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ANTIBODY-DRUG CONJUGATES IN UROTHELIAL CANCER *AND AN OVERVIEW IN OTHER GENITOURINARY CANCERS*

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ANTIBODY-DRUG CONJUGATES: BACKGROUND

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- **Antibody Drug Conjugates** (ADCs) are an **emerging class of targeted anticancer drug** delivery agent that **confer selective and sustained cytotoxic drug delivery to tumours**
- **ADCs** are structured from **three main structural units**:
  - **monoclonal antibody** against a specific target
  - **linker molecule**
  - **Payloads:** cytotoxic agent or drug
- Selection of an appropriate target, a monoclonal antibody, cytotoxic payload, and the manner in which the antibody is linked to the payload are key determinants of the safety and efficacy of ADCs

Sau S, et al. Drug Discovery Today 2017;22:1547-1556

ANTIBODY-DRUG CONJUGATES FOR UROTHELIAL CANCERS

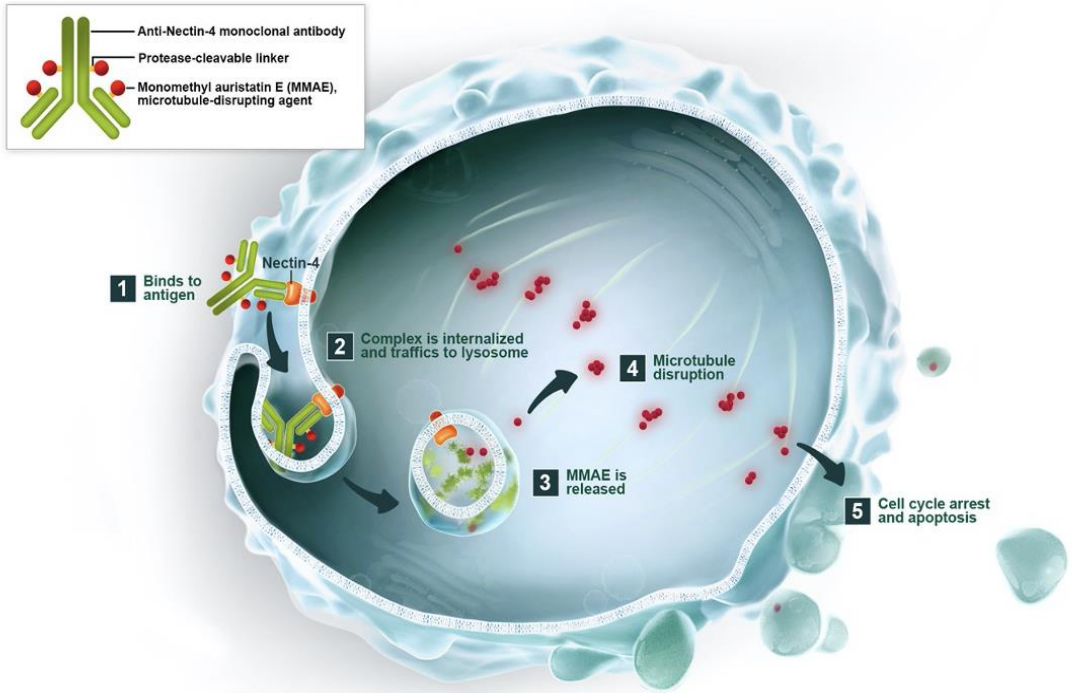
BACKGROUND

- Patients with mUC who progress after platinum-based chemotherapy and immune checkpoint inhibitors have poor outcomes and limited treatment options
- UC is characterised by the expression of multiple cell surface antigens suitable for specific therapeutic targeting with antibody-drug conjugates (ADCs)
- **Two ADCs** in advanced development for **advanced urothelial cancer**:
  - **Enfortumab vedotin** (recently FDA approved)
  - **Sacituzumab govitecan** (late stage development)

ADC, Antibody drug conjugate; mUC, metastatic urothelial cancer; UC, urothelial cancer

