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MEETING SUMMARY
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PROSTATE CANCER UPDATE

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INTERESTING ORAL PROSTATE CANCER PRESENTATIONS AT ASCO GU 2020

ANALYSIS OF SMALL NON-CODING RNAs IN URINARY EXOSOMES TO CLASSIFY PROSTATE CANCER INTO LOW-GRADE (GG1) AND HIGHER GRADE (GG2-5)

Klotz L, et al. ASCO GU 2020. Abstract #277
Oral Presentation

INTRODUCTION

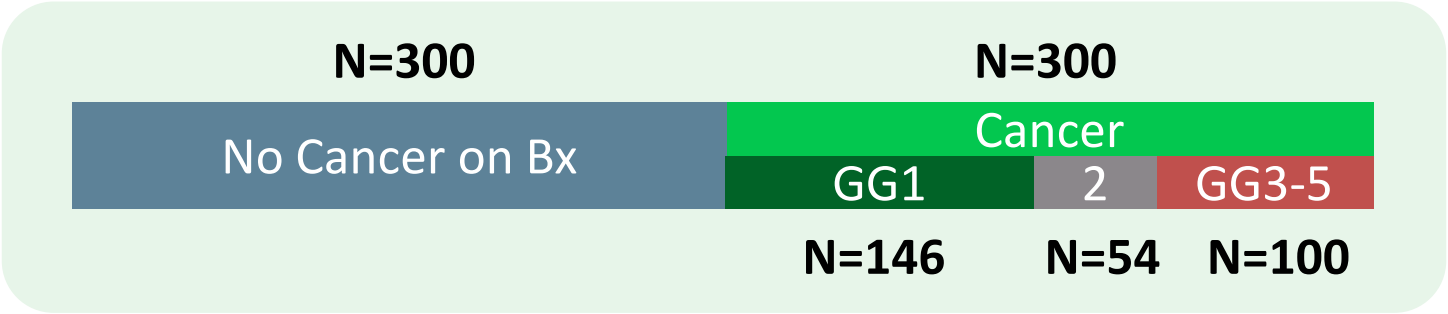
- **A new predictive test for prostate cancer was developed** based on **small non-coding RNAs (sncRNA)** isolated from urinary exosomes
- The **test is non-invasive** for diagnosis and prognosis of prostate cancer
  - Based on urine samples
  - Does not require DRE or first pass urine
- **Three tests were developed**, each using 200-280 selected sncRNA to classify disease status:
  - **PCa Assay** – distinguishes patients with prostate cancer (GG1-GG5) from those with no evidence of prostate cancer
  - **CS Assay** – distinguishes low-risk and low-grade prostate cancer (GG1) from higher-grade and higher-risk (GG2-GG5) disease
  - **HG Assay** – distinguishes low and favourable-intermediate grade (GG1-GG2) from high-grade (GG3-GG5) disease
- All 3 tests **can be performed on a single 20mL urine sample**

CS, clinically significant; DRE, Digital rectal examination; HG, high grade; Pca, prostate cancer; sncRNA, small non-coding RNA

Klotz L, et al. ASCO GU 2020 Abstract #277 Oral Presentation

STUDY DESIGN

- **Discovery cohort** – interrogated 6599 sncRNAs from 235 patients
- **Validation cohort** – 1436 patients
  - 836 patients in training dataset (fully cross-validated)
  - 600 separate patients in testing dataset



- PCa, CS and HG tests performed on separate customised OpenArrays containing informative sncRNAs specific for each test

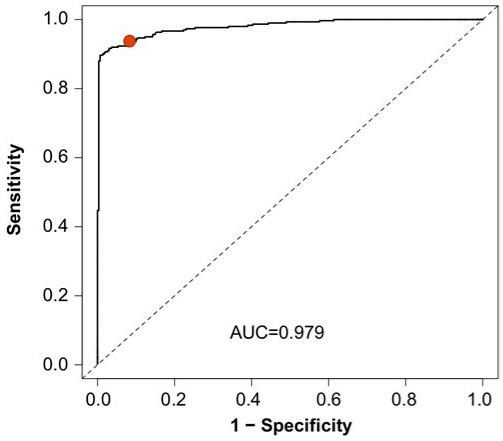
Bx, biopsy; CS, clinically significant; GG, grade group classification; HG, high grade; Pca, prostate cancer; sncRNA, small non-coding RNA

Klotz L, et al. ASCO GU 2020 Abstract #277 Oral Presentation

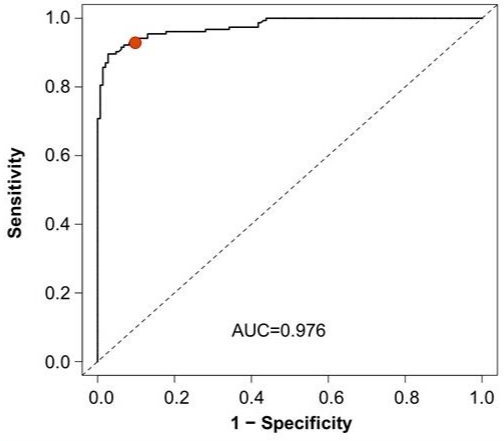
RESULTS

- **Pca Test:** sensitivity 94%; specificity 92%; PPV 92%; NPV 94%
- **CS Test (GG1 vs GG2-5):** sensitivity was 93%; specificity 90%; PPV 91% and NPV 92%
- **HG Test (GG1-2 vs GG3-5):** sensitivity was 94%; specificity 96%; PPV 91% and NPV 97%

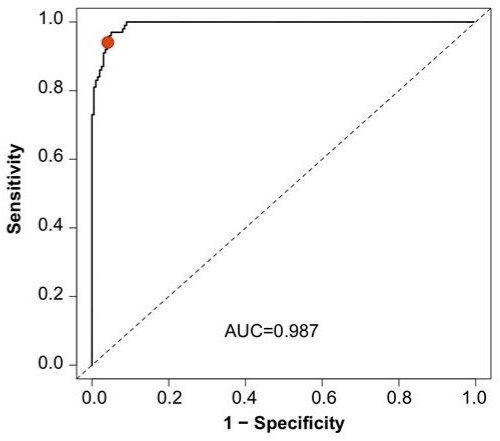
Pca test



CS test



HG test



AUC, area under the curve; CS, clinically significant; HG, high grade; NPV, negative predictive value; Pca, prostate cancer; PPV, positive predictive value

