Tumores raros en una sesión presidencial: ¿Qué está cambiando?

Dr Angela Lamarca

Consultant in Medical Oncology
ENETS Centre of Excellence
The Christie NHS Foundation Trust
University of Manchester
Manchester; United Kingdom

VII Simposio GETTHI

GETTHI
Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

Disclosures

- Receipt of honoraria or consultation fees: Eisai, Nutricia, Ipsen, Roche, QED, Servier, Boston Scientific and Albireo Pharma
- Participation in company sponsored speaker bureau: Pfizer, Ipsen, Merck, Incyte, Servier, QED, AstraZeneca and EISAI
- Travel, education funding: Ipsen, Pfizer, Bayer, AAA, Sirtex, Delcath, Novartis, Mylan
- Research funding from Ipsen and Roche

Tumores raros en una sesión presidencial: ¿Qué está cambiando?

What is this about?

2021 ESMO congress

16-21 September 2021

ESMO daily REPORTER

CANCER IN SPECIAL SITUATIONS / POPULATION

Rare tumours make it to a Presidential Symposium

20 Sep 2021 / *Angela Lamarca* **ESMO Congress 2021**

Rare tumours have been neglected for decades, with lack of funding, lack of research and lack of visibility. It is encouraging to see how this is changing and how research in rare tumours is not only taking place, but also being highlighted in Presidential Symposium 3 at this year's ESMO Congress.

MANCHESTER 1824
The University of Manchester

NHS Foundation Trust

What is this about?

Presidential symposium

Presidential symposium 3

Date Mon, 20.09.2021
Time 15:05 - 16:35
Location Channel 1
Chairs Solange Peters (Lausanne, Switzerland), Pasi A. Jänne (Boston, MA, United States of America)

567O_PR - First International Randomized Study in Malignant Progressive Pheochromocytoma and Paragangliomas (FIRSTMAPPP): An academic double-blind trial investigating sunitinib

Presentation Number 567O_PR
Speakers Eric Baudin (Villejuif, CEDEX, France)
Lecture Time 15:05 - 15:20

Abstract

Background

Malignant pheochromocytoma and paraganglioma (MPP) is a very rare cancer (annual incidence < 1 per million). Here, we report the first academic randomized double-blind phase II study results assessing Sunitinib efficacy compared to placebo.

The FIRSTMAPPP study – Why is it so special?

Represents a **proof of principle**

Rare cancers or rare clinical scenarios are **NOT** un **excuse** for well-designed and good-quality clinical research (including clinical trial) to be undertaken

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

The North American Neuroendocrine Tumor Society Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors

Pheochromocytoma, Paraganglioma, and Medullary Thyroid Cancer

Herbert Chen, MD, Rebecca S. Sippel, MD,* M. Sue O'Dorisio, MD, PhD,† Aaron I. Vinik, MD, PhD,‡ Ricardo V. Lloyd, MD, PhD,§ and Karel Pacak, MD, PhD, DSc||*

Management of Advanced Disease

Palliative surgery is usually performed to release tumor pressure on surrounding tissues or to decrease tumor mass. Decreased tumor burden can lead to a significant decrease in catecholamine secretion and organ damage as well as α- and β-blockade dosage. Reduced tumor burden can also facilitate subsequent radiotherapy or chemotherapy. However, a survival advantage of surgical debulking is not proven. In some patients with organ metastatic lesions (not if numerous or very small), radiofrequency ablation and cryoablation are current attractive options.

[^{131}I]-MIBG is used for patients in whom [^{123}I]-MIBG scintigraphy is positive (only approximately one third of patients will respond). Biochemical or symptom response rates as high as 67% and 89%, respectively, have been published.[40] Multicenter studies are required to reach consensus on the efficacy of high-dose versus fractionated usually medium doses of [^{131}I]-MIBG and of monotherapy versus combination with other radionuclides or modes of chemotherapy. In patients with rapidly growing tumors, even if [^{123}I]-MIBG scintigraphy shows positive lesions, chemotherapy is a preferable treatment option (only approximately one third of patients will respond).

Chemotherapy, with a combination of cyclophosphamide, vincristine, and dacarbazine, can provide tumor regression and symptom relief in up to 50% of patients, but the responses are usually short and in only 30% of patients.[41] Chemotherapy is preferred in patients with negative [^{123}I]-MIBG scintigraphy and in those with rapidly progressing tumors.

The effect of [^{177}-Lu-DOTA]-octreotate in malignant paragangliomas or pheochromocytomas has been described only in case reports.[42] External-beam irradiation of bone metastases or radiofrequency and cryoablation may provide additional treatment alternatives in selected cases only. External radiation therapy may represent an appropriate approach to treat some bone lesions, especially those that are rapidly growing.

