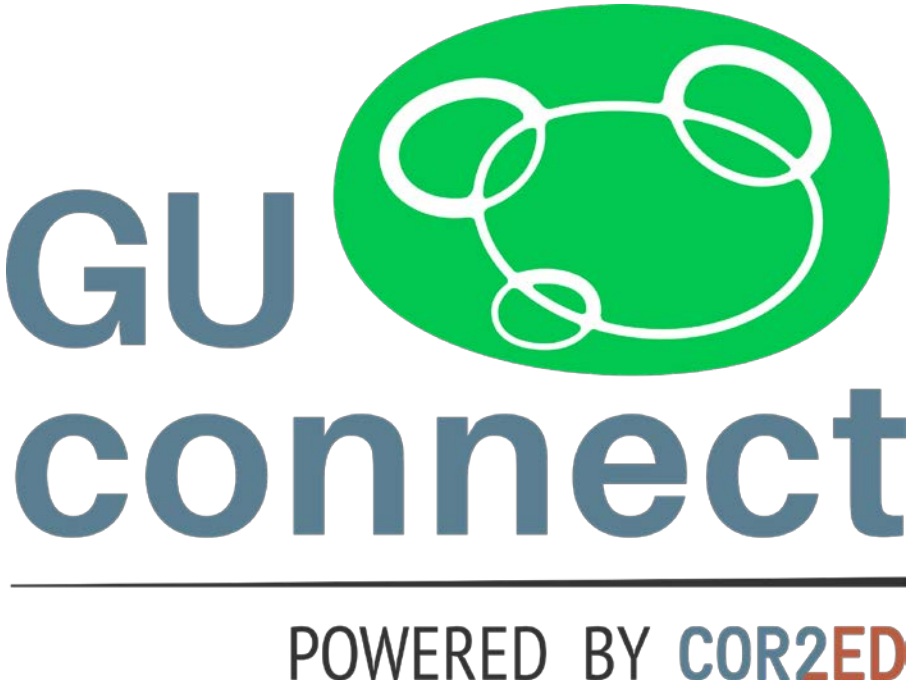
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OLIGOMETASTATIC PROSTATE CANCER: EVOLVING TREATMENT PARADIGMS MAY 2019

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WHAT IS OLIGOMETASTATIC PROSTATE CANCER AND HOW COMMON IS IT?

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- **APCCC 2017** suggested a **clinically meaningful definition** may be **three or fewer bone or lymph node metastases**[1]
  - Newer imaging modalities (MRI, PET or combination) felt to be superior to CT/bone scan

- From TROG 03.04 RADAR trial, **8.8% of patients being followed for biochemical failure developed 1–3 bone mets**[2] at the time of recurrence
  - There was no association between higher stage or Gleason score and number of bone metastases that developed
  - PCSM is increased for men with 2-3 bone metastases compared to 1

APCCC, Advanced Prostate Cancer Consensus Conference; CT, computed tomography; MRI, magnetic resonance imaging; PCSM, prostate cancer-specific mortality; PET, positron emission tomography; T/N, Tumour/Node