Klotz L, et al. ASCO GU 2020 Abstract #277 Oral Presentation

CONCLUSIONS

- **Sequential analysis of small non-coding RNAs** from single urine samples without DRE **has enabled development of 3 assays for the presence of prostate cancer:**
  - **PCa test:** cancer versus no cancer
  - **CS test:** low risk cancer (GG1) versus higher grade, higher risk cancer (GG2-GG5)
  - **HG test:** low to intermediate cancer (GG1-GG2) versus high grade cancer (GG3-GG5) (HG test)
- **Initial evaluation of these assays** in a validation cohort of 1436 men **demonstrated a high level of accuracy and AUC**
- **Further validation studies are ongoing** including validation of radical prostatectomy pathology

AUC, area under the curve; CS, clinically significant; DRE, digital rectal exam; HG, high grade; Pca, prostate cancer

Klotz L, et al. ASCO GU 2020 Abstract #277 Oral Presentation

TRANSCRIPTOME PROFILING OF NRG/RTOG 9601: VALIDATION OF A PROGNOSTIC GENOMIC CLASSIFIER IN SALVAGE RADIOTHERAPY PROSTATE CANCER PATIENTS FROM A PROSPECTIVE RANDOMISED TRIAL

Feng FY, et al. ASCO GU 2020. Abstract #276
Oral Presentation

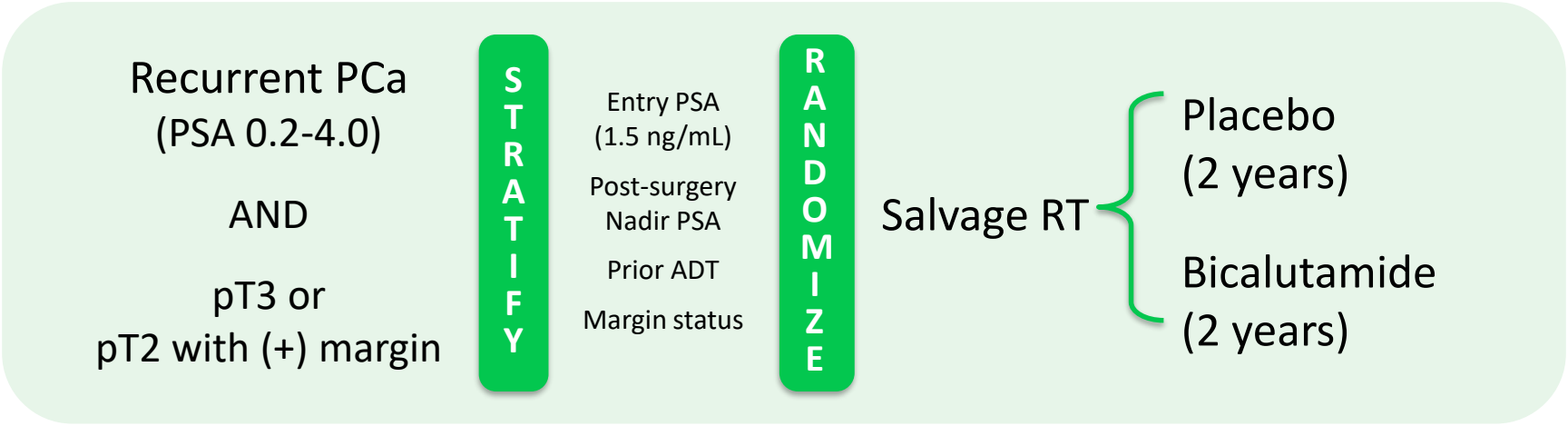
INTRODUCTION

- **Decipher is a 22-gene genomic classifier** (GC) that estimates the **risk of distant metastases in prostate cancer** patient's post-radical prostatectomy (RP)
- Decipher has been used in > 130 manuscripts:
  - Single & multicenter retrospective studies
  - Meta-analyses
  - Prospective registries
  - Prospective single-arm trials
- It has **not been validated in the context of a post-prostatectomy trial**
- **The GC was calculated in a randomised, phase 3 clinical trial of salvage radiotherapy (sRT) with and without 2 years of bicalutamide treatment**
  - Test the hypothesis that the Decipher GC will be independently prognostic for the development of distant metastases and overall survival

GC, genomic classifier; RP, radical prostatectomy; sRT, salvage radiotherapy

Feng FY, et al. ASCO GU 2020 Abstract #276, Oral Presentation

NRG/RTOG 9601 STUDY DESIGN



Sample size: 760 patients
Median follow up: 13 years

Primary endpoint: Overall survival (HR 0.77, p=0.04)

- FFPE tissue from RP specimens from patients enrolled in the NRG/RTOG 9601 trial were examined
- 352 samples passed quality control
  - 176 samples were from patients assigned to sRT + Plb
  - 176 samples were from patients assigned to sRT + bicalutamide

