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MEETING SUMMARY
ASCO GU 2020, San Francisco, USA

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UROTHELIAL CANCER UPDATE

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STUDY EV-103: PRELIMINARY DURABILITY RESULTS OF ENFORTUMAB VEDOTIN PLUS PEMBROLIZUMAB FOR LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

Rosenberg JE, et al.
ASCO GU 2020. Abstract #441 (Oral presentation)

INTRODUCTION

- **Platinum chemotherapy is the standard of care for patients** with metastatic Urothelial Carcinoma (UC) in the first line setting
- **Gemcitabine/carboplatin is a standard therapy in patients who are cisplatin ineligible** but it is poorly tolerated and associated with limited durability and survival.
- **Enfortumab vedotin is an antibody-drug conjugate** comprised of the nectin-4 antibody enfortumab coupled to the microtubule disrupting agent monomethyl auristatin E (MMAE). Nectin-4 is highly expressed in UC
- Results from EV-103 were presented at ESMO 2019. EV-103 evaluated **enfortumab as a first-line agent in combination with pembrolizumab**, and the **results from the cisplatin-ineligible (cohort A) demonstrated a 62% objective response rate with 14% of patients achieving a complete response**[1]
- **This presentation presents updated durability, progression-free survival and overall survival data** for enfortumab vedotin and pembrolizumab in the first-line setting for patients who could not receive cisplatin as first line therapy for locally advanced or metastatic disease

MMAE, monomethyl auristatin E; UC, urothelial carcinoma

1. Hoimes C, et al. Annals of Oncology (2019) 30 (suppl_5): v356-v402. 10.1093/annonc/mdz249;
2. Rosenberg JE, et al. ASCO GU 2020. Abstract #441 (Oral presentation)

EV-103 STUDY DESIGN

EV-103 FIRST-LINE COHORTS OF ENFORTUMAB VEDOTIN PLUS PEMBROLIZUMAB

Enfortumab vedotin 1.25 mg/kg + pembrolizumab (200 mg) in 1L cisplatin-ineligible la/mUC patients (N=45)

Patient Population

Locally Advanced or Metastatic Urothelial Carcinoma

Dose Escalation[1]

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=5)

Dose Expansion Cohort A

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=40)

Dosing: Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle

Enfortumab vedotin exposure: Comparable to enfortumab vedotin monotherapy on 4-week schedule (Days 1, 8 and 15)[2]

Primary endpoints: safety and tolerability

Key secondary endpoints: dose-limiting toxicities, ORR, DOR, PFS OS

[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembrolizumab 200 mg

[2] Rossenberg et al. J Clin Oncol. 2019;37(29)2592-600.

- Data is presented on 45 patients, who have received a median of 9 cycles of therapy (range 1-22)

1L, first-line; 2L, second-line; DOR, duration of response; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Rosenberg JE, et al. ASCO GU 2020. Abstract #441 (Oral presentation)

EV-103 BASELINE DATA

Enfortumab vedotin 1.25 mg/kg + pembrolizumab in 1L setting 8 Oct 2019 data cut-off	Patients (N=45) n (%)
Male sex, n (%)	36 (80)
Age, yrs, median (min, max)	69 (51, 90)
ECOG performance status, n (%)	
0	16 (36)
1	23 (51)
2	6 (13)
Primary tumor location, n (%)	
Lower tract	31 (69)
Upper tract	14 (31)
Metastasis sites, n (%)	
Lymph nodes only	4 (9)
Visceral disease	41 (91)
Liver	15 (33)
PD-L1 status by combined positive score,[1] n (%)	
<10	19 (42)
≥10	14 (31)
Not evaluable/not available	12 (27)

[1] Unselected patient population; PD-L1 tested using the 22C3 PharmDx assay from Agilent/Daklo

- The majority of patients were men with visceral disease
- Patients with low and high PD-L1 status were balanced

1L, first-line; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed ligand death-1

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SAFETY AND TOLERABILITY

TREATMENT-RELATED ADVERSE EVENTS (TRAE)

TRAEs by preferred term 8 Oct 2019 data cut-off	Patients (N=45) n (%)	
	Any Grade ≥20% of patients	≥Grade 3 ≥10% of patients
Overall	43 (96)	26 (58)
Fatigue	22 (49)	4 (9)
Alopecia	22 (49)	–
Peripheral sensory neuropathy	22 (49)	2 (4)
Diarrhea	20 (44)	3 (7)
Decreased appetite	17 (38)	0
Dysgeusia	15 (33)	–
Rash maculo-popular	14 (31)	4 (9)
Nausea	13 (29)	0
Pruritus	13 (29)	1 (2)
Anemia	9 (20)	3 (7)
Weight decreased	9 (20)	0
Lipase increased	8 (18)	8 (18)

- 7 patients (16%) had treatment related SAEs
  - 1 patient (2%) died due to multiple organ failure