1. Gillessen S et al. Eur Urol 2018; 73:178-211; 2. Sridharan S et al. Radiother Oncol 2016; 121:98-102

THE IMPORTANCE OF IMAGING TO CORRECTLY CATEGORISE OLIGOMETASTASES

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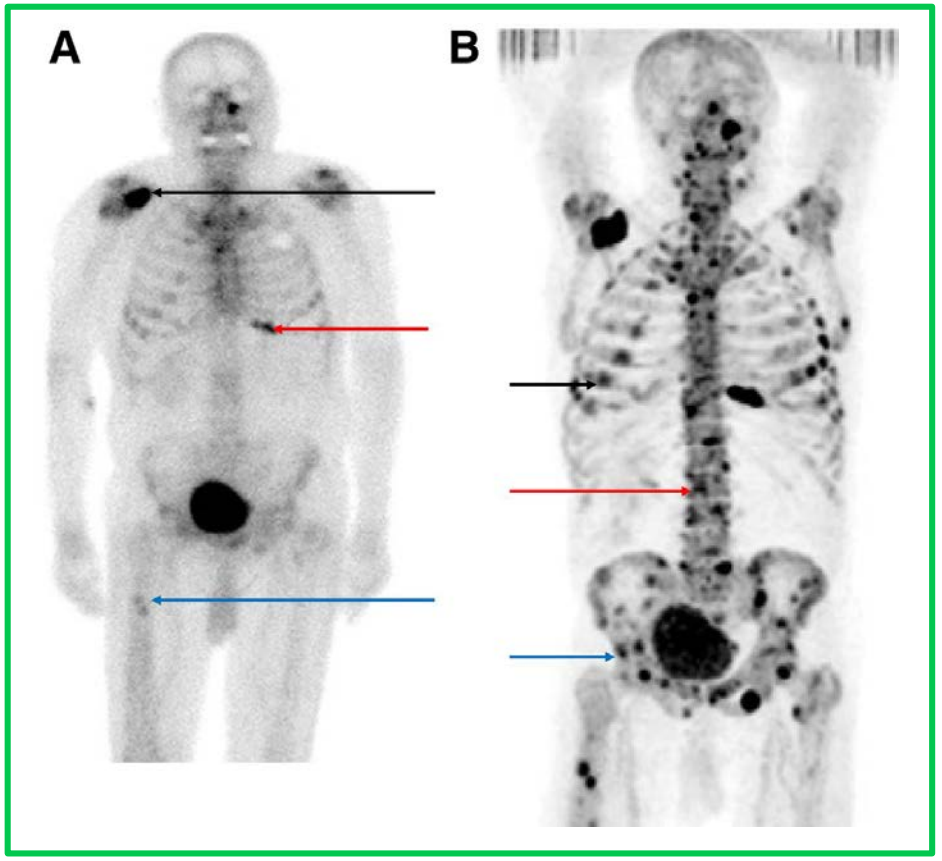
a) Conventional ^{99m}Tc-MDP planar scintigraphy shows bone metastases in right scapula (black arrow), left lower anterior ribcage (red arrow), and right proximal femoral shaft (blue arrow)

b) 18-F NaF PET/CT obtained shortly afterward shows greater burden of metastases



18F-NaF: sodium fluoride tracer; ^{99m}Tc-MDP, technetium 99m-methyl diphosphonate; CT, computed tomography; PET, positron emission tomography