Debulking strategies	Case series
MIBG (I +ve)	Phase II (2009)
Chemotherapy	Phase II (2009)
PRRT (SRS +ve)	Case series (not lincensed in this indication)

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

Acknowledgements

All the people involved in the FIRSTMAPPP trial that are more numerous than the number of patients enrolled : third last definition of a rare cancer at the time of trial development

SPONSOR	FRANCE		GERMANY		ITALY	NETHERLAND
D. Vuillier	A. Tabarin	L. Siegel	C. Strasburger	S. Zopp	A. Berruti	H. Timmers
T. Motreff	B. Goichot	M. Abdi	F. Beuschlein	T. Deutschbein	A. Faggiano	A. VanBerkel
S. Pravong	C. Castinetti	M. Reinteau	K. Balthasar	T. Kienitz	G. Moratello	
A. Lelec	C. Delafourchardiere	S. Lozaic	M. Fassnacht	U. Ubbelohde	M. Boglioni	
F. Ngadjeua	P. Caron	S. Cazenave	M. Haaf		S. Zavato	
R. Magadevane	P. Niccoli	V. Wetta	G. Brabant			
C. Janin	P-F. Plouin	S. Laboureau	G. Folprecht			
M. Angokai	V. Rhomer	J Hadoux	S. Noelting			
M. Texier	F. Quiblier	L Lamartina	S. Schmid			
S. Laghouati	G. Ligocki	S Leboulleux				
G. Genzizalp	J. Onezime	M Schlumberger				
	K. Piton					
	L. Amar					
	N=24		N=13		N=5	N=2

Scentific Comitee and Translational research board :
Y Anouar, F Beuschlein, M Buyse, C Dromain, G Eisenhofer,M Fassnacht , J Favier, AP Gimenez-Roqueplo, A Grossman, C Jimenez, R de Krjger, M Mannelli, A Laplanche, K Pacak, PF Plouin, A Tischler, H Timmers

Private contributor and Facilitator

Patients and Family

The FIRSTMAPPP study – Why is it so special?

Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

ENDPOINTS AND STATISTICS

Analysis on the ITT population

- ✓ The basic assumption was a 20% increase – from 20% to 40% of the 12-months PFS.
- ✓ Two-stage Simon design (Simon R, 1989) with alpha=10% and power=90%. Number of patients without progression at one year required to consider Sunitinib as effective (Simon design conclusion):
  - ✓ **4 out of 17 patients in the first stage analysis and**
  - ✓ **11 out of 37 in the second stage analysis**
- ✓ The placebo group will serve as an internal control : 90% Confidence Interval (90%CI) of the 12 months PFS will be calculated
  - ✓ **If 20% is included in the 90%CI, the final conclusion will be the Simon design conclusion.**
- ✓ IDMC was implemented to monitor : safety, accrual rate and interim fist stage analysis

2021 ESMO congress

Baudin E et al 2021

FIRSTMAPPP : PRIMARY ENDPOINT

Progression-free survival at 12 months per central review

Patient in the Sunitinib arm with :	N	%
No progression at one year	14	35.90
Progression or death at one year	25	64.10

- ✓ Simon design hypothesis for the Sunitinib arm was met: at least 11 out of 37 patients showing no progression at one year
- ✓ The placebo group serves as an internal control

  The 90% Confidence Interval (90%CI) of the 12 month-PFS was estimated on the 37 patients of the placebo group: **18.9% [10.7 ; 31.4]**
  - ✓ As 20% is included in the 90%CI, the final conclusion is the Simon design conclusion. **We can conclude Sunitinib as effective.**

2021 ESMO congress

Baudin E et al. 2021

MANCHESTER 1824
The University of Manchester

The Christie NHS
NHS Foundation Trust

The FIRSTMAPPP study – Why is it so special?

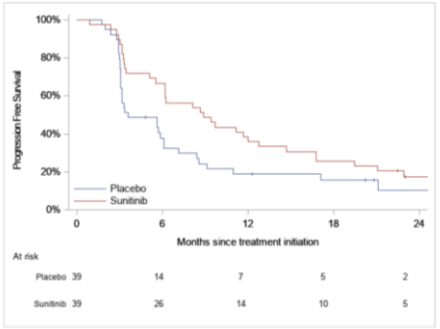
Trial-related characteristics	Population being explored
Unmet need	No prior randomised studies to inform best practice in this disease group (first of its kind) → new SOC
Prospective	Malignant pheochromocytoma and paraganglioma (metastatic disease)
Randomised (1:1) phase II study (Simon-two stage); double-blind	
Good study design: sample size calculation and efficacy assumptions provided – rare cancers and NOT an excuse	Rare cancer: incidence <1 per million
Academic (pharma provided drug free-of-charge)	
Independent Data Monitoring Committee to monitor study accrual	
Multiple countries (4) /centres	
Long recruitment period: 8 years to enrol 78 patients (10/ yr or 0.6 pt/ year /centre)	

The FIRSTMAPPP study – Why is it so special?

FIRSTMAPPP : MEDIAN PFS

median PFS in both arms

Median PFS is
- 8.9 months in Sunitinib arm (95% CI: [5.5; 12.7])
- 3.6 months in Placebo arm (95% CI: [3.1; 6.1]).

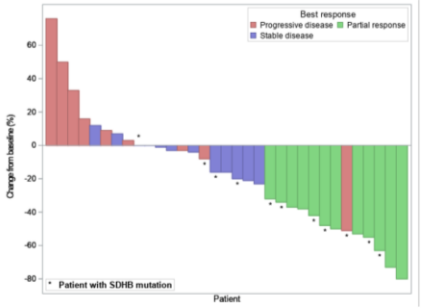


2021 ESMO congress

Baudin E et al. 2021

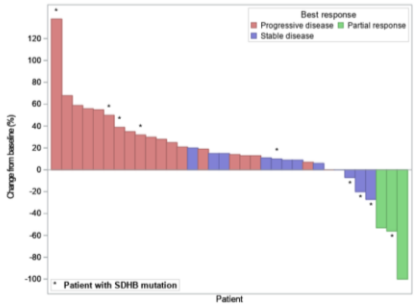
FIRSTMAPPP : WATERFALL PLOT

Sunitinib arm : 33 patients (PR:31%)



