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AR-V7 splice variant and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer: Overall survival results

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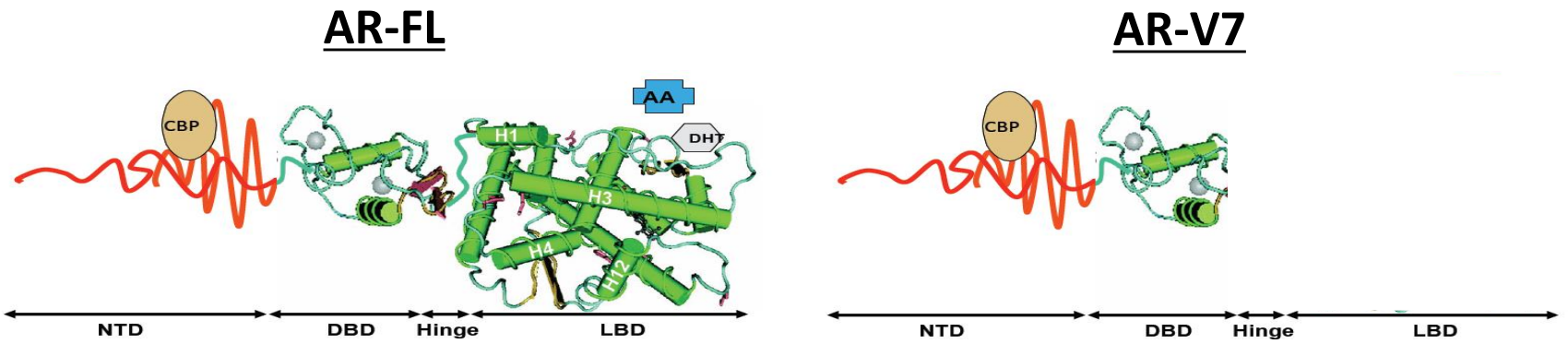
Background

- Androgen receptor variant-7 (AR-V7) is a truncated isoform of the AR that lacks the LBD, the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor



Background

- We previously reported that detection of AR-V7 in CTCs from men with mCRPC was associated with resistance to enzalutamide and abiraterone *(ASCO 2014, NEJM 2014)*
  - PSA_{50} rates and PFS were inferior in AR-V7(+) men
- Here, we present overall survival (OS) data from this study

Design: Prospective biomarker study

- We planned to enroll 30 men (each) with CRPC who were about to begin therapy w/ enzalutamide or abiraterone
- 85% Power to detect a difference in PSA response rates from 10% (in AR-V7[+] men) to 60% (in AR-V7[–] men), using a 2-sided α=0.10
- CTC samples were collected at 3 time points
  - *Baseline*/pretreatment
  - At time of *Response* to enzalutamide/abiraterone
  - At time of *Resistance* to enzalutamide/abiraterone