Kulshrestha RK et al. J Nucl Med Technol 2016; 44:217-222

SELECT DATA SHOWING SENSITIVITY OF NOVEL IMAGING

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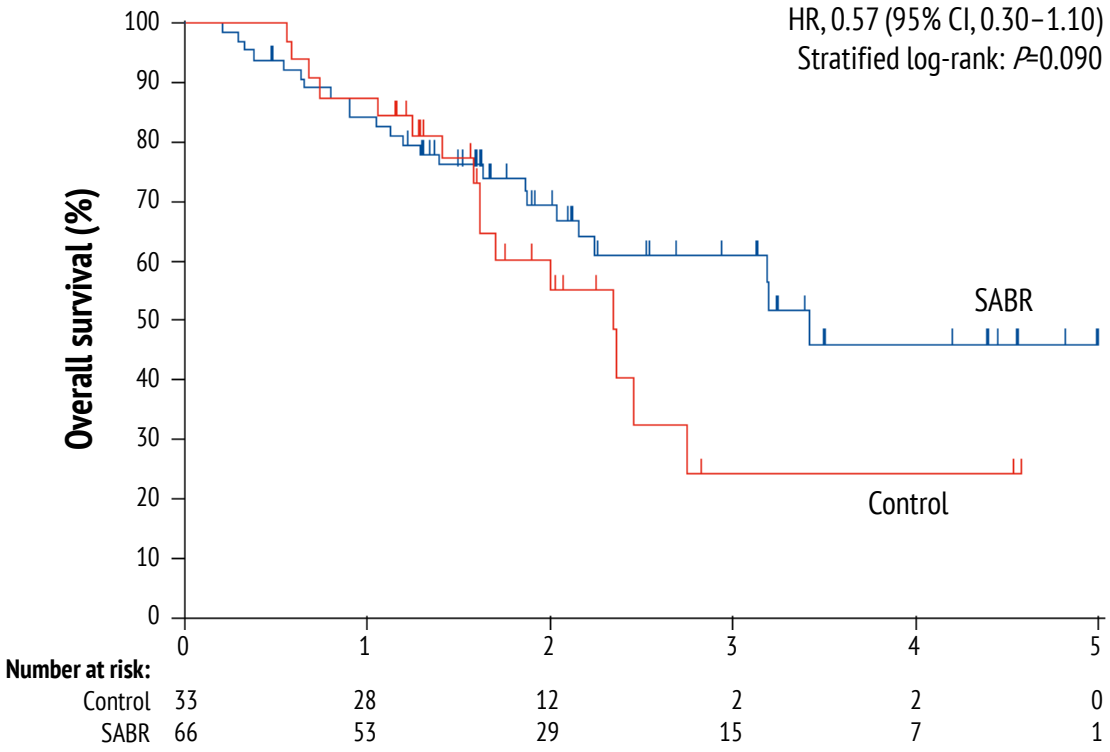
- Who is "oligo" metastatic and who has "high volume" metastatic disease must be viewed in the context of the imaging study used to identify metastases

PET tracer	Detection rate in biochemical recurrence	Accuracy	Reference(s)
FDG / NaF	8% / 16% *	64% PPV (combined)	Jadvar H et al. Clin Nucl Med 2012; 37:637-643
Fluciclovine	57%	97% PPV, specificity 67%	Andriole GL et al. J Urol 2019; 201:322-331 Nanni et al, Eur J Nucl Med Molec Imag 2016; 43:1601
Choline	49%	90% PPV, specificity 40%	Evangelista L et al. Eur Urol 2013; 63:1040-1048 Nanni et al, Eur J Nucl Med Molec Imag 2016; 43:1601
Gallium PSMA	50%	85% PPV, specificity 95% in lymph nodes	Calais J et al. J Nucl Med 2018; 59:434-441 van Leeuwen PJ et al. BJU Int 2017; 119:209-215

*True positives, higher PSA levels compared to the other studies

FDG, fludeoxyglucose; NaF, sodium fluoride; PPV, positive predictive value; PSMA, prostate-specific antigen

SABR-COMET: METASTASIS-DIRECTED THERAPY IMPROVES OS



- N=99 total (n=16 prostate)
- Maximum 5 mets
- Randomized 2:1 standard care +/- SBRT to all mets

CI, confidence interval; HR, hazard ratio; OS, overall survival; SABR, stereotactic ablative radiotherapy

Palma DA et al. Lancet 2019; Epub ahead of print

SBRT TO OLIGOMETASTATIC SITES IN PROSTATE CANCER WAS ASSOCIATED WITH PSA DECLINES (A) AND DELAYED RECURRENCE (B)

