Case 1

Dr Simone Albisinni

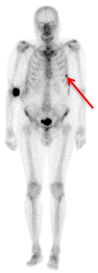
CASE 1

- 71 yo male
- PSA 10,7ng/ml
- DRE: non suspicious, ±40cc
- Mp-MRI: negative
- Biopsies: 13/16 +; Gleason 8(4+4)

- PMH: hypertension; sarcoidosis; appendectomy; erectile dysfunction

CASE 1

- CT scan:
  - One lesion on the VI left rib,
  - 1 suspicious enlarged lymph node, external iliac, left
- Bone scan:
  - Confirms one lesion on the VI left rib,
  - Suspicious for a lesion on the V right rib,

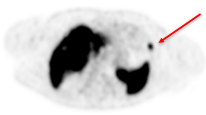


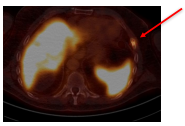
WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Local Radiotherapy+ADT
5. Local Radiotherapy+stereotaxic radiotherapy on ribs and nodes+ADT
6. Prostatectomy+stereotaxic radiotherapy on ribs±ADT
7. Whole body MRI
8. PSMA PET/CT
9. Inclusion in protocol

CASE 1

- PSMA confirms single osteous lesion on VI left rib, (seen on bone scan)
- PSMA is negative on right side (suspicious on CT scan)
- PSMA is positive for 2 enlarged nodes in the pretracheal region





WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Local Radiotherapy+ADT
5. Local Radiotherapy+stereotaxic radiotherapy on ribs and nodes+ADT
6. Prostatectomy+stereotaxic radiotherapy on ribs±ADT
7. Biopsy of tracheal nodes and rib lesion

CASE 1

Hôpital Erasme ULB

- The view of the Urologist

INSTITUT JULES BORDET INSTITUUT

Hôpital Erasme ULB

Guideline for staging of prostate cancer

Hôpital Erasme ULB

High-risk localised PCa/locally advaned PCa	LE	Strength rating
Use prostate mpMRI for local staging.	2b	Strong
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

EAU 2017

[^{68}Ga]PSMA PET/CT Improves Initial Staging and Management Plan of Patients with High-Risk Prostate Cancer

Nader Hirmas,[1] Akram Al-Ibraheem,[1] Ken Herrmann,[2] Abedalatif Alsharif,[1] Haider Muhsin,[1] Jamal Khader,[3] Ali Al-Daghmin,[4] Samer Salah[5] Mol Imaging Biol. 2018

Table 3.. Diagnostic utility of the different imaging modalities (per-lesion-site analysis)

Imaging modality: region	Sensitivity (%)	Specificity (%)	*PPV* (%)	*NPV* (%)	Accuracy (%)
CT: pelvic LNs	66.7	87.5	88.9	63.6	75
CT: extra-pelvic LNs	57.1	84.6	66.7	78.6	75
MRI: prostate gland	86.7	N/A	100	N/A	86.7
MRI: pelvic LNs	75	85.7	85.7	75	80
Bone scan	62.5	87.5	83.3	70	75
[^{68}Ga]PSMA PET/CT: prostate gland	85.7	N/A	100	N/A	85.7
[^{68}Ga]PSMA PET/CT: pelvic LNs	92.3	100	100	88.9	95.2
[^{68}Ga]PSMA PET/CT: extra-pelvic LNs	100	100	100	100	100
[^{68}Ga]PSMA PET/CT: bone metastases	100	91.7	90	100	95.2

LNs lymph nodes, *N/A* not applicable, *NPV* negative predictive value, *PPV* positive predictive value

(PS)MA-PET?

Summary of the published reports on incidental detection of non-prostatic benign PSMA-avid lesions in the staging/restaging work-up of prostate cancer (false-positive findings)

