Mr Bill Cross

Consultant
Urological Surgeon

Leeds Teaching
Hospitals NHS Trust

Advances in Prostate Cancer

1. Prostate cancer diagnostics
2. Management of advanced disease

Two-week fast track referral

62 years old

PSA 5.5ng/ml

IPSS – 9/2

Comorbidity – hypertension

Performance status – 0

No family history of prostate cancer

DRE – firm right lobe

What next?

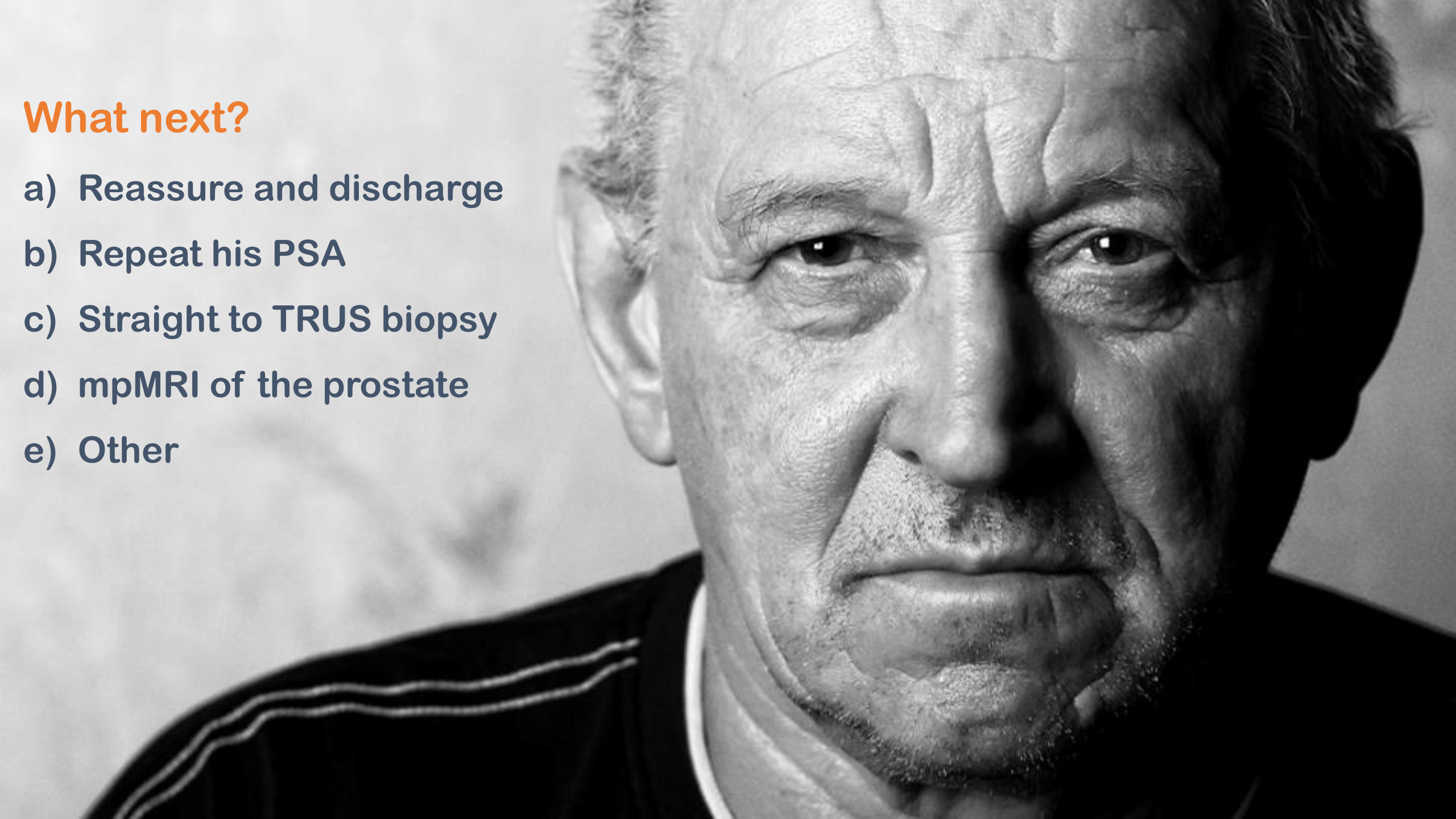
a) Reassure and discharge

b) Repeat his PSA

c) Straight to TRUS biopsy

d) mpMRI of the prostate

e) Other



NICE guideline [NG131] - May 2019

- Do not automatically offer a prostate biopsy on the basis of serum PSA level alone
- Offer multiparametric MRI as the first-line investigation for people with suspected clinically localised prostate cancer
- Do not routinely offer mpMRI to people with prostate cancer who are not going to be able to have radical treatment

“How accurate is mpMRI?”

