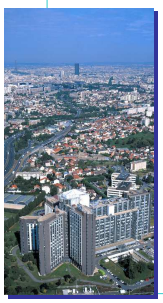
Biphosphonates et anti-RANK

Dans le cancer de la prostate



Early clinical trial unit SITEP www.igr.fr

Dr Christophe Massard
Département de Médecine Oncologique

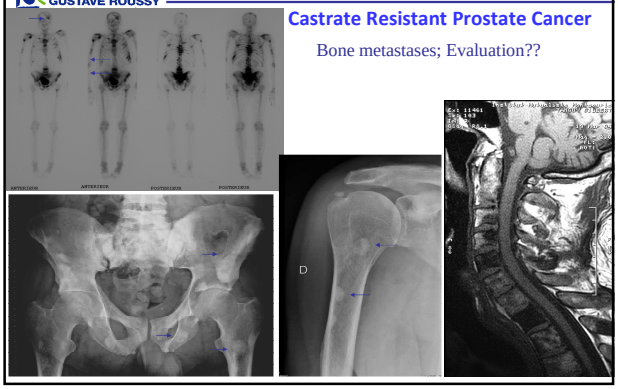
Onco Bretagne, Actualités et controverses, Samedi 1er Octobre 2011

Institut de cancérologie GUSTAVE ROUSSY VILLEJUIF - www.igr.fr · Inserm French Institute of Health and Medical Research U98 · UNIVERSITÉ PARIS-SUD 11

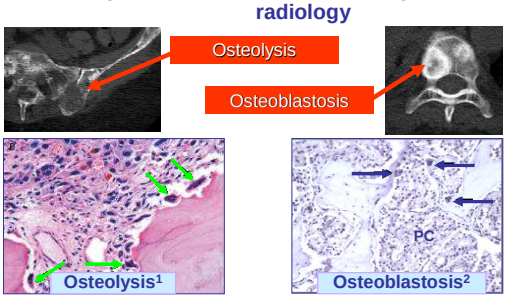
- Principes
- Biphosphonates
- RANK-RANKL
- Perspectives

Castrate Resistant Prostate Cancer

Bone metastases; Evaluation??



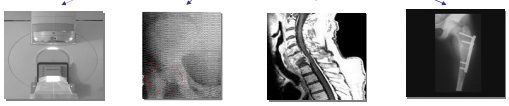
Osteolytic and osteoblastic bone metastases: presence of osteoclasts irrespective of radiology



Black arrows = osteoclasts

1. Roodman GD. *N Engl J Med* 2004;350:1655–1664
2. Amgen, data on file

Defining Skeletal Related Events (SRE)

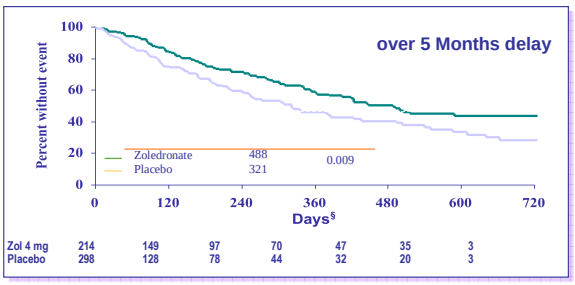


Radiation to Bone (Major pain) · Pathologic Fracture · Spinal Cord Compression · Surgery to Bone

Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* 2001;27:165-76.

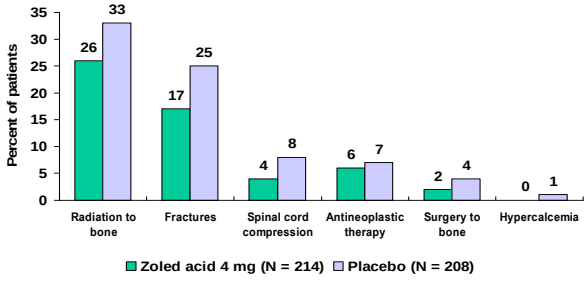
- Principes
- Biphosphonates
- RANK-RANKL
- Perspectives

Zoledronate: Time to Skeletal Related Event

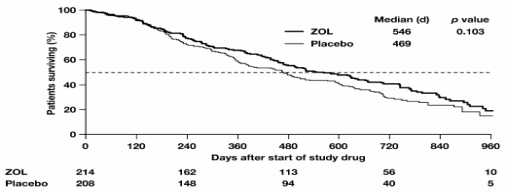


Saad et al. *JNCI 2004; 96:879*

Proportion (%) of Patients With Each SRE



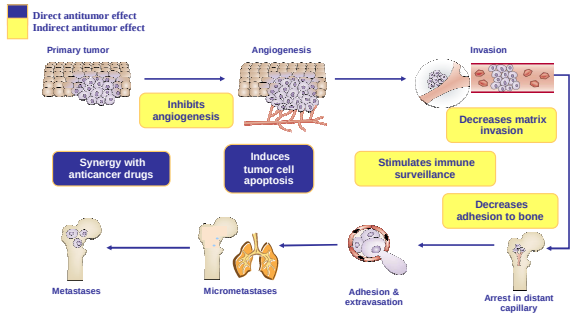
Zoledronic Acid for CRPC: Overall survival



- Median OS: 18.2 vs 15.6 months
- 1-year survival 85.2% vs. 78.3% (P = 0.21)[2]

[1]Saad F. Cancer Treatment Reviews (2008) 34, 183– 192
[2]Weinfurt KP, et al. *Annals of Oncology*. 2006;17: 986-989.