Tagawa S, et al. Journal of Clinical Oncology 2019;37(7_suppl):354; Vlachostergios P, et al. Bladder Cancer 2018;4(3):247-259; Enfortumab vedotin Prescribing Information Dec 2019

ENFORTUMAB VEDOTIN



Immuno-drug Conjugate

- Antibody target: Nectin-4
- Linker: Protease Cleavable
- Payload: MMAE - microtubule disrupting agent

EV-101 phase 1 study – initial assessment of efficacy and safety:

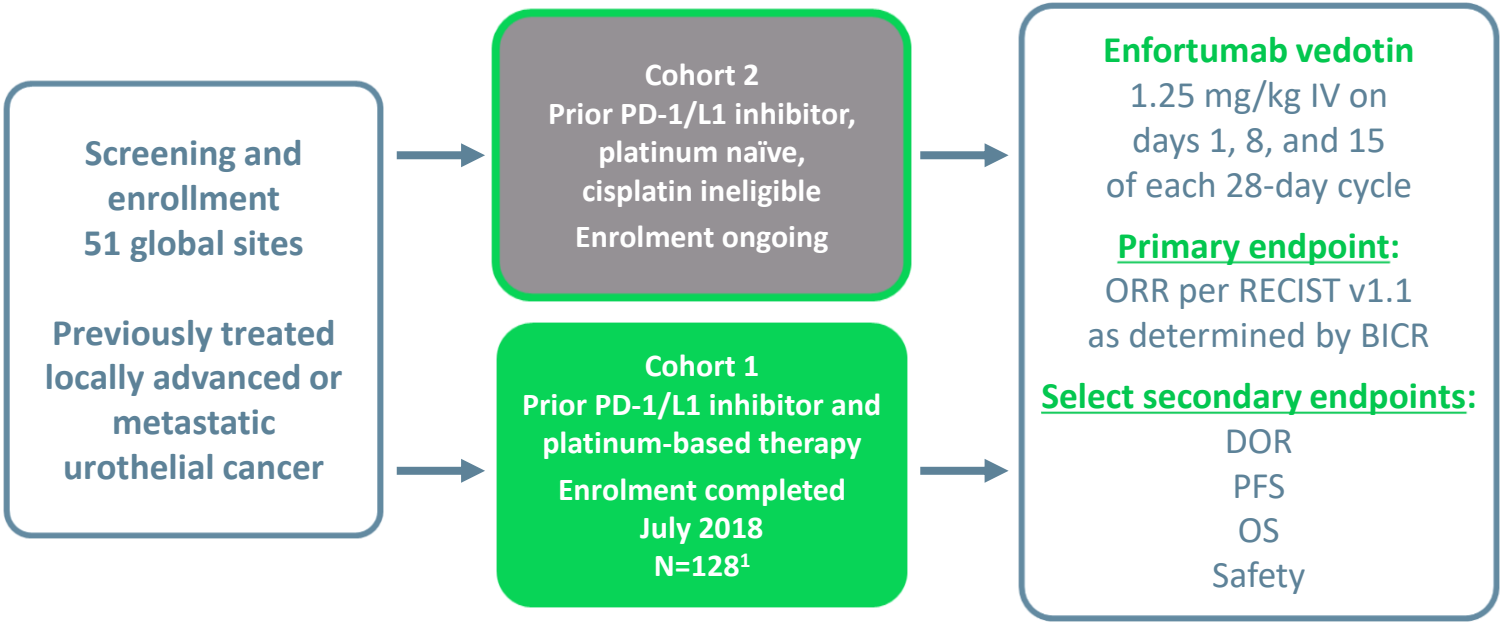
- 112 patients
- ORR: 43%
- PFS: 5.4 months

MMAE, monomethyl auristatin E; ORR, objective response rate; PFS, progression free survival

Rosenberg J, et al. Journal of Clinical Oncology 2020;38(10):1041-1049; https://www.seattlegenetics.com/pipeline/enfortumab-vedotin. Accessed 02Jul2020

EV-201 STUDY DESIGN

- Single arm, pivotal phase 2 trial



[1]3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low haemoglobin after enrolment

BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed cell death 1/programmed cell death ligand 1; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Petrylak D, et al. Journal of Clinical Oncology 2019;37(18_suppl):4505; Rosenberg JE, et al. Journal of Clinical Oncology 2019;37(29):2592-2600

EV-201: COHORT 1 DEMOGRAPHICS AND DISEASE CHARACTERISTICS

	Patients (N=125)
Male sex, n (%)	88 (70)
Age, years	
Median (min, max)	69 (40,84)
≥75 years, n (%)	34 (27)
ECOG PS of 1, n (%)	85 (68)
Primary tumour location, n (%)	
Bladder/other	81 (65)
Upper tract	44 (35)
Number of prior systemic therapies[1], median (min,max)	3 (1, 6)
≥2 Bellmunt adverse prognostic factors	52 (42)
Metastasis sites, n (%)	
Lymph nodes only	13 (10)
Visceral disease	112 (90)
Liver	50 (40)
PD-L1 status by combined positive score[2]	
<10	78/120 (65)
≥10	42/120 (35)

[1]Patients with 1 prior therapy had platinum and a PD-1/L1 inhibitor in combination;
[2]Five patients were not evaluable for PD-L1

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1

Petrylak D, et al. Journal of Clinical Oncology 2019;37(18_suppl):4505; Rosenberg JE, et al. Journal of Clinical Oncology 2019;37(29):2592-2600.

EV-201: RESPONSE RATES

- EV-201 results highly consistent with phase 1 EV-101 trial in same patient population

COHORT 1 ORR per RECIST v 1.1 assessed by BICR	Patients (N=125)
Confirmed objective response rate, n (%) **95% confidence interval[1]**	55 (44) (35.1, 53.2)
Best overall response per RECIST v. 1.1, n (%)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[2]	12 (10)

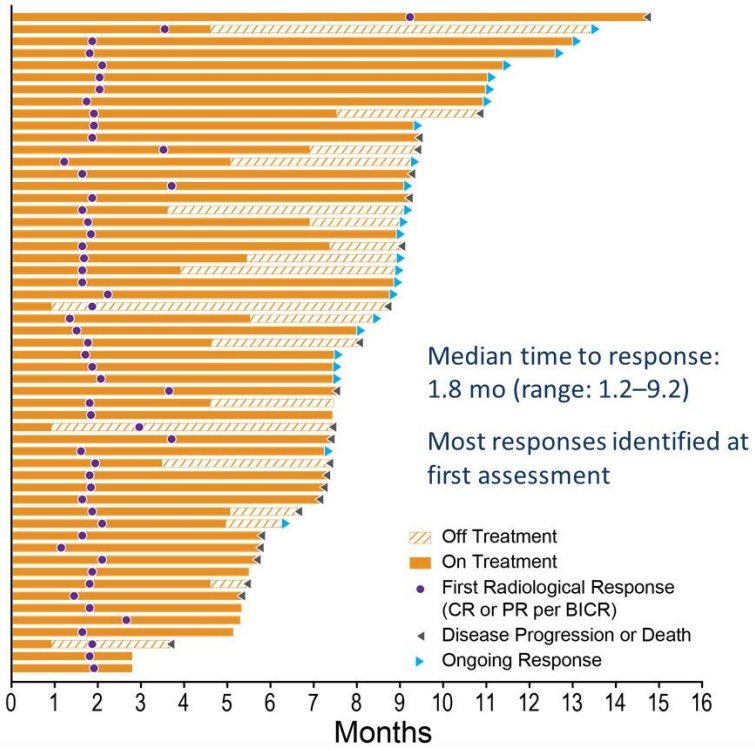
[1]Computed using the Clopper-Pearson method; [2]Includes 10 patients who discontinued study prior to post-baseline response assessment, 1 patient who had uninterpretable post-baseline assessment and 1 patient whose post-baseline assessment did not meet the minimum interval requirement for stable disease