“If I have prostate cancer, will the scan always detect it?”

“If the scan is negative does this mean I don’t have cancer?”

All prostate cancers are not equal

Risk to the patient

Low risk cancer

Increased PSA

Higher Gleason score

Increased tumour volume (stage)

High risk cancer

"At what PSA, Gleason score and tumour volume does a prostate cancer become clinically significant?"

Definitions – clinically significant prostate cancer

- **Gleason score ≥4+3 or cancer core length ≥6 mm**
- **Gleason score ≥3+4 or cancer core length ≥4 mm**
- **Any Gleason score 7 (≥3+4)**

The art and science of prostate mpMRI reporting

Prostate MRI reporting

PIRADS 1	Very low probability of clinically significant cancer
PIRADS 2	Low probability of clinically significant cancer
PIRADS 3	Intermediate probability of clinically significant cancer
PIRADS 4	High probability of clinically significant cancer
PIRADS 5	Very high probability of clinically significant cancer

(PIRADS - **Prostate Imaging Reporting and Data System**)

“If I have prostate cancer, will the scan always detect it?”

Test sensitivity

“If I have prostate cancer, will the scan always detect it?”

	MRI %	TRUS Biopsy %
Gleason score ≥4+3 or cancer core length ≥6 mm		
Gleason score ≥3+4 or cancer core length ≥4 mm		
Any Gleason score 7 (≥3+4)		

Ahmed *et al.* Lancet 2017 (PROMIS Study)

“If I have prostate cancer, will the scan always detect it?”

	MRI %	TRUS Biopsy %
Gleason score ≥4+3 or cancer core length ≥6 mm		
Sensitivity		48
Gleason score ≥3+4 or cancer core length ≥4 mm		
Sensitivity		60
Any Gleason score 7 (≥3+4)		
Sensitivity		48

Ahmed *et al.* Lancet 2017 (PROMIS Study)

“If I have prostate cancer, will the scan always detect it?”

	MRI %	TRUS Biopsy %
Gleason score ≥4+3 or cancer core length ≥6 mm		
Sensitivity	93	48
Gleason score ≥3+4 or cancer core length ≥4 mm		
Sensitivity	87	60
Any Gleason score 7 (≥3+4)		
Sensitivity	88	48

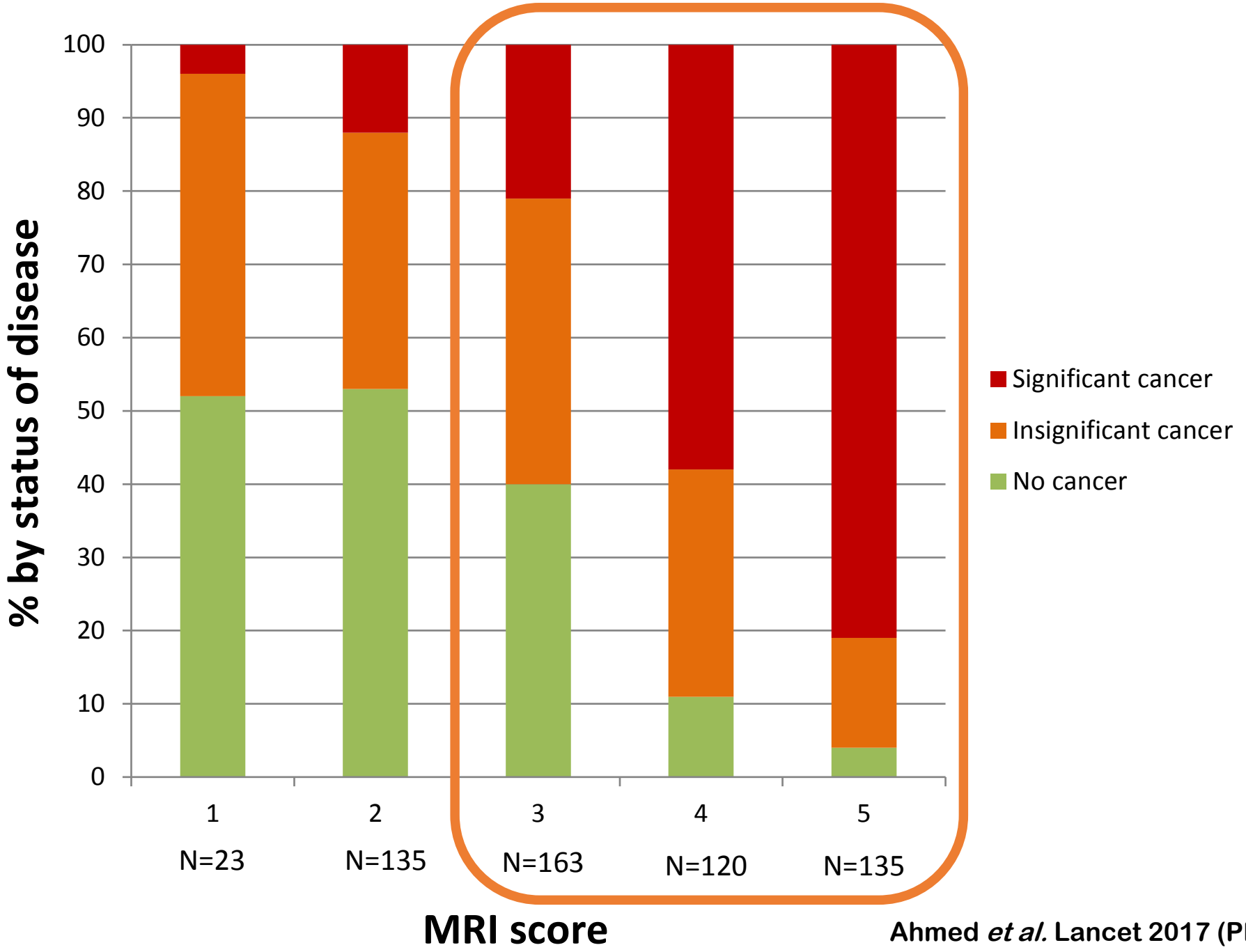
Ahmed *et al.* Lancet 2017 (PROMIS Study)