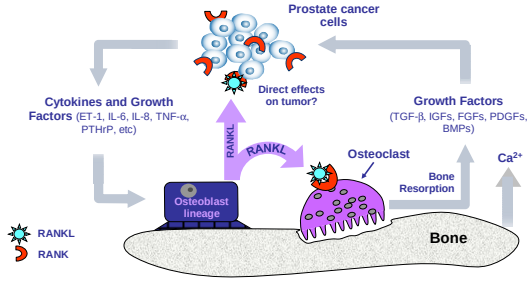
Zoledronic Acid Can Inhibit this Process at Several Key Steps



Adapted from Mundy GR, et al. *Nature Reviews Cancer*. 2002;2:584-593.

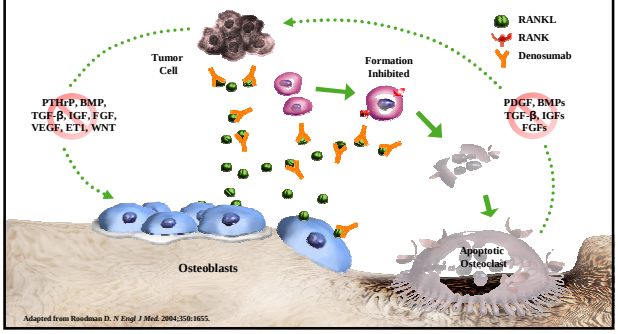
- **Principes**
- **Biphosphonates**
- **RANK-RANKL**
- **Perspectives**

The "vicious circle" of bone metastases



Adapted from Roodman GD. *N Engl J Med.* 2004;350:1655-64.

Denosumab may interrupt the "vicious cycle" of bone metastases



Targeting RANK-L with Denosumab: randomized phase II study

- Bone metastases from solid tumours
- Patients receiving bisphosphonates and **uNTX >50 nM/mM Cr**
- 45 patients per group (n=135)

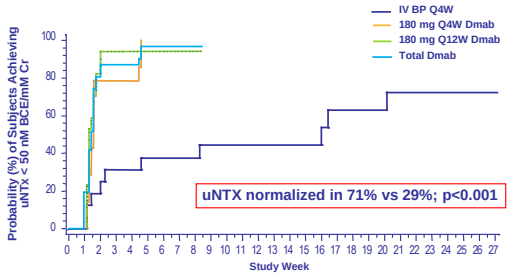
uNTx >50

Randomization

- Denosumab 180 mg SC Q4W
- Denosumab 180 mg SC Q12W
- Bisphosphonate IV Q4W

Primary endpoint:
uNTx <50
(at week 13)

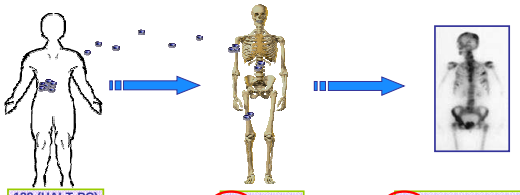
Denosumab vs bisphosphonate: Time to achieve uNTx < 50



Fizazi et al., J Clin Oncol 2009; 27: 1564-71

Denosumab is being studied in multiple stages of cancer

Early cancer → Advanced cancer



138 (HALT-PC) 135 (HALT-BC)	147 protocol	103/136/244 protocols
ADT-induced bone loss	Prevention of bone metastases	Prevention of SREs Delay of progression

Prostate cancer SRE Phase III Study

Key Inclusion
- Castration-resistant prostate cancer and bone metastases

Key Exclusion
- Current or prior intravenous bisphosphonate administration

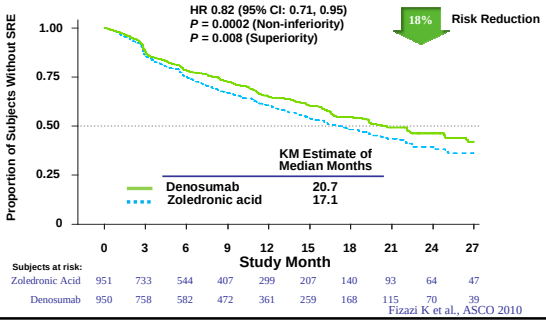
→ Denosumab 120 mg SC and Placebo IV* every 4 weeks

→ Zoledronic acid 4 mg IV* and Placebo SC every 4 weeks

Supplemental Calcium and Vitamin D

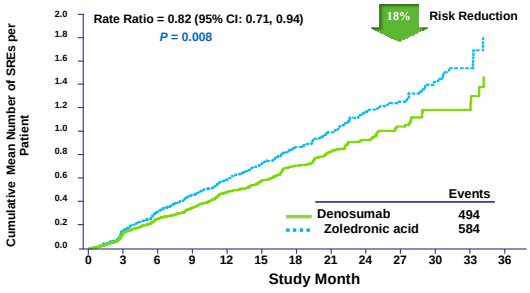
*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa® label)