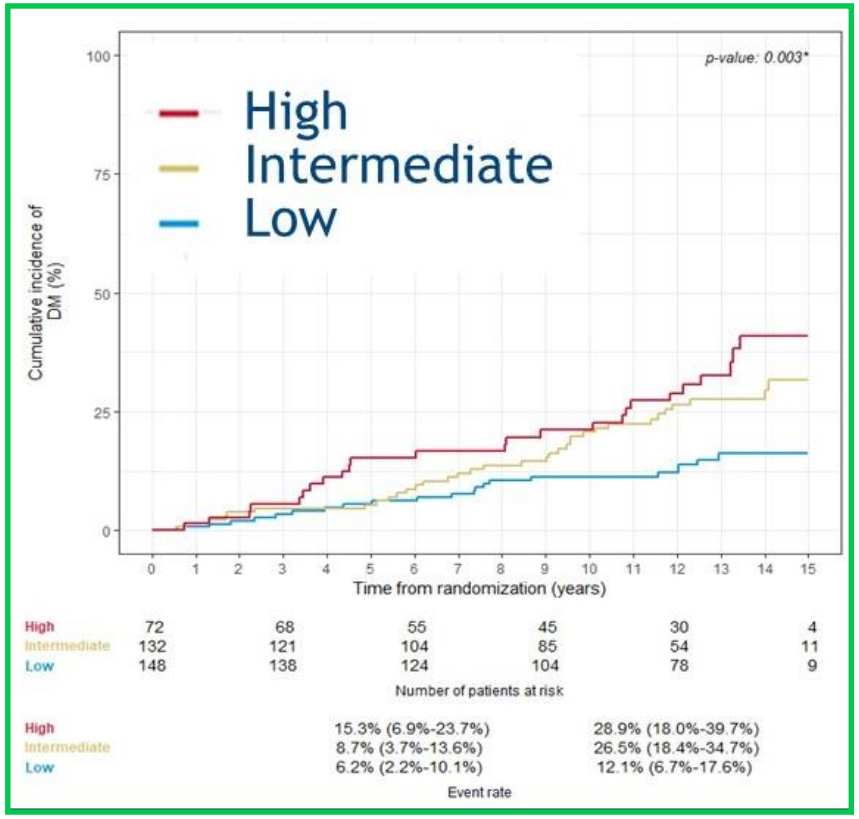
ADT, androgen deprivation therapy; HR, hazard ratio; Pca, prostate cancer; Plb, placebo; PSA, prostate specific antigen; RT, radiotherapy; sRT, salvage radiotherapy

Shipley W, et al. NEJM 2017;376:417-28; Feng FY, et al. ASCO GU 2020 Abstract #276, Oral Presentation

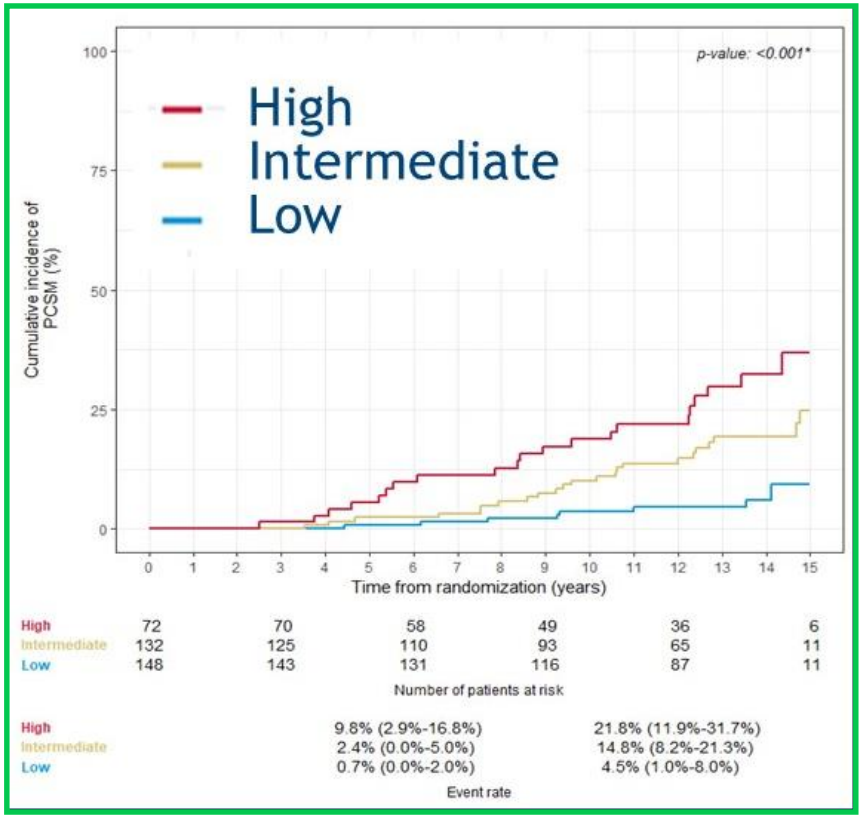
RESULTS

22-GENE DECIPHER GENE CLASSIFIER RISK STRATIFIES ALL OUTCOMES

Distant metastases



Prostate cancer specific mortality



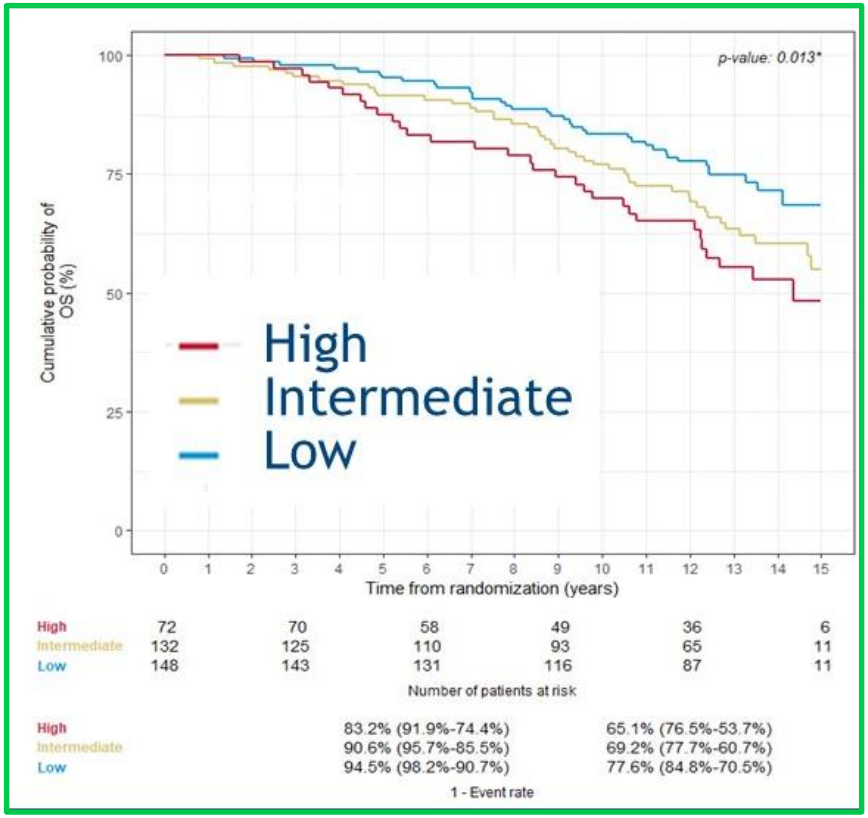
DM, distant metastases; PCSM, prostate cancer –specific mortality