Take Home Messages

- TRUS-biopsy performs poorly as a diagnostic test for clinically significant prostate cancer
- mpMRI improves the detection of clinically significant cancer

But not all men with a ‘positive’ scan have prostate cancer

False positive test



Ahmed *et al.* Lancet 2017 (PROMIS Study)

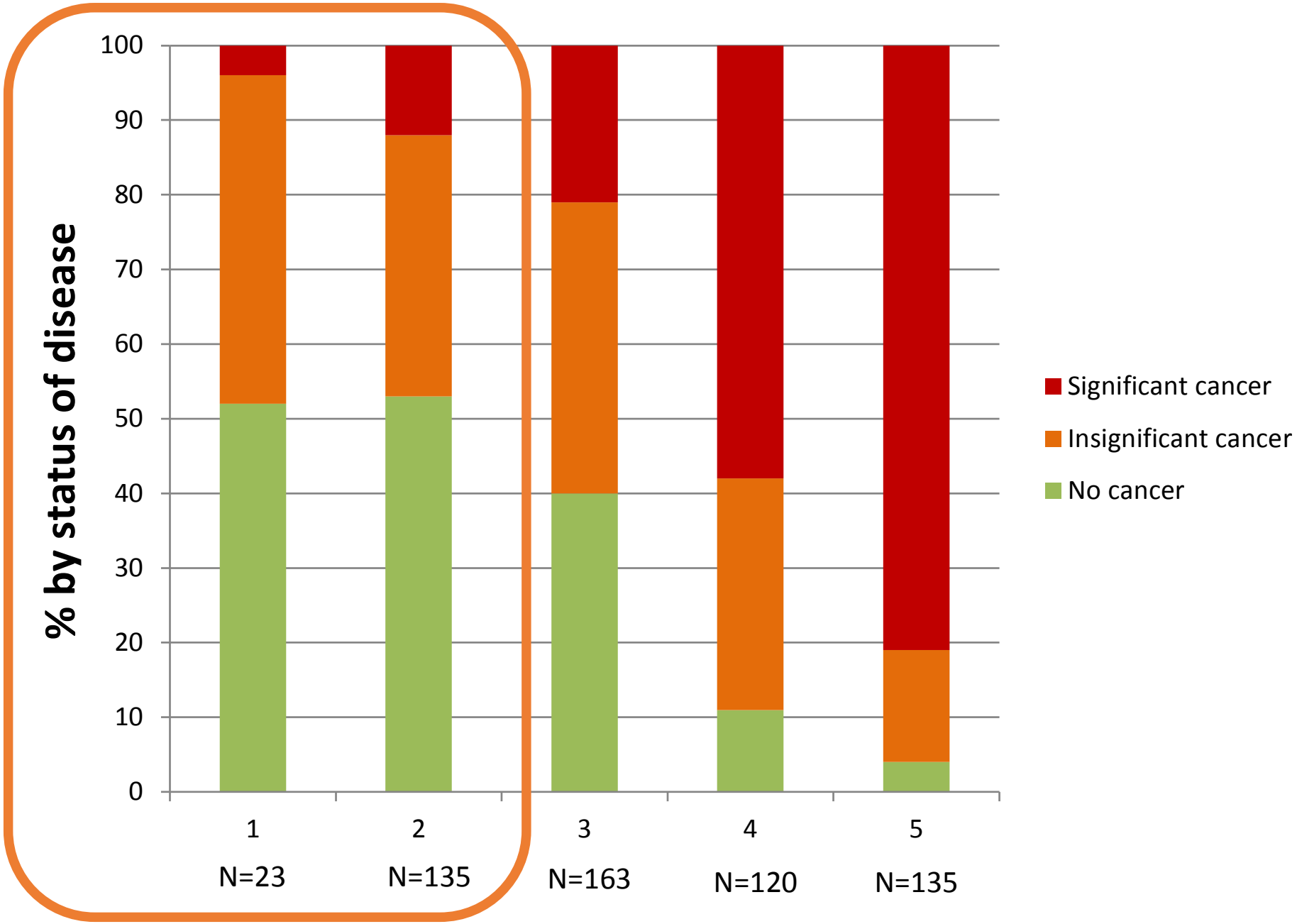
“If the scan is negative does this mean I don’t have cancer?”