Hôpital Erasme ULB

Author, year	PSA level	Imaging finding	Diagnosis	Reference standard
Granulomatous and inflammatory pathologies				
Dias et al. [110]	> 0.3 & 17 µg/L	Staging/ Restaging ^{68}Ga-PSMA: symmetrical bilateral uptake in mediastinal and hilar LNs (Two patients)	Sarcoidosis	Pathology (biopsy)
Hermann et al. [76]	1.4 ng/mL	Restaging ^{68}Ga-PSMA: Avid area in the liver segment VIII CE Ultrasound: No pathological area or tumor in the liver	Sarcoidosis	2-year FU, PMH sarcoidosis
Kobe et al. [77]	0.2 ng/mL	Restaging ^{68}Ga-PSMA: intense uptake in spleen MRI: hypo intense lesion (T2-weighted); not specific for a benign splenic lesion	Sarcoidosis	Pathology (biopsy)
Ardies et al. [78]	elevated	Staging ^{68}Ga-PSMA: uptake in numerous thoracic and intra-abdominal LNs	Sarcoidosis	History of sarcoidosis, remained stable on CT imaging over 50 years
Pyka et al. [73]	NR	^{68}Ga-PSMA: uptake in lung lesions (Two patients) (SUVmax: 7.8 and 2.5)	Reactivated tuberculosis	Sputum analysis

Pearls and pitfalls in clinical interpretation of prostate-specific membrane Antigen (PSMA) targeted PET imaging

Sara Sheikhbahaei 1 & Ali Afshar-Oromieh2 & Matthias Eiber3,4 & Lilja B. Solnes1 & Mehrbod S. Javadi1 & Ashley E. Ross5 & Kenneth J. Pienta5 & Mohamad E. Allaf5 &Uwe Haberkorn2 & Martin G. Pomper1 & Michael A. Gorin5 & Steven P. Rowe1 Eur J Nucl Med Mol Imaging. 2017

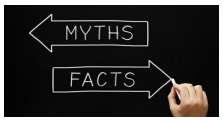
Bouchelouche and Vendelbo [111]	**23.7 ng/mL**	**Staging ^{68}Ga-PSMA: opacities and bronchiectasis, airway wall thickening with moderate uptake**	**Benign lung opacities and bronchiectasis**	**Endoscopic bronchoalveolar lavage, FU CT in 3 months**
Elri et al. [112] (Spanish)	21.4 ng/mL	Restaging ^{68}Ga-PSMA: intense uptake in hilar mass in the left lung and accompanying mediastinal lymphadenopathies (in addition to liver and bone metastases)	Anthracosis	Pathology (bronchoscopic biopsy)
Benign bone pathologies				
Froehner\ et al. [85, 113]	6.7 ng/mL	Staging ^{68}Ga-PSMA: moderate uptake in left pubic bone	Paget's disease	Pathology (biopsy)
Sasikumaret al. [82, 114, 115]	0.5 ng/mL	Staging ^{68}Ga-PSMA: heterogeneous moderate to intense uptake in sclerotic changes in the left iliac bone	Paget's disease	Pathology (biopsy)
Derlin et al. [80]	1.1 ng/mL	Restaging ^{68}Ga-PSMA: intense uptake in the right iliac bone and in multiple LNS	Paget's disease	Imaging correlate, PMH Paget's disease
Blazak and Thomas [81]	elevated	^{68}Ga-PSMA: intense uptake within the left ischial tuberosity and the posterior right inferior pubic ramus	Paget's disease	Bone scan/SPECT/CT
Artigas et al. [79]	rising	Restaging ^{68}Ga-PSMA: uptake in the proximal phalanx of the finger	Paget's disease	Bone scan and X-ray
Bourgeois et al. [83]	6.5 ng/mL	Restaging ^{68}Ga-PSMA: intense uptake in left humeral head, several LNs	Paget's disease	Imaging correlate (CT, stable appearance over 8 yrs)
Rowe et al. [7, 54, 84, 116]	0.3 ng/mL	Restaging ^{18}F–DCFPyL: Diffuse uptake in sacrum (SUVmax 4.6)	Paget's disease	contrast-enhanced CT, bone scan, and pelvic MRI
Vamadevan et al. [88, 102]	8.9 µg/L	Staging 68Ga-PSMA: tracer uptake localized to an undisplaced transverse fracture of the L1 vertebral body (SUVmax, 6.3)	Vertebral body fracture	Imaging correlate (CT, history of fall)
Gykiere et al. [87]	1.8 µg/L	Restaging ^{68}Ga-PSMA: moderately and diffuse tracer uptake in the sacrum	Healing Sacral Fracture	Imaging correlate (MRI, history of fall)
De Coster et al. [86]	5.7 ng/mL	Staging ^{68}Ga-PSMA: mild focal uptake in the posterior arch of the sixth right rib	Benign fibrous dysplasia	Pathology (surgical resection)