Median treatment duration :11 months [0 ; 37]

Placebo arm : 34 patients (PR:8%)



Median treatment duration:4 months [0 ; 35]
87% crossed over

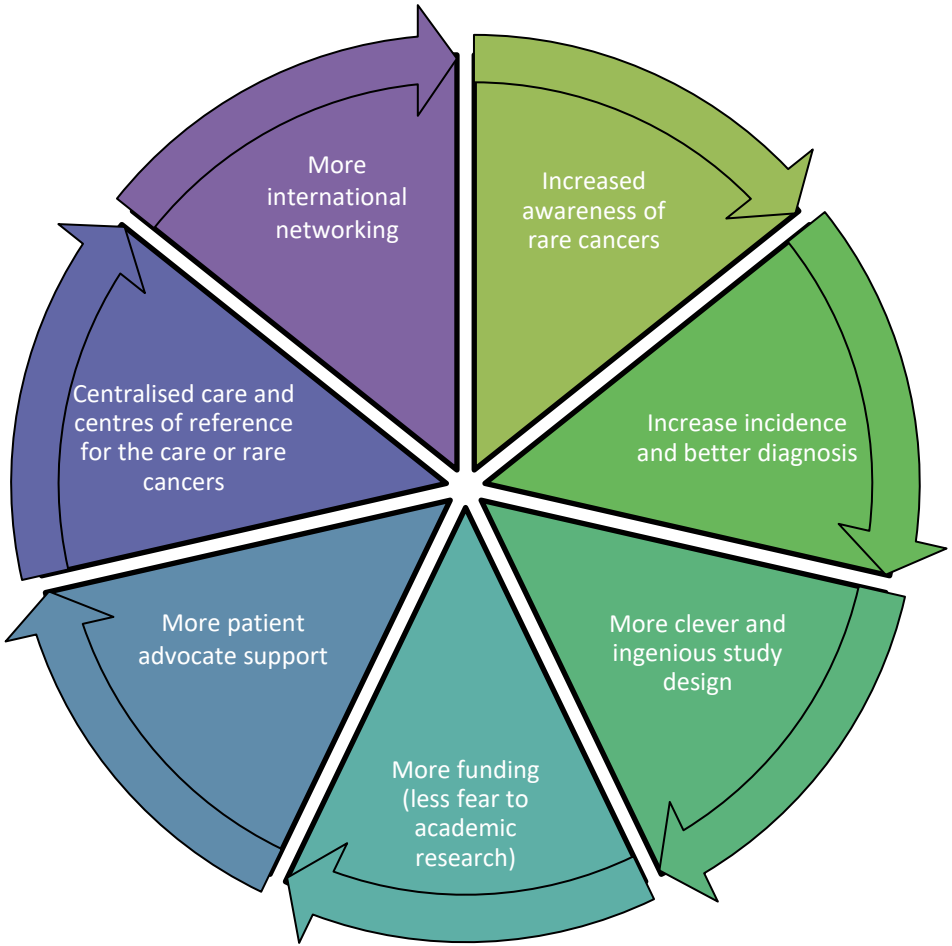
2021 ESMO congress

Baudin E et al. 2021

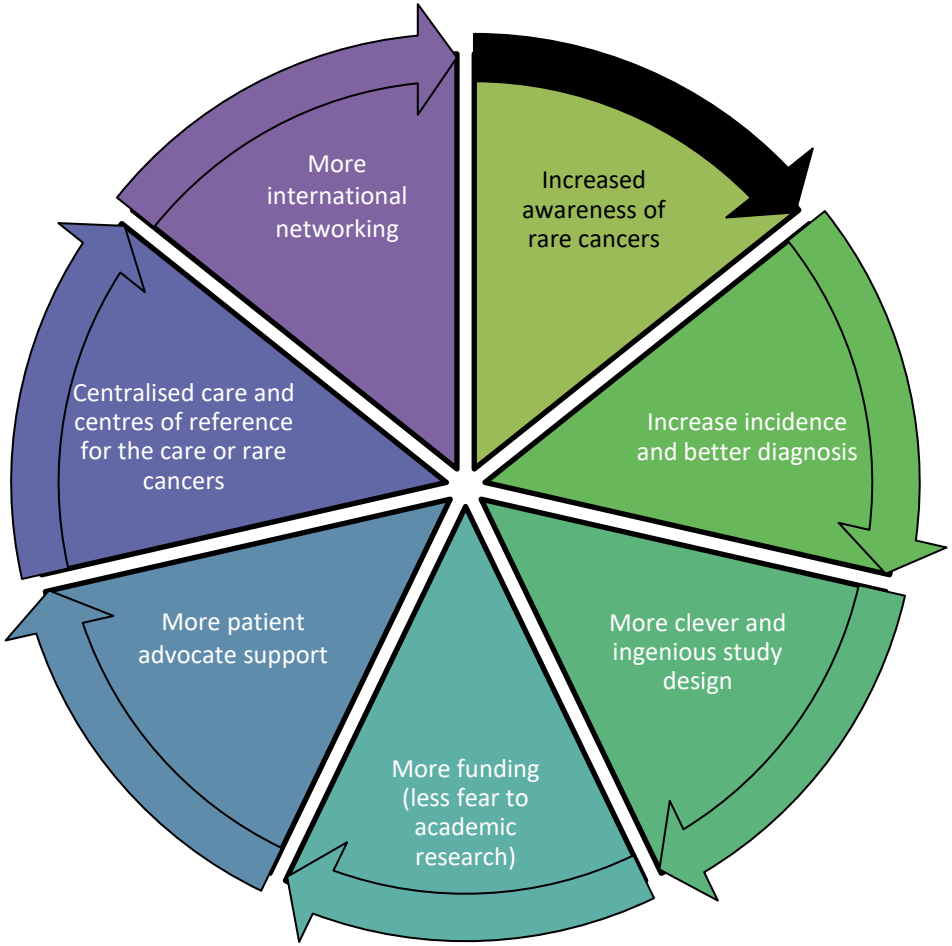
MANCHESTER 1824
The University of Manchester