Negative predicitive value

“If the scan is negative does this mean I don’t have cancer?”

	MRI %	TRUS Biopsy %
Gleason score ≥4+3 or cancer core length ≥6 mm		
Sensitivity	93	48
Negative Predictive value	89	74
Gleason score ≥3+4 or cancer core length ≥4 mm		
Sensitivity	87	60
Negative Predictive value	72	65
Any Gleason score 7 (≥3+4)		
Sensitivity	88	48
Negative Predictive value	76	63

Ahmed *et al.* Lancet 2017 (PROMIS Study)



Ahmed *et al.* Lancet 2017 (PROMIS Study)

mpMRI - PIRADS 2

What next?

a) Discharge, no follow up

b) Discuss option of a biopsy

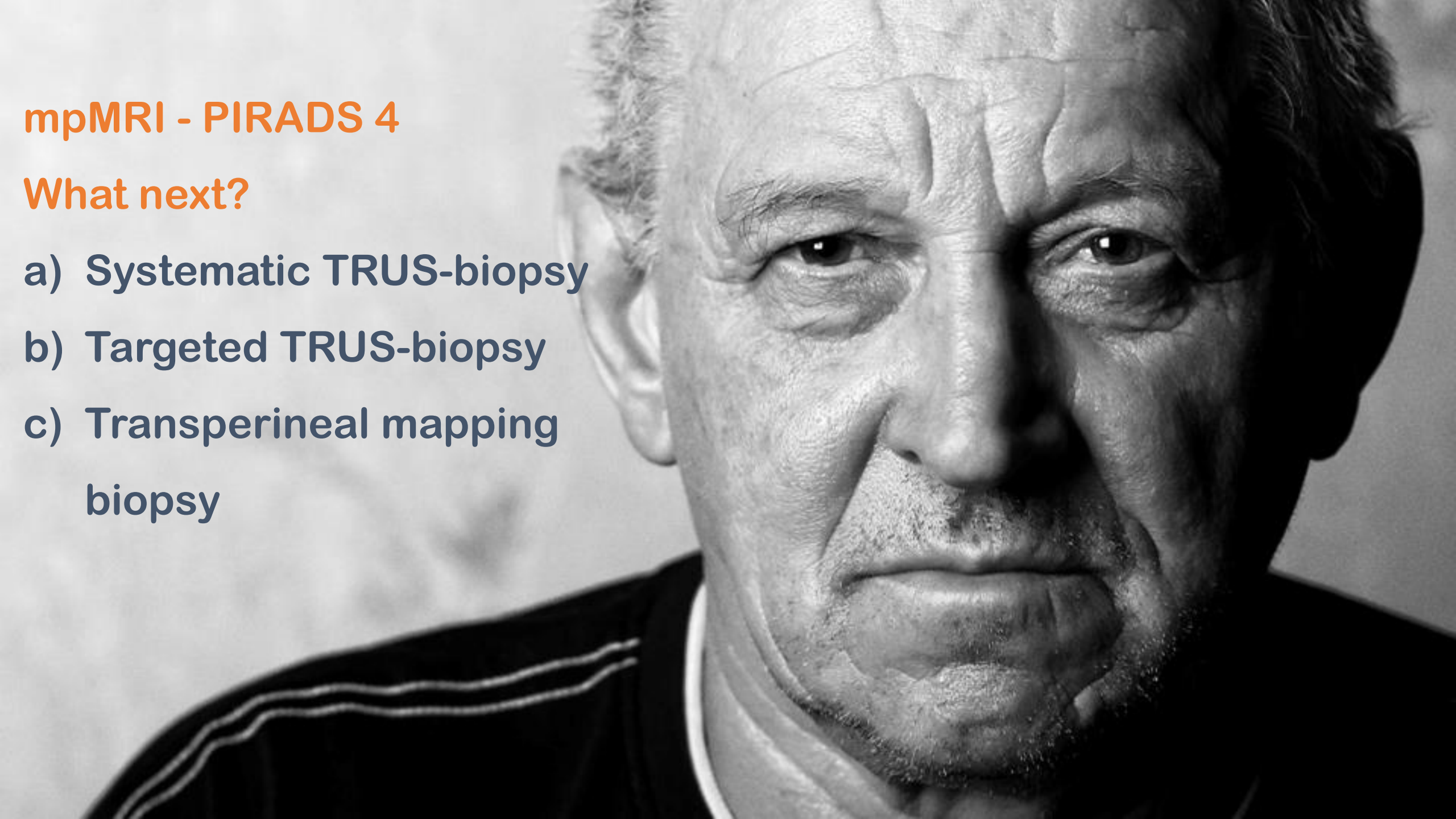
c) Discharge, PSA surveillance

NICE guideline [NG131] - May 2019

- **Consider omitting a prostate biopsy for people whose multiparametric MRI Likert score is 1 or 2,** but only after discussing the risks and benefits with the person and reaching a shared decision
- **For people who have a raised PSA and MRI Likert score of 1 or 2, and who have not had a prostate biopsy, repeat PSA test at 3 to 6 months and:**
  - **offer prostate biopsy if there is a strong suspicion of prostate cancer** (for example, PSA density greater than 0.15 ng/ml/ml or PSA velocity greater than 0.75 ng/year, or strong family history), taking into account their life expectancy and comorbidities
  - **discharge the person to primary care if the level of suspicion is low; advise PSA follow-up at 6 months and then every year, and set a PSA level for primary care at which to re-refer based on PSA density (0.15 ng/ml/ml) or velocity (0.75 ng/year)**

Take Home Messages

- Approximately 25% of men may be able to avoid a prostate biopsy if mpMRI is used as a triage test
- If PIRADS 1-2, discuss option of biopsy or PSA surveillance



mpMRI - PIRADS 4