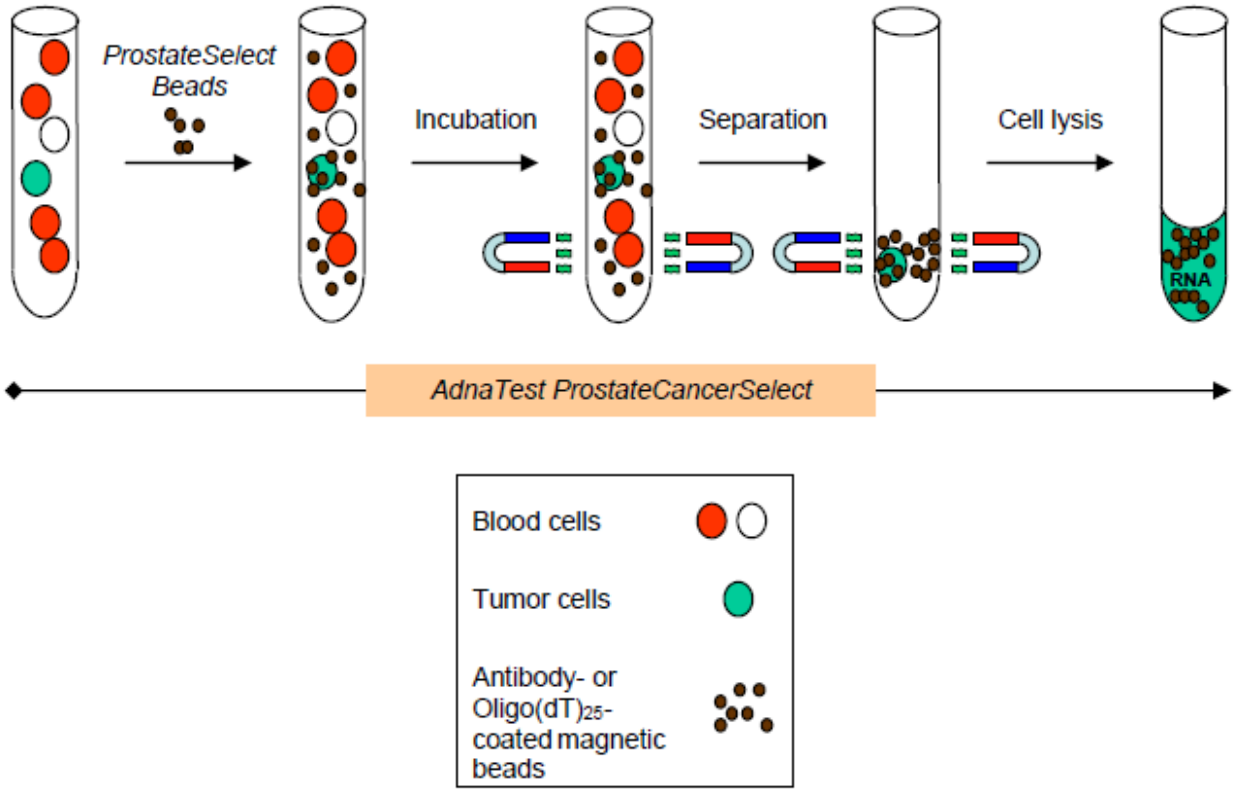
Outcome Measures

- PSA_{50} response rate *(presented previously)*
- PSA progression-free survival *(presented previously)*
- Progression-free survival *(presented previously)*
- Overall survival

