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SUMMARY OF KEY CONGRESSES ASCO 2020, AACR 2020, WCGIC 2020 VIRTUAL MEETINGS

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HIGHLIGHTS FROM NET CONNECT
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EFFICACY AND SAFETY OF SURUFATINIB IN UNITED STATES PATIENTS WITH NEUROENDOCRINE TUMOURS

Dasari A, et al.

ASCO 2020. Abstract #4610. Poster presentation

BACKGROUND

- **surufatinib** is a targeted **inhibitor of tyrosine kinases VEGFR1, 2, and 3, FGFR1, and CSF-1 R**
- Efficacy and safety of surufatinib have been confirmed in two randomised, phase 3, placebo-controlled trials in Chinese patients; both met the primary endpoint and stopped at the planned interim analysis
  - **SANET-ep** (NCT02588170)[1]
    - Median progression-free survival (mPFS) 9.2 vs 3.8 months with placebo in **patients with extrapancreatic NET (epNET)**
  - **SANET-p** (NCT02589821)[2]
    - Demonstrated superior efficacy vs placebo in terms of mPFS in **patients with advanced pancreatic NET (pNET)**
- Data reported here are from an **ongoing dose escalation and expansion study** evaluating the effects of surufatinib **in US patients**
  - Dose escalation is complete; **maximum tolerated dose** and recommended phase 2 dose: **300 mg once daily**
  - **Objective: to evaluate anticancer activity in select indications**, including advanced or metastatic epNET and pNET
  - **Primary endpoint** of expansion study: **PFS**
  - **Secondary endpoints:** objective response rate (ORR), disease control rate (DCR), time to response, duration of response, safety, pharmacokinetics

CSF-1 R, colony-stimulating factor 1 receptor; FGFR, fibroblast growth factor receptor; NET, neuroendocrine tumour; SANET, surufatinib in advanced neuroendocrine tumours; VEGFR, vascular endothelial growth factor receptor

1. Xu J, et al. Ann Oncol. 2019;30 suppl 5:v911, abstract LBA76; 2. www.chi-med.com/surufatinib-phase-iii-sanet-p-study-achieved-primary-endpoint/, accessed 25 Jun 2020

EFFICACY RESULTS

- At data cut-off, 32 patients with heavily pre-treated progressive NETs were included:
  - Previous lines of therapy: median 3, range 1–8
  - All patients had received everolimus or sunitinib (or both)
- 15 patients remain on active treatment
  - pNET: 5 patients (31%); epNET: 10 patients (63%)
- Tumour growth was controlled in all patients
  - In pNET patients: ORR was 18%
  - In epNET patients: no confirmed partial responses (PRs) had been achieved at the time of data cut-off
- surufatinib showed clinical efficacy regardless of previous therapies
  - pNET: median 4 prior lines
  - epNET: median 2 prior lines

Best tumour assessment	pNET (n = 16)	epNET (n =16)
Complete response (CR), n	0	0
PR, n (%)	3 (18.8)	0
Stable disease (SD), n (%)	13 (81.2)[a]	16 (100)[b]
Progression of disease (PD), n	0	0
ORR, %	18.8	0
DCR, %	100	100
Median (range) duration of treatment, months	7.1 (2.0–17.5)	4.9 (1.0–10.2)

[a] One pNET patient had an unconfirmed PR.
[b] One epNET patient had an unconfirmed PR.

DCR, disease control rate; epNET, extrapancreatic neuroendocrine tumour; NET, neuroendocrine tumour; ORR, objective response rate; pNET, pancreatic neuroendocrine tumour

Dasari A, et al. ASCO 2020, abstract 4610, poster presentation

SAFETY RESULTS

- Safety profile of surufatinib is consistent with that seen in completed trials
- 30 patients (93.8%) had at least one adverse event (AE)
- 22 patients (68.8%) had AEs of grade ≥ 3
- 5 patients discontinued treatment because of AEs
  - pNET: 1; epNET: 4

TEAE in > 15% of patients	pNET, n (%) (n = 16)		epNET, n (%) (n = 16)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension	6 (37.5)	2 (12.5)	13 (81.3)	7 (43.8)
Fatigue	8 (50.0)	0	8 (50.0)	0
Proteinuria	3 (18.8)	0	13 (81.3)	1 (6.3)
Diarrhoea	8 (50.0)	3 (18.8)	5 (31.3)	1 (6.3)
Abdominal pain	1 (6.3)	0	7 (43.8)	0
AST increase	4 (25.0)	0	4 (25.0)	0
Haematuria	3 (18.8)	1 (6.3)	5 (31.3)	1 (6.3)
Rash	2 (12.5)	0	6 (37.5)	0
Headache	2 (12.5)	1 (6.3)	4 (25.0)	0
ALT increase	2 (12.5)	0	3 (18.8)	0
Peripheral oedema	1 (6.3)	0	4 (25.0)	0
Platelet count decreased	1 (6.3)	0	4 (25.0)	0
Urinary retention	0	0	5 (31.3)	1 (6.3)
Vomiting	3 (18.8)	0	2 (12.5)	1 (6.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; epNET, extrapancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour

Dasari A, et al. ASCO 2020, abstract 4610, poster presentation

SUMMARY

- surufatinib has shown promising antitumour activity in US patients with progressing NETs
- Its safety profile has been manageable and is comparable with the larger pool of surufatinib safety data
- Previously reported pharmacokinetics and dose exposure data are also consistent with those from patients in the US and China[1]

NET, neuroendocrine tumour

1. Dasari A, et al. AACR I 2020, abstract CT115; Dasari A, et al. ASCO 2020, abstract 4610, poster presentation

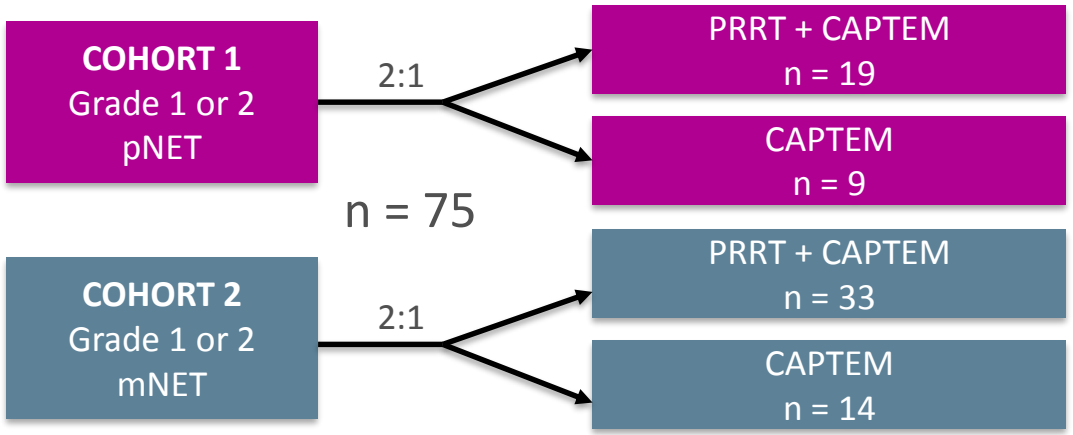
AGITG CONTROL NET STUDY: PHASE 2 STUDY EVALUATING THE ACTIVITY OF LuTate PRRT AND CAPTEM – FIRST RESULTS FOR pNETs AND mNETs

Pavlakis N, et al.
ASCO 2020. Abstract #4608. Poster presentation

AGITG, Australasian Gastrointestinal Trials Group; CAPTEM, capecitabine + temozolomide; LuTate, ^{177}lutetium-octreotate; mNET, midgut neuroendocrine tumour; NET, neuroendocrine tumour; pNET; pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

BACKGROUND

- capecitabine + temozolomide (CAPTEM) is an accepted regimen for patients with advanced pNETs[1]
- ^{177}lutetium-octreotate (LuTate) peptide receptor radionuclide therapy (PRRT) is recommended for progressing mNETs grade 1 or 2 after failure of medical therapy[1]
- High activity of LuTate–CAPTEM has been observed in a single-arm, phase 1–2 trial[2]
- The CONTROL NET study investigated whether, after progression on somatostatin analogues, LuTate–CAPTEM is sufficiently active to evaluate further in a phase 3 trial[3]
  - Open label, non-comparative, parallel group, phase 2, cohort study



Primary endpoint

- PFS (*aim: 12-month PFS 75% for pNETs; 15-month PFS 80% for mNETs*)

Secondary endpoints

- Objective tumour response rate (OTRR)
- Clinical benefit rate (CBR)
- Toxicity
- Quality of life (QoL)

CAPTEM: twice daily oral capecitabine 750 mg/m^2 on days 1–14 and temozolomide 75 mg/m^2 on days 10–14, 8 weekly x 4
PRRT: 7.8 GBq LuTate on day 10, 8 weekly x 4

mNET, midgut neuroendocrine tumour; NET, neuroendocrine tumour; PFS, progression free survival; pNET; pancreatic neuroendocrine tumour

1. Pavel M, et al. Neuroendocrinology. 2016;103:172-85; 2. Claringbold PG, et al. Cancer Biother Radiopharm. 2012;27:561-9;
3. Pavlakis N, et al. ASCO 2020, abstract 4608, poster presentation