What next?

a) Systematic TRUS-biopsy

b) Targeted TRUS-biopsy

c) Transperineal mapping biopsy

MRI-targeted *vs* standard biopsy

	Standard biopsy	MRI-guided biopsy
Number of men recruited	248	252

Kasivisvanathan *et al.* NEJM 2018 (PRECISION Study)

MRI-targeted *vs* standard biopsy

	Standard biopsy	MRI-guided biopsy
Number of men recruited	248	252
% which avoided a biopsy (MRI PIRADS <3)		28%

Kasivisvanathan *et al.* NEJM 2018 (PRECISION Study)

MRI-targeted *vs* standard biopsy

	Standard biopsy	MRI-guided biopsy
Number of men recruited	248	252
% which avoided a biopsy (MRI PIRADS <3)		28%
Median number of biopsies	**12**	**4**

Kasivisvanathan *et al.* NEJM 2018 (PRECISION Study)

MRI-targeted *vs* standard biopsy

	Standard biopsy	MRI-guided biopsy
Number of men recruited	248	252
% which avoided a biopsy (MRI PIRADS <3)		28%
Median number of biopsies	12	4
Clinically significant disease (Gleason 7)	**26%**	**38%**
Insignificant disease	**22%**	**9%**

Kasivisvanathan *et al.* NEJM 2018 (PRECISION Study)

MRI-targeted *vs* standard biopsy

	Standard biopsy	MRI-guided biopsy
Number of men recruited	248	252
% which avoided a biopsy (MRI PIRADS <3)		28%
Median number of biopsies	12	4
Clinically significant disease (Gleason 7)	26%	38%
Insignificant disease	22%	9%
Quality of life/side-effects	**Did not differ significantly**	

Kasivisvanathan *et al.* NEJM 2018 (PRECISION Study)

Take Home Message

- MRI, with or without targeted biopsy, results in
  - fewer men undergoing biopsy
  - more clinically significant cancers being identified
  - less over detection of clinically insignificant cancer
  - fewer prostate biopsies

“If I only have a targeted biopsy will you miss disease in the other parts of the prostate?”