SAE, serious adverse event; TRAE, treatment-related adverse event

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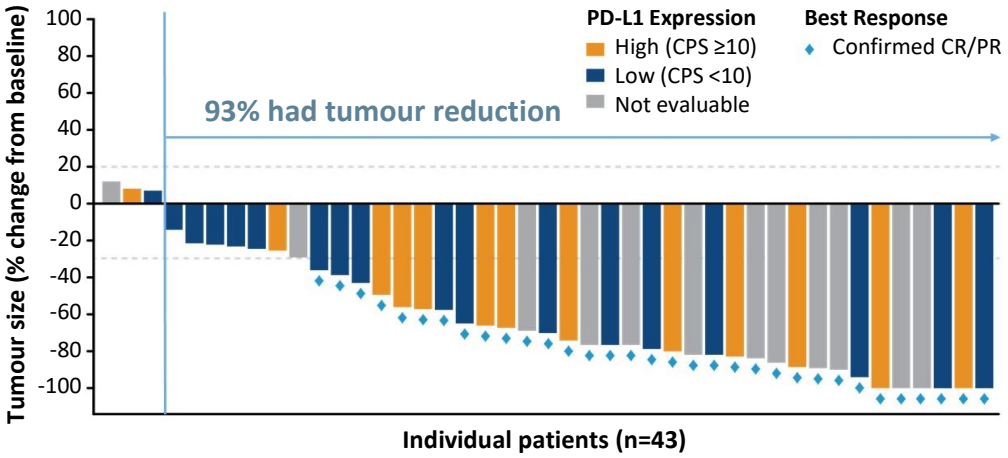
OBJECTIVE RESPONSE RATE

MAXIMAL TARGET LESION REDUCTION BY PD-L1 STATUS



- Responses observed regardless of PD-L1 expression level

ORR PER INVESTIGATOR

Confirmed ORR 95% CI	**73.3% (33/45)** (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

Best Overall Response Per RECIST v 1.1 by investigator (N=45)

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above.

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

- Median follow-up of 11.5 months
- Confirmed investigator-assessed ORR of 73.3% (95% CI: 58.1-85.4)
  - Includes 15.6% CR and 93.3% DCR

CI, confidence interval; CPS, combined positive score; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD-L1. Programmed death-ligand 1; PR, partial response; RECIST, Response evaluation criteria in solid tumors

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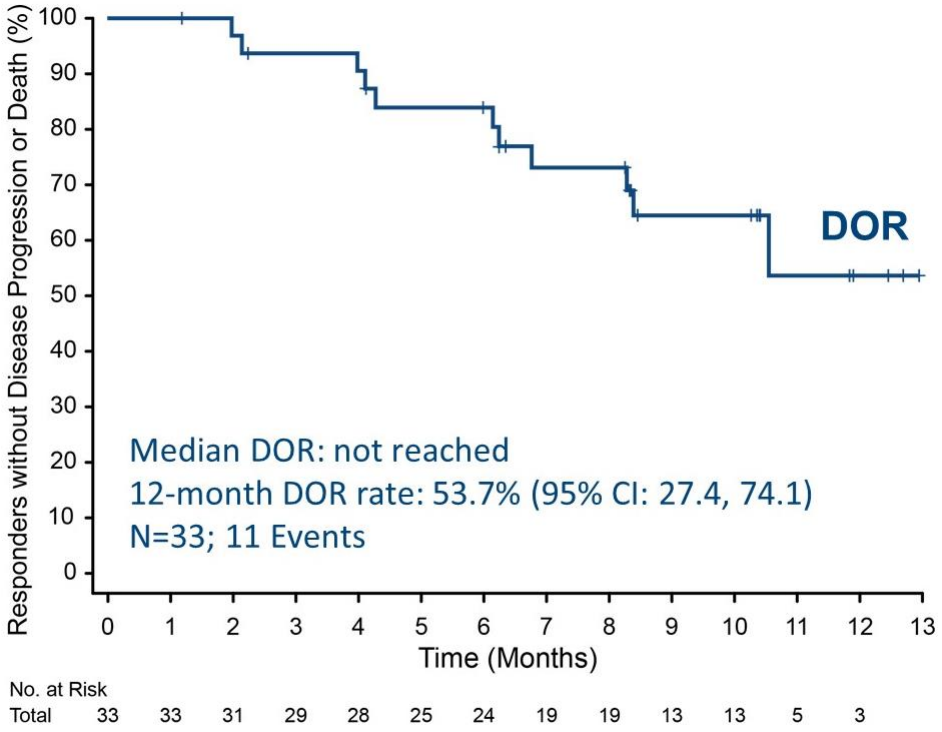
DURATION OF RESPONSE

ENFORTUMAB VEDOTIN + PEMBROLIZUMAB

- Median follow up of 10.4 months
  - Median DOR not been reached (range: 1.2-12.9+ months)