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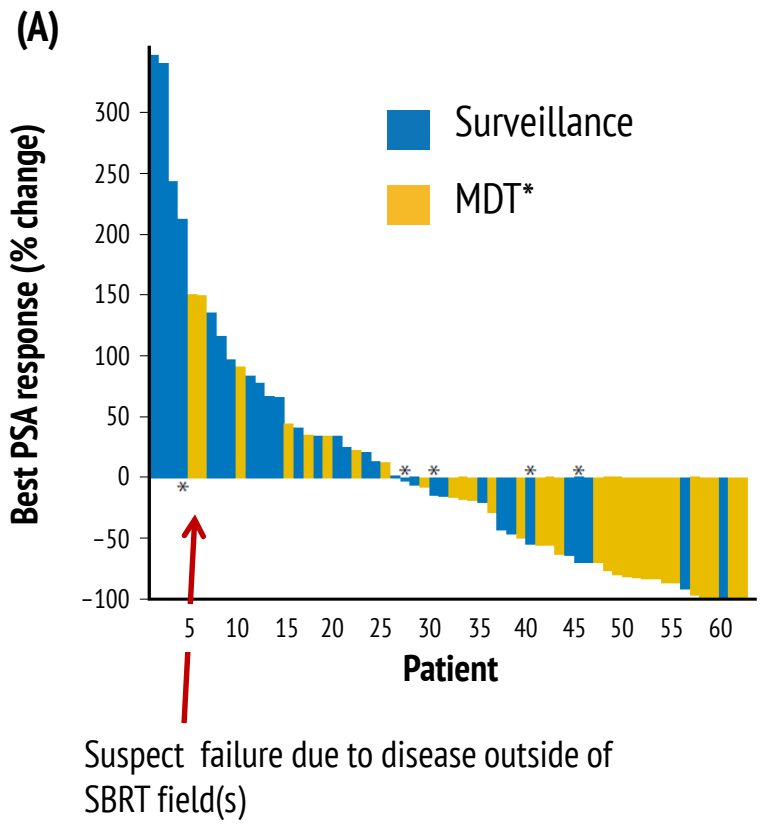
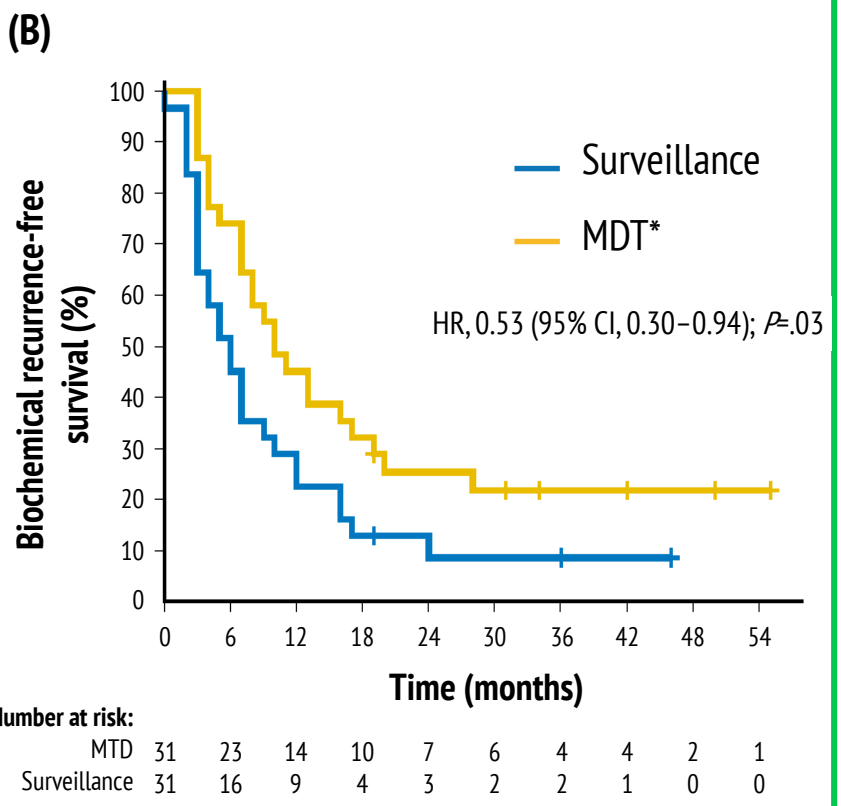