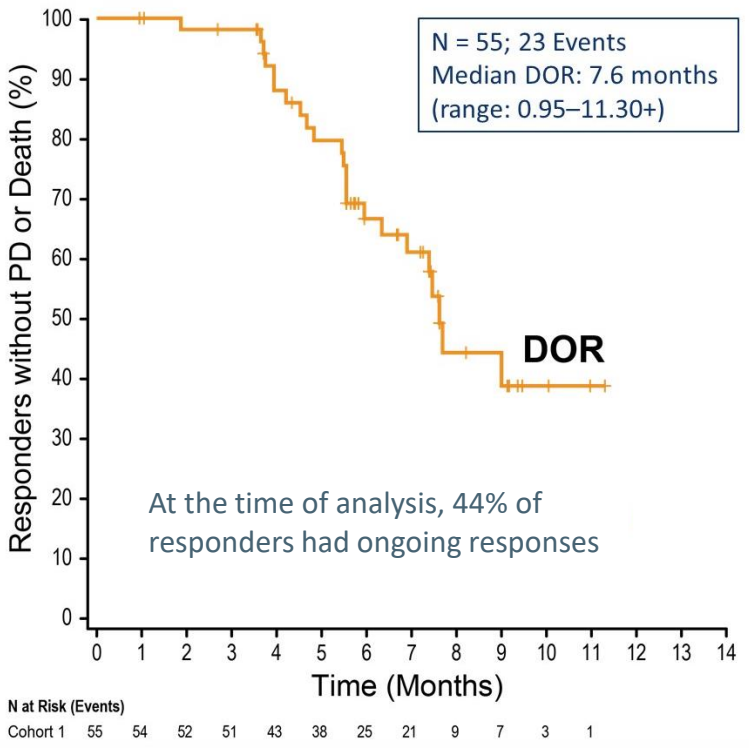
BICR, blinded independent central review; RECIST, Response Evaluation Criteria In Solid Tumors

Petrylak D, et al. Journal of Clinical Oncology 2019;37(18_suppl):4505; Rosenberg JE, et al. Journal of Clinical Oncology 2019;37(29):2592-2600

EV-201: DURATION OF RESPONSE

EV-201: COHORT 1 DURATION OF RESPONSE WITH ENFORTUMAB VEDOTIN





BICR, blinded independent central review; CR, complete response; DOR, duration of response; PR, partial response

Petrylak D, et al. Journal of Clinical Oncology 2019;37(18_suppl):4505; Rosenberg JE, et al. Journal of Clinical Oncology 2019;37(29):2592-2600

EV-201: TREATMENT RELATED ADVERSE EVENTS

Cohort 1 Treatment-related AEs by preferred term in ≥20% of patients (any Grade)[1,2]	Patients (N=125) n (%)	
	Any Grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhoea	40 (32)	3 (2)
Dry skin	28 (22)	0
Weight decreased	28 (22)	1 (1)
Rash maculo-popular	27 (22)	5 (4)

- Most common adverse reactions (≥ 20%) included fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin[3]
- Recommend holding treatment if blood glucose >250mg/dL[3]
- Permanently discontinue for peripheral neuropathy ≥ grade 3[3]