Feng FY, et al. ASCO GU 2020 Abstract #276, Oral Presentation

RESULTS

22-GENE DECIPHER GENE CLASSIFIER RISK STRATIFIES ALL OUTCOMES

Overall survival



OS, overall survival

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RESULTS

DECIPHER GC REMAINS A SIGNIFICANT PREDICTOR OF OUTCOME IN A MULTIVARIABLE MODEL

Variable	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
	Distant Metastases		PCSM		OS	
Decipher score	**1.17 (1.05-1.32)**	**0.006***	**1.39 (1.20-1.63)**	**<0.001***	**1.17 (1.06-1.29)**	**0.002***
Treatment vs. placebo	0.62 (0.39-0.97)	0.037*	0.53 (0.30-0.92)	0.024*	0.82 (0.57-1.19)	0.293
Age 65+ vs. 65-	1.30 (0.83-2.06)	0.247	1.52 (0.88-2.66)	0.136	1.95 (1.33-2.91)	<0.001*
Black vs. non-black	0.88 (0.28-2.13)	0.798	0.86 (0.17-2.73)	0.827	1.35 (0.57-2.77)	0.467
Gleason 8-10 vs. ≤7	2.11 (1.24-3.47)	0.007*	2.53 (1.38-4.49)	0.003*	1.87 (1.20-2.85)	0.007*
T3 vs. T2	1.42 (0.82-2.58)	0.220	2.01 (0.97-4.62)	0.061	1.24 (0.79-1.97)	0.350
Entry PSA	1.16 (0.88-1.49)	0.264	1.37 (1.01-1.80)	0.041*	1.08 (0.84-1.35)	0.530
Positive surgical margins	0.71 (0.44-1.16)	0.167	1.26 (0.68-2.44)	0.465	0.98 (0.64-1.53)	0.919
Non-nadir vs. nadir PSA (<0.5 ng/ml)	1.31 (0.62-2.51)	0.456	2.10 (0.92-4.26)	0.074	1.98 (1.13-3.30)	0.019*

Hazard ratios of GC were per 0.1 unit increased. *indicates statistical significance

CI, confidence interval; GC, gene classifier; OS, overall survival; PCSM, prostate cancer-specific mortality; PSA, prostate specific antigen

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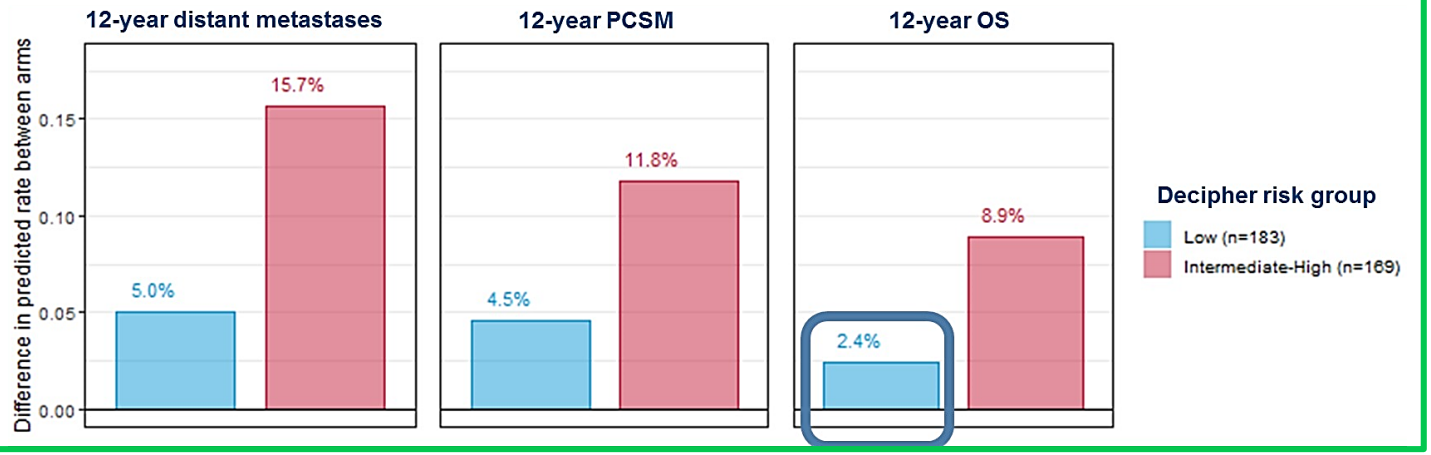
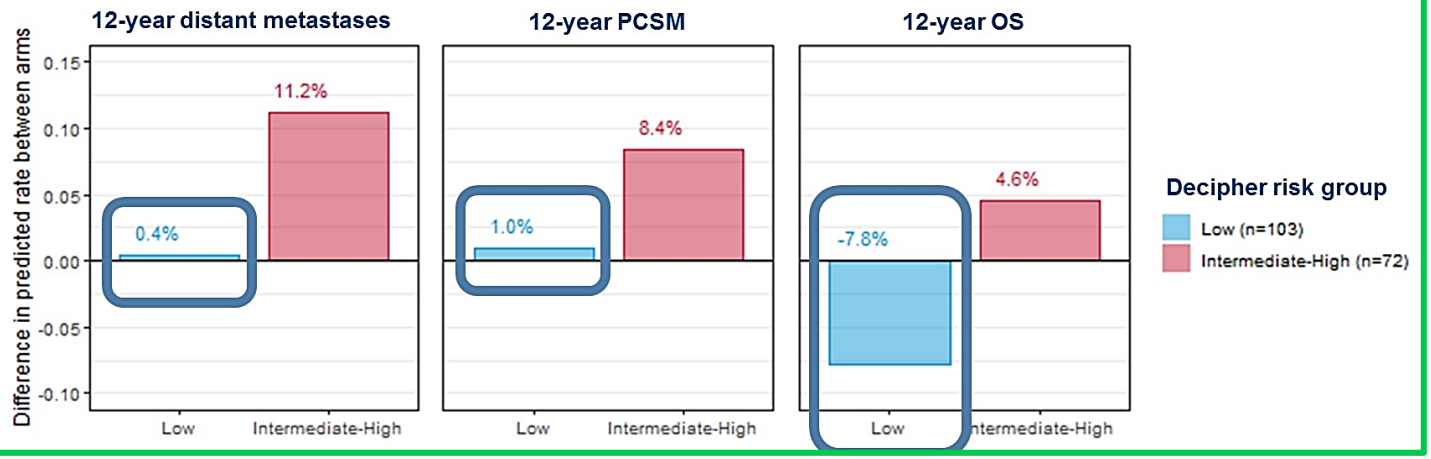
ABSOLUTE BENEFIT