RESULTS

EFFICACY

pNET cohort	CAPTEM n = 9	PRRT + CAPTEM n = 18	Difference in proportions (95% CI)
PFS proportion (range) at 12 months, %	66.7 (28.2–87.8)	75.9 (47.6–90.3)	9.3 (−27.9–46.4)
OTRR (CR or PR), n (%)[a]	3 (33.3)	12 (66.7)	33 (−4.4–71)
CBR (OTRR or SD), %	100	100	–

Median follow-up 34 months
[a] ITT population.

mNET cohort	PRRT n = 13	PRRT + CAPTEM n = 32	Difference in proportions (95% CI)
PFS proportion (range) at 15 months, %	92.3 (56.6–98.9)	90.4 (73.1–96.8)	−1.9 (−19.7–15.9)
OTRR (CR or PR), n (%)[a]	2 (15.4)	10 (31.3)	15.9 (−9.5–41.5)
CBR (OTRR or SD), %	92	97	–

Median follow-up 35 months
[a] ITT population.

CAPTEM, capecitabine + temozolomide; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; mNET, midgut neuroendocrine tumour; OTRR, objective tumour response rate; PFS, progression free survival; pNET; pancreatic neuroendocrine tumour; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease

Pavlakis N, et al. ASCO 2020, abstract 4608, poster presentation

RESULTS

SAFETY

- AEs were mainly haematological in the mNETs group

pNET cohort	CAPTEM n = 9		PRRT + CAPTEM n = 18	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any AE, n (%)	9 (100)	4 (44)	18 (100)	8 (44)

mNET cohort	PRRT n = 13		PRRT + CAPTEM n = 32	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any AE, n (%)	13 (100)	6 (46)	32 (100)	28 (88)

Proportion of patients with ≥ 1 grade 3+ AE or SAE: any or related	pNET cohort, n (%)		mNET cohort, n (%)	
	CAPTEM n = 9	PRRT + CAPTEM n = 18	PRRT n = 13	PRRT + CAPTEM n = 32
Any grade 3+ AE	4 (44)	8 (44)	6 (46)	28 (88)
Any treatment-related grade 3+ AE	3 (33)	8 (44)	6 (46)	26 (81)
Any SAE	0	5 (28)	1 (8)	10 (31)
Any treatment-related SAE	0	4 (22)	1 (8)	7 (22)

AE, adverse event; CAPTEM, capecitabine + temozolomide; mNET, midgut neuroendocrine tumour; pNET; pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SAE, serious adverse event

Pavlakis N, et al. ASCO 2020, abstract 4608, poster presentation

SUMMARY

- This analysis showed that **15-month PFS with CAPTEM + PRRT in the mNET cohort and 12-month PFS with CAPTEM + PRRT in the pNET cohort are similarly high** vs PRRT alone
- PFS in both cohorts is higher than expected from initial estimates
- **OTRR** is numerically **higher with combined therapy** but at the cost of **greater grade 3 or 4 toxicity, mainly haematologic**
- The AE profile in pNET patients is similar to that in mNET patients
- Longer follow-up is required to determine whether phase 3 evaluation is warranted

AE, adverse event; CAPTEM, capecitabine + temozolomide; mNET, midgut neuroendocrine tumour; OTRR, objective tumour response rate; PFS, progression free survival; pNET; pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