Take Home Message

- Omission of standard biopsies in men having a targeted biopsy may miss up to 10% of cases of clinically significant disease

Management of advanced disease

Prostate Clinic

69 years old

PSA 110ng/ml

IPSS – 11/2

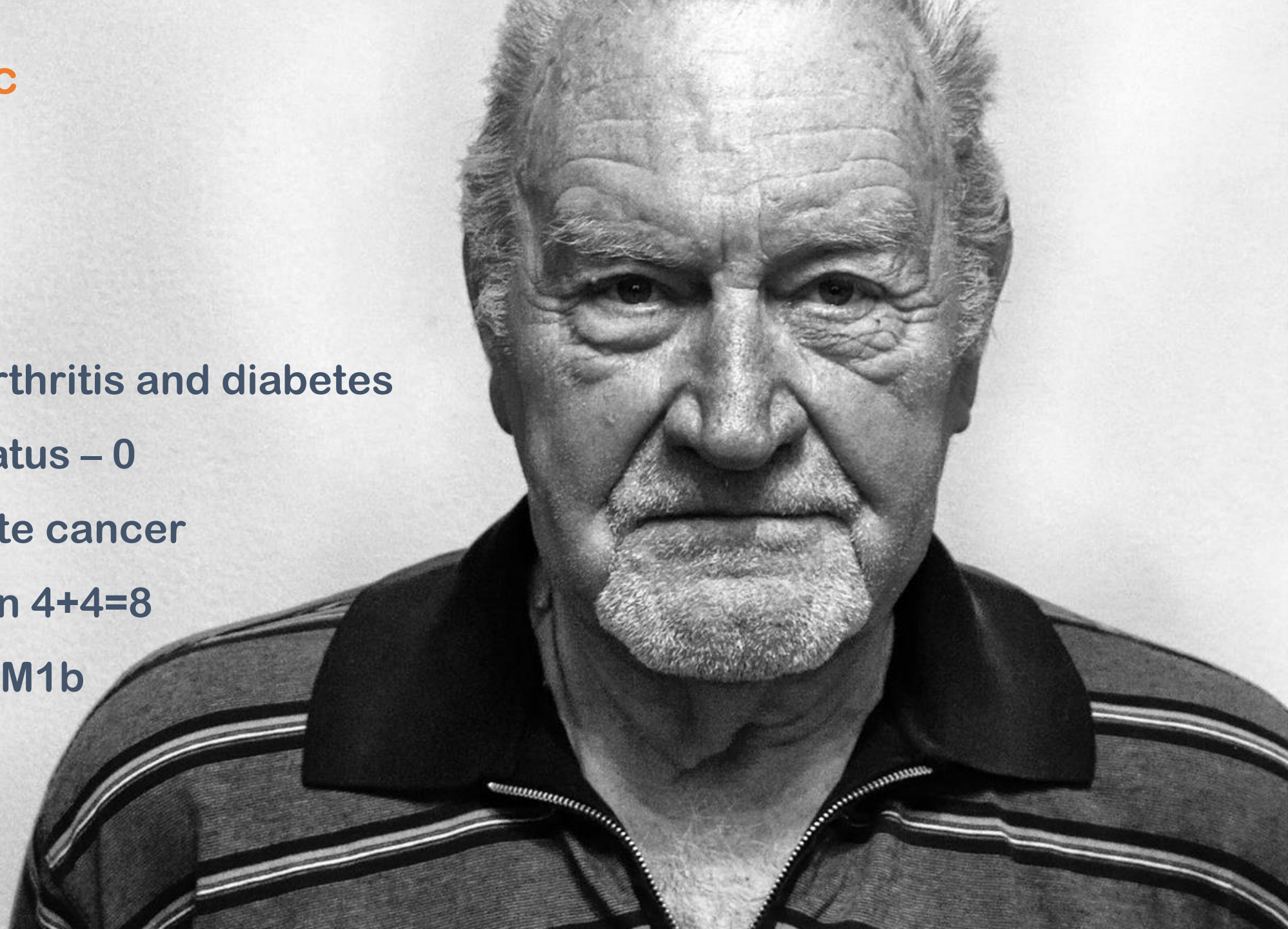
Comorbidity – arthritis and diabetes

Performance status – 0

DRE – T3 prostate cancer

Biopsy – Gleason 4+4=8

Staging – T3 N1 M1b



Recommended management

Gleason 8 T3 N1 M1b (PSA 110)