Entire cohort



Early salvage RT (PSA <0.7 ng/mL)



The absolute benefit from hormone therapy is smaller in the low Decipher GC risk group

GC, gene classifier; OS, overall survival; PCSM, prostate cancer-specific mortality; PSA prostate specific antigen; RT, radiotherapy

Feng FY, et al. ASCO GU 2020 Abstract #276, Oral Presentation

CONCLUSIONS

- **This prospective randomised trial cohort demonstrated association of the GC with DM and PCSM** independent of standard clinicopathologic variables
- GC may help personalise shared decision-making to weigh the absolute benefit from the addition of bicalutamide to sRT
- **At this time, biomarkers are not referenced in any prostate cancer guidelines**
  - Without guidance, it is unclear how these should be operationalised in the context of clinical variables
- Ongoing randomised trials will support the use of biomarkers:
  - NRG GU 006 study
  - PREDICT-RT (NRG-GU 009)
  - ERADICATE

DM, distant metastases; GC, genomic classifier; PCSM, prostate cancer –specific mortality; sRT, salvage radiotherapy

Feng FY, et al. ASCO GU 2020 Abstract #276, Oral Presentation ; Lin, D. Presentation at ASCO GU 2020

KEY PROSTATE CANCER POSTER PRESENTATIONS AT ASCO GU 2020

PROs FROM A PHASE 1/2 DOSE-ESCALATION STUDY OF FRACTIONATED DOSE ^{177}LU-PSMA-617 FOR PROGRESSIVE mCRPC

Panagiotis J, et al.
ASCO GU 2020. Abstract #45 (Poster presentation)

mCRPC, metastatic castration resistant prostate cancer; PSMA, prostate specific membrane antigen

INTRODUCTION

- **Radionuclide therapy may be able to treat symptoms related to tumour and therefore may improve patient-reported outcomes (PROs)**
- This was the **first dose-escalation study** of PSMA-targeted radionuclide therapy **with ^{177}Lu-PSMA-617**
- Dose fractionation was used to deliver a dose-intense regimen intended to minimise radioresistance due to repopulation

METHODOLOGY

- **Patients with progressive mCRPC** following potent ARPI, (e.g. abi/enza) and taxane (or unfit/refuse chemo) **without limit of number of prior therapies**, adequate organ function, ECOG performance status 0-2, **without preselection for PSMA expression were included**
- Treatment was a single cycle of fractionated dose ^{177}Lu-PSMA-617 on D1 and D15 (7.4 to 22 GBq in phase 1; 22.2 GBq in phase 2)
- PRO tools included FACT-P and BPI-SF at baseline and follow up

Abi, abiraterone; BPI-SF, Brief Pain Inventory – Short Form; ECOG, Eastern Cooperative Oncology Group; enza, enzalutamide; FACT-P, Functional Assessment of Cancer Therapy Prostate Module; GBq, gigabecquerel; Lu, Lutetium; mCRPC, metastatic castration resistant prostate cancer; PRO, patient reported outcomes; PSMA, prostate specific membrane antigen

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

BASELINE DATA

Baseline data	N=44
Median age (range)	69 (55-91)
Median PSA	182.97 (0.89-5541)
Sites of metastases:	
Bone	93%
Nodal	45%
Lung	18%
Liver	9%
Other visceral metastases	9%
Prior therapies:	
At least 1 prior CT regimen	55%
⩾2 prior ARPI	52%
Ra-223	27%
Sipuleucel-T	30%
^{177}Lu-J591	5%

ARPI, androgen receptor pathway inhibitior; CT, chemotherapy; Lu, Lutetium; PSA, prostate specific antigen; Ra-223, Radium-223

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

RESULTS

Efficacy endpoints	Result
> 50% decline PSA 22.2 GBq (600mCi)	59.1% 66.7%
Median overall survival	16 mo 95% CI: 11-NR

Safety endpoints	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Treatment emergent AEs:			
Pain	19 (43.2%)	17 (38.6%)	0
Xerostomia	25 (56.8%)	2 (4.5%)	0
Fatigue	6 (13.6%)	12 (27.3%)	0
Nausea	21 (47.7%)	1 (2.3%)	0
Thrombocytopenia	9 (20.5%)	5 (11.4%)	1 (2.3%)
AST elevation	8 (18.2%)	1 (2.3%)	0
Anaemia	4 (9.1%)	6 (13.6%)	3 (6.8%)
Neutropenia	2 (4.5%)	3 (6.8%)	0