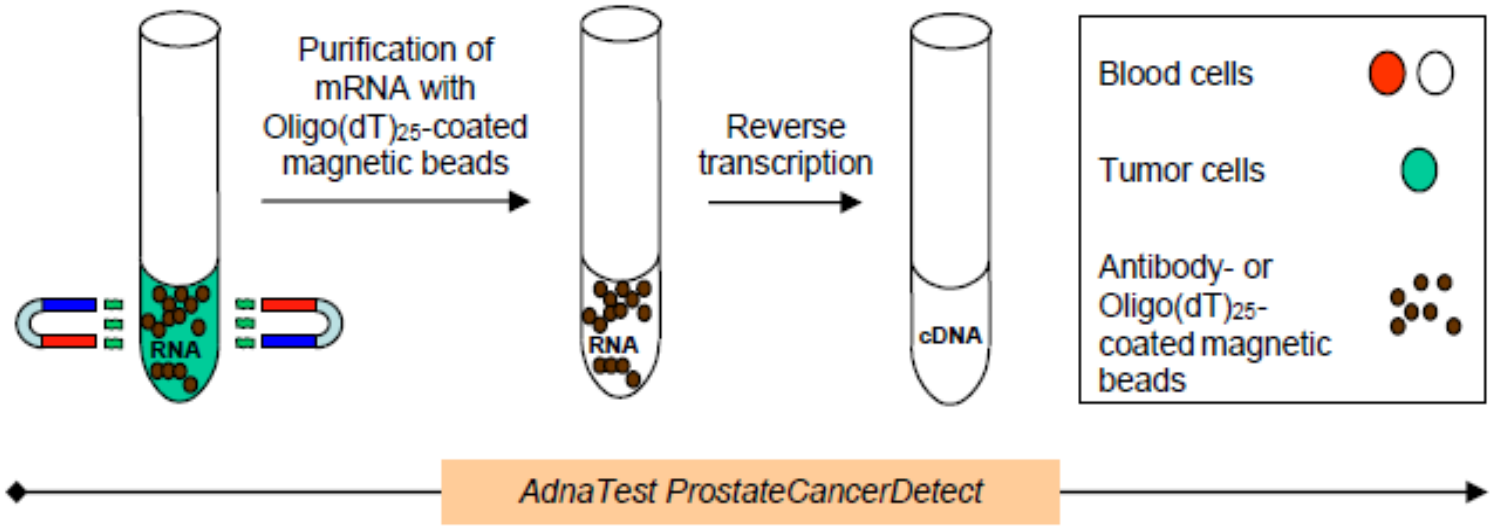
CTC-Based qRT-PCR AR-V7 Assay

- AdnaTest ProstateCancer*Select* kit
  - isolation and enrichment of CTCs
  - immunomagnetic capture via epithelial and tumor-associated antigens
- AdnaTest ProstateCancer*Detect* kit
  - mRNA expression analysis by qRT-PCR
  - multiplexed RT-PCR probe sets to detect prostate CTCs
    - PSA, PSMA, EGFR, Actin (control)
  - we have developed custom primers for AR and AR-V7