Time to First SRE



Fizazi K et al., ASCO 2010

Time to First and Subsequent SRE

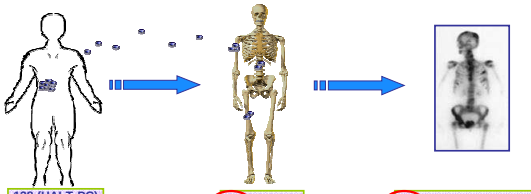


*Events occurring at least 21 days apart

Fizazi K et al., ASCO 2010

Denosumab is being studied in multiple stages of cancer

Early cancer → Advanced cancer



138 (HALT-PC) 135 (HALT-BC)	147 protocol	103/136/244 protocols
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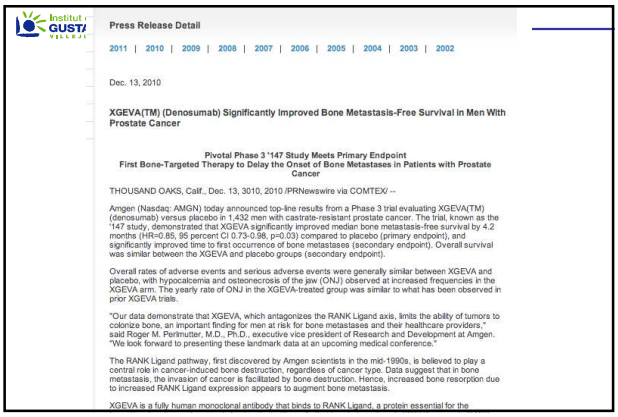


Press Release Detail

2011 | 2010 | 2009 | 2008 | 2007 | 2006 | 2005 | 2004 | 2003 | 2002

Dec. 13, 2010

XGEVA(TM) (Denosumab) Significantly Improved Bone Metastasis-Free Survival in Men With Prostate Cancer

Pivotal Phase 3 '147 Study Meets Primary Endpoint
First Bone-Targeted Therapy to Delay the Onset of Bone Metastases in Patients with Prostate Cancer

THOUSAND OAKS, Calif., Dec. 13, 3010, 2010 /PRNewswire via COMTEX/ --

Amgen (Nasdaq: AMGN) today announced top-line results from a Phase 3 trial evaluating XGEVA(TM) (denosumab) versus placebo in 1,432 men with castrate-resistant prostate cancer. The trial, known as the '147 study, demonstrated that XGEVA significantly improved median bone metastasis-free survival by 4.2 months (HR=0.85, 95 percent CI 0.73-0.98, p<0.03) compared to placebo (primary endpoint), and significantly improved time to first occurrence of bone metastases (secondary endpoint). Overall survival was similar between the XGEVA and placebo groups (secondary endpoint).

Overall rates of adverse events and serious adverse events were generally similar between XGEVA and placebo, with hypocalcemia and osteonecrosis of the jaw (ONJ) observed at increased frequencies in the XGEVA arm. The yearly rate of ONJ in the XGEVA-treated group was similar to what has been observed in prior XGEVA trials.

"Our data demonstrate that XGEVA, which antagonizes the RANK Ligand axis, limits the ability of tumors to colonize bone, an important finding for men at risk for bone metastases and their healthcare providers," said Roger M. Perlmutter, M.D., Ph.D., executive vice president of Research and Development at Amgen. "We look forward to presenting these landmark data at an upcoming medical conference."

The RANK Ligand pathway, first discovered by Amgen scientists in the mid-1990s, is believed to play a central role in cancer-induced bone destruction, regardless of cancer type. Data suggest that in bone metastasis, the invasion of cancer is facilitated by bone destruction. Hence, increased bone resorption due to increased RANK Ligand expression appears to augment bone metastasis.

XGEVA is a fully human monoclonal antibody that binds to RANK Ligand, a protein essential for the

Bone Metastases Prevention Phase III trial (147)

Key Inclusion Criteria

- Castrate-resistant prostate cancer
- Total serum testosterone level < 50 ng/dL
- High risk for bone metastasis:
  - PSA value ≥ 8.0 ng/mL within 3 mo before randomization **and/or**
  - PSA doubling time ≤ 10.0 mo

Key Exclusion Criteria

- Bone metastasis detected radiographically
- Metastatic involvement of distant organs (except lymph node)
- IV bisphosphonates

Denosumab 120 mg SC every 4 weeks (N = 716)

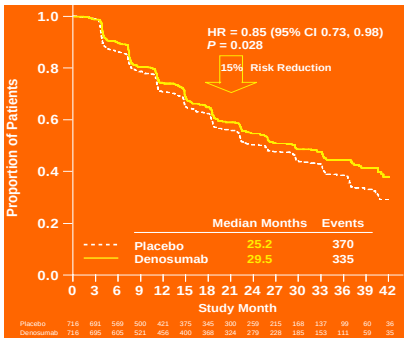
Calcium and Vitamin D Supplementation

Placebo SC every 4 weeks (N = 716)