- Of the 33 responders:
  - 18 (55%) had an ongoing response
  - 11 (33%) had progressed or died
  - 4 (12%) started new treatment prior to PD

CI, confidence interval; DOR, duration of response; PD, progressive disease

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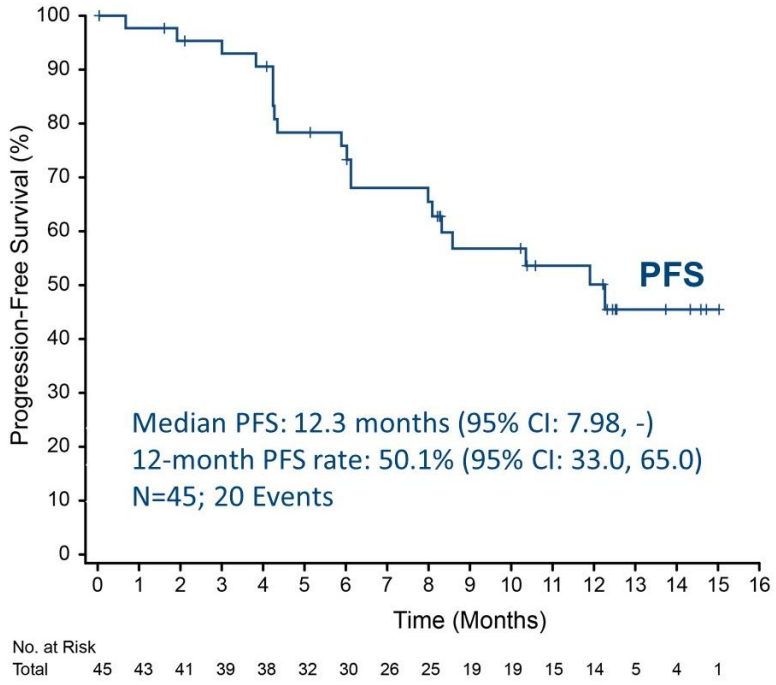
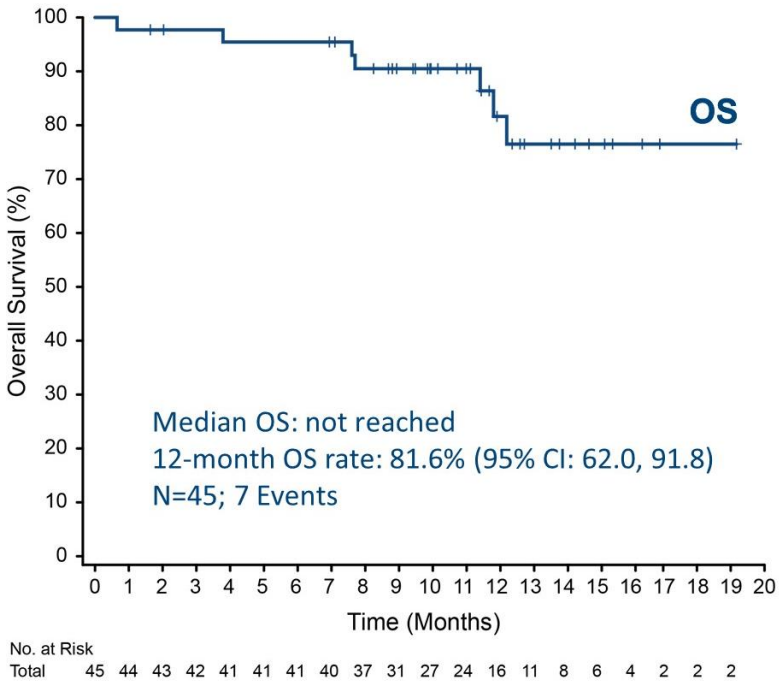
SURVIVAL DATA

ENFORTUMAB VEDOTIN + PEMBROLIZUMAB

Progression-free survival



Overall survival



CI, confidence interval; OS, overall survival; PFS, progression-free survival

Rosenberg JE, et al. ASCO GU 2020. Abstract #441 (Oral presentation)

CONCLUSIONS

- **In first-line cisplatin-ineligible patients,** combination therapy with **enfortumab vedotin and pembrolizumab shows promising activity and durability**
- **A high overall response rate was observed**, with 88% of patients having responded at first assessment and responses being evident within 2 months (median) of treatment
- **Combination therapy was associated with a manageable safety profile** and no new safety concerns were identified
- Further evaluation of the enfortumab vedotin and pembrolizumab combination in metastatic UC and muscle-invasive UC is ongoing

UC, urothelial carcinoma

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PHASE II RANDOMIZED PLACEBO-CONTROLLED NEOADJUVANT TRIAL OF NINTEDANIB OR PLACEBO WITH GEMCITABINE AND CISPLATIN IN LOCALLY ADVANCED MUSCLE INVASIVE BLADDER CANCER (NEO-BLADE)