Pavlakis N, et al. ASCO 2020, abstract 4608, poster presentation

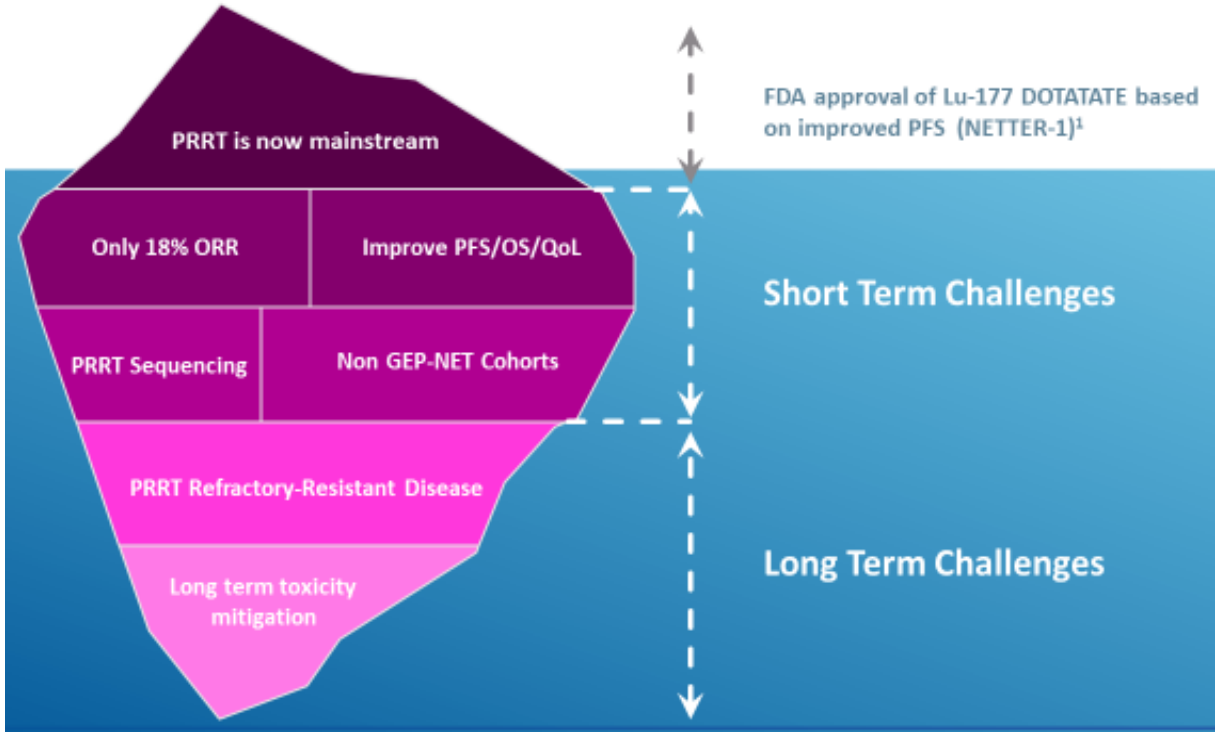
DNA-PK INHIBITOR, M3814, AS A RADIATION SENSITISER IN THE TREATMENT OF NEUROENDOCRINE TUMOURS

Rychahou P, et al.
AACR II 2020. Abstract #6402. Poster presentation

DNA-PK, deoxyribonucleic acid-dependent protein kinase

BACKGROUND

PRRT-CURRENT ADVANCES AND CHALLENGES



- **Advanced GEP-NETs remain a difficult therapeutic challenge** due to their high malignant potential and resistance to conventional chemotherapy
- Peptide Receptor Radionuclide Therapy (**PRRT**) **is a potential treatment option** for inoperable and metastatic **GEP-NETs**
- The DNA-dependent protein kinase (**DNA-PK**) complex **plays a pivotal role in** non-homologous endjoining (**NHEJ**) **repair after radiation therapy**
- A novel, clinical-stage **DNA-PK inhibitor, M3814** (peposertib), **potently and selectively blocks the NHEJ repair pathway** for DNA double strand breaks
- **This study investigated** the feasibility of radiosensitising NET cells **with M3814, both in vitro and in preclinical NET models**

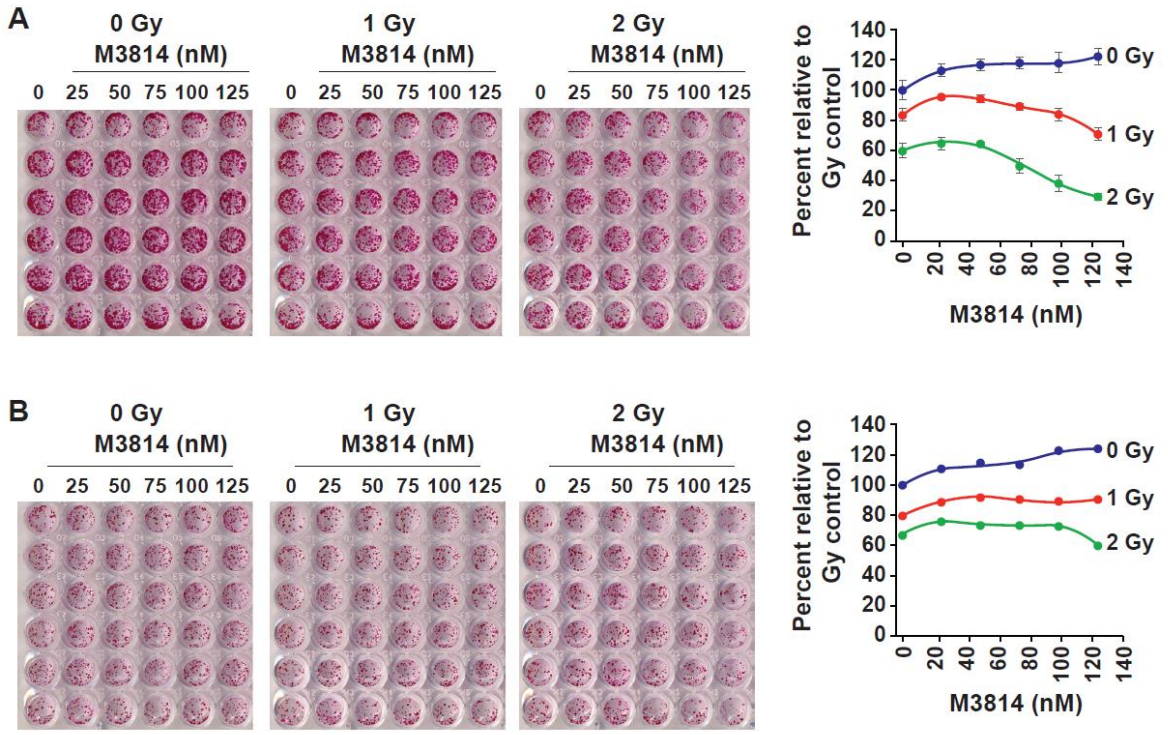
DNA-PK, deoxyribonucleic acid –dependent protein kinase; GEP-NET, gastroenteropancreatic neuroendocrine tumours; NET, neuroendocrine tumours; NHEJ, non-homologous endjoining; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy; QoL, quality of life