Benign neurogenic tumors				
Kanthan et al. [92, 100, 104, 117]	6.9 µg/L	Staging ^{68}Ga-PSMA: avid right pelvic mass anterior to the sacrum (SUVmax:4)	Schwannoma	Pathology (Surgical resection), MRI
Rischpler et al. [72, 101]	11.3 ng/ml	^{68}Ga-PSMA: intense uptake right paravertebral soft-tissue mass	Schwannoma	MRI
Bilgin et al. [98]	16.4 ng/mL	Restaging ^{68}Ga-PSMA: Moderate uptake in left orbitofrontal region (SUVmax: 3.1)	Meningioma	Imaging correlate (FU MRI)
Jain et al. [99]	NR	Staging ^{68}Ga-PSMA: uptake in a meningioma	Meningioma	NR
Vamadevan et al. [88, 102]	7.5 µg/L	Staging ^{68}Ga-PSMA: intense uptake in prostate gland and increased uptake localized to a soft tissue density in the left adductor compartment (SUVmax 4.7)	Peripheral nerve sheath tumor	Pathology (biopsy)
Hemangiomas and benign soft tissue pathologies				
Artigas et al. [90]	2.1 ng/mL	Restaging 68Ga-PSMA: intense uptake in the 12th thoracic vertebra without morphological correlation in CT	Vertebral hemangioma	Spinal MRI and 1-year FU
Jochumsen et al. [91]	0.5 µg/L	Restaging ^{68}Ga-PSMA: intense uptake in the abdominal wall	Subcutaneous capillary hemangioma	Pathology (resection)
Bhardwaj et al. [89]	NR	Staging ^{68}Ga-PSMA: intense uptake in hepatic segment IVa (SUVmax: 20.6)	Benign liver hemangioma	Imaging FU (CT, MRI; no growth over 3 months)
Zacho et al. [96, 118]	0.2 ng/mL	Restaging ^{68}Ga-PSMA: uptake in left vastus medialis muscle (SUVmax: 3)	Intramuscular myxoma	Pathology (surgical resection)
Daglioz Gorur et al. [97]	19.62 ng/mL	Staging ^{68}Ga-PSMA: moderate uptake in a protruded lesionleft lower quadrant of abdomen (SUVmax: 3.8)	Acrochordon	Consistent with history and physical exam
Aydin et al. [94]	elevated	Restaging ^{68}Ga-PSMA: uptake in subcutaneous masses in the frontal region of the cranium, abdomen, thigh and trunk (SUVmax: 12.8)	Dermatofibroma	Pathology (excisional biopsy)
Malik et al. [95]	18.2 µg/L	Staging ^{68}Ga-PSMA: Focal increased uptake in left chest (SUVmax 3.1)	Pseudo-angiomatous stromal hyperplasia of breast	Pathology (breast biopsy)
Kanthan et al. [92, 100, 104, 117]	6.9 µg/L	Staging ^{68}Ga-PSMA: large intensely avid soft tissue mass in the right pelvis abutting the cecum and terminal ileum (SUVmax:15.9)	Desmoid tumor	Pathology (Surgical resection)

Henninger et al. [93]	**19.86 ng/mL**	**Staging 68Ga-PSMA: intense uptake in soft-tissue mass in the left rectus femoris muscle (PET/MRI)**	**Fasciitis nodularis**	**Pathology (biopsy)**
Other benign pathologies				
Chan et al. [119]	NR	Staging ^{68}Ga-PSMA: Focal uptake in the pancreatic head (SUVmax: 10.1)	Pancreatic serous cystadenoma	1-year clinical and imaging FU (MRI)
Kanthan et al. [92, 100, 104, 117]	rising	Restaging ^{68}Ga-PSMA: intense uptake in a mixed density nodule in the left lower pole of the thyroid (SUVmax: 25.3)	Follicular thyroid adenoma	Pathology (left hemi thyroidectomy)
Derlin et al. [105]	NR	Restaging 68Ga-PSMA: uptake in thyroid lesion (SUVpeak: 2.9)	Follicular thyroid adenoma	Pathology (surgical resection)
Law et al. [107]	1.3 µg/L	Restaging ^{68}Ga-PSMA: mild-to-moderate tracer uptake in the left adrenal gland	Lipid-rich adrenal adenoma	Stable lesion on CT for 9 years
Malik D, 2017	6.6 ng/mL	Restaging ^{68}Ga-PSMA: intense uptake in a soft tissue lesion at the base of the urinary bladder (SUVmax 15.3- local recurrence), intense uptake in the left hemithorax (SUVmax 15.5)	Herniated spleen	^{99m}Tc-labeled sulfur colloid scintigraphy, history of congenital hiatal hernia
Stephens et al. [103]	NR	Staging 68Ga-PSMA: Symmetrical intense uptake in the seminal vesicles bilaterally	Senile seminal vesicle amyloidosis	Pathology (surgical resection)
Noto et al. [109]	NR	Restaging ^{68}Ga-PSMA: Focal cerebral tracer uptake in the right frontal lobe (SUVmax 1.2)	Cerebral infarction	MRI, 6-month FU, consistent with history
Chan et al. [106]	NR	Restaging ^{68}Ga-PSMA: additional focus of uptake in the left cerebral hemisphere	Acute cortical Infarct of embolic nature	MRI, consistent with history