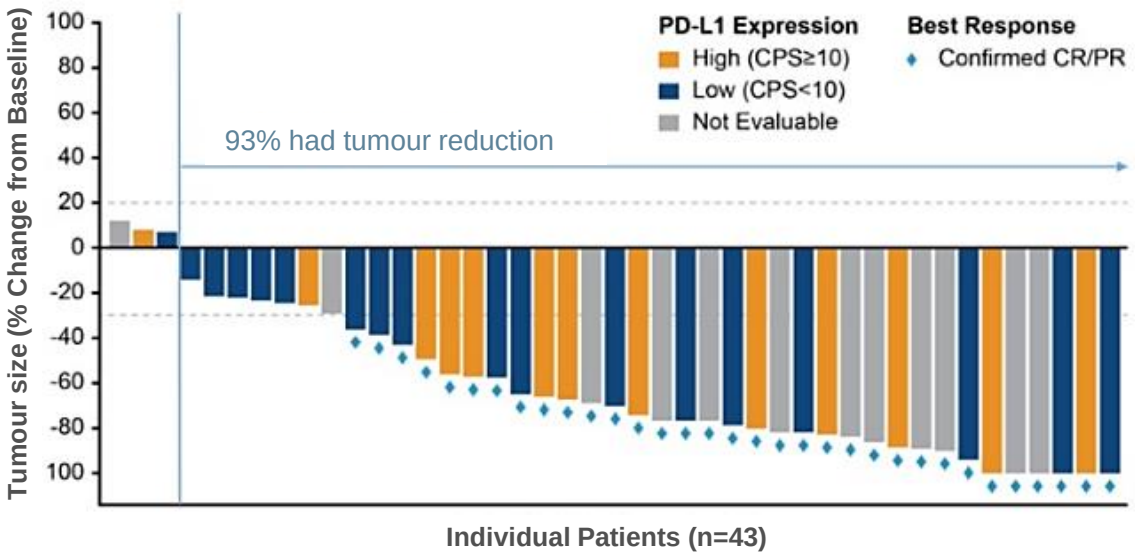
AEs, adverse events

1. Petrylak D, et al. Journal of Clinical Oncology 2019;37(18_suppl):4505; 2. Rosenberg JE, et al. Journal of Clinical Oncology 2019;37(29):2592-2600; 3. Enfortumab vedotin prescribing information, Dec 2019

EV-103: EV PLUS PEMBROLIZUMAB IN FIRST LINE CISPLATIN-INELIGIBLE mUC PATIENTS

MAXIMAL TARGET LESION REDUCTION BY PD-L1 STATUS AND BEST RESPONSE

- Responses observed regardless of PD-L1 expression level



The horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively

OBJECTIVE RESPONSE RATE

Best overall response by RECIST v 1.1 (Investigator assessed), N=45	
Confirmed ORR 95% CI	73.3% (33/45) (58.1, 85.4)
CR	15.6% (7/45)
PR	57.8% (26/45)

CI, confidence interval; CPS, combined positive score; CR, complete response; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate; PD-L1, Programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors

Rosenberg JE, et al. Journal of Clinical Oncology 2020, 38,suppl 6: abstr 441

SACITUZUMAB GOVITECAN

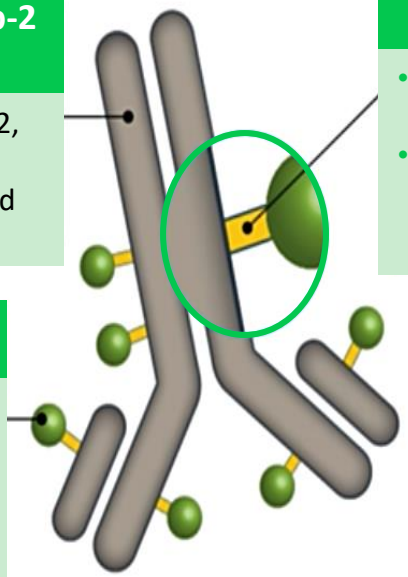
- Antibody target: Trop-2
- Linker: Hydrolysable linker
- Payload: SN-38-parent compound - irinotecan
- Trop-2 is an epithelial cell surface antigen highly expressed in UC
- Shown activity across multiple tumour types: NSCLC, SCLC, mTNBC

Humanised Anti-Trop-2 Antibody (hRS7)

- Directed towards Trop-2, an epithelial antigen expressed on many solid tumours

SN-38 Payload

- Metabolite of topoisomerase I inhibitor
- SN-38 more potent than parent compound, irinotecan



Linker for SN-38

- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.6:1)

ADC, antibody drug conjugate; mTNBC, metastatic triple-negative breast cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; UC, urothelial cancer

Tagawa S, et al. Annals of Oncology 2019;30(suppl_5):v851-v934; Rugo S, et al. Future Medicine 2020; doi:10.2217/fon-2020-0163