Rychahou P, et al. AACR II 2020, abstract 6402, poster presentation; Strosberg, et al. N Engl J Med 2017;376:125-35; Chauhan A, et al. ASCO 2020; poster presentation: abstract TPS4660

RESULTS

- Combination therapy with M3814 and radiation was effective in the low-dose range (100 nM) in selected NET cell lines

Radio-sensitising effect of M3814 in QGP-1 cells



Representative photographs of clonogenic assays in (**A**) BON and (**B**) QGP-1 cells. BON and QGP-1 cells were treated with M3814 (25, 50, 75, 100, or 125 nM) and irradiated at doses of 1 or 2 Gy. Graphs show the mean value ± SD; each value was read in sextuplicate.

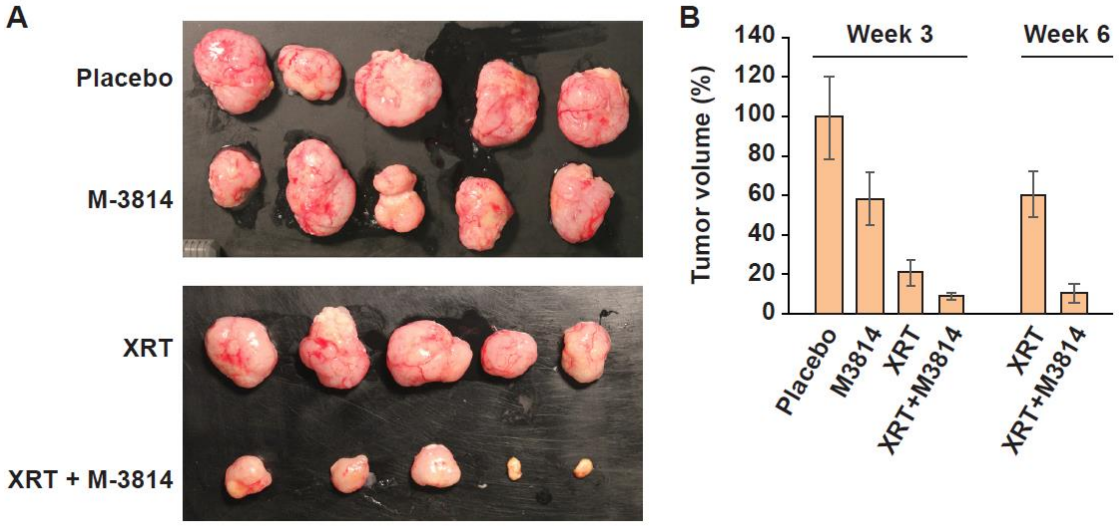
NET, neuroendocrine tumour; SD, standard deviation

Rychahou P, et al. AACR II 2020, abstract 6402, poster presentation

RESULTS

EFFECTS OF M3814 ON RADIATION-INDUCED DELAY OF TUMOUR GROWTH

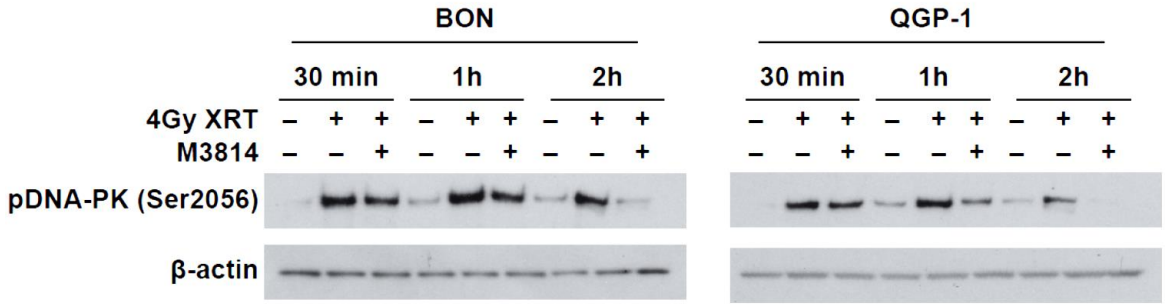
- Combination therapy with M3814 and radiation effectively suppressed proliferation of QGP and BON xenografts