RATIONAL OF LOCAL TREATMENT IN THE METASTATIC SETTING

- Oncological rational: Reduction of tumor burden
  - Reduction of shedding of metastatic cells
  - Reduction of paraneoplastic effect
  - Reduction of immunosuppressive effect
- Non oncological rational: Reduction of local complications



Background – Cytoreductive Prostatectomy???

- Cytoreductive surgery increases survival in multiple cancers (Ovarian; Kidney; colon)[1-2]

Gleham D Lancet Oncol. 2006
Britton JCO 2002
Hyng 2014

- For PCa, idea supported by population-based studies.
  - •Culp 2014: CSS 75.8% vs 48.7%

- Reduce lethal clone
- Reduce CTCs
- Block self-seedin

THEORY!

Shao Eur Urol 2014

- Reduce intratu al androgen synthesis

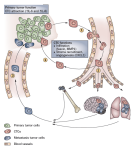
Mostaghel Cancer Res 2007

- An intact primitive may be fundamental for M+ development

Weckermann et al, J Clin Oncol 2009

- Reduce local symptoms

Poelart Urology 2017



Real life - Cytoreductive Prostatectomy???

No strong evidence to date of survival benefit

Need of prospective randomized trials

No test to evaluate in which patients cytoreduction can be beneficial vs useless

Morbidity+++ Overall complication rate 30%
Post-operative incontince remains a potential significant burden on QoL
Possibly higher compared to radical prostatectomy

Kim et al 2017: 8% overall complications; 4% major complications; 43% (>1 pad/day)

Castration combined with any local treatment	Radiotherapy/Surgery	Use castration combined with local treatment in an investigational setting only.	3	A

EVIDENCE SUPPORTING LOCAL TREATMENT

Survival advantage for local therapy in the metastatic setting

- RRP: all reports showed the benefit on OS and CSS with HR of 0.27–0.51 and 0.26–0.38, respectively.
- Radiotherapy: all but one study confirmed the benefit on CSS with a HR of 0.38–0.85

Tilki, Int J Urol 2018

Study	Design	Cohort	outcome	Results
Culp, 2014	Retrospective	SEER	OS	✓
Artel, 2014	Retrospective	SEER	OS	✓
Gratzke, 2014	Retrospective	MCR	OS	✓
Fossati, 2015	Retrospective	SEER	CSS	✓
Satkunasivam, 2015	Retrospective	SEER	OS	✓
Heidenreich, 2015	Retrospective	Single center	OS	
Sooriakumaran, 2015	Retrospective	Multicenter	OS	
Gandaglia, 2016	Retrospective	Single center	CSS	
Rusthoven, 2016	Retrospective	NCDB	OS	✓
Loppenberg, 2016	Retrospective	NCDB	OS	✓
Sooriakumaran, 2017	Retrospective	PCABaSe Sweden	OS	✓
Leyh-Bannurah, 2017	Retrospective	SEER	OS	✓
Steuber, 2017	Prospective	Martini Klinik	OS	?
Bianchini, 2017	Retrospective	Single center	OS	✓
Parikh, 2017	Retrospective	NCDB	OS	✓
Jang, 2017	Retrospective	Single center	OS	✓
Pomp, 2018	Retrospective	SEER	OS	✓

EVIDENCE SUPPORTING LOCAL TREATMENT

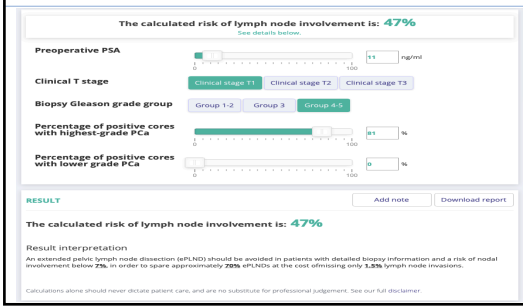
Safety, feasibility and non oncological benefit of RP in the metastatic setting