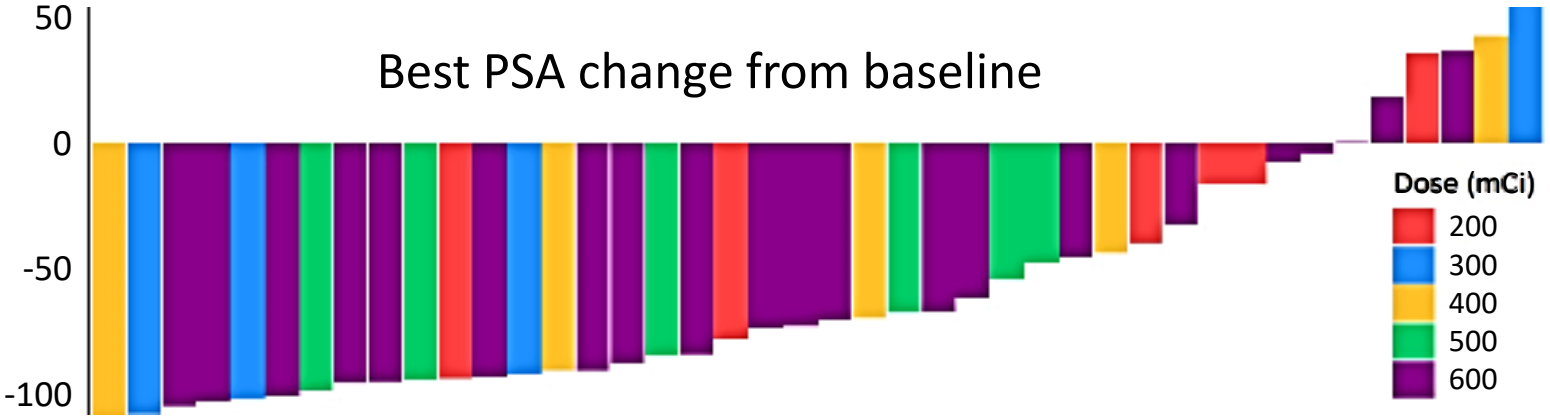
- Pain flare and xerostomia were the most common AEs, occurring in 81.8% and 61.4% of subjects respectively (both generally low grade and temporary)

AE, adverse event; CI, confidence interval; GBq, gigabecquerel; NR, not reached; PSA, prostate specific antigen

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

PSA RESPONSE

- 81.8% of patients experienced any PSA decline, despite no selection for PSMA+
- 59.1% of patients had a >50% PSA decline
- At phase 2 dose (600mCi), 66.7% patients had > 50% PSA decline



mCi, millicuries; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

PATIENT-REPORTED OUTCOMES

- **FACT-P scores improved in all categories by D22** (1 week later)
- Overall FACT-P scores improved by a mean of 8.9 points (p=0.07) at D22 and remained improved at 12 weeks
- **All BPI scores improved**
  - BPI overall severity score improved by a mean of 3.0 at D22 (p=0.008) and remained better than baseline at 12 weeks
- There was **no clear association with any AE and PRO changes**
  - Those with a PSA decline tended to have improved pain scores (p=0.1)

AE, adverse event; BPI, Brief Pain Inventory; FACT-P, Functional Assessment of Cancer Therapy Prostate Module; PRO, patient reported outcomes; PSA, prostate specific antigen

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

CONCLUSION

- **A single cycle of up to 22.2 GBq of ^{177}Lu-PSMA-617 is safe** with fractionated (D1 & D15) dosing
- **Encouraging early efficacy signals were observed** in a population unselected for PSMA expression and improved QoL and pain scores by validated PRO instruments

GBq, gigabecquerel; PRO, patient reported outcomes; PSMA, prostate specific membrane antigen; QoL, quality of life

Panagiotis J, et al. ASCO GU 2020 Abstract #45 (Poster presentation)

CLINICAL OUTCOMES AND PATIENT PROFILES IN REASSURE: AN OBSERVATIONAL STUDY OF RADIUM-223 IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Higano CS, et al.
ASCO GU 2020. Abstract #32 (Poster presentation)

mCRPC, metastatic castration resistant prostate cancer

INTRODUCTION

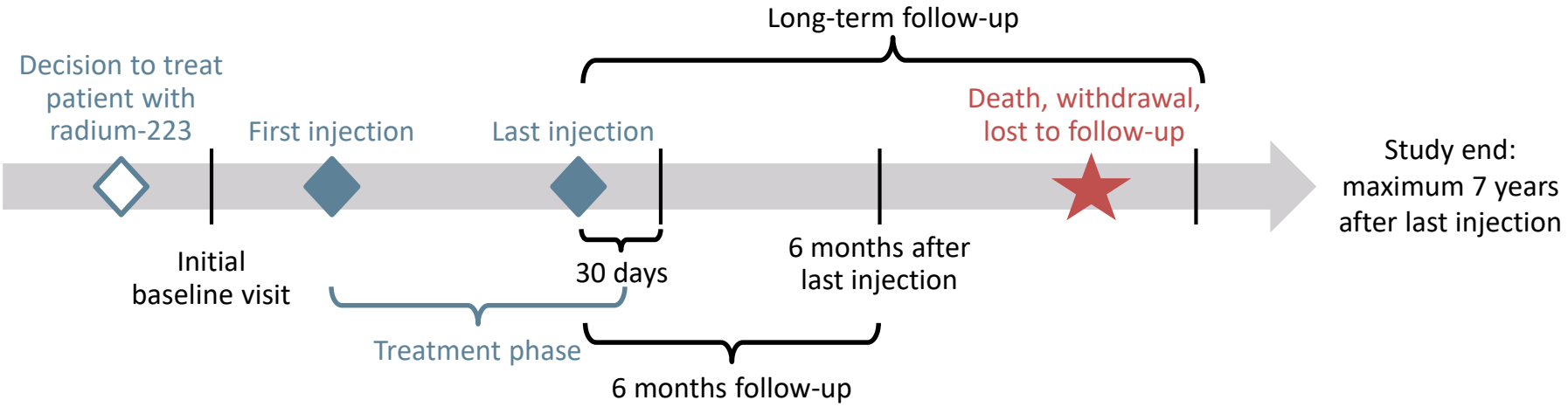
- **Radium-223 is a targeted alpha therapy** that demonstrated a survival advantage and favourable safety profile in the ALSYMPCA trial[1]
- **Treatment with Ra-223 leads to radiation exposure**, therefore long-term follow up of patients is important to determine the **long-term risk of developing a second primary malignancy (SPM)**[2]
- **The REASSURE trial evaluated the short and long-term safety of Ra-223 in patients with mCRPC in routine clinical practice over a 7-year follow-up period** [2]
  - Results from the second planned interim analysis are presented

mCRPC, metastatic castration resistant prostate cancer; Ra-223, Radium-223; SPM, second primary malignancy