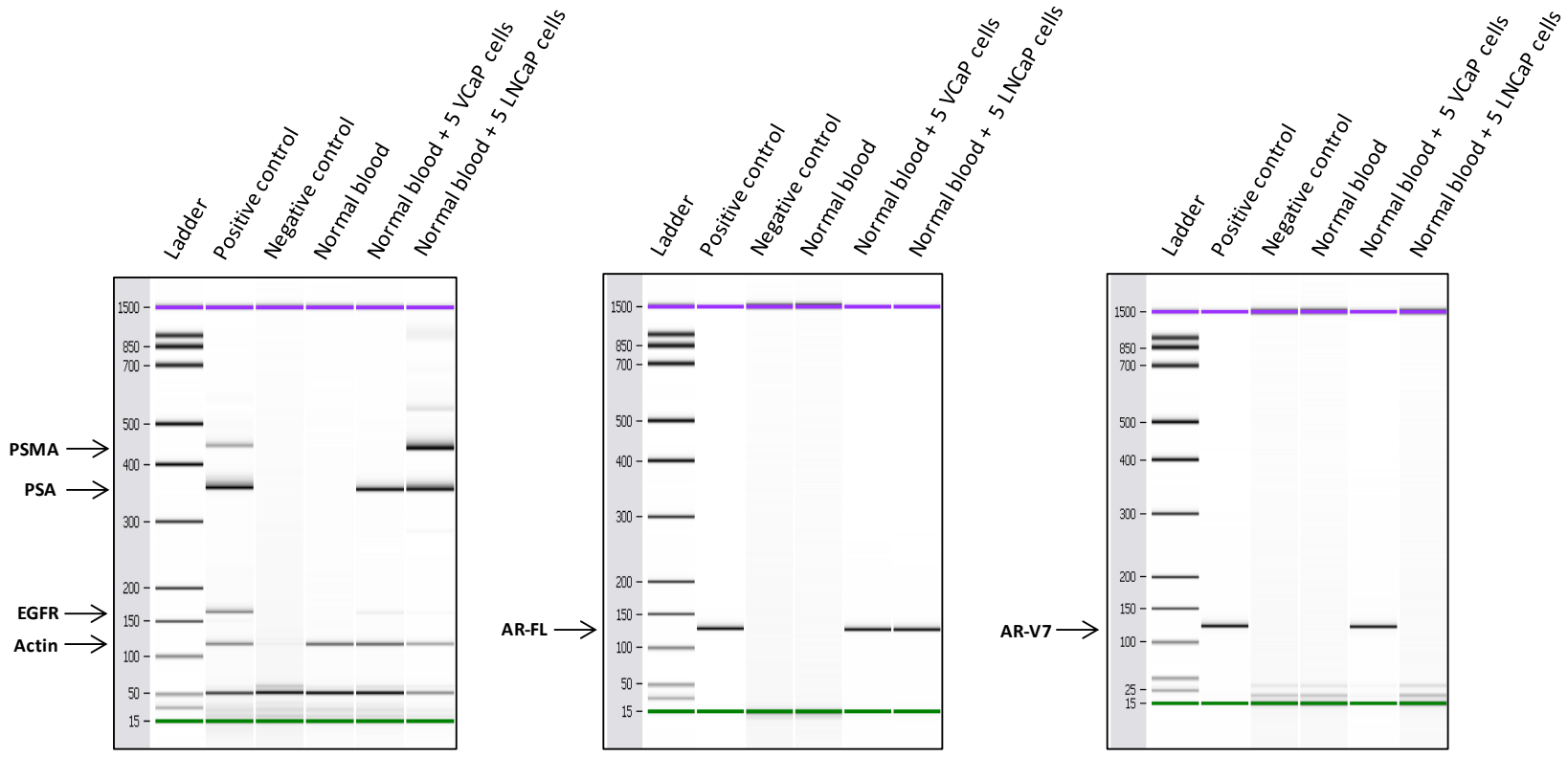
AdnaTest ProstateCancer*Select*



AdnaTest ProstateCancer*Detect*

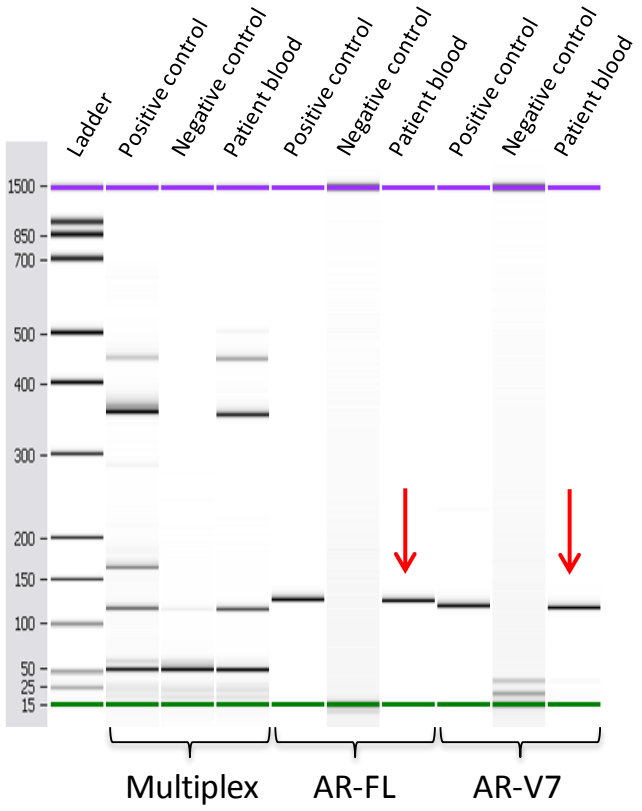