Primary Endpoint:
- **Bone Metastasis-Free Survival**
  Time to first bone metastasis (symptomatic or asymptomatic) or death

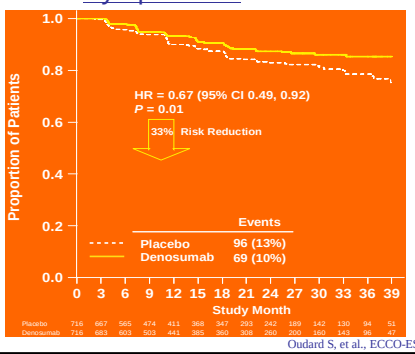
Secondary Endpoints:
- **Time to First Bone Metastasis**
  Either symptomatic or asymptomatic
- **Overall Survival**

Bone Metastasis-Free Survival



Oudard S, et al., ECCO-ESMO 2011

Time to Symptomatic Bone Metastasis



Oudard S, et al., ECCO-ESMO 2011

- Principes
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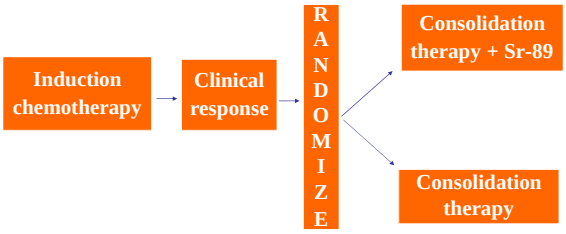
Radiopharmaceuticals

- Phase III **Strontium-89 vs placebo** after radiotherapy:
  - → Improvement in time to pain (n=126) (Porter 1993)
  - → No improvement (n=95) (Smeland 2003)
- Phase III **Strontium-89 vs radiotherapy**:
  - → Similar pain control (n=284) (Quilty 1994)
  - → Better OS: 7 months vs 11 months ($p<0.05$) (n=101) (Oosterhof 2003)
- Phase III **Samarium-153 vs placebo**:
  - → Better pain control (n=118) (Serafini 1998); (n=152) (Sartor 2004)

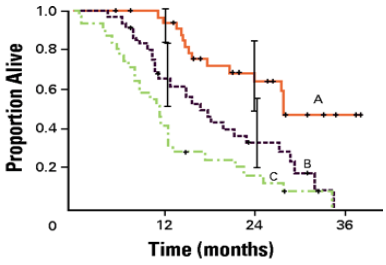
Chemotherapy + radiopharmaceuticals: Randomized phase II MDACC



Tu S-M, Lancet, 357, 336-341, 2001

n= 103

Median OS: 27.7 vs 17.5 months



A) Doxorubicin and Sr-89	36	35	34	26	21	15	5	3	0
B) Doxorubicin alone	36	35	27	18	7	7	3	0	0
C) Not randomly assigned	31	26	17	8	6	4	1	0	0

Tu S-M, Lancet, 357, 336-341, 2001

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CRPC and bone metastases

Induction regimen: n=43
- docetaxel 70 mg/m² day 2
- estramustine 10 mg/Kg/day, day 1-5

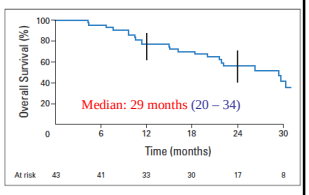
(1 cycle every 3 weeks)

Response (n=31) or stabilization (n=11) | Progression n=1

Consolidation regimen: n=42
- docetaxel 20 mg/m²/w x 6 w
- samarium 1 injection week 1 (37 MBq/Kg)

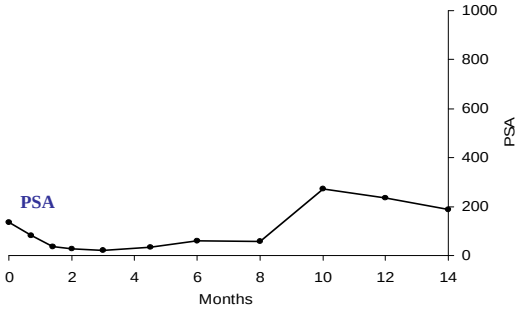
Phase II Trial of Consolidation Docetaxel and Samarium-153 in Patients With Bone Metastases From Castration-Resistant Prostate Cancer

Karim Fizazi, Philippe Beuzeboc, Jean Lumbroso, Vincent Haddad, Christophe Massard, Marine Gross-Goupil, Marie-Th Palma, Bernard Escudier, Christine Theodore, Yohann Loriot, Elodie Tourtay, Jeannine Bouzy, and Agnes Laplanche