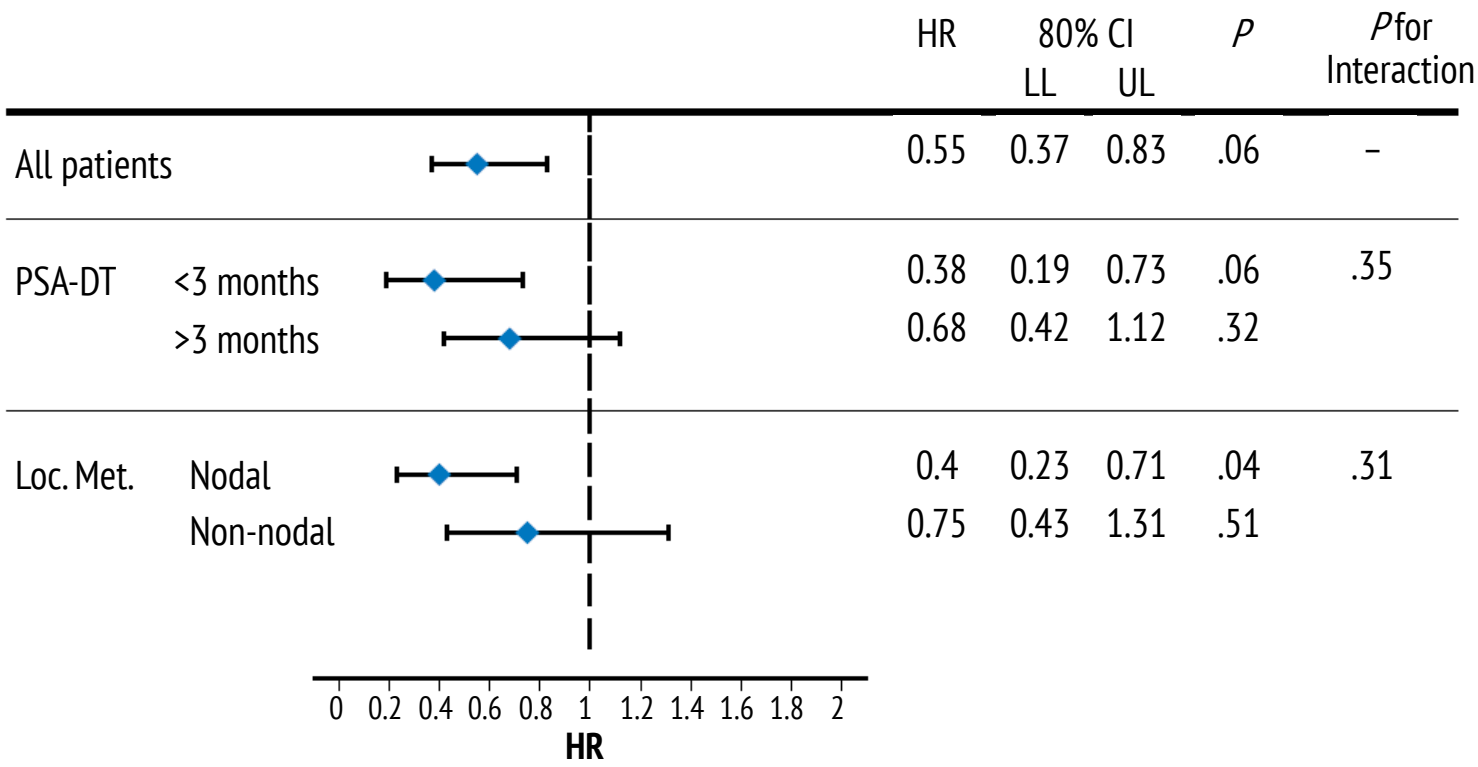
*MDT was either surgery (n=6) or SBRT (n= 25)

CI, confidence interval; HR, hazard ratio; MDT, metastasis-directed therapy; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy

Ost P et al. J Clin Oncol 2018; 36:446-453

ASSOCIATION BETWEEN MDT* AND ADT-FREE SURVIVAL

- Need larger experiences to learn which patients are most likely to benefit from SBRT to oligometastases



*MDT was either surgery (n=6) or SBRT (n= 25), Intent to treat population

ADT, androgen deprivation therapy; CI, confidence interval; DT, doubling time; HR, hazard ratio; LL, lower limit of the 80% CI, Loc. Met., location of metastases; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy; UL, upper limit of the 80% CI

Ost P et al. J Clin Oncol 2018; 36:446-453

MINIMAL TOXICITY WITH SBRT TO OLIGOMETASTASES (SABR-COMET)