Detection of CTCs, AR-FL, AR-V7

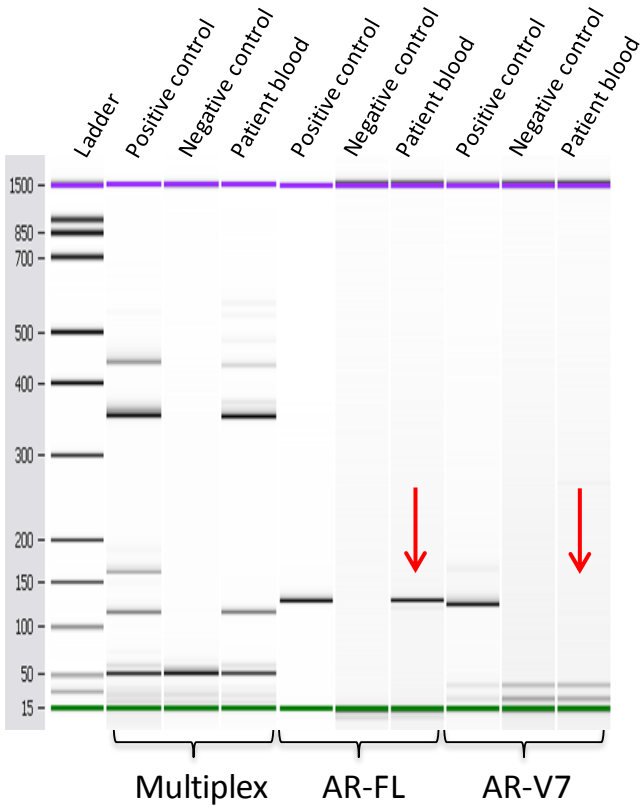


CTC Detection: Set 1 | AR-FL: Set 2 | AR-V7: Set 3

Detection of AR-V7: (+) and (–)



