Where's the good news in cancer research?

Pan Pantziarka

July 28 1993 – April 25 2011

Cancer Risk in LFS

- LFS is associated with a germline mutation in TP53 (around 70% of patients)
- Cumulative cancer incidence 50% by age 31 years among females and 46 years among males
- Nearly 100% by age 70 years for both sexes
- Approximately 49% of those with a first cancer develop one or more cancers after a median of 10 years
- Risk management strategies revolve around active surveillance protocols and risk-reducing mastectomy

TAILORx – Breast Cancer

- TAILORx (Trial Assigning Individualized Options for Treatment) is a very large international breast cancer trial
- The trial enrolled 10,273 women at 1,182 sites in the United States, Australia, Canada, Ireland, New Zealand, and Peru
- The aim was specifically to assess the best treatment for women with early stage hormone responsive breast cancer (ER/PR+, HER2-, axillary lymph node-negative)
- The trial used the Oncotype DX Breast Recurrence Score to assess risk – with a score below 10 as low-risk, 11 – 25 as intermediate and 26 and over as high-risk

TAILORx - Results

- Women in the low-risk group were treated with hormone therapy, the high-risk group received chemo and hormone therapy
- The trial randomly assigned women in the intermediate risk group to either hormone therapy alone OR hormone therapy with chemo – reflecting current practice where there is no clear evidence on what's best
- The results clearly show chemotherapy ***can be avoided*** for the majority of women in the intermediate group
- This means around 70% of women with early stage breast cancer can avoid chemotherapy

TAILORx and LFS

Why is this relevant to women with LFS?

Table 3 Joint ER and HER2 status of the tumors in the cohort

	N	ER+/ HER2+	ER−/ HER2+	ER+/ HER2−	ER−/ HER2−
DCIS	11	3	5	3	–
IDC	32	17	3	10	2
Total	43	20 (47%)	8 (19%)	13 (30%)	2 (5%)

Masciari et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat 2012

Avoiding chemotherapy, like avoiding radiotherapy, can decrease the risk of subsequent cancers for women with LFS – this isn't just about avoiding the horrible side effects of chemo, it could have longer term positive effects

Childhood Rhabdomyosarcoma

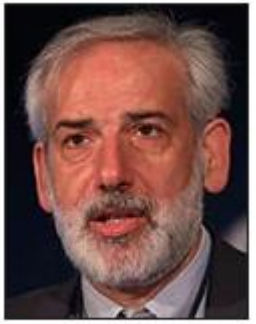
- Rhabdomyosarcoma (RMS) is one of the 'signature' childhood LFS cancers
- The most common soft tissue sarcoma in children – more than half diagnosed before the age of 10
- Treatment has not changed in almost 30 years: Surgery, Chemotherapy, Radiotherapy
- Around 20 – 30% of children relapse after treatment –their outlook is grim and has not improved in 30 years

A step forward – at last!

- The RMS 2005 is an international (14 countries) randomised trial in children with RMS, it took 11 years to complete!
- It recruited 371 children with high risk RMS, with half receiving the standard treatment, and the other half receive standard treatment followed by six months of ‘maintenance therapy’
- The maintenance therapy was low-dose (non-toxic) chemotherapy (daily tablets and weekly outpatient chemotherapy)

RMS2005 - Results

"This study establishes the new standard of treatment for patients with high-risk rhabdomyosarcoma, at least in Europe," said lead author Gianni Bisogno, MD, of the University Hospital of Padova, Italy.



