<br>2.8% |
| Wound disruption(Gr≥3) | 0% | 0.8% |
| Bleeding<br>CNS<br>Non CNS(Gr≥3) | <br>0.4%<br>0.9% | <br>0.8%<br>5.7% |
| Toxic death | 0.4% | 0.4% |

Aghajanian C, et al J Clin Oncol. 2012 Jun 10;30(17):2039-45

## Bevacizumab

- Bevacizumab improves progression free survival in patients with ovarian cancer
- No benefit on overall survival
- Limited number of elderly patients in these trials
- Toxicity can be severe and caution should be taken when used in elderly patients

## Conclusions

- New drugs have been approved in pelvic tumours based on phase III trials
- Older patients have been enrolled in these trials:
  - however very **selected**
  - use of these drugs in the general elderly population is not always easy and should be done **carefully**
- Need for **specific trials** with geriatric evaluation especially with targeted agents and new chemotherapies

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