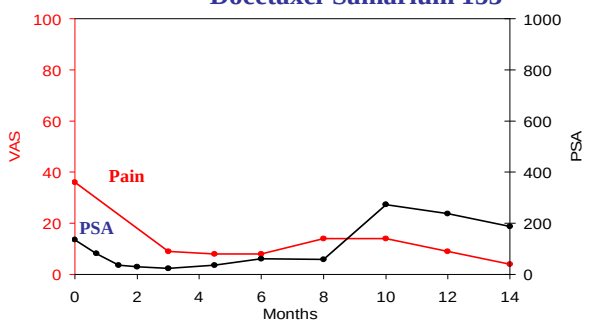
1-year survival rate: 76% (62%-87%)
2-year survival rate: 63% (47%-77%)

Docetaxel-Samarium 153



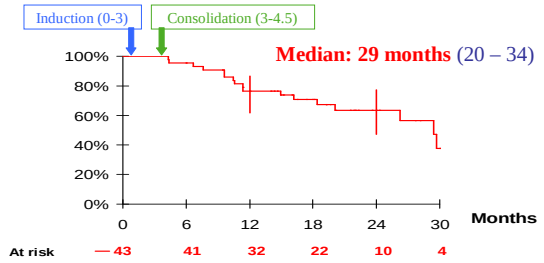
Fizazi et al., J Clin Oncol 2009; 27: 2429-35

Docetaxel-Samarium 153



Fizazi et al., J Clin Oncol 2009; 27: 2429-35

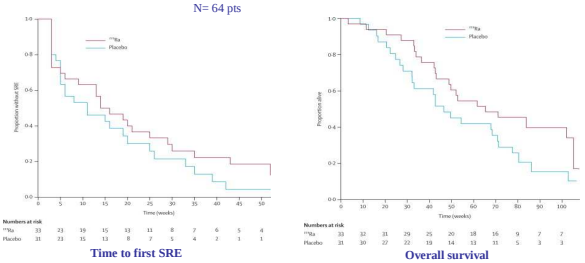
Docetaxel-Samarium: Overall survival



Fizazi et al., J Clin Oncol 2009; 27: 2429-35

Radium-223 vs Placebo in CRPC

N= 64 pts



Nilsson et al., Lancet Oncol 2007, 8: 587-94

Alpharadin Improves Survival in Phase III Trial in Patients with CRPC That Has Spread to the Bone

Press release June 6, 2011

The overall survival result was statistically significant (**p-value = 0.0022, HR = 0.699**, the median overall survival was 14.0 months for Alpharadin and 11.2 months for placebo).

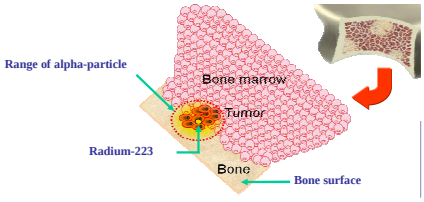
ESMO 36 ECCO 16 ESTRO 30

Overall Survival Benefit of Radium-223 Chloride (Alpharadin) in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer (CRPC): A Phase III Randomised Trial (ALSYMPCA)

C. Parker,[1] D. Heinrich,[2] J.M. O'Sullivan,[3] S. Fosså,[4] A. Chodacki,[5] T. Demkow,[6] A. Cross,[7] B. Bolstad,[8] J. Garcia-Vargas,[9] and O. Sartor,[10] on behalf of the ALSYMPCA Investigators

[1]The Royal Marsden Hospital, Surrey, UK; [2]Haukeland Univ Hospital, Bergen, Norway; [3]Centre for Cancer Research and Cell Biology, Queen's Univ, Belfast, Northern Ireland; [4]Radiumhospitalet, Oslo, Norway; [5]Hospital Kochova, Chomutov, Czech Republic; [6]Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; [7]PharmaNet, Hemel Hempstead, UK; [8]Algeta ASA, Oslo Norway; [9]Bayer HealthCare Pharmaceuticals, Montville, NJ, USA; [10]Tulane Cancer Center, New Orleans, LA, USA

Radium-223 Targets Bone Metastases



- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells[1]
  - → Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue

1. Perez et al. *Principles and Practice of Radiation Oncology.* 5th ed. Lippincott Williams & Wilkins; 2007:103.

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

→ RANDOMISED 2:1

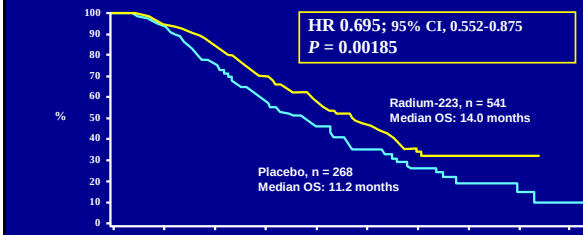
- Total ALP: < 220 U/L vs ≥ 220 U/L
- Bisphosphonate use: Yes vs No
- Prior docetaxel: Yes vs No

→ Radium-223 (50 kBq/kg) + Best standard of care

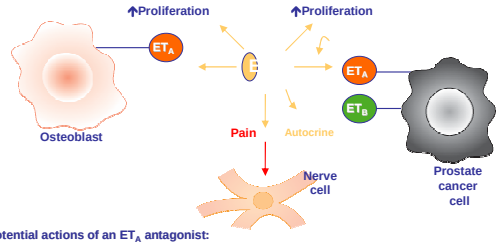
→ Placebo (saline) + Best standard of care

Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Overall Survival



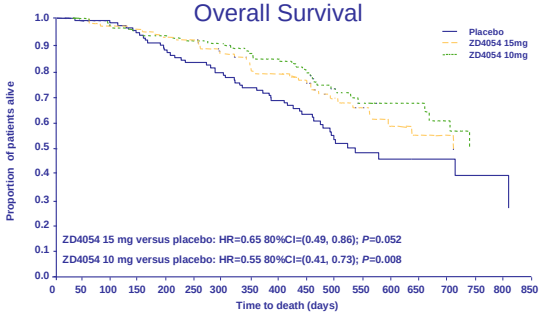
Endothelin-1 and Prostate cancer



Potential actions of an ET_A antagonist:

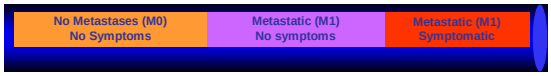
- Inhibition of prostate tumour cell proliferation
- Promotion of tumour cell apoptosis
- Inhibition of osteoblast proliferation
- Reduction in pain

Zibotentan: Targeting Endothelin-1 Overall Survival



James ND, Eur Urol 2009, 55: 1112-23

Zibotentan Phase III Programme



	ENTHUSE M0 (15) ZD4054 vs placebo	ENTHUSE M1 (14) ZD4054 vs placebo	ENTHUSE M1C (33) docetaxel +/- ZD4054
PI:	C. Higano K. Miller	M. Gleave J. Nelson	K. Fizazi J. Moul
	Ongoing	Accrual completed	Accrual completed

Results of Zibotentan Phase III trial in castration resistant prostate cancer

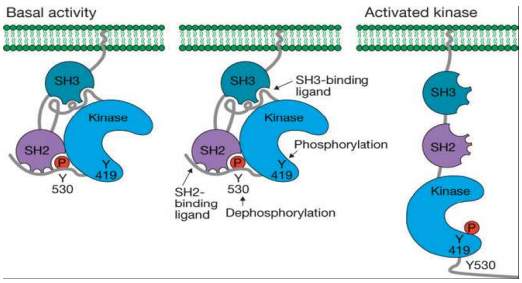
Monday, 27 September 2010

AstraZeneca today announced that a study evaluating zibotentan for the treatment of men with metastatic castration resistant prostate cancer (CRPC) did not show a significant improvement in the primary endpoint of overall survival (OS).

Study 14 was a randomised, placebo controlled phase III study which evaluated zibotentan 10mg added to standard of care treatment in 594 patients with metastatic CRPC. The safety and tolerability profile of zibotentan in this trial was in line with previous studies.

Based on this study result, AstraZeneca plans no regulatory submissions for zibotentan at this time. The zibotentan ENTHUSE trial programme includes two other ongoing studies with zibotentan in different CRPC settings. The full results of study 14 will be published in 2011.

Activation of Src

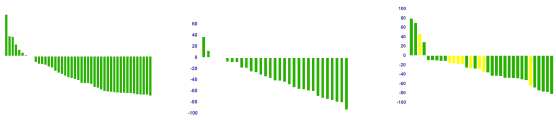


Fizazi K. The role of Src in prostate cancer. Ann Oncol 18:1765-1773, 2007

Phase I-II trial Docetaxel-Dasatinib

n= 46 CRPC patients (including 14 with previous chemotherapy)

PSA response:49% RECIST response: 42% uNTx response: 50%



Araujo et al., ASCO 2009, Abstr 5061

Docetaxel-Dasatinib Phase III READY trial

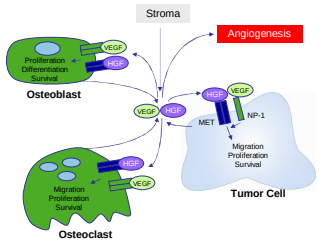
- n=1380 planned

R

- Docetaxel 75 mg/m^2 + prednisone 5 mg BID + **dasatinib 100 mg QD**
- Docetaxel 75 mg/m^2 + prednisone 5 mg BID + placebo

Role for HGF and VEGF in Tumor-Bone Interactions

- **HGF is highly expressed in bone metastases**
- **Osteoblasts and osteoclasts express MET and VEGFRs—respond to HGF and VEGF**
- **HGF and VEGF promote angiogenesis**



HGF and VEGF may be key factors mediating cross-talk between tumor cells, osteoblasts, and osteoclasts

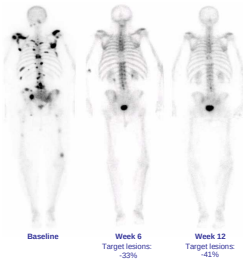
XL184 Biochemical and Cellular Activity

Kinase	IC_{50} (nM)
MET	1.8
VEGFR2	0.035
KIT	4.6
RET	5.2
AXL	7.0
TIE2	14
FLT3	14
PDGFRβ	234
IRK	1140
S/T Ks (47)	>200

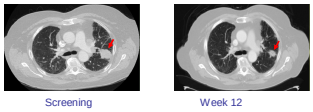
RTK	Cellular IC_{50} (nM) Autophosphorylation
MET	8
VEGFR2	4
FLT3-ITD	7.5
TIE2	106
PDGFRβ	2150