A. Mice with QGP-1 subcutaneous tumours were randomised into four groups: vehicle, M3814 (200 mg/kg delivered via gavage), radiation therapy (2 Gy), and a combination of radiation therapy (2 Gy) and M3814 (200 mg/kg). M3814 was administered 30 minutes before radiation therapy daily for 5 consecutive days. **B**. Mice treated with vehicle and M3814 were euthanised 3 weeks after the start of treatment because of large tumours. Mice treated with radiation therapy alone or radiation therapy and M3814 combined were euthanised 6 weeks after the start of treatment.

DNA-PK INHIBITION AFTER M3814 TREATMENT OF BON AND QGP CELLS

- M3814 treatment in vitro resulted in short-term DNA-PK inhibition



BON and QGP-1 cells were irradiated with 4 Gy gamma rays and treated with 1,000 nM M3814 30 minutes after irradiation. Protein was collected at 30 minutes, 1 hour, and 2 hours after M3814 treatment and analysed for phospho-DNA-PK (Ser2056) expression.

DNA-PK, deoxyribonucleic acid-dependent protein kinase; XRT, radiation therapy

Rychahou P, et al. AACR II 2020, abstract 6402, poster presentation

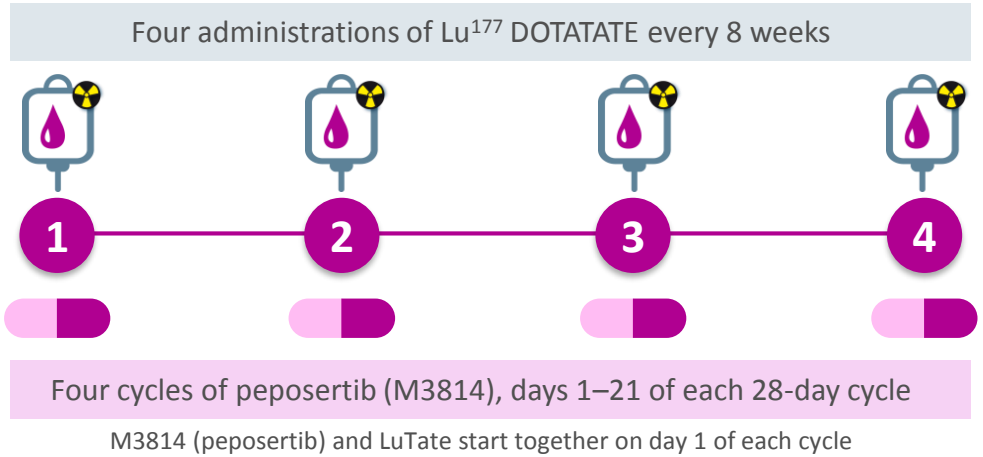
SUMMARY

- These results demonstrate a benefit of adding MK3814 (peposertib) to radiation therapy[1]
- Selective DNA-PK inhibition by MK3814 provides a potent therapeutic strategy for disruption of NHEJ repair of double-strand breaks and may offer a novel therapeutic approach in advanced NET[1]
- The combination of MK3814 and Lu^{177} DOTATATE PRRT will be investigated further in a phase 1 trial which is under development at the Markey Cancer Center[2]

BOIN design

- Four peposertib (M3814) dose cohorts
- Target 25% toxicity
- n = 12–15
- (n = 14 expansion cohort after phase 1 completion)

PHASE 1 TREATMENT SCHEMA



BOIN, Bayesian optimal interval; DNA-PK, deoxyribonucleic acid-dependent protein kinase; NET, neuroendocrine tumour; NHEJ, non-homologous endjoining; PRRT, peptide receptor radionuclide therapy

1. Rychahou P, et al. AACR II 2020, abstract 6402, poster presentation; 2. Chauhan A, personal communication 2020

YOUNG ADULTS WITH NEUROENDOCRINE TUMOURS PRESENT HIGH RATE OF PATHOGENIC OR LIKELY PATHOGENIC GERMLINE VARIANTS IN CANCER-PREDISPOSING GENES