- Heidenreich et al.: No increase in surgery-related complications in well-selected patients
- Steuber et al.: Local treatment resulted in a reduced complication rate (7.0%) compared with that of the best supportive treatment group (35.0%)
- Sooriakumaran et al.: 80 % of the patients did not have any complications

ROLE OF LOCAL THERAPY: RANDOMIZED TRIALS AND THEIR CHARACTERISTICS

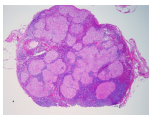
Study name	Country Primary investigator	Phase	Design	Primary endpoint	Start	Close to recruitment in	NCI/NRT number
Stampede	UK, N.D.James,MD University Hospital Birmingham	Phase II and Phase III	SOC (ADT) and prostate RT, (two possible RT schedules)	OS	January 2013 (Arm H)	September 2016 (Arm H)	NCT 00268476
Horrad	Netherlands, G van Andel, MD Onze lieve Amsterdam	Phase II	SOC (ADT)	OS	June 2004	August 2014	NCT 271
PEAGE 1	Europe, K Fizazi, MD PhD Gustave Roussy, Paris	Phase III	SOC (ADT +/- Docetaxel) +/- abiraterone acetate with or without Prostate RT	OS, PFS	October 2013	May 2017	NCT01957436
ENROS 1932	USA, B F Chapin, MD M.D. Anderson Cancer Center, Houston	Phase II I	RP or EBRT + SoC vs SoC	OS	December 2015	March 2018	NCT01751438
g-RAMPP	Germany Markus Graefen Martini-Klinik Hamburg	Phase III	BST With RP or BST Alone	CSS	May 2015	April 2020	NCT02454543
TROMBone	UK Freddie Hamdy Oxford University Hospitals London	Feasibility	RP+eLND + SoC vs SoC	Feasibility	February 2017	November 2018	ISRCTN 15704862

BRIGANTI NOMOGRAM

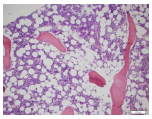


CASE 1

- Biopsy of pretracheal lymph node shows granulations, compatible with sarcoidosis



- Biopsy of the rib lesion is inconclusive

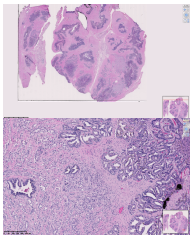


WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Local Radiotherapy+ADT
5. Local Radiotherapy+stereotaxic radiotherapy on ribs and nodes+ADT
6. Prostatectomy+stereotaxic radiotherapy on ribs+ADT

CASE 1

- Patient undergoes robotic assisted radical prostatectomy (Dec 2016)
  - Pathology: adenocarcinoma, Gleason 7 (4+3), pT3bN0R0.
  - 28 negative nodes
  - Surgery uneventful, excellent recovery of continence by 6 weeks post-op
  - PSA at 6 weeks: **0,48ng/ml**



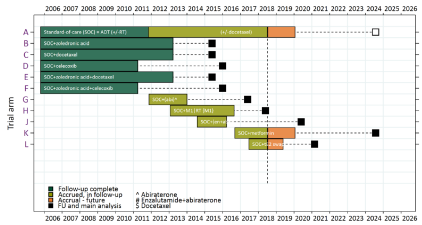
WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Adjuvant Radiotherapy+ADT
5. Adjuvant Radiotherapy+stereotaxic radiotherapy on rib + ADT
6. Stereotaxic radiotherapy on rib + ADT
7. Restaging

CASE 1

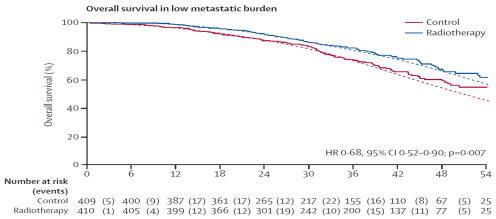
- The view of the Radiation Oncologist

STAMPEDE TRIAL



http://www.stampedetrial.org/ 25

RT to the primary prolongs OS in low-volume mHSPC

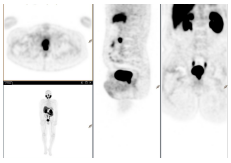


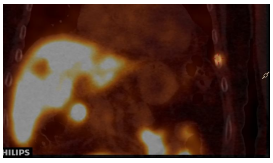
RT to the primary works as systemic treatment in prostate cancer