Hussain SA, et al.
ASCO GU 2020. Abstract #438 (Oral presentation)

INTRODUCTION

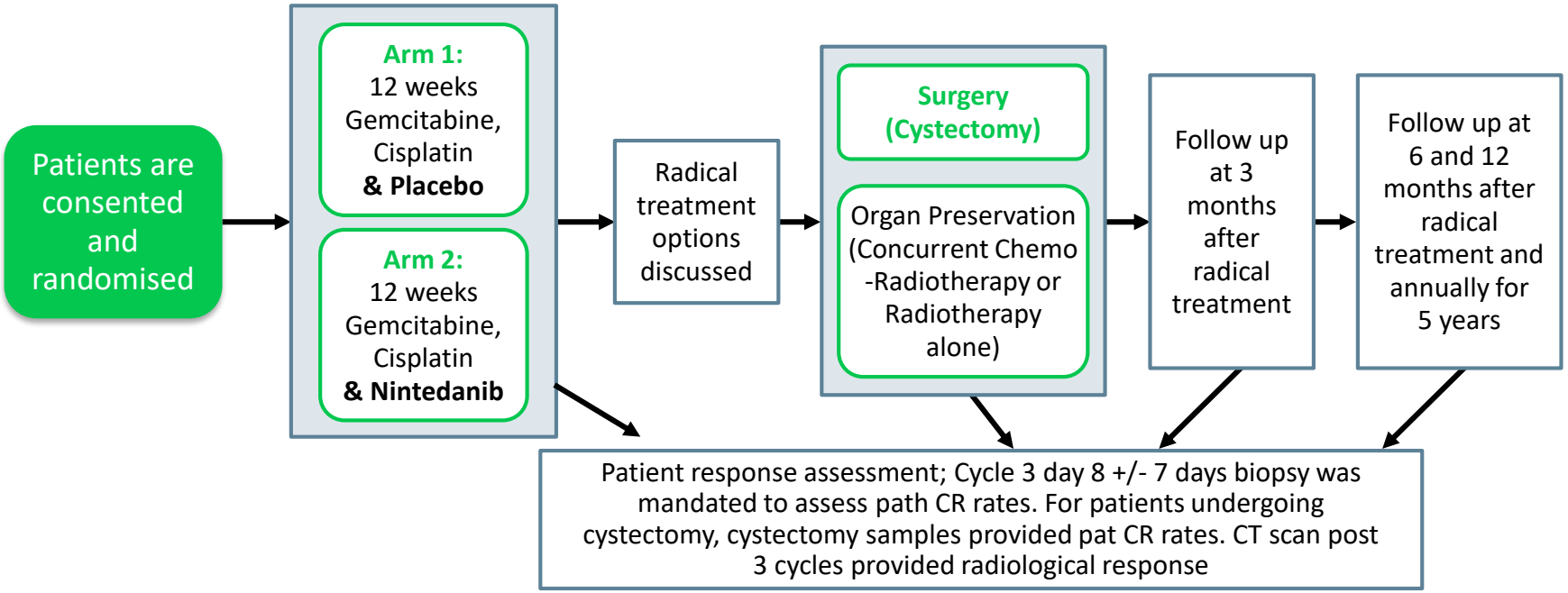
- **Neo-adjuvant chemotherapy** (gemcitabine and cisplatin) **improves overall survival in patients with MIBC**
- **Nintedanib** is a small molecule tyrosine-kinase inhibitor, targeting vascular endothelial growth factor receptor-2, fibroblast growth factor receptor-1 and platelet derived growth factor receptor
- The **NEO-BLADE study, investigates the toxicity and efficacy** effects **of adding nintedanib to the usual neo-adjuvant chemotherapy combination** of gemcitabine and cisplatin **in patients with MIBC**

MIBC, muscle invasive bladder cancer

Hussain SA, et al. ASCO GU 2020. Abstract #438 (Oral presentation)

STUDY DESIGN

- Randomised, placebo controlled, phase 2 study
- 120 patients with MITCC, T2-T4 N0M0, GFR >60ml/min



- Co-primary endpoint: Pathological CR rate and Overall CRR (pathological & radiological)
- Secondary endpoints: PFS, OS and toxicity

CR, complete response; CRR, complete response rate; CT, computerised tomography; GFR, glomerular filtration rate; MITCC, muscle invasive transitional cell carcinoma; OS, overall survival; PFS, progression-free survival

Hussain SA, et al. ASCO GU 2020. Abstract #438 (Oral presentation)

RESULTS

PRIMARY ENDPOINT: PATHOLOGICAL/OVERALL CRR

Pathological CRR

(Evaluable n= 86; ITT n=120)