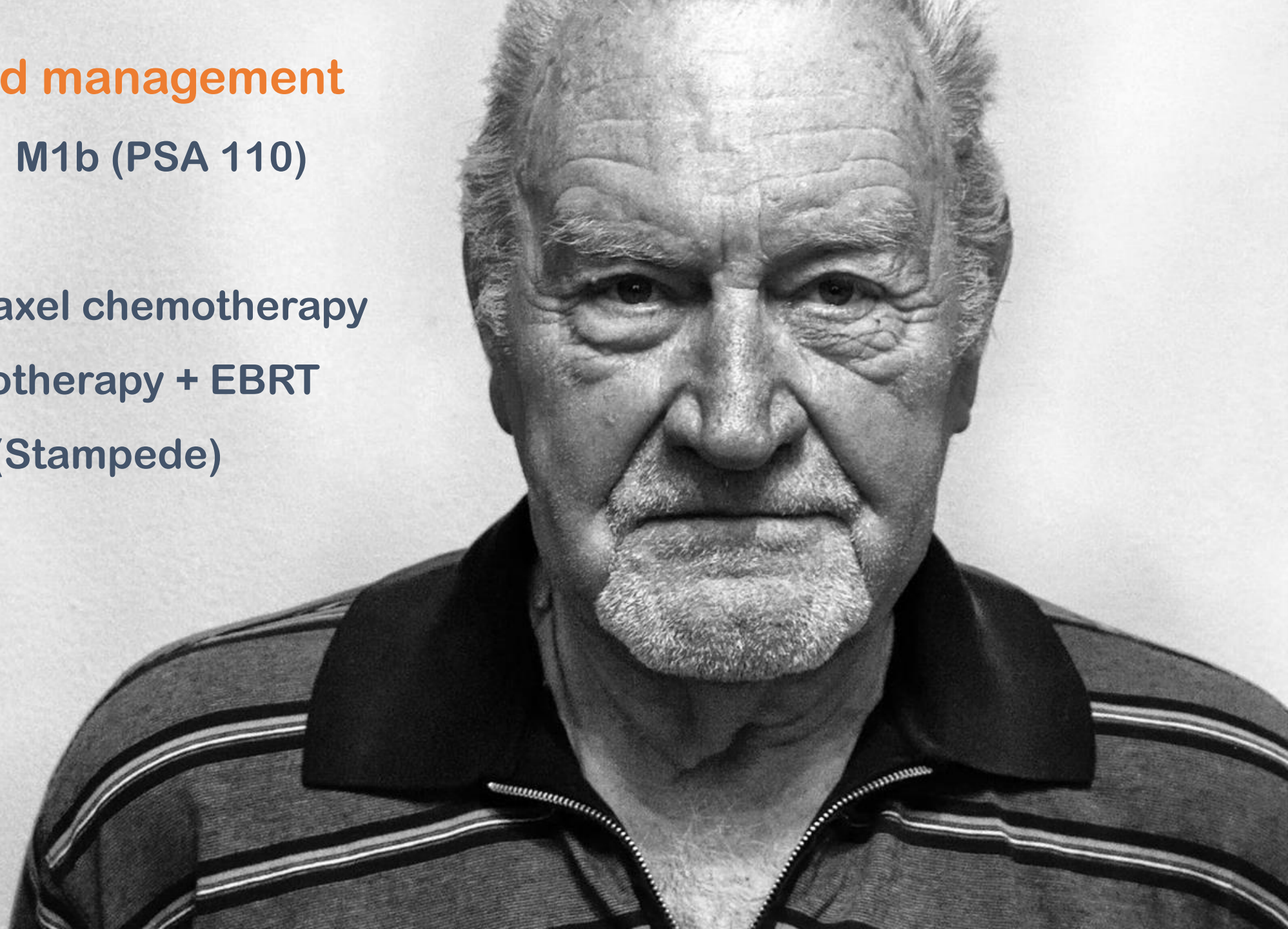
a) ADT only

b) ADT + Docetaxel chemotherapy

c) ADT + Chemotherapy + EBRT

d) Clinical trial (Stampede)

e) Other



“What is my prognosis if I just have hormone treatment (primary ADT)?”

