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MEETING SUMMARY
ENETS 2020
VIRTUAL MEETING

Dr Alia Munir MBBCH MRCP PhD FRCP
Consultant Endocrinologist
Sheffield Teaching Hospitals NHS Foundation Trust, UK

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DISCLOSURES DR. MUNIR

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PRESIDENTIAL ABSTRACT CLINICAL SCIENCE:

SOMATOSTATIN ANALOGS (SSA) IN PATIENTS WITH SYMPTOMATIC DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE CELL HYPERPLASIA (DIPNECH)

Al-Toubah T, et al. ENETS 2020. Abstract #H01

BACKGROUND

- **DIPNECH is a very rare lung disorder considered a precursor of tumourlets and typical/atypical carcinoids[1]**
- A typical patient is a **middle aged non-smoking woman** presenting with **decades of chronic cough and dyspnoea**
- Radiological signs include:
  - Multifocal pulmonary nodules
  - Mosaic attenuation with air trapping
  - Ground glass appearance
  - Endobronchial wall thickening
  - Atelectasis
- This multi-institution **retrospective chart review** on outcomes of **SSA treatment in DIPNECH**

DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; SSA, somatostatin analogues

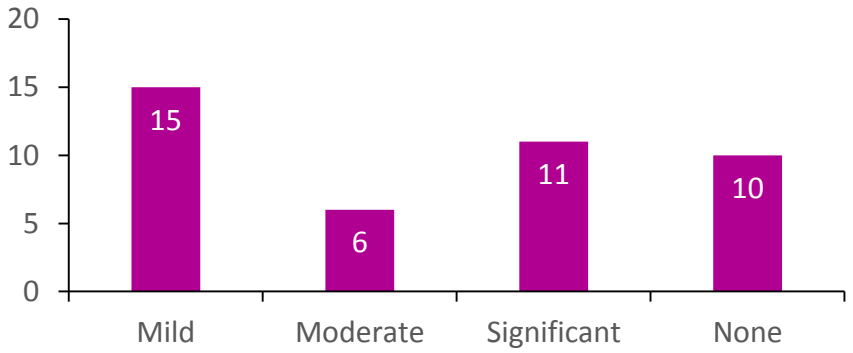
1. Brambilla B, et al. Eur Respir J 2001;18:1059-68; 2. Gorshtein A, et al. Cancer 2012;118:612-9;
3. Chauhan A and Ramirez RA. Lung 2015;193:653-7 ; 4. Al-Toubah T, et al. ENETS 2020. Abstract #H01 (Oral presentation)

KEY RESULTS

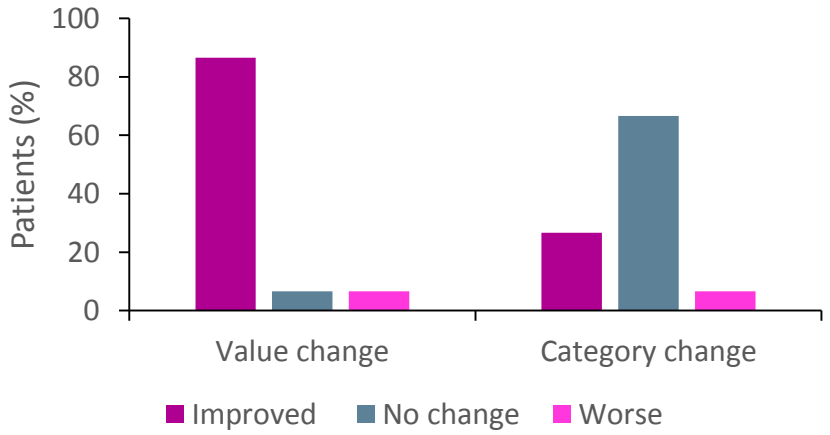
PATIENT CHARACTERISTICS

	N (%)
Sex	
Female	40 (95.2)
Male	2 (4.8)
Age	
<50	4 (9.6)
50-59	13 (30.9)
60-69	10 (23.8)
70+	15 (35.7)
Ki-67% (on biopsy or surgical specimen)	
Not reported	25 (59.5)
≤2%	16 (38.1)
3-20%	1 (2.4)
Smoking history	
Yes	10 (23.8)
No	32 (76.2)
Other therapies for respiratory symptoms	
0	11 (26.2)
1	9 (21.4)
2-3	18 (42.9)
>3	4 (9.5)
Baseline symptoms	
Cough	34 (80.9)
Dyspnea	27 (64.2)
Fatigue	6 (14.3)
Wheezing	5 (11.9)
Palpitations	4 (9.5)
Chest tightness	2 (4.7)
Hot flashes	1 (2.4)
Hirsutism	1 (2.4)
Abdominal pain	1. (2.4)