SACITUZUMAB STUDIES

- **IMMU-132 Phase 1 study[1]**
  - Initial assessment of efficacy and safety in 45 mUC patient's pts who progressed after ≥1 prior systemic therapy
  - ORR 31%
  - Grade ≥3 AEs in ≥5% of pts were neutropenia/neutrophil count decreased (38%), anaemia (11%), hypophosphatemia (11%), diarrhoea (9%), fatigue (9%), and febrile neutropenia (7%).
- **TROPHY-U-01 : Phase 2 ongoing study[2]**
  - 35 patients post platinum and post CPI included in interim analysis
  - ORR 29%; CR 6%

TROPHY-U-01: TRAE ≥ 20% ANY GRADE OR ≥ 5% GRADE ≥3 (N=35)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic	Neutropenia	66	29	26
	Leukopenia	40	20	9
	Anaemia	34	17	0
	Febrile neutropenia	11	9	3
	Lymphocyte count decreased	11	6	3
Gastrointestinal	Diarrhoea	57	6	3
	Nausea	43	0	0
	Abdominal pain	20	3	0
General disorders & administrative site conditions	Fatigue	54	6	0
Infections & infestations	Urinary tract infection	14	11	0
Skin & subcutaneous tissue	Alopecia	74	0	0
Metabolism & nutrition	Decreased appetite	20	0	0

AE, adverse event; CPI, checkpoint inhibitors; CR, complete response; ORR, objective response rate; TRAE, treatment related adverse event

1. Tagawa S, et al. Journal of Clinical Oncology 2019;37(7_suppl):354; 2. Tagawa S, et al. Annals of Oncology 2019; 30 (suppl_5): v851-v934

CONCLUSIONS

- Immuno-drug conjugates are a new class of drugs in urothelial cancer
- Enfortumab vedotin approved in advanced or metastatic urothelial cancer post platinum, post checkpoint inhibitor
- Promising data of enfortumab in first line in combination with check point inhibitors
- Ongoing studies with sacituzumab govitecan which targets Trop-2
- Await larger phase 3 confirmatory studies

Enfortumab vedotin Prescribing Information Dec 2019; Sau S, et al. Drug Discov Today 2017;22:1547-1556; Tagawa S, et al. Annals of Oncology 2019; 30 (suppl_5): v851-v934; Vlachostergios P, et al. Bladder Cancer 2018;4(3):247-259; Rosenberg JE, et al. Journal of Clinical Oncology 2020, 38,suppl 6: abstr 441

ANTIBODY-DRUG CONJUGATES FOR OTHER GENITOURINARY CANCERS

ANTIBODY-DRUG CONJUGATES IN OTHER GU TUMOUR TYPES

- Prostate Cancer[1]
  - Prostate-specific membrane antigen (**PSMA**) **is over expressed on the surface of cancer cells** and is therefore a suitable target for selective drug delivery through conjugated antibodies
  - There are a number of **PSMA-ADC drugs in development for mCRPC** that have shown promising activity in phase I/II trials
  - Clinical trials are ongoing to investigate the effects of **sacituzumab govitecan** which targets TROP-2 **in patients with mCRPC** (NCT03725761)[2]
- Renal Cell Carcinoma[3]
  - ENPP3 is a novel target specific to renal cell carcinoma (RCC) with minimal expression in normal tissue
    - **ADCs targeting ENPP3** in initial human studies **warrant further investigation**
  - **Other antigen targets** for ADCs under investigation in **RCC include: CD70, CD27L, TIM-1**[4,5]

ADC, Antibody drug conjugate; CD, cluster of differentiation;ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase 3; GU, genitourinary; IL, interleukin; mCRPC, metastatic castration resistant prostate cancer; PSMA, prostate-specific membrane antigen; TIM-1, T-cell immunoglobulin and mucin domain 1

1. Niaz M, et al. Cureus 2020;12(2):e7147. doi:10.7759/cureus.7147; 2. www.clinicaltrials.gov; 3. Thompson J, et al. Clinical Cancer Research 2018;24(18):4399-4406; 4. Sau S, et al. Drug Discov Today 2017;22:1547-1556; 5. Thomas L, et al. Mol Cancer Ther 2016;15(12):2946-2954