NHS Foundation Trust

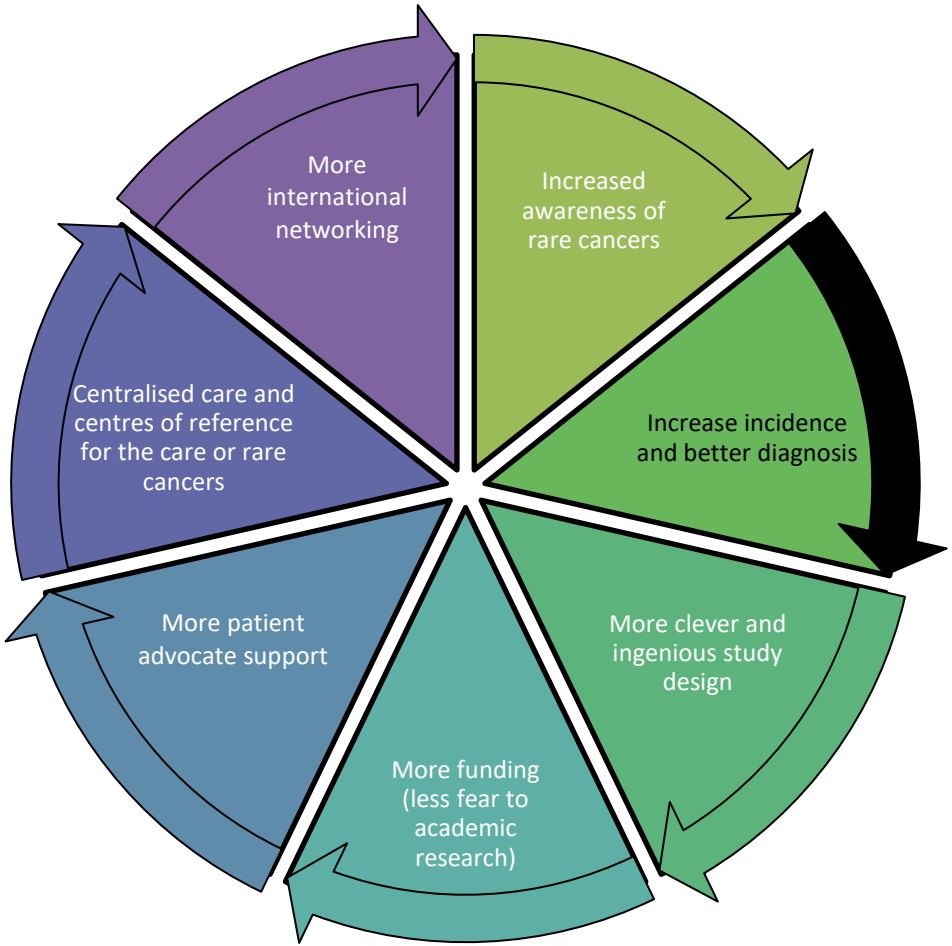
What is changing?



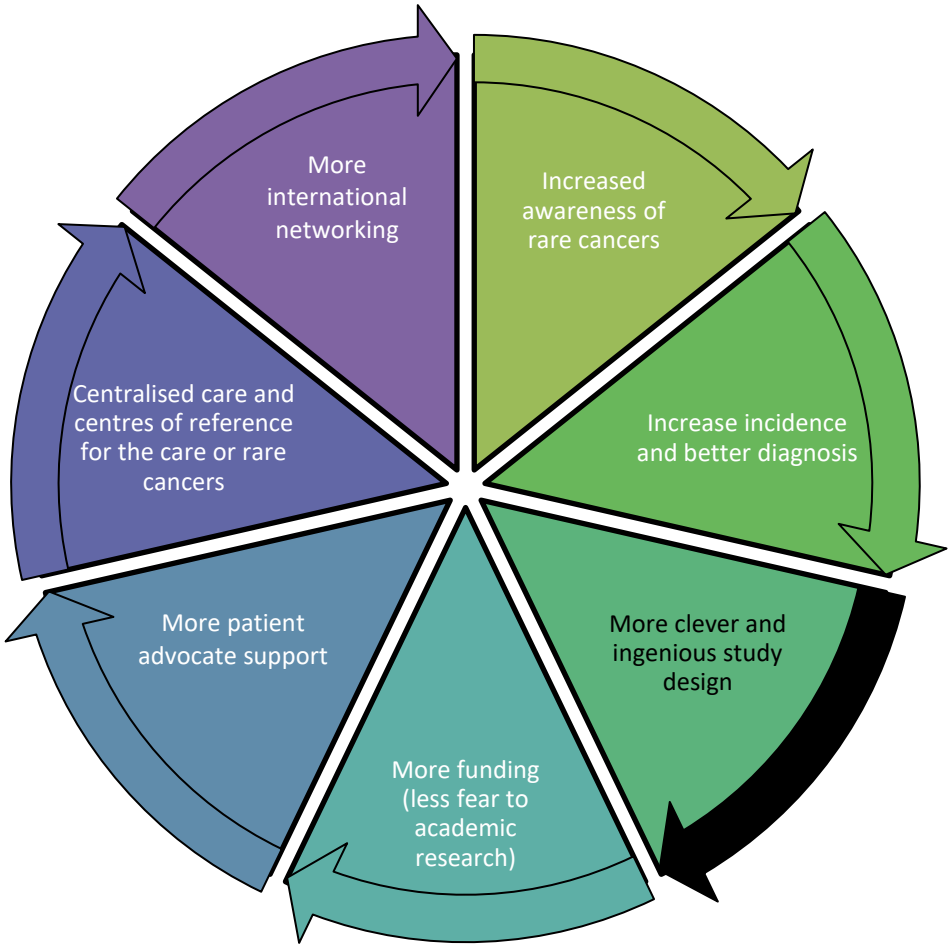
What is changing?