Dr Gianni Bisogno

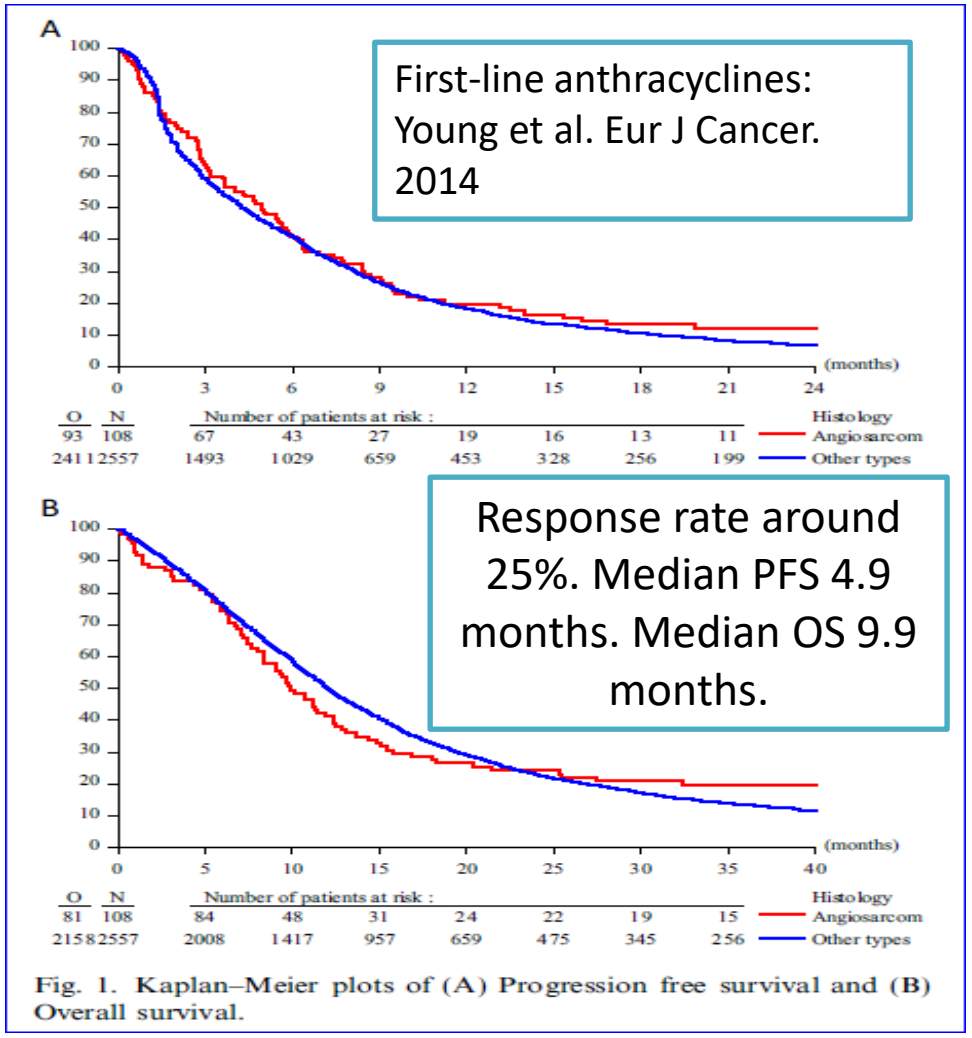
Disease free survival at five years (i.e. five years without recurrence after treatment has ended) was 68.8% in the standard therapy group, and 77.6% in the maintenance therapy group

Overall survival was 73.7% in the standard therapy group and 86.5% in the maintenance therapy group.

This is the first advance in more than 30 years – and is the new standard of care in the UK and other European countries

Angiosarcoma

- A rare soft tissue sarcoma – not one of the 'signature' LFS sarcomas
- More common in LFS as a secondary primary caused by radiotherapy for breast cancer
- Treatment has not changed in decades – chemo, surgery, radiotherapy
- **Could an old non-cancer drug called propranolol improve outcomes?**



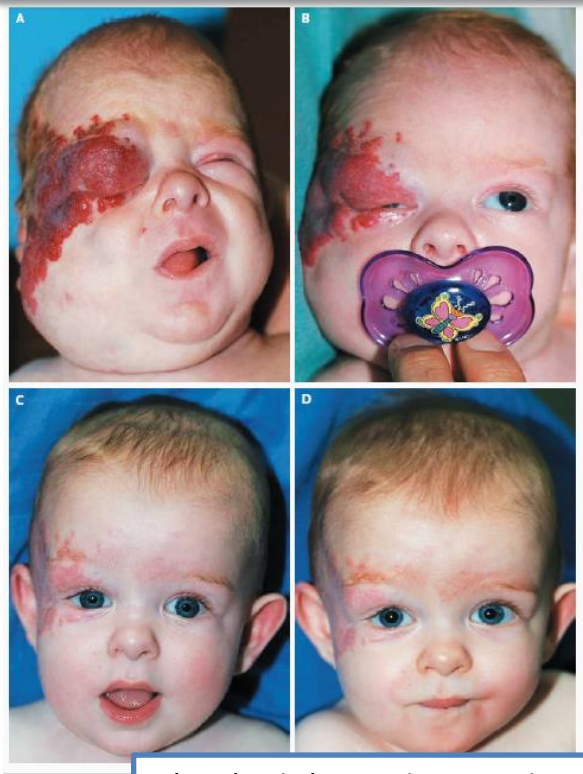
First-line anthracyclines: Young et al. Eur J Cancer. 2014

Response rate around 25%. Median PFS 4.9 months. Median OS 9.9 months.

Fig. 1. Kaplan–Meier plots of (A) Progression free survival and (B) Overall survival.

The hemangioma story…

Incidental observation in a child treated with propranolol shows rapid and sustained effects on infantile hemangioma – results repeated in 10 other children.



Léauté-Labrèze et al. 2008. *The New England Journal of Medicine* 358:2649–51.