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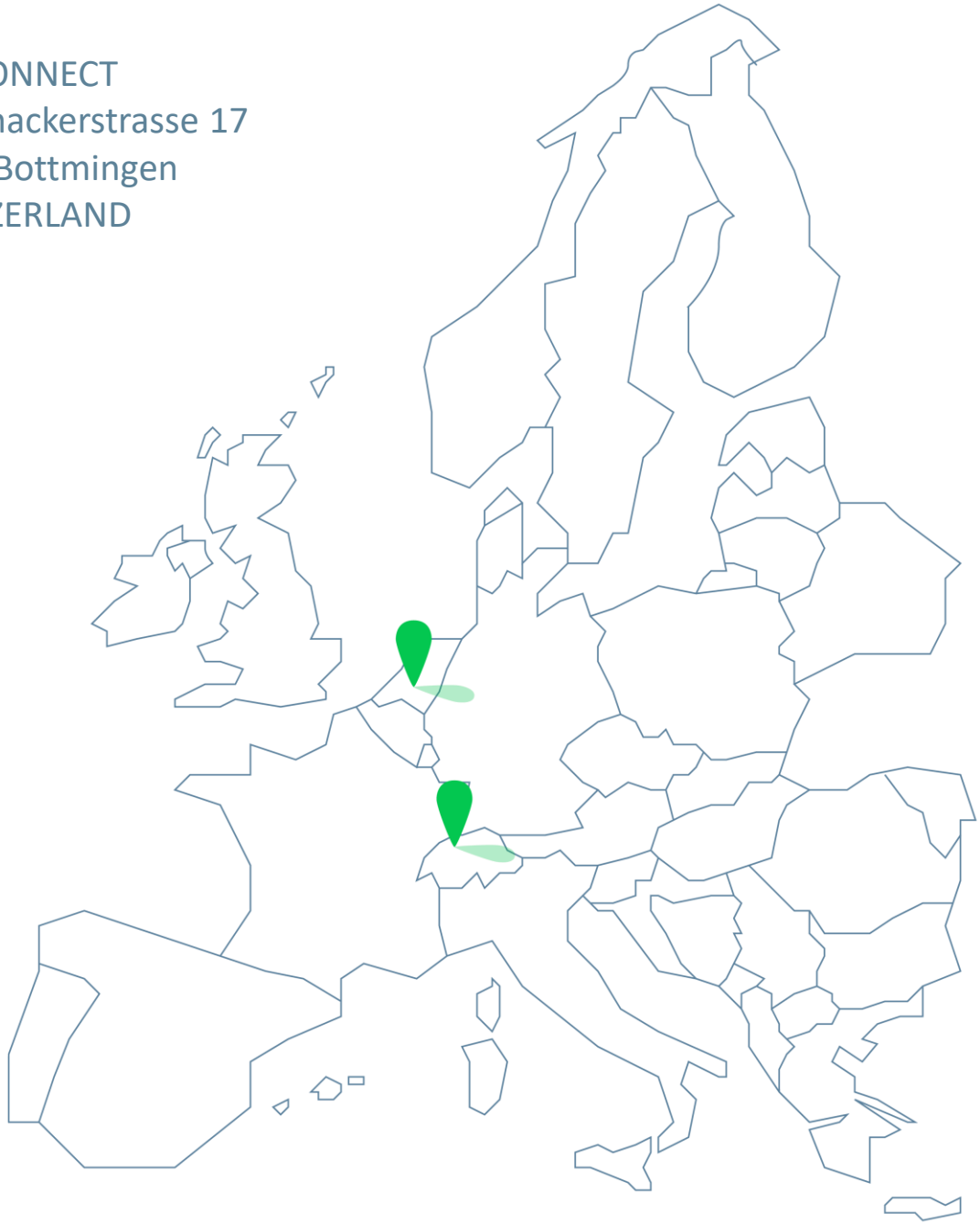

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