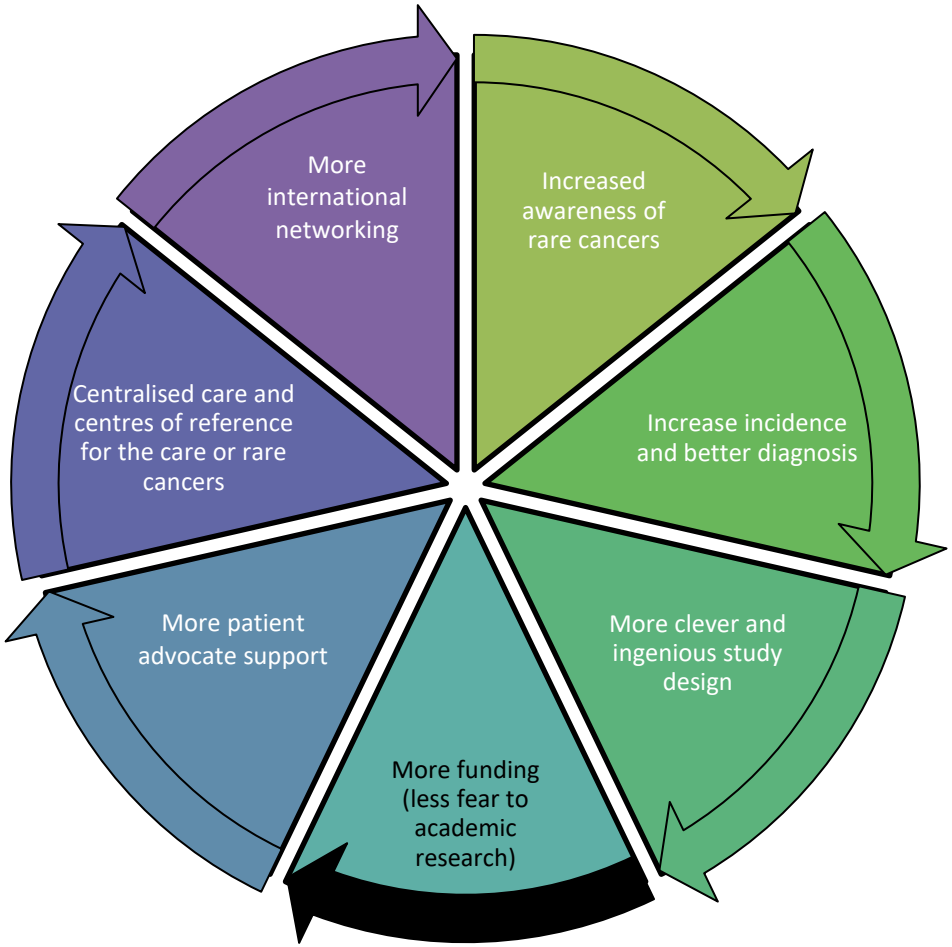
What is changing?