SYMPTOM IMPROVEMENT



CHANGE IN FEV1 TEST RESULTS[a]



[a]15 patients had pre and post treatment FEV1 data

DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; FEV1, forced expiratory volume in 1 second; SSA, somatostatin analogues. Al-Toubah T, et al. ENETS 2020. Abstract #H01 (Oral presentation)

CONCLUSION

- This was the largest cohort study of SSA therapy for DIPNECH
- SSA therapy was effective at palliating symptoms
  - 76% had a degree of improvement
  - 26% reported significant improvement
- 13 of 15 (87%) showed an improvement in PFTs
- **The mechanism of SSA remains uncertain**
  - Inhibit PNEC autocrine/paracrine secretion
  - Diminished airway reactivity
- **Malignant/metastatic transformation of DIPNECH is rare**
- **SSA should be considered standard of care in DIPNECH patients**
- Further work to investigate aetiology and larger clinical studies are needed

DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; PFT, pulmonary-function test; PNEC, pulmonary neuroendocrine cell; SSA, somatostatin analogue

Al-Toubah T, et al. ENETS 2020. Abstract #H01 (Oral presentation)

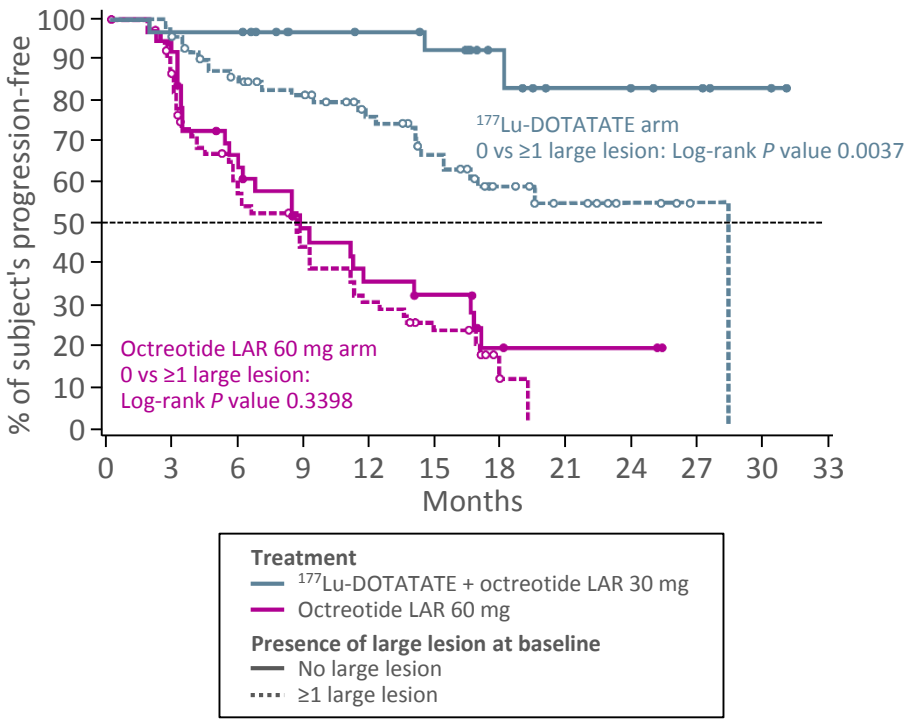
^{177}Lu-DOTATATE PLUS ^{166}Ho-RADIOEMBOLIZATION IN PATIENTS WITH NEUROENDOCRINE TUMOURS; A SINGLE CENTER, PROSPECTIVE, INTERVENTIONAL, NON-COMPARATIVE, OPEN LABEL, PHASE II STUDY (HEPAR PLuS STUDY)

Braat A, et al. ENETS 2020. Abstract #K04

BACKGROUND

- **Liver disease in NENs is a major factor which impacts survival[1]**
- Treatment options include[1]:
  - Surgical resection
  - TAE
  - PRRT
- In general clinical practice **PRRT outcomes are good but could be better[1]**
- **HEPAR PLuS** is the **first prospective** single arm phase II **trial of combination ^{177}Lu-DOTATATE PRRT and ^{166}Ho-radioembolization in NEN**

BULKY LIVER METASTASES (>30 mm) DECREASES SURVIVAL[2]