Median survival

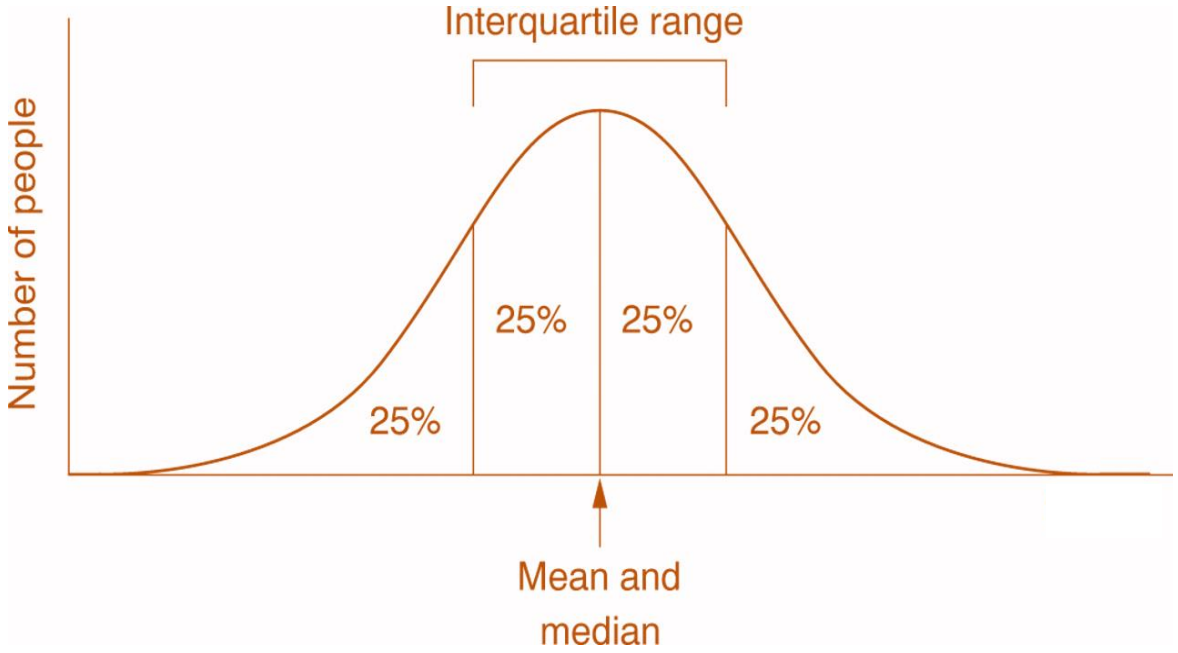
42.1 months

James et al. Eur Urol 2015 (STAMPEDE Trial)

Median survival

42.1 months

IQR: 22.7–90.7 months



IQR – Interquartile range (middle 50%)

James et al. Eur Urol 2015 (STAMPEDE Trial)

Median survival

42.1 months

IQR: 22.7–90.7 months

Survival impacted negatively by

- presence of non-regional N+
- worse performance status
- higher Gleason score
- younger age at diagnosis

IQR – Interquartile range (middle 50%)

James et al. Eur Urol 2015 (STAMPEDE Trial)

“I have concerns about chemotherapy. What are the benefits of treatment?”

Median survival (M1)

SOC - 45 months

SOC+chemotherapy - 60 months

SOC – standard of care

James et al. Lancet 2015 (STAMPEDE Trial)

Chemotherapy side effects

- Neutropenia/Febrile Neutropenia (12-15%)
- Gastrointestinal symptoms (8%)

- Few men stop treatment due to side-effects (13%)

James et al. Lancet 2015 (STAMPEDE Trial)

“Can I have anything else other than chemotherapy?”

Abiraterone

Abiraterone

3-year overall survival (M1)

SOC – 49%

SOC+Abiraterone – 66%

Fizazi et al. NEJM 2017 (LATITUDE Trial)

Abiraterone

Radiographic Progression Free Survival

SOC – 14.8 months

SOC+Abiraterone – 33 months

Fizazi et al. NEJM 2017 (LATITUDE Trial)

Abiraterone

Safety (Grade 3-4 adverse events)
SOC – 48%
SOC+Abiraterone – 63%

Most frequent events – hypertension and hypokalemia

Fizazi et al. NEJM 2017 (LATITUDE Trial)

“Should I have chemotherapy or Abiraterone?”

NICE currently reviewing Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer

Docetaxel *vs* Abiraterone

Overall Survival

No significant difference between the treatments

Safety

Similar % of men experienced side-effects

Side effects specific to the individual drugs

Sydes et al. Annal Oncol 2018 (STAMPEDE Trial)

“I have read about Enzalutamide. Can I have this instead of chemotherapy?”

Enzalutamide

Benefits

Improved progression free survival

Longer overall survival

Safety

Increased fatigue and small risk of seizures

Peripheral neuropathy (Enzalutamide + Docetaxel)

Davis et al. NEJM 2019 (ENZAMET Trial)

NICE currently reviewing Enzalutamide for treating metastatic hormone-sensitive prostate cancer with androgen deprivation therapy

(Expected publication date - May 2020)

“What is the benefit of prostate radiotherapy if my cancer has already spread?”

Take Home Messages

- Radiotherapy to the prostate does not improve overall survival for unselected patients
- But there is a benefit for men with low volume disease

High metastatic burden

4 or more bone metastases with one or more outside the vertebral bodies or pelvis or visceral metastases or both

3-year survival (low volume metastatic burden)

SOC – standard of care

Parker et al. Lancet 2018 (STAMPEDE Trial)

High metastatic burden

4 or more bone metastases with one or more outside the vertebral bodies or pelvis or visceral metastases or both

3-year survival (low volume metastatic burden)

SOC - 73%

SOC+prostate radiotherapy - 81%

SOC – standard of care

Parker et al. Lancet 2018 (STAMPEDE Trial)

Take Home Messages

- The new standard of care is ADT+Docetaxel
- Evidence to support Abiraterone and Enzalutamide as an alternative to Docetaxel (NICE considering these)
- Addition of prostate radiotherapy in low volume metastatic disease improves survival
- Studies ongoing looking at combinations (eg STAMPEDE and PEACE-1)

Questions?