- Nin 51% (21/41); ITT 37% (21/57)
- Plb 44% (20/45); ITT 32% (20/63)
- **OR(CI): 1.31 (0.84, 2.06)**

Overall CRR (n=109)*

- Nin 40% (22/54); ITT 38% (22/57)
- Plb 45% (25/55); ITT 39% (25/63)
- **OR(CI): 0.90 (0.60, 1.35), p=0.893**

Pathological Complete Response

Response	Nintedanib	Placebo	Total
CR	21 (51%)	20 (44%)	41
Non-CR	20 (49%)	25 (56%)	45

Radiological Response

Response	Nintedanib	Placebo	Total
CR	**22 (40%)**	**25 (45%)**	**47**
PR	3 (6%)	4 (7%)	7
SD	25 (46%)	19 (35%)	44
PD	4 (7%)	7 (13%)	11

*109 (91%) patients were evaluable for complete response

CI, confidence interval; CR, complete response; CRR, complete response rate; ITT, intention-to-treat; Nin, nintedanib; OR, odds ratio; PD, progressive disease; Plb, placebo; PR, partial response; SD, stable disease

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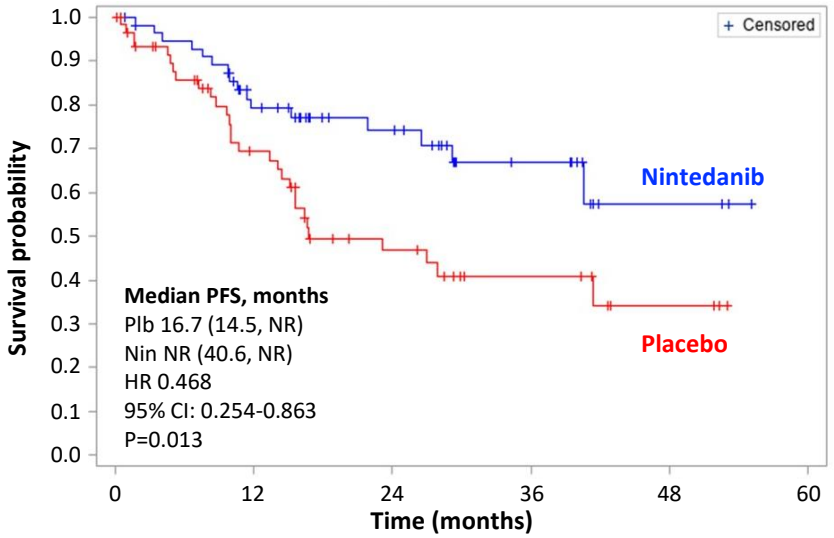
SECONDARY ENDPOINT RESULTS

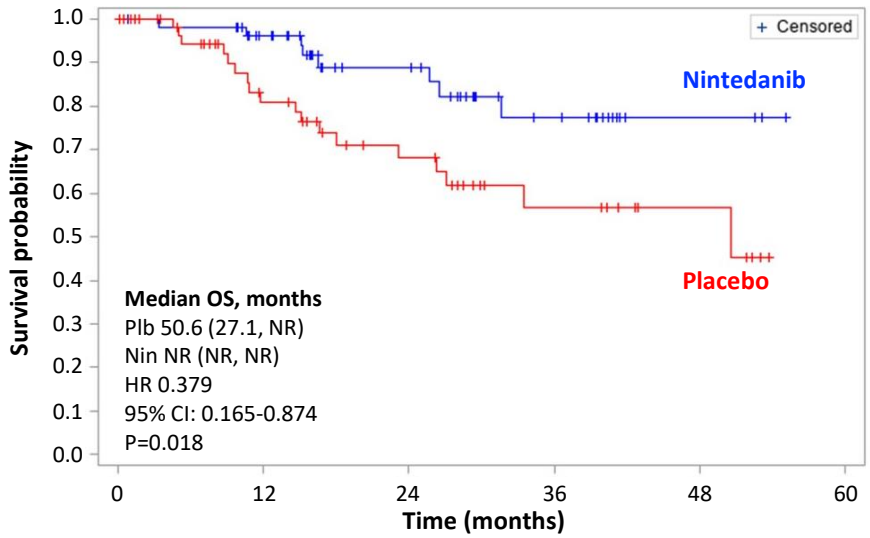
PROGRESSION-FREE SURVIVAL



Nintedanib	57	38	25	13	3	0
Placebo	63	33	17	9	3	0

- 12-month PFS: Plb 74%, Nin 89%
- 24-month PFS: Plb 61%; Nin 82%

OVERALL SURVIVAL



Nintedanib	57	46	29	15	3	0
Placebo	63	36	23	11	5	0

- 12-month OS: Plb 83%, Nin 96%
- 24-month OS: Plb 69%; Nin 89%

CI, confidence interval; HR, hazard ratio; Nin, nintedanib; OS, overall survival; Plb, placebo; PFS, progression free survival