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- There is concern for future fracture risk when bone is radiated - this outcome should be measured in future trials

	All patients (n=99)	Control group (n=33)	Stereotactic ablative radiotherapy group (n=66)	*P* value
Adverse event grade ≥2	55 (56%)	15 (46%)	40 (61%)	0.15
Related adverse event grade ≥2	22 (22%)	3 (9%)	19 (29%)	0.026
Adverse event associated with death (grade 5)	3 (3%)	0	3 (5%)	0.55
Fatigue*	–	–	–	0.45
Grade 2	6 (6%)	2 (6%)	4 (6%)	–
Grade 3	1 (1%)	1 (3%)	0	–
Dyspnoea*	–	–	–	1.00
Grade 2	1 (1%)	0	1 (2%)	–
Grade 3	1 (1%)	0	1 (2%)	–
Pain (any type)*	–	–	–	0.14
Grade 2	5 (5%)	0	5 (8%)	–
Grade 3	3 (3%)	0	3 (5%)	–

*Treatment related
SBRT, stereotactic body radiotherapy

Palma DA et al. Lancet 2019; Epub ahead of print http://dx.doi.org/10.1016/S0140-6736(18)32487-5

MORE ON TOXICITY WITH SBRT FROM THE "POPSTAR" TRIAL

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Adverse event (CTCAE v4.0)	Grade 1	Grade 2	Grade 3	Total
Fatigue	14			14
Diarrhoea	5	1		6
Nausea	6			6
Abdominal pain	2			2
Back pain		2		2
Dermatitis radiation	2			2
Fracture		2	1	3
Myositis	1	1		2
Neuralgia		1		1
Pain	1			1
Skin hyperpigmentation	1			1
Urinary incontinence	1			1
Vomiting	1			1
Any AE	16	5	1	22

CTCAE, Common terminology criteria for adverse events

- N=33
- Median age = 70
- 22/33 patients on ADT
- 1-3 metastases detected by CT, bone scan and NaF PET scan
- 1 instance of grade 3 vertebral fracture
- **There is concern for future fracture risk when bone is radiated - this outcome should be measured in future trials**

ADT, androgen deprivation therapy; CT, computed tomography; NaF, sodium fluoride; PET, positron emission tomography

Siva S et al. European Urology 2018; 74:455-462

ONGOING CLINICAL TRIALS

Name	Intervention	Inclusion	Primary Endpoint
ORIOLE NCT02680587	SBRT in 1–5 fractions	1–3 asymptomatic mets, bone + ST (⩽5 cm) PSA 1.0–50	Time to progression
NCT01859221 University of Florida	SBRT	mHSPC and mCRPC cohorts	PFS
NCT02206334 NRG Oncology	SBRT	NSCLC, Breast, Prostate cancer	Optimal dose of SBRT
PEACE V NCT03569241	LN dissection or SBRT +/- pelvis XRT	Prostate – pelvic lymph node recurrence	Metastasis free survival
ARTO NCT03449719	ADT +/- SBRT	1–3 metastases	PSA response at 6 months
City of Hope NCT03361735	ADT + SBRT + Radium 223	Up to 4 mets, at least 1 in bone. <5 cm for non-visceral lesions; <2 cm for visceral lesions (limited to 1 LN/lung met)	Time to treatment failure

www.clinicaltrials.gov

ADT, androgen deprivation therapy; LN, lymph node; mets, metastases; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy; ST, soft tissue; XRT, radiotherapy

IN SUMMARY

- **Imaging tools** are a **critical component for MDT** of oligometastatic disease
  - Work is ongoing to determine which PET scanner tracers are most sensitive/specific

- **SBRT** associated with **improved survival** in patients **with oligometastatic prostate cancer**[1,2]

- Future goal may be to avoid long-term ADT therapy by using MDT; more data are needed and studies are ongoing

ADT, androgen-deprivation therapy; MDT, metastasis-directed therapy; PET, positron emission tomography; SBRT, stereotactic body radiotherapy