Riechelmann R, et al.
WCGIC 2020. Abstract #O-14. Oral presentation

BACKGROUND

- **Hereditary cancer predisposing syndromes are characterised by germline mutations** that increase the risk of developing tumours
- **Recent advances in genomics**, especially in next generation sequencing (NGS), **have enabled the recognition of new cancer predisposing genes** (CPGs)
- **Little is known about the role of CPGs in neuroendocrine tumours** (NETs), beyond the known hereditary syndromes:
  - multiple endocrine neoplasia (MEN) type 1, MEN type 2, von Hippel–Lindau disease, neurofibromatosis syndrome and tuberous sclerosis complex, which are caused by the presence of germline mutations in the *MEN1*, *RET*, *VHL*, *NF1* and *TSC1/TSC2* genes, respectively
- **New germline mutations have been reported in 17% of pancreatic NETs** , including *BRCA* and *PALB2*[1]
- **Consecutive patients with lung or GEP NETs diagnosed under 40 years were prospectively screened** without known history of cancer hereditary syndromes for germline variants in a panel of 113 CPGs of high to moderate penetrance. The results are reported here

GEP, gastroenteropancreatic; MEN, multiple endocrine neoplasia; NETs, neuroendocrine tumours

1. Scarpa A, et al. Nature 2017; 543(7643):65-71; 2. Riechelmann R, et al. WCGIC 2020. Abstract #O-14. Oral presentation

RESULTS

DEMOGRAPHIC DATA

Variable	Pts with PV/LPV (N=14)	Pts without PV/LPV (N=52)
Median age (years) of NET onset	35 (24-40)	35.5 (14-40)
Female sex	9 (56.3%)	36 (69.2%)
NET type:		
Pancreas	4 (25%)	22 (42.3%)
Midgut	5 (31.25%)	15 (28.2)
Rectum	1 (6.25%)	4 (7.7%)
Appendix	1 (6.25%)	1 (1.9%)
Gastric	1 (6.25%)	3 (5.7%)
Lung	0 (0%)	4 (7.7%)
Unknown primary	1 (6.25%)	3 (5.7%)
Kidney	1 (6.25%)	0
Family history of any cancer	11 (68.7%)	29 (55.7%)
Family history of NET	1 (6.25%)	3*
Other neoplasms	1**	3***
Tumour grade: 1/2/3	8/4/2	27/21/4
Stage IV at diagnosis	7 (43.7%)	25 (48%)

*Gastric G1, midgut and NE pulmonary hyperplasia;
** myofibroblastic tumour; *** ovarian malignant teratoma, pituitary adenoma; breast and papillary thyroid (both in one patient)

VARIANTS IN CANCER PREDISPOSING GENES BY PATIENT

ID	Age	Sex	Type of NET	Family history	Gene	Variant	Classification
GRY_109	38	F	G2 functioning pNET	Father skin cancer, mother thyroid cancer	MUTYH	p.Gin29Ter	LPV
GRY_112	34	M	G1 non-functioning midgut	Mother multiple myeloma	POLE	p.Ala895Profs*3	LPV
GRY_118	32	F	G3 unknown primary	No	SDHB	Deletion exon 1	PV
GRY_122	39	F	G1 non-functioning midgut	No	MUTYH	p.Gly396Asp	PV
GRY_133	36	M	G2 non-functioning pNET	2 grandfathers with prostate cancer (70 and 80yo) + grandmother with leukaemia (75yo)	XPC	p.Val548Alafs*25	PV
GRY_135	40	M	G3 non-functioning pNET	Father and brother with prostate cancer (69 and 44yo); grandmother with colon cancer (65yo)	SLX4	p.His1290Profs*45	LPV
GRY_141	33	M	G2 kidney NET	Maternal grandfather and paternal uncle with lung cancer (heavy smokers); paternal cousin with breast cancer	XPC	p.spl?	LPV
GRY_143	28	F	G1 appendix NET	Grandfather with colorectal cancer (70yo)	MUTYH/ ERCC3	p.spl?; p.Arg530Ter	PV/LPV
GRY_145	33	F	G2 rectum NET	Paternal grandmother with uterus cancer; paternal grandfather with gastric cancer	FH	p.Lys477_Lys477dup	LPV
GRY_147	40	M	G1 non-functioning midgut	No	ERCC2	p.Phe568Tyrfs*2	LPV
GRY_155	39	F	G1 non-functioning midgut	Father with prostate cancer	ERCC3	p.Asp474Glufs*2	PV
GRY_159	37	F	G1 non-functioning pNET	Father with pancreatic cancer (58yo); maternal aunt with breast cancer (60yo); maternal grandmother with lung cancer (smoker); maternal cousin with thyroid cancer (35yo)	MEN1 RECQL4	p.Ser555Asn; p.Phe850Profs*33	LPV
GRY_165	24	F	G1 gastric NET	Paternal grandmother with oesophageal cancer (70yo)	MUTYH	p.Gly396Asp	PV
GRY_176	33	F	G1 non-functioning midgut	Mother with NET; maternal grandfather with prostate cancer	CHEK2	p.Arg117Gly	LPV

F, female; G, grade; LPV, likely pathogenic; M, male; NE, neuroendocrine; NET, neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; pts, patients; PV, pathogenic; yo, years old