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TOXICITY

Grade 3+ adverse events	Gemcitabine; Cisplatin & Nintedanib	Gemcitabine; Cisplatin & placebo	Total
Thromboembolic event	16 (28%)	13 (21%)	29
Neutrophil count decreased	6 (10%)	1 (2%)	6
Febrile neutropenia	2 (4%)	4 (6%)	6
Vomiting	1 (2%)	3 (5%)	4
Acute kidney injury	1 (2%)	3 (5%)	4
Skin infection	2 (4%)	1 (2%)	3
Nausea	1 (2%)	2 (3%)	3
Hypotension	1 (2%)	2 (3%)	3
Hyponatremia	1 (2%)	2 (3%)	3
Alanine aminotransferase increased	3 (5%)	0 (0%)	3
Wound infection	1 (2%)	1 (2%)	2
Renal and urinary disorders – Other	0 (0%)	2 (3%)	2
Myocardial infarction	0 (0%)	2 (3%)	2
Fatigue	1 (2%)	1 (2%)	2

- 111 SAEs observed
  - 74 grade 3, 11 grade 4, 1 grade 5
  - Nintedanib associated with more neutropenia and hypertension

SAE, serious adverse event

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CONCLUSION

- **NEO-BLADE failed to reach its primary endpoint** in demonstrating an improvement in CRR between nintedanib and placebo when given alongside gemcitabine/cisplatin
- **Secondary endpoints of PFS and OS showed significant benefits** for patients treated with nintedanib
- The **safety data from this trial confirms that triplet therapy can be administered safely**
- The efficacy signals indicate that the treatment regimen warrants further investigation in a phase 3 trial

CRR, complete response rate; OS, overall survival; PFS, progression-free survival

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RESULTS FROM BLASST-1 (BLADDER CANCER SIGNAL SEEKING TRIAL) OF NIVOLUMAB, GEMCITABINE, AND CISPLATIN IN MUSCLE INVASIVE BLADDER CANCER (MIBC) UNDERGOING CYSTECTOMY

Gupta S, et al.
ASCO GU 2020. Abstract #439 (Oral presentation)

INTRODUCTION

- MIBC is a highly aggressive disease with high relapse rates post-cystectomy
- Cisplatin-based neoadjuvant chemotherapy (NAC) in MIBC improves survival which correlates with pathologic response
- Survival advantage with NAC primarily occurs in patients who achieve pathological downstaging[1,2]
- Anti PD-1/PD-L1 inhibitors have revolutionalised the therapeutic landscape in mUC and neoadjuvant IO-chemo combination has been shown to be active in MIBC[3]
- The phase 2 BLASST-1 study evaluated the efficacy and safety of the PD-1 inhibitor nivolumab plus gem/cis as neoadjuvant therapy for MIBC

Gem/cis, gemcitabine/cisplatin; IO, immuno-oncology; MIBC, muscle invasive bladder cancer; mUC, metastatic urothelial cancer; NAC; neoadjuvant chemotherapy; PD-1, Programmed cell death protein 1; PD-L1, programmed death ligand-1

1. Sonpavde G, et al. Cancer 2009;115:4104-9; 2. Bhindi B, et al. Eur Urol 2017;72(5):660-4; 3. Hoimes C. ESMO 2018. Abstract#LBA33;
4. Gupta S, et al. ASCO GU 2020. Abstract #439 Oral presentation

BLASST-1 STUDY DESIGN

ELIGIBLE PATIENTS

- cT2-T4aN≤1MO
- Predominantly UC histology
- Fit and planned for radical cystectomy
- ECOG PS 0-1
- Cisplatin-eligible
- Cr Cl ≥50 ml/min