1. Parker C, et al. NEJM 2013;369:213-23; 2. Higano CS, et al. ASCO GU 2020 Abstract #32 (Poster presentation)

REASSURE STUDY DESIGN

- Global, prospective, single-arm, observational study
- 1465 patients enrolled



Second prespecified interim analysis: data cut-off March 20, 2019; Median FU 11.5 months

Patient population:
- mCRPC with bone metastases
- Scheduled to receive Ra-223 prior to study enrolment
- No previous treatment with Ra-223 or other radiopharmaceuticals

Primary endpoints:
- Incidence of second primary malignancies (SPM)
- Bone marrow suppression
- Short and long-term safety in patients with ≥ 1 dose Ra-223

Key secondary endpoint:
- Overall Survival
- Incidence of bone fractures
- No. of bone-associated events
- PROs (BPI-SF scores)

BPI-SF, brief pain inventory – short form; FU, follow-up; PRO, patient reported outcomes; Ra-223, Radium-223; SPM, second primary malignancies

Higano CS, et al. ASCO GU 2020 Abstract #32 (Poster presentation)

BASELINE DATA

Safety population (N=1465)	Baseline data
Laboratory values	
Median PSA (n=1053)	59 ng/mL
Median ALP (n=1048)	135 U/L
Median LDH (n=555)	269 U/L
Extent of disease, n (%)	
Patients with bone metastases only	1193 (81)
Patients with metastases at other sites*	272 (19)
Patients with <6 metastatic sites	259 (19)
Patients with 6-20 metastatic sites	636 (47)
Patients with >20 metastatic sites	270 (20)
Superscan	81 (6)
Prior therapy, n (%): Abiraterone/prednisone Docetaxel Enzalutamide Cabazitaxel Sipuleucel-T	 665 (45) 555 (38) 548 (37) 132 (9) 123 (8)
Median number of Ra-223 doses	6
Patients with ≥5 dose of Ra-223	67%

*predominantly in lymph nodes

ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen; Ra-223, Radium-223

Higano CS, et al. ASCO GU 2020 Abstract #32 (Poster presentation)

RESULTS

Primary Endpoints	N=1465 N (%)
Secondary Primary Malignancy	14 (1)
Any AE	701 (48)
Treatment-emergent drug-related AE	510 (35)
Grade ≥3	155 (11)
Resulting in Ra-223 discontinuation	82 (6)
Bone marrow suppression	178 (12)
Most common TEAE any grade: Diarrhoea Nausea Anaemia	 157 (11) 127 (9) 122 (8)
Treatment emergent SAE	311 (21)
Drug-related SAE	80 (5)
Death due to drug-related SAE	11 (1)

Secondary Endpoints	N=1465 N (%)
Median Overall Survival	15.6 months (95% CI: 14.6-16.5)
Fractures	70 (5)

AE, adverse event; CI, confidence interval; Ra-223, Radium-223; SAE, serious adverse event; TEAE, treatment emergent adverse event

Higano CS, et al. ASCO GU 2020 Abstract #32 (Poster presentation)

CONCLUSIONS

- Following treatment with **Ra-223 in the REASSURE study there was a low incidence of:**
  - Second primary malignancy
  - Bone fractures
  - Bone marrow suppression
- **No new AEs were identified**
- The REASSURE study confirms that in routine clinical practice the Ra-223 AE rates were low, and most patients completed the full course (6 injections) of Ra-223 treatment

AE, adverse event; Ra-223, Radium-223

Higano, CS et al. ASCO GU 2020 Abstract #32 (Poster presentation)

ADVERSE EVENT PROFILES OF APALUTAMIDE, ENZALUTAMIDE AND DAROLUTAMIDE IN SPARTAN, PROSPER AND ARAMIS: HOW CONFIDENT ARE WE ABOUT WHICH DRUG IS SAFEST?

Drago JZ, et al.
ASCO GU 2020. Abstract #318 (Poster presentation)

INTRODUCTION

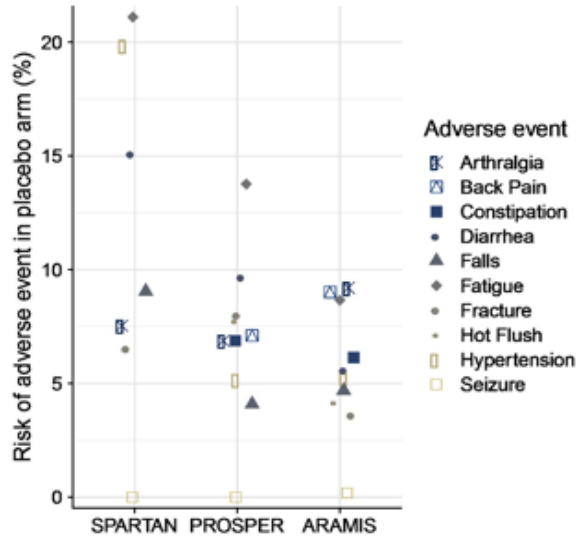
- **Apalutamide, enzalutamide and darolutamide were approved for non-metastatic castration-resistant prostate cancer (nmCRPC)** based on 3 randomised trials:
  - SPARTAN[1]
  - PROSPER[2]
  - ARAMIS[3]
- **Similar efficacy was observed in these trials** whereas **differences in adverse event profiles** have been observed and used to differentiate the drugs
- **The safety profiles of these drugs have only been informally compared**
- This analysis accounts for baseline characteristics, AE collection & reporting and statistical uncertainty when comparing the AE profiles from the 3 trials

AE, adverse event; nmCRPC, non-metastatic castration resistant prostate cancer

1. Smith M, et al. NEJM 2018;378:1408-18; 2. Hussain M, et al. NEJM 2018;378:2465-74; 3. Fizazi K, et al. NEJM 2019;380:1235-46;
4. Drago JZ, et al. ASCO GU 2020 Abstract #318 (Poster presentation)