Parker C. et al. Lancet 2018. 26

CASE 1

- Restaging by PSMA confirms single uptake by costal lesion on VI left rib,
- Urinary activity +++
- Impossible to exclude prostatic bed recurrence





WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Adjuvant Radiotherapy±ADT
5. Adjuvant Radiotherapy+stereotaxic radiotherapy on rib ± ADT
6. Stereotaxic radiotherapy on rib ± ADT

- Patient undergoes Adjuvant radiotherapy to prostatic fossa (74Gy)
- Stereotaxic radiotherapy (3x10Gy) to costal lesion

- PSA 1 month after radiotherapy: 0,12ng/ml

WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Surveillance

CASE 1

- PSA
- 3/17: 0,08
- 6/17: 0,07
- 9/17: 0,12
- 12/17: 0,14
- 03/18: 0,24

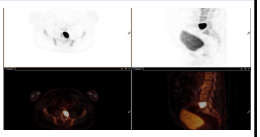
- PSMA PET/CT: persistant activity on costal lesion
- PSA-DT: 6 months

WHAT TO DO?

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Surveillance
5. Orthopaedic Surgery

CASE 1

- Patient is kept on surveillance
- PSA 9/18: 2,68ng/ml
- Bone scan: 3 bone lésions (L5, Th10, scapula)



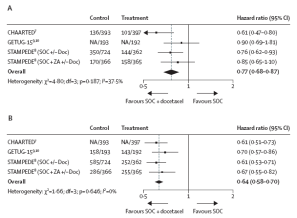
CASE 1

- The view of the Medical Oncologist
  - Gleason 8
  - Rapidly rising PSA
  - Long life expectancy

=> Treatment needed

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Claire L Vale*, Sarah Burdett*, Laryssa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Joyce F Tierney, for the STOPCaP Steering Group



Effect of the addition of docetaxel in **M1** patients

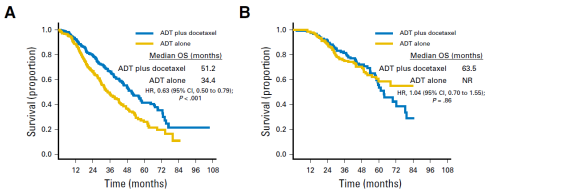
A: on OS

B: on DFS

Vale et al, Lancet Oncol, 2016, 17, 243-56

mHNPC : Docetaxel and volume disease in CHAARTED

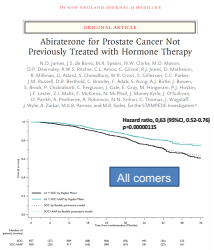
Addition of docetaxel to ADT benefits high-volume disease ONLY

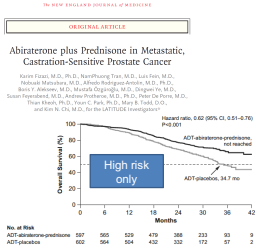


Sweeney et al, N Engl J Med, 2015, 373, 737-46
Kyriakopoulos et al, J Clin Oncol, 2018, 36, 1080-7

mHNPC : WHAT WE KNOW FOR ABIRATERONE!

- 2 randomised controlled trials and 1 meta-analysis

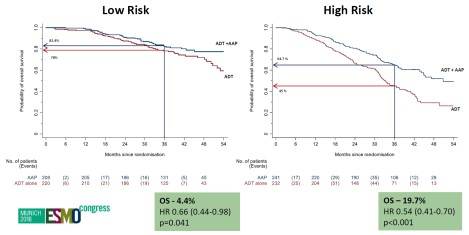




James N, et al. N Engl J Med. 2017, 377, 338-51
Fizazi K, et al. N Engl J Med. 2017, 377, 352-60

DOES SIZE MATTER ?
STAMPEDE AAP SUB-ANALYSIS

RESULTS: OVERALL SURVIVAL



MUNICH 2018 ESMO congress

OS - 4.4%
HR 0.66 (0.44-0.98)
p=0.041

OS – 19.7%
HR 0.54 (0.41-0.70)
p<0.001

Hoyle et al, ESMO meeting, Munich, Oct 2018

WHAT TO DO?

Hôpital Erasme | ULB

1. ADT
2. ADT+docetaxel
3. ADT+Abi/P
4. Stereotaxic radiotherapy ± ADT
5. Surveillance