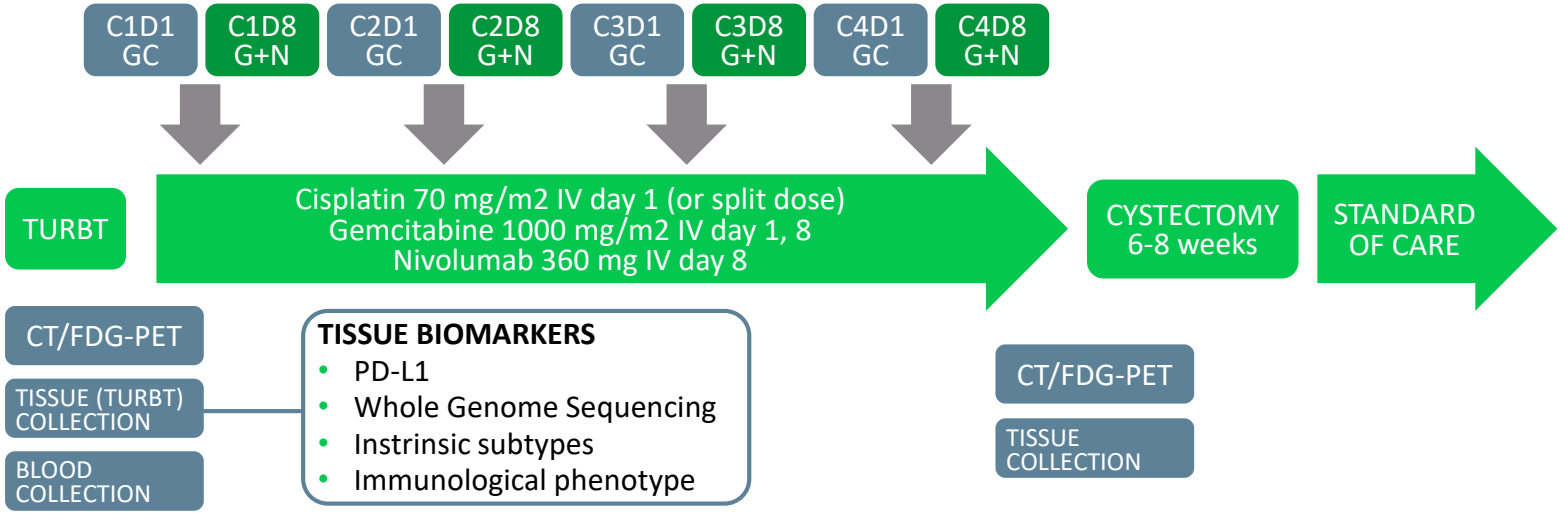
OBJECTIVES

Primary objective:

- Pathologic response = pathological non muscle-invasive rates <pT2N0

Secondary objectives:

- Safety
- PFS at 2 years



- 41 patients received Gem/Cis + Nivolumab
  - 38 received 4 cycles, 2 received 2 cycles and 1 received cycle
  - 40 underwent cystectomy

CrCl, creatinine clearance; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG-PET, fluorodeoxyglucose - positron emission tomography; GC, gemcitabine cisplatin; Gem/Cis, gemcitabine/Cisplatin; G+N, gemcitabine plus nivolumab; IV, intravenous; PD-L1, programmed death ligand-1; PFS, progression-free survival

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RESULTS

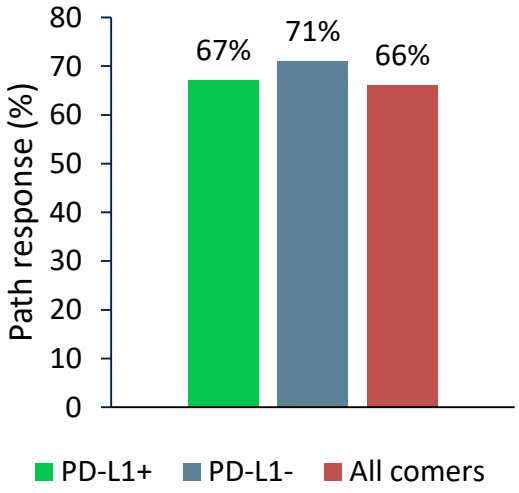
PATHOLOGICAL RESPONSES

	N (%)		
PRIMARY ENDPOINT **PaR: Pathologic non muscle-invasive rate (<pT2N0)**	**27/41 (66)**		
	pT0	14	51.8%
	pT1	2	7.4%
	pTa*	5	18.5%
	pTis	6	22.2%
pCR: Pathologic complete response (pT0, pTis)	**20/41 (49)**		

*1 patient with T4N1 disease had a downstaging to pTaN0

- There was no correlation between PD-L1 status and pathologic response
  - 67% of patients with PD-L1 positive tumours achieved a pathologic response
  - 71% of patients with PD-L1 negative tumours achieved a pathologic response

- 66% of patients achieved a pathologic response



PaR, pathologic response; pCR, pathologic complete response; PD-L1, programmed death ligand-1

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RESULTS – SAFETY

TREATMENT-RELATED AEs

Drug related AEs	Grade 1-2	Grade 3-4	Total
Anemia	7 (17%)	2 (7%)	10 (24%)
Neutropenia	17 (41%)	3 (7%)	20 (48%)
Febrile neutropenia	0	1 (2%)	1 (2%)
Thrombocytopenia	12 (29%)	2 (2%)	13 (31%)
Fatigue	25 (60%)	0	25 (60%)
ALT increase	10 (24%)	1 (2%)	11 (26%)
AST increase	10 (24%)	0	10 (24%)
Rash	14 (34%)	0	14 (34%)
Diarrhea	7 (17%)	0	7 (17%)
Nausea	29 (70%)	0	29 (70%)
Acute kidney injury	5 (12%)	1 (2%)	6 (14%)