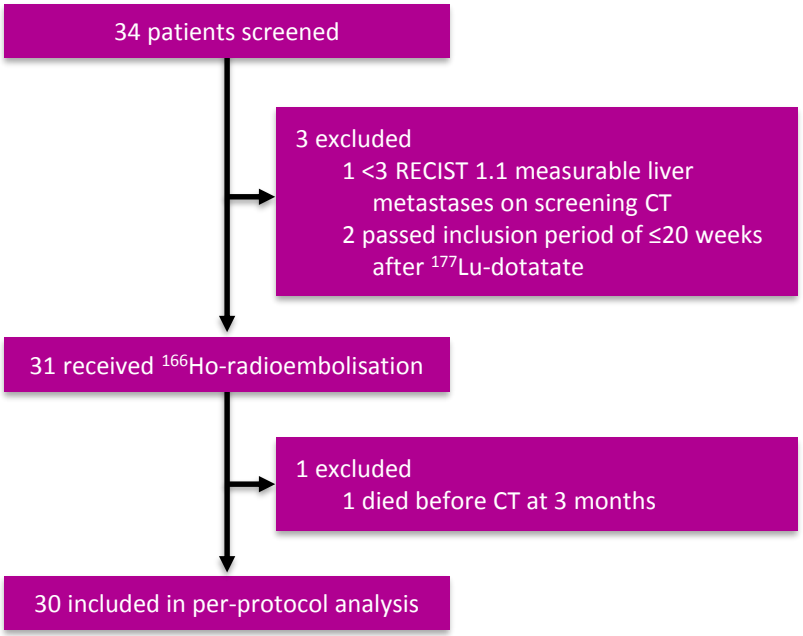


^{166}Ho, holmium-166; LAR, long-acting release; ^{177}Lu, lutenium-177; NEN, neuroendocrine neoplasm; PRRT, peptide receptor radionuclide therapy; TAE, trans-arterial embolisation

Braat A, et al. BMC Gastroenterol 2018;18:84; 2. Strosberg J, et al. Annals of Oncology (2018) 29 (suppl_8): viii467-viii478; 3.Strosberg J, et al. EurJ Nucl Med Mol Imaging 2018; 45 (suppl 1): OP-180
Braat A, et al. ENETS 2020. Abstract #K04, Oral Presentation

STUDY ENROLMENT AND KEY DISEASE CHARACTERISTICS

PATIENT DISPOSITION



TUMOUR CHARACTERISTICS

	N (%)
Primary tumour	
Pancreas	9 (30)
Ileum or jejunum	9 (30)
Unknown	5 (17)
Colon, caecum, or rectum	4 (13)
Bronchus or lung	3 (10)
Functioning neuroendocrine neoplasms	9 (30)
Neuroendocrine neoplasm grade	
1	12 (40)
2	18 (60)
Fractional liver involvement	
<25%	22 (73)
25 to 50%	6 (20)
>50 to 70%	2 (7)
Extrahepatic disease	
Yes	24 (80)
No	6 (20)

CT, computed tomography; ^{166}Ho, holmium-166; RECIST, response evaluation criteria in solid tumours

Braat A, et al. Lancet Oncol 2020; DOI: https://doi.org/10.1016/S1470-2045(20)30027-9
Braat A, et al. ENETS 2020. Abstract #K04, Oral Presentation

PRIMARY EFFICACY ENDPOINT

- Efficacy outcomes
  - Additional durable CR/PR after PRRT (mRECIST)
- Clinical toxicity
  - Similar to radioembolisation of other tumour types in salvage setting
- Biochemical toxicity
  - Peak in liver enzymes at 3 weeks
- QoL reductions peaked at 3-6 weeks
  - Peak in fatigue at 3 weeks
  - Resolution at 3 months

PRIMARY EFFICACY OUTCOMES

	3 months		6 months	
	Liver-specific response	Patient-based response	Liver-specific response	Patient-based response
RECIST 1.1 (n=30)				
Complete response	0	0	0	0
Partial response	13 (43%)	12 (40%)	14 (47%)	10 (33%)
Stable disease	15 (50%)	14 (47%)	11 (37%)	13 (43%)
Progressive disease	2 (7%)	4 (13%)	4 (13%)	6 (20%)
NA	0	0	1 (3%)	1 (3%)
mRECIST (n=30)				
Complete response	3 (10%)	–	2 (7%)	–
Partial response	15 (50%)	–	15 (50%)	–
Progressive disease	0	–	1 (3%)	–
NA	4 (13%)	–	5 (17%)	–

PRIMARY SAFETY OUTCOMES

	Grade 1–2	Grade 3	Grade 4	Grade 5
Related toxicity				
Radioembolisation-induced liver disease	0	0	0	1 (3%)
Abdominal pain	21 (68%)	3 (10%)	0	0
Fatigue	18 (58%)	1 (3%)	0	0
Nausea	19 (61%)	1 (3%)	0	0
Vomiting	13 (42%)	0	0	0
Malaise	8 (25%)	0	0	0
Subfebrile	4 (13%)	0	0	0
Shivering	3 (10%)	0	0	0
Oedema	2 (6%)	0	0	0