Patient 2: Pre-treatment sample



Patient 5: Pre-treatment sample

Characteristics - Enzalutamide

Baseline Characteristic	All Patients (N=31)	AR-V7 Negative (N=19)	AR-V7 Positive (N=12)
Age (years) Median	**70**	72	69
Gleason sum at diagnosis, (%) ≥8	**60.0%**	52.6%	72.7%
No. of prior hormonal therapies Mean	**3.3**	3.2	3.4
Prior use of abiraterone, (%) Yes	**64.5%**	47.4%	91.7%
Prior use of docetaxel, (%) Yes	**64.5%**	52.6%	83.3%
Presence of visceral metastases, (%) Yes	**32.3%**	15.8%	58.3%
Baseline PSA (ng/mL) Median	**44.3**	29.8	144.3

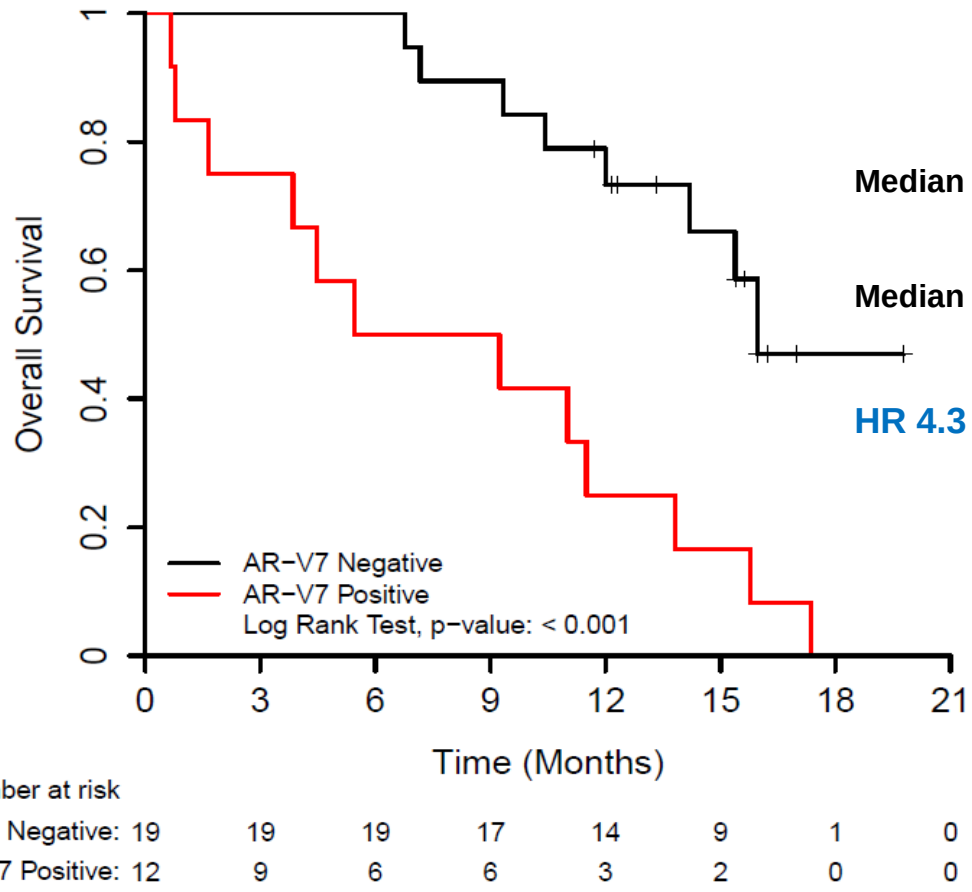
Characteristics - Abiraterone

Baseline Characteristic	All Patients (N=31)	AR-V7 Negative (N=25)	AR-V7 Positive (N=6)
Age (years) Median	**69**	69	69
Gleason sum at diagnosis, (%) ≥8	**73.3%**	76.0%	60.0%
No. of prior hormonal therapies Mean	**2.5**	2.2	3.7
Prior use of enzalutamide, (%) Yes	**12.9%**	8.0%	33.3%
Prior use of docetaxel, (%) Yes	**16.1%**	16.0%	16.7%
Presence of visceral metastases, (%) Yes	**25.8%**	32.0%	0%
Baseline PSA (ng/mL) Median	**37.8**	31.4	86.9

Maturity of OS analysis

- Enzalutamide cohort (n=31)
  - 20/31 death events
  - 65% maturity
- Abiraterone cohort (n=31)
  - 8/31 death events
  - 26% maturity

Overall Survival - Enzalutamide

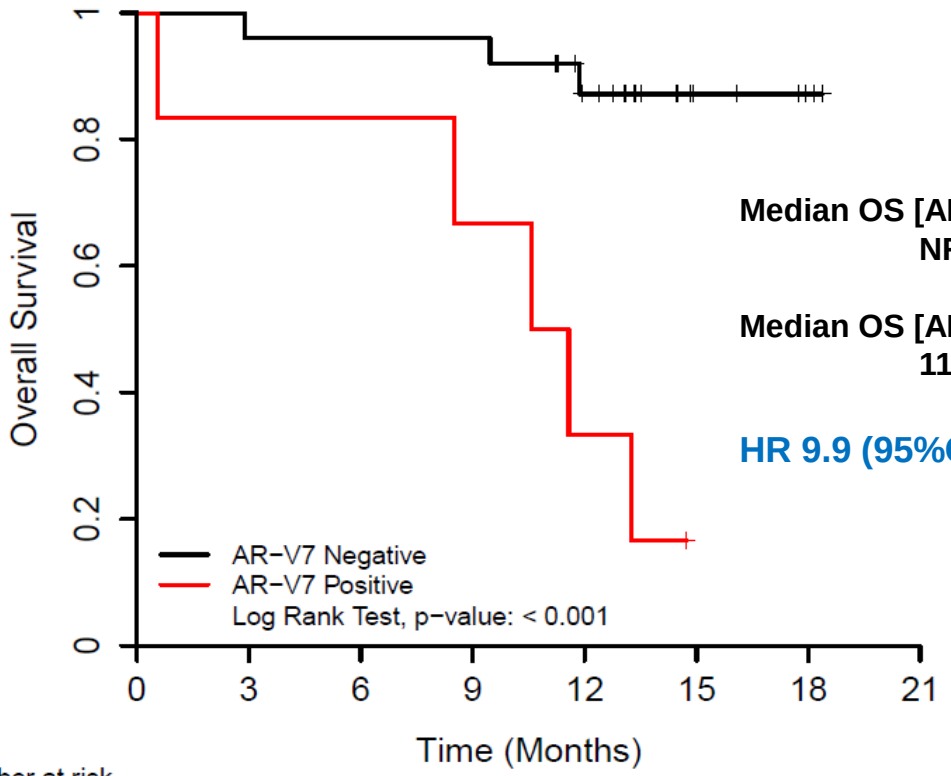


Median OS [AR-V7-Negative]:
16.0 mo (95%CI, 14.2–NR)

Median OS [AR-V7-Positive]:
7.4 mo (95%CI, 3.9–NR)