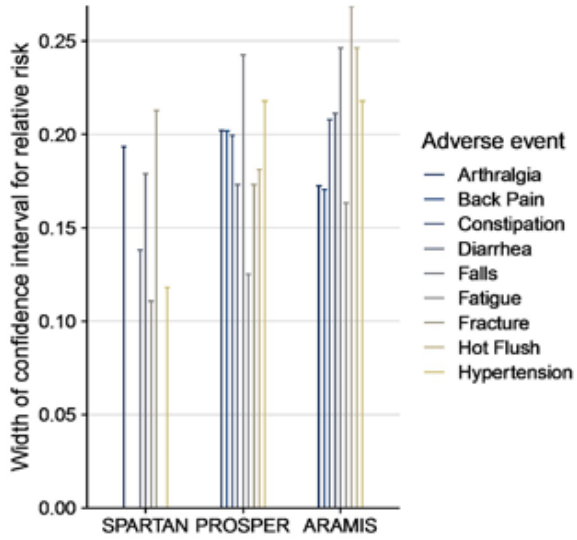
RESULTS

Absolute risks of adverse events in the placebo arms differed considerably.



Compared to the placebo arm of SPARTAN, adverse events were on average 44% less common in the placebo arm of PROSPER (95% CI, 28–56%) and 54% less common in the placebo arm of ARAMIS (95% CI, 41–64%).

Lower event numbers decrease confidence in relative risk estimates.



Across all adverse event types, compared to SPARTAN, relative risks from PROSPER were 23% less precise and relative risks from ARAMIS were 30% less precise.

CI, confidence interval

Drago JZ, et al. ASCO GU 2020 Abstract #318 (Poster presentation)

CONCLUSIONS

- Patients in **SPARTAN, PROSPER and ARAMIS** had similar baseline characteristics but **AE reporting differed widely between the trials**
  - Of 34 adverse event types reported overall, only 10 were reported in all three trials
- Low absolute adverse event numbers decrease confidence in AE profiles
- **Published data are insufficient to differentiate the AE profiles of these drugs in nmCRPC patients**
- Standardisation of AE reporting and analysis in phase 3 clinical trials will improve the interpretation of safety data across different therapeutic agents

AE, adverse event; nmCRPC, non-metastatic castration resistant prostate cancer

Drago JZ, et al. ASCO GU 2020 Abstract #318 (Poster presentation)

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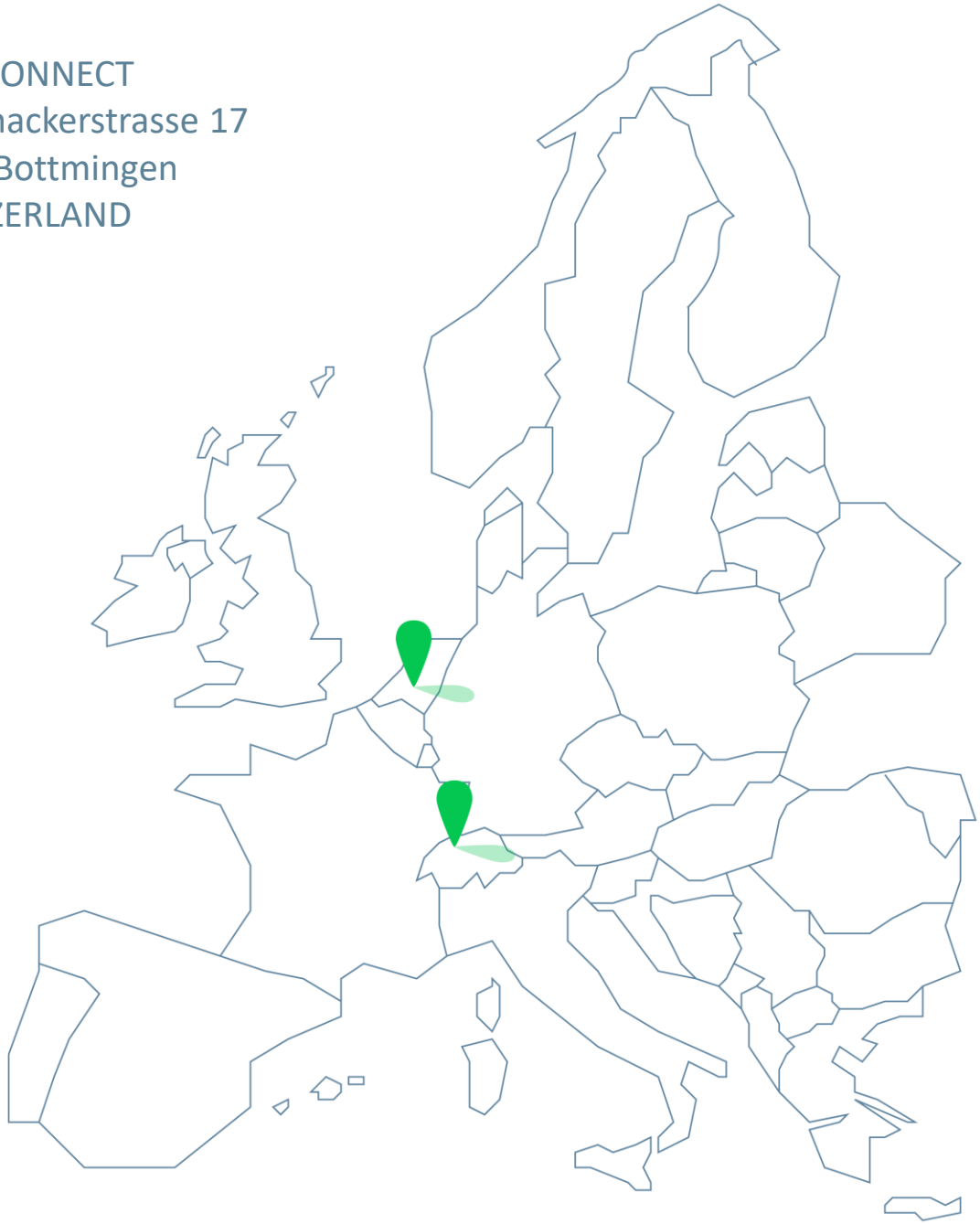

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