CR, complete response; NA, not applicable; PR, partial response; QoL, quality of life; RECIST, response evaluation criteria in solid tumours; mRECIST, modified RECIST

Braat A, et al. Lancet Oncol 2020; DOI: https://doi.org/10.1016/S1470-2045(20)30027-9; Braat A, et al. ENETS 2020. Abstract #K04, Oral Presentation

CONCLUSIONS SO FAR..

- **Additional ^{166}Ho-radioembolization**
  - Effective in bulky liver disease after PRRT
  - Is safe and effective after PRRT1
  - Toxicity profile comparable to literature[2]
- **QoL** was temporarily decreased and fully recovered at **3 months**
- OS and PFS have not been reached, long term follow up is needed
- Dosimetric analysis results are very exciting

^{166}Ho, holmium-166; OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; QoL, quality of life

1. Braat A, et al. Lancet Oncol 2020; DOI: https://doi.org/10.1016/S1470-2045(20)30027-9; 2. Braat A and Lam M. Cardiovasc Intervent Radiol 2019; 41:200-1; Braat A, et al. ENETS 2020. Abstract #K04, Oral Presentation

ASSESSING RESPONSE TO PRRT

Prasad V, et al. ENETS 2020

RESPONSE ASSESSMENT

- **Assesses the efficacy of drugs in clinical trials** in order **to avoid or reduce**
  - **Cost** of drug development
  - **Unnecessary public health risk** by early identification **of drug failure** and reduction of **biases and statistical errors**
- In NETs, the **Gold Standard is pre- and post-therapy tumour tissue sampling**
- Response assessment criteria vary by cancer type
- Both clinical endpoints and surrogate biomarkers can be used to assess response
  - Biomarker endpoints
    - Measured objectivelyy
    - Surrogate for clinical endpoints
  - Clinical endpoints
    - Variables of subjects health and well-being
    - Valuable to assess OS and QoL

NET, neuroendocrine tumour; OS, overall survival; QoL, quality of life

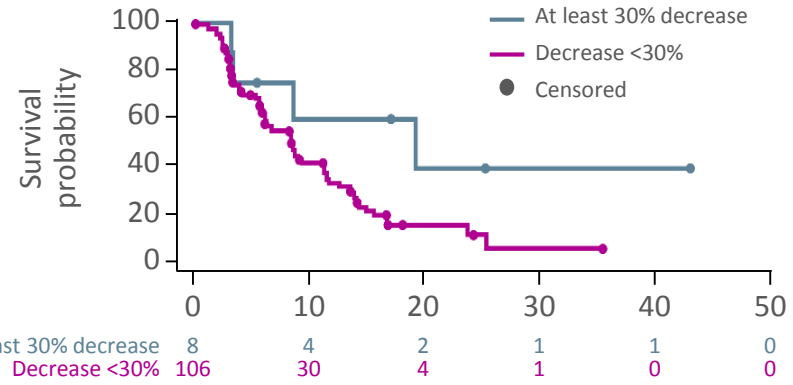
1. Faraji F and Gaba RC. Front Oncol 2019;4;9:471; 2. DiMasi JA, et al. J Health Econ 2016;47:20-33; Prasad V. ENETS 2020, Oral Presentation

RESPONSE ASSESSMENT IN NEUROENDOCRINE TUMOURS

REDUCED TUMOUR SIZE AS AN OUTCOME

- Reduction in tumour size can act as an objective response measure[1]

KAPLAN-MEIER CURVE OF PFS IN RELATION TO TUMOUR RESPONSE



CgA, chromogranin A; MR; minor response; NET, neuroendocrine tumour; PD, disease progression; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease

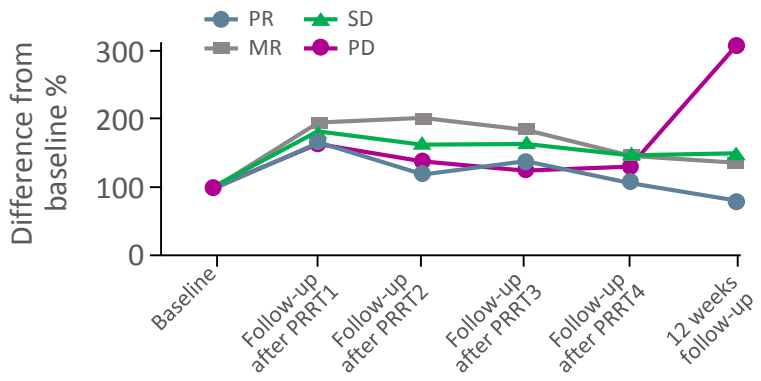
1. Pavel M, et al. Ann Oncol 2019;30(Supp. 5):v564-73; Prasad V. ENETS 2020, Oral Presentation