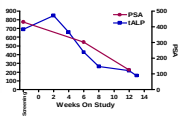
ATP competitive, reversible

Activity of XL184 in a Docetaxel-pretreated CRPC pt



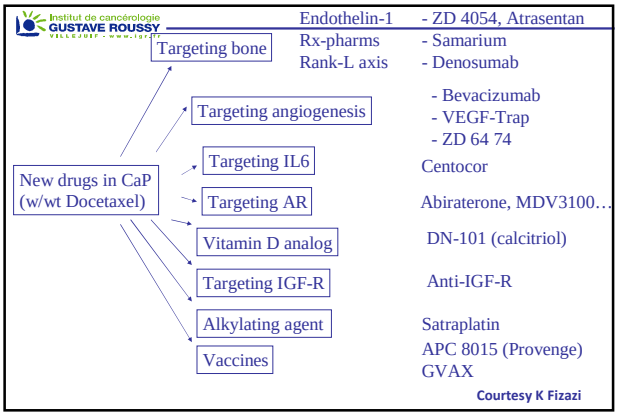
CT scan: confirmed PR with 41% tumor decrease at Week 12





Age: 77 years
Diagnosis: 8/93
Prior treatments: Casodex/Lupron (4/01-11/05),
DES (11/06 – 1/10),
Taxotere (1/08 – 6/08, SD),
Casodex (10/08 -4/09),
Trelstar (10/08 – present)
XL184: Start 2/12/10; Open label extension 5/7/10; D/C due to AE (diarrhea) 6/18/10

+ pain improvement

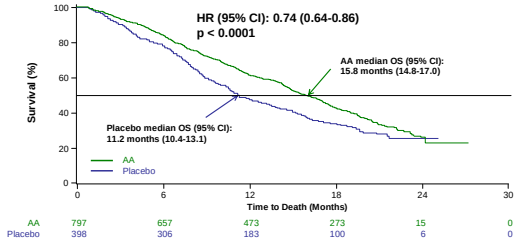


Overall Survival Benefit in Recent CRPC Trials

Agent (trial, year)	Disease State	Comparator	Hazard Ratio	*P* value
Radium-223/Alpharadin (ALSYMPCA 2011)	Bone metastases CRPC	Placebo + best standard of care	0.695	0.00185
Docetaxel/Taxotere[1] (TAX327 2004)	Chemo-naive CRPC	Mitoxantrone Prednisone	0.76	0.009
Cabazitaxel/Jevtana[2] (TROPIC 2010)	Post-docetaxel CRPC	Mitoxantrone Prednisone	0.70	<0.0001
Sipuleucel-T/Provenge[3] (IMPACT 2010)	Chemo-naive CRPC	Placebo	0.775	0.032
Abiraterone/Zytiga[4] (COU-AA-301 2010)	Post-docetaxel CRPC	Placebo Prednisone	0.65	<0.001

1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. de Bono. *Lancet.* 2010;376:1147-1154.
3. Kantoff et al. *N Engl J Med.* 2010;363:411-422.
4. de Bono. *N Engl J Med.* 2011;364:1995-2005.

Updated Analysis (775 Events): The OS Benefit of AA Increased From 3.9 to 4.6 Months

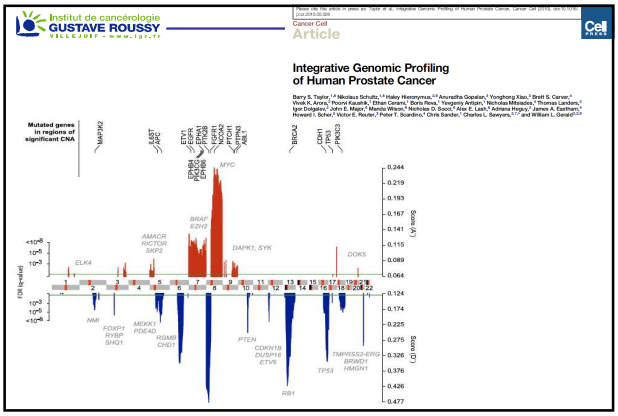


AA	797	657	473	273	15	0
Placebo	398	306	183	100	6	0

- Median duration of follow-up: 20.2 months
- Median duration of treatment: 8 months with AA vs 4 months with placebo

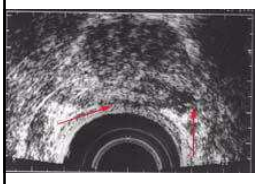
What is Prostate Cancer ? An Old view

The same treatment for everybody?
For different disease?