1. Ost P et al. J Clin Oncol 2018; 36:446-453; 2. Palma DA et al. Lancet 2019; Epub ahead of print

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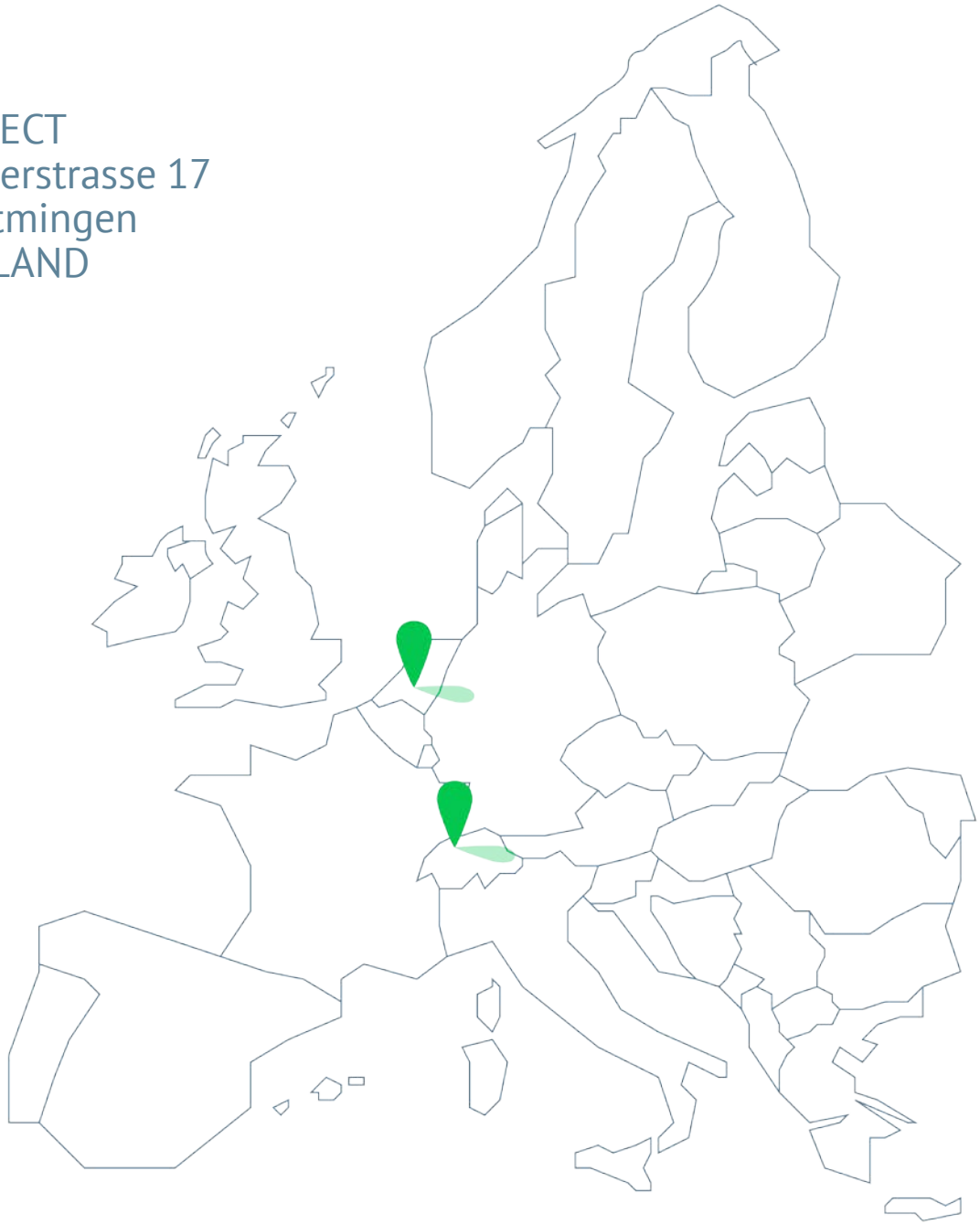

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