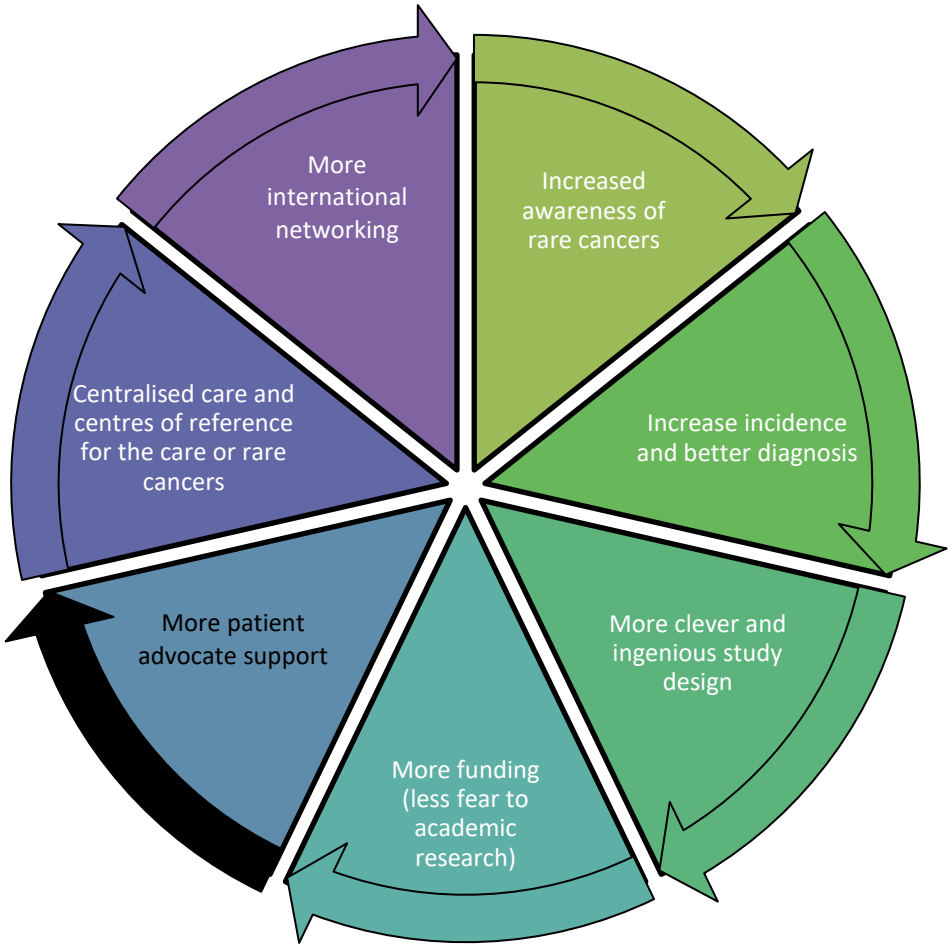
What is changing?



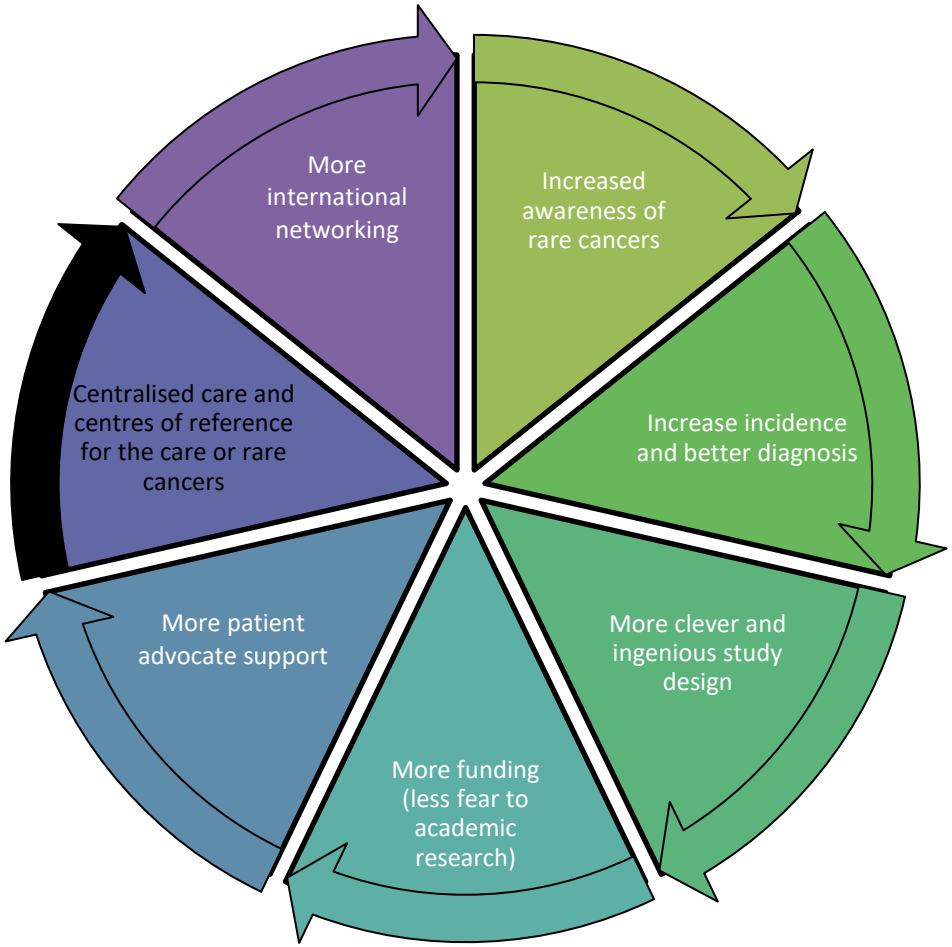
What is changing?