Riechelmann R, et al. WCGIC 2020. Abstract #O-14. Oral presentation

SUMMARY

- **Nearly 70% of young adults with NETs have a family history of cancer**
- **Nearly one fifth present a pathogenic or probably pathogenic germline variant in cancer predisposing genes**, with most affected genes being involved in DNA repair mechanisms
  - Midgut and pancreas were the most common tumour sites
  - Except for 1 case, all were G1/G2 NETs
  - Compared to sporadic cases, those with germline mutations were similar in terms of sex and age of onset
- **For future analyses, the cohort will be expanded to 200 pts** and include pts whose biological samples are already collected and stored

DNA, deoxyribonucleic acid; G, grade; NETs, neuroendocrine tumours; pts, patients

Riechelmann R, et al. WCGIC 2020. Abstract #O-14. Oral presentation

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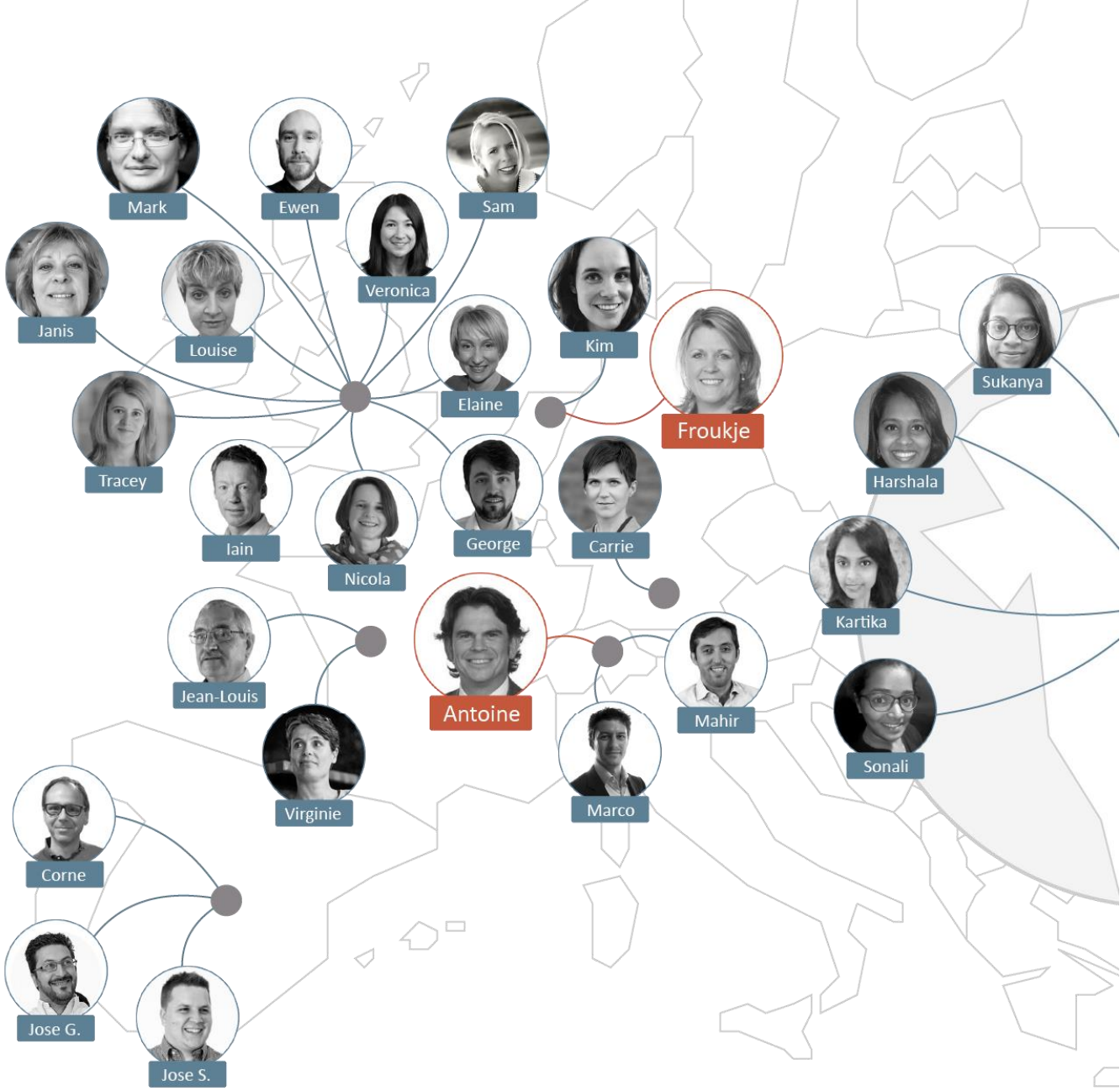

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