Pathology-based therapy

cytotoxic

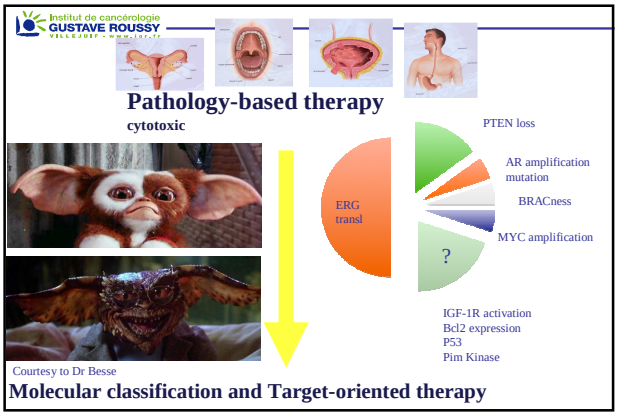


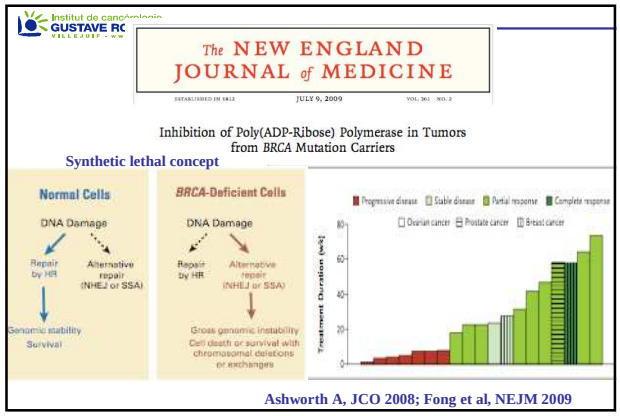
ERG transl

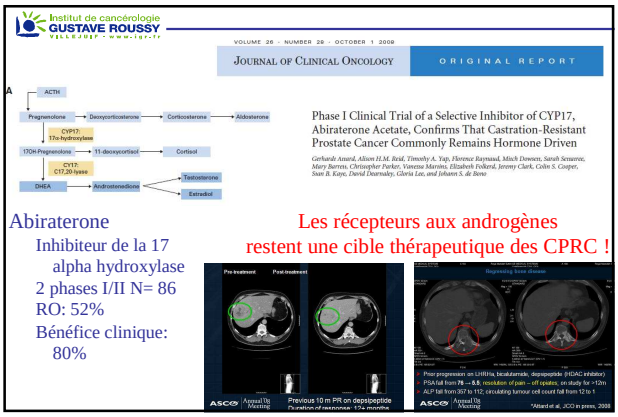
PTEN loss
AR amplification mutation
BRACness
MYC amplification
?

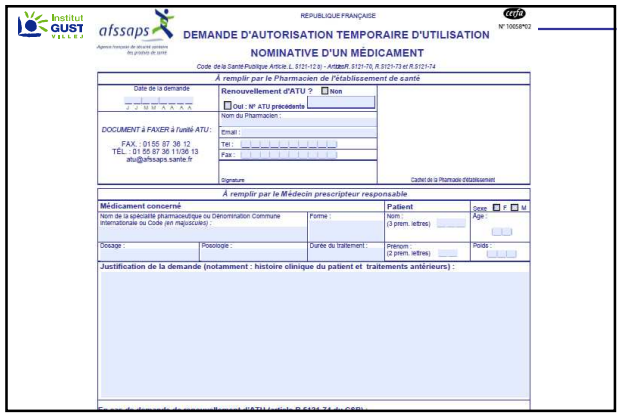
IGF-1R activation
Bcl2 expression
P53
Pim Kinase

Molecular classification and Target-oriented therapy









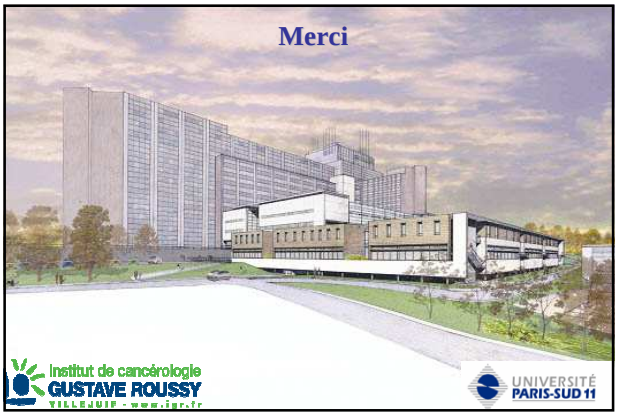
Conclusion

- **Zoledronic acid:**
  - → Delays Skeletal-Related Events
  - → Anti-tumor effect?
  - → Phase III trials in localized prostate cancer awaited (2011?)
- **Denosumab (Rank-L):**
  - → Delays Skeletal-Related Events better than Zoledronic Acid
  - → Approval awaited
  - → Phase III trial for prevention of bone metastases in non-metastatic CRPC awaited (2011?)
- **Radio-pharmaceuticals:**
  - → Samarium-153 and Strontium-89 used for palliation
  - → Role on survival?
  - → Ongoing phase III trial with Radium-223
  - → Safe, and likely more active in combination with chemo

Conclusion-2

- **Zibotentan (Endothelin-1):**
  - → Promising randomised phase II data
  - → 3 phase III trials ongoing (2011)
- **Others drugs**

- **The Futur: Personalized Medicine…**


Merci
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