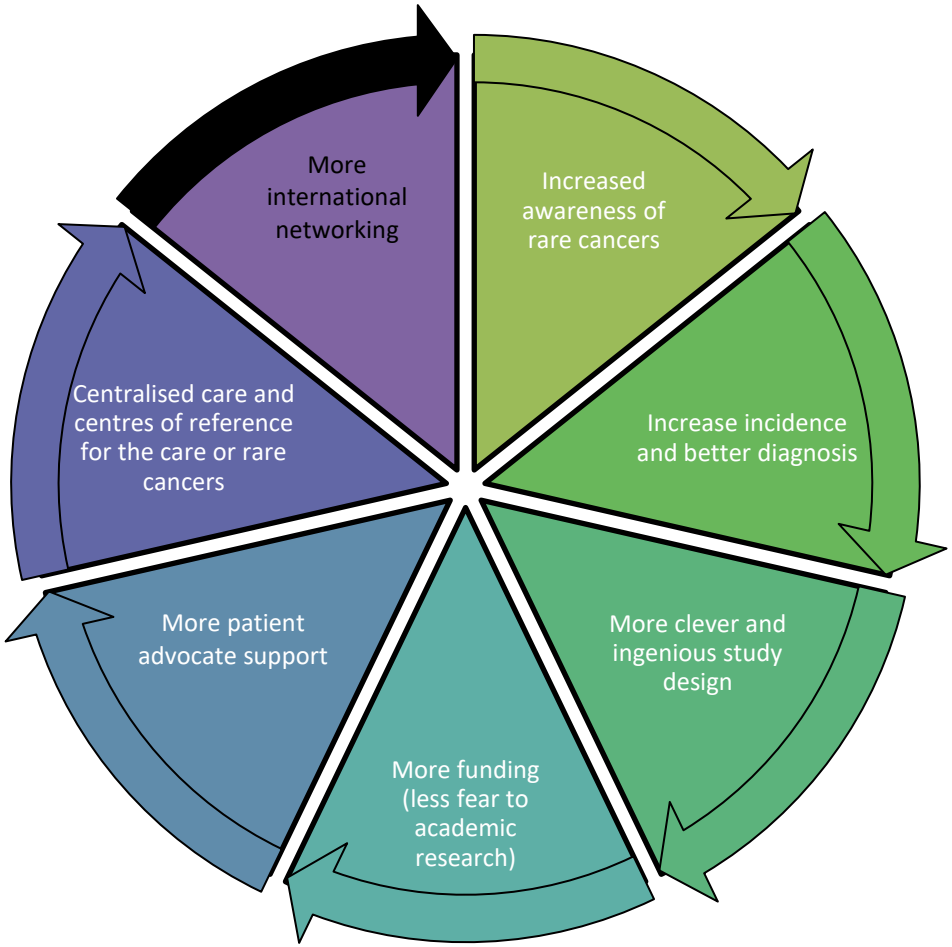
What is changing?



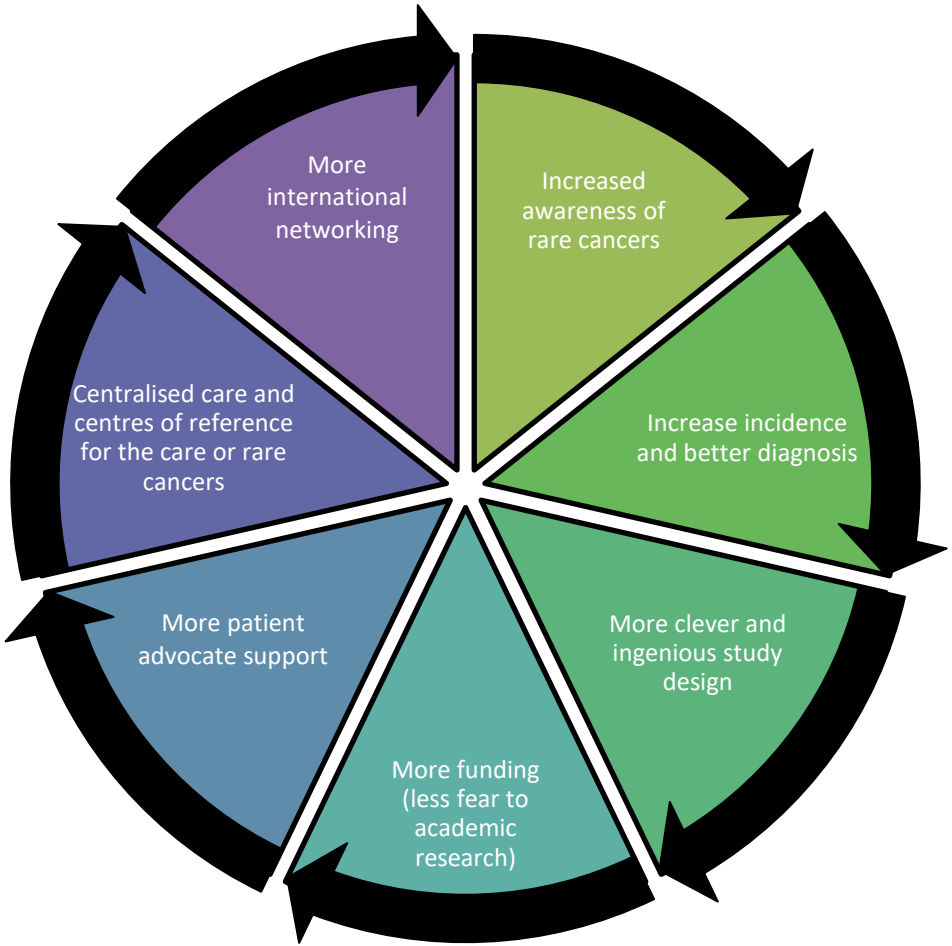
What is changing?



What is changing?



What is changing?