RESPONSE ASSESSMENT IN NEUROENDOCRINE TUMOURS

RADIOLOGY AND PSEUDO-PROGRESSION

- Progression markers like CgA may be caused by radiology-induced cell damage[2]
  - **Liver function parameters and CgA should be interpreted with caution**
- Transient increase in metastasis size (≥10%) may occur post-PRRT
  - **True progression is almost always reflected by new metastases**

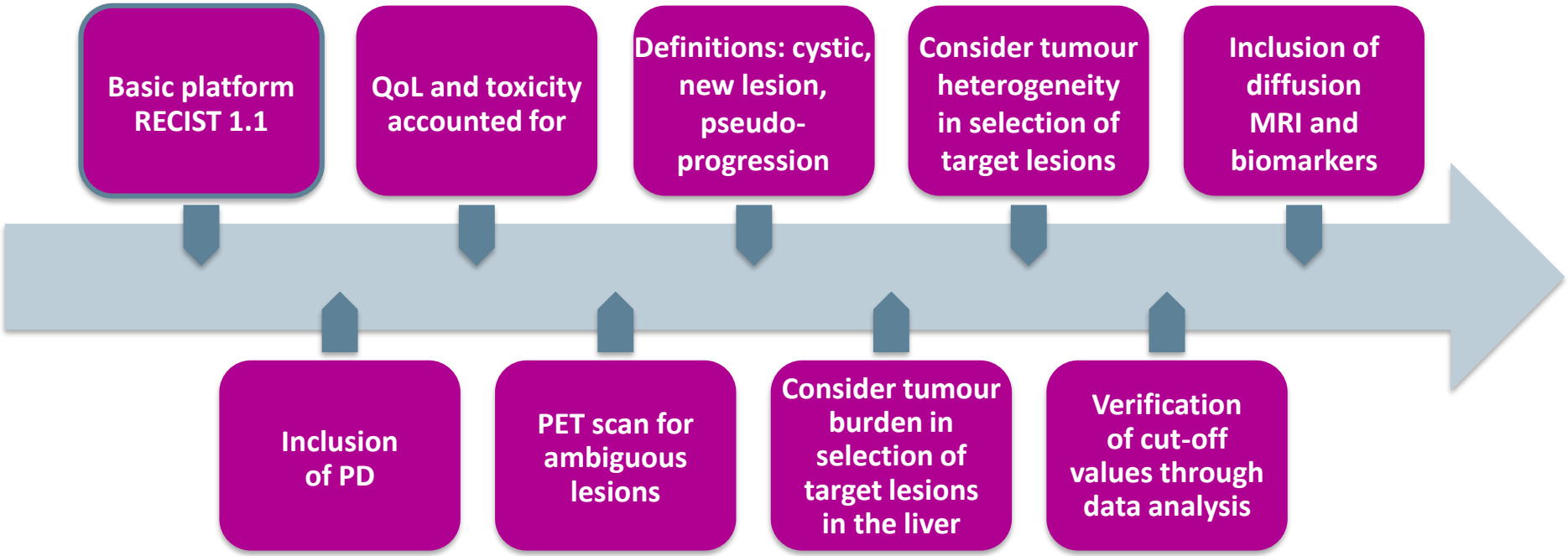
TRANSIENT INCREASE IN CgA POST-THERAPY



CgA, chromogranin A; MR; minor response; NET, neuroendocrine tumour; PD, disease progression; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease

Brabander T, et al. Endocr Relat Cancer 2017;24:243-51; Prasad V. ENETS 2020, Oral Presentation

ROAD MAP TO NEW RESPONSE IN PEPTIDE RECEPTOR RADIONUCLIDE THERAPY



MRI, magnetic resonance imaging; PD, disease progression; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; QoL, quality of life; RECIST, Response evaluation criteria in solid tumours

CONCLUSION

- **Optimal criteria for the response of PRRT is a challenge**
- Process requires a **collective effort collect to prospectively study** and **real world data** to find the best response criteria for PRRT
- **PET must be included in the response assessment of PRRT**

PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy
Prasad V. ENETS 2020, Oral Presentation

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NET CONNECT

Email
antoine.lacombe
@cor2ed.com

NET CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com