HR 4.3 (95%CI, 1.7–10.7); P<0.001

Overall Survival - Abiraterone



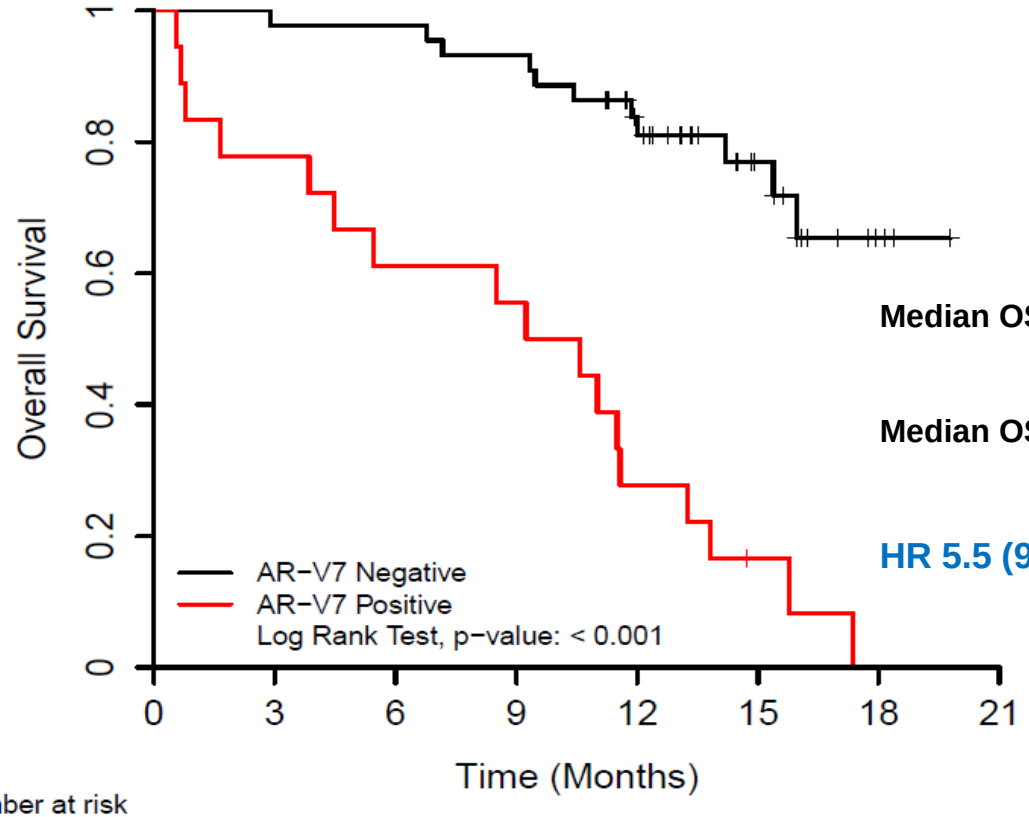
Number at risk							
AR−V7 Negative: 25	24	24	24	17	6	3	0
AR−V7 Positive: 6	5	5	4	2	0	0	0

Median OS [AR-V7-Negative]:
NR after 18 mo

Median OS [AR-V7-Positive]:
11.1 mo (95%CI, 8.5–NR)

HR 9.9 (95%CI, 2.3–41.6); P<0.001

Overall Survival - Combined



Number at risk								
AR−V7 Negative:	44	43	43	41	31	15	4	0
AR−V7 Positive:	18	14	11	10	5	2	0	0

Median OS [AR-V7-Negative]:
>16.0 mo (95%CI, 16.0–NR)

Median OS [AR-V7-Positive]:
9.9 mo (95%CI, 4.5–13.8)

HR 5.5 (95%CI, 2.5–12.0); P<0.001

Multivariable Cox Model for OS (stratified by treatment type)

- AR-V7 (+)
  - HR 2.58 (95%CI, 1.10–6.04); *P=0.029*
- Prior use of Abi/Enza
  - HR 4.09 (95%CI, 1.41–11.88); *P=0.010*
- AR-FL level (continuous)
  - HR 1.17 (95%CI, 0.94–1.45); *P=0.152*