Summary of Phase III–IV trials in NETs

Author	Phase / type	*N*	Disease	Treatment	Response (%)	TTP / PFS† (months)	OS (months)
Somatostatin analogues							
PROMID Rinke et al.[1]	IIIB	85	GEP-NET	Octreotide vs. placebo	SD at 6 months: 66.7 vs. 37.2	14.3 vs. 6 (p<0.001)	
CLARINET Caplin et al.[2]	III	204	P-NET, mid-gut, hind-gut NET	Lanreotide* vs. placebo	Rate of PFS at 24 months 65.1% vs. 33.0%	Not reached vs. 18.0 months, (p<0.001)	
PRRT							
NETTER-1 Strosberg et al.[3]	III	229	Intestinal (midgut) NET	Lutetium-177 (177Lu)–Dotatate vs. octreotide	18 vs 3 (p<0.001)	NR vs 8.4 (p<0.001)	*Data immature at time of analysis*
Targeted therapies							
SU1111 Raymond et al.[4–6]	III	171	Pancreatic NET	Sunitinib vs. placebo	ORR: 9.3 vs. 0 p=0.007	11.4† vs. 5.5† p<0.001	38.6 vs. 29.1 *p=0.094*
RADIANT-2 Pavel et al.[7]	III	429	Carcinoid	Everolimus vs. placebo		16.4† vs. 11.3† p=0.026	
RADIANT-3 Yao et al.[8]	III	410	Pancreatic NET	Everolimus vs. placebo		11.0† vs. 4.6† p<0.001	
RADIANT-4 Yao et al.[9]	III	302	Lung or GI NET	Everolimus vs. placebo	Estimated PFS rate at 12 months 44% vs. 28%	11.0 vs.3.9	
PhIV Raymond et al.[9]	IV	106	Pancreatic NET	Sunitinib	ORR: 24.5	13.2	37.8 (not yet mature)

1. Rinke A, et al. J Clin Oncol 2009;27:4656–4663; 2. Caplin N Engl J Med 2014;371:224-33.ME et al.; 3. Strosberg J, et al. N Engl J Med 2017; 376:125-135; 4. Raymond E, et al. N Engl J Med 2011;364:501–513; 5. Vinik A, et al. ASCO Meeting Abstracts 2012;30:4118; 6. Faivre S et al. Ann Oncology 2017;28:339–343; 7. Pavel ME, et al. Lancet 2011;378:2005–2012; 7. Yao JC, et al. N Engl J Med 2011;364:514–523; 8.Yao JC et al. Lancet. 2016; 387):968–977; 9. Raymond E, et al. Neuroendocrinology 2018;107:237–45.

Rare tumours beyond NETs…

EURACAN

Who we are | Rare adult solid cancers | Patients | Health professionals | Expert centres & referral pathways | Research | Contact

About rare adult solid cancers

More than 300 rare cancers have been identified. ERN EURACAN covers all rare adult solid tumour cancers, grouping them into 10 areas.

- Connective tissue (sarcomas)
- Female genital organs and placenta
- Male genital organs and urinary tract
- Neuroendocrine system
- Digestive tract
- Endocrine organs
- Head and neck
- Thorax
- Skin and eye melanoma
- Brain and spinal cord

View the **patient body map** to locate your rare cancer.

Translate »

Take home messages

- Clinical trials in rare cancers are challenging, but not impossible to deliver
  - ❑ Funding sources for academic research
  - ❑ Attracting pharmaceutical companies to niche areas
  - ❑ Resilience to pursue the study until completion
  - ❑ International networking

Take home messages

- Clinical trials in rare cancers are challenging, but not impossible to deliver
  - ❑ Funding sources for **academic / investigator-led research**
  - ❑ Attracting pharmaceutical companies to niche areas
  - ❑ Resilience to pursue the study until completion
  - ❑ International networking

Take home messages

- Clinical trials in rare cancers are challenging, but not impossible to deliver
  - ❑ Funding sources for academic / investigator-led research
  - ❑ Attracting **pharmaceutical companies** to niche areas
  - ❑ Resilience to pursue the study until completion
  - ❑ International networking

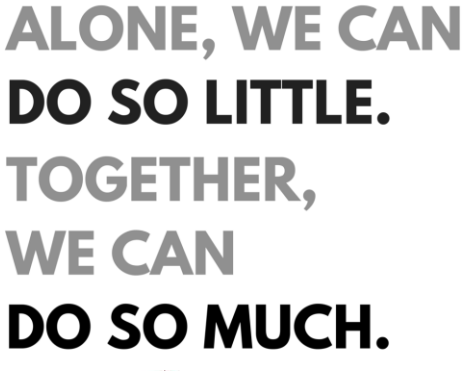
Priorities and definition of success may differ between parties
Transparency and understanding of both sides is the key

Take home messages

- Clinical trials in rare cancers are challenging, but not impossible to deliver
  - ❑ Funding sources for academic / investigator-led research
  - ❑ Attracting pharmaceutical companies to niche areas
  - ❑ **Resilience** to pursue the study until completion
  - ❑ International networking

Take home messages

- Clinical trials in rare cancers are challenging, but not impossible to deliver
  - ❑ Funding sources for academic / investigator-led research
  - ❑ Attracting pharmaceutical companies to niche areas
  - ❑ Resilience to pursue the study until completion
  - ❑ **International networking**



THANK YOU to Prof Eric Baudin for his permission to utilise his slides from ESMO 2021

Thank you for your attention

Angela.Lamarca@nhs.net