The combination was safe with manageable toxicities and no deaths from treatment

IMMUNE-RELATED AEs

Drug related AEs	Grade	Total	Systemic steroids
Rash	1	1 (2%)	No
Hypothyroidism	1	1 (2%)	
Inflamed lymph-nodes	1	2 (4%)	No
Guillain Barre Syndrome		1 (2%)	No

AEs, adverse events; ALT, alanine aminotransferase; AST, Aspartate transaminase

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CONCLUSION

- **Neoadjuvant nivolumab + gemcitabine/cisplatin resulted in significant pathological non-muscle invasive rates of 66%** (49% pCR)
- **The combination treatment was safe and effective in patients with MIBC** and no added toxicities or deaths were observed
  - No cystectomy delays occurred and there were no unexpected surgical complications
- **PD-L1 status did not correlate with pathologic response**
- The randomised, phase 3 ENERGIZE study will further investigate the combination treatment in patients with MIBC

MIBC, muscle invasive bladder cancer; pCR, pathologic complete response; PD-L1, programmed death ligand-1

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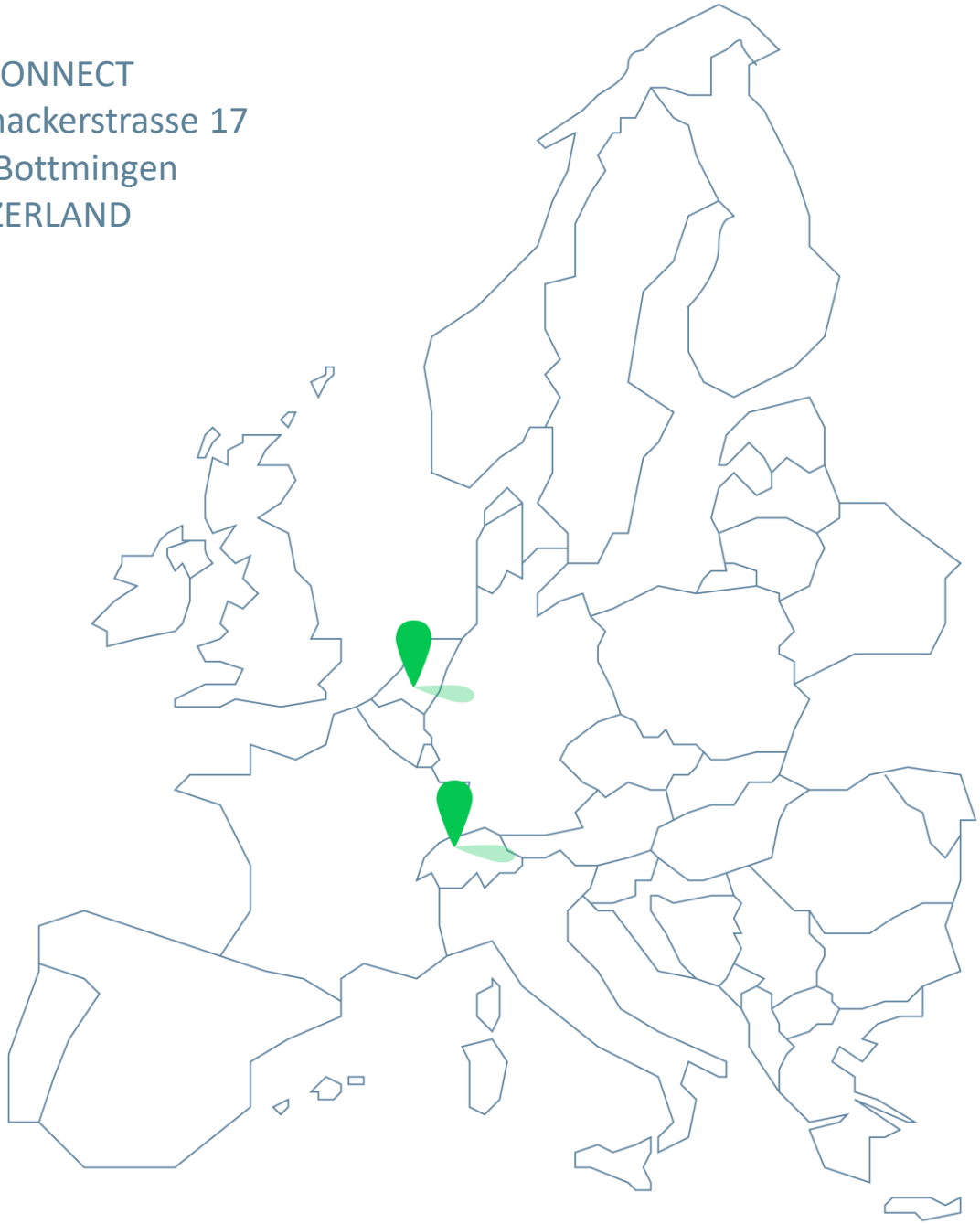

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