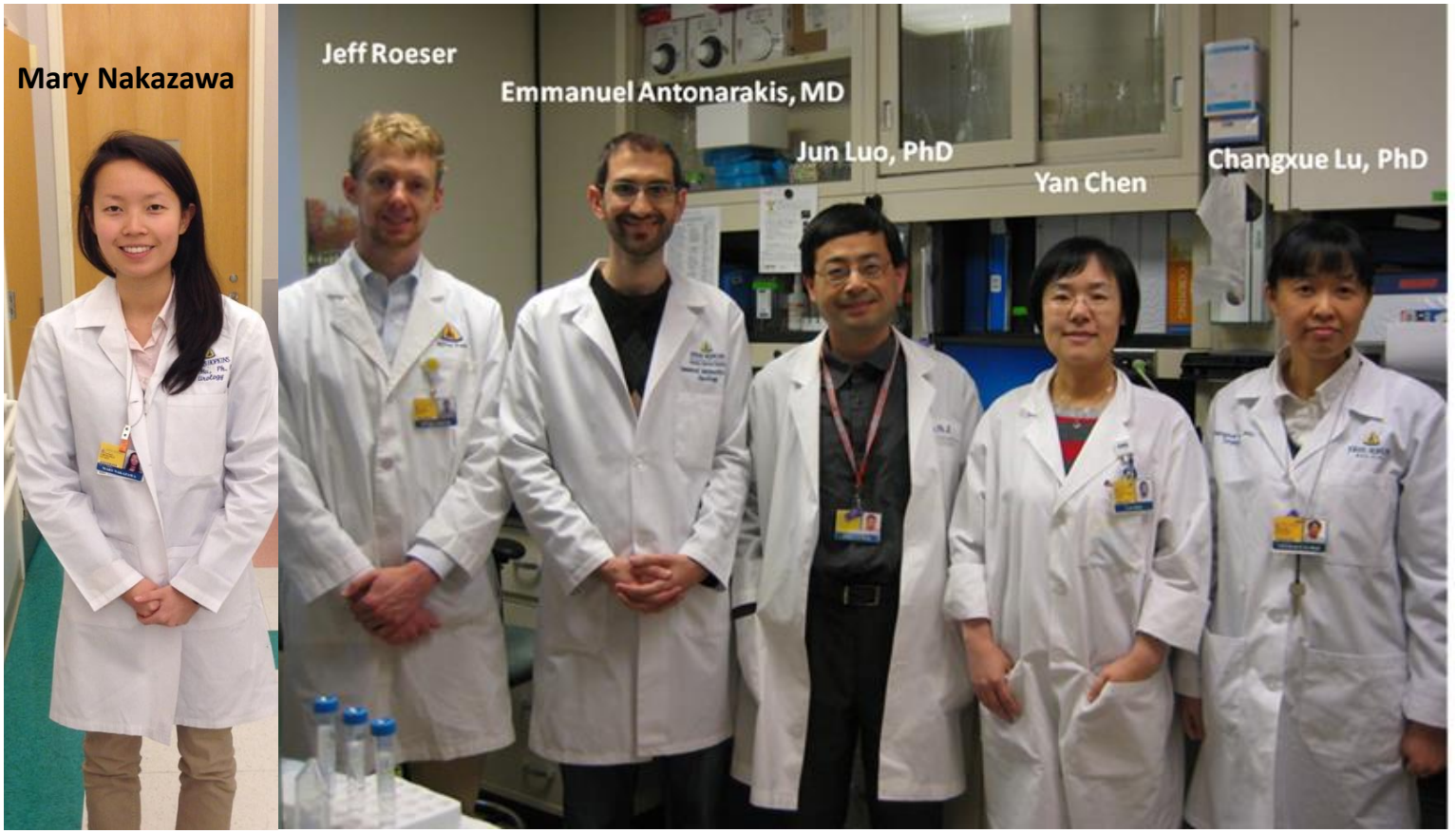
Conclusions

- Detection of AR-V7 in CTCs from men with mCRPC is associated with resistance to both enzalutamide and abiraterone, as evidenced by inferior PSA_{50} response rates, PFS *and OS*
- AR-V7 status may be used as a non-invasive biomarker to predict resistance to AR-targeting agents, facilitate treatment selection, and fuel the development of AR-NTD inhibitors

Limitations

- These findings require replication and validation in multi-center studies using larger patient numbers
- It is still not known whether AR-V7 status is a predictive (*i.e.* treatment-selection) biomarker, or just a prognostic marker: its role should be determined in the context of other therapies

Laboratory of Jun Luo, PhD



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