Results confirmed in numerous patients and trials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ORIGINAL ARTICLE

A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma

Christine Léauté-Labrèze, M.D., Peter Hoeger, M.D., Juliette Mazereeuw-Hautier, M.D., Laurent Guibaud, M.D., Eulalia

Léauté-Labrèze et al. 2015. A randomized, controlled trial of oral propranolol in infantile hemangioma. *The New England journal of medicine* 372:735–46.

Drug reformulated for infants

Hemangeol – FDA Approved March 2014

Hemangiol – EMA Approved Feb 2014

Successfully repurposed

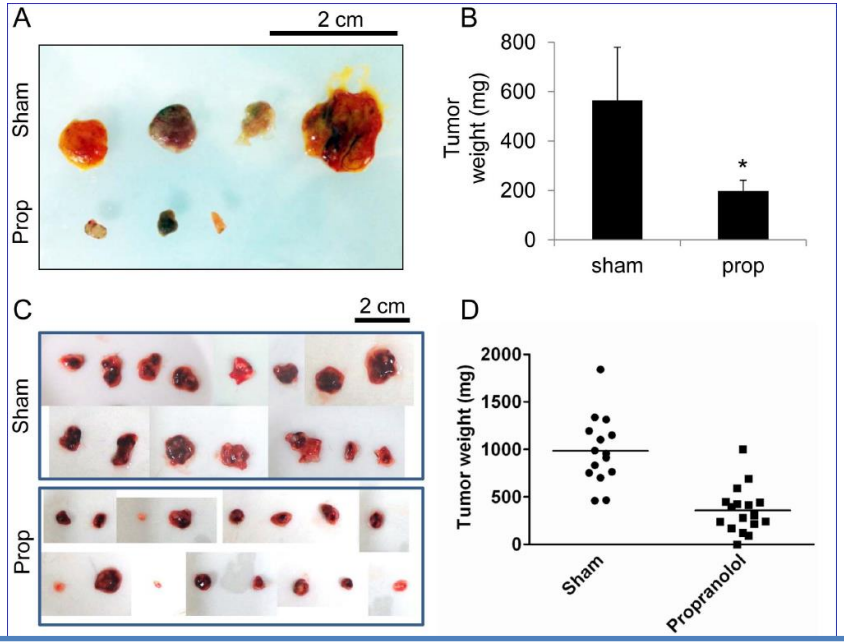
But what about angiosarcoma?

Investigators look at expression of beta receptors in range of benign and malignant tumours

Vascular lesion	*B2-AR*		*B2-ARP*		*B3-AR*	
	N[a]	%[b]	N[a]	%[b]	N[a]	%[b]
Infantile hemangioma	5	100	5	80	4	100
Epithelioid hemangioma	4	50	4	100	4	75
Spindle cell hemangioma	2	100	4	50	3	67
~~Bone hemangioma~~	~~1~~	~~100~~	~~2~~	~~50~~	~~1~~	~~100~~
Epithelioid hemangioendothelioma	14	50	14	87	13	69
Kaposiform hemangioendothelioma	3	67	4	75	2	50
Bone hemangioendothelioma	1	100	1	0	1	0
Hobnail hemangioendothelioma	1	0	1	0	1	0
~~Retiform hemangioendothelioma~~	~~1~~	~~0~~	~~1~~	~~100~~	~~1~~	~~0~~
Angiosarcoma	44	41	44	48	38	21
Intimal sarcoma	4	100	4	50	4	50
Kaposi sarcoma	4	75	5	60	3	33
Hemangiopericytoma	3	33	3	67	3	33
Littoral cell angioma	4	25	6	83	5	20
Pyogenic granuloma	2	50	2	50	1	0
Glomus tumor	5	40	5	40	5	20
Masson's	1	0	2	100	2	100
Vascular malformation, venous	7	57	7	71	6	33
Vascular malformation, lymphatic	4	50	7	57	3	33
Vascular malformation, mixed small and large vessel	1	100	1	100	1	100
Vascular malformation, not otherwise specified	1	100	1	100	1	0
Intramuscular vascular malformation	1	100	2	50	1	100
Lymphangioleiomyomatosis	1	0	1	100	1	0
Reactive vascular proliferation	0	n.a.	1	0	1	0

Chisholm KM et al. 2012. β-Adrenergic receptor expression in vascular tumors. *Modern pathology* 25:1446–51.

Brad Bryan and co-workers at Texas Tech University test propranolol in animal models of angiosarcoma



Stiles JM et al. 2013. Targeting of Beta Adrenergic Receptors Results in Therapeutic Efficacy against Models of Hemangioendothelioma and Angiosarcoma. *PloS one* 8:e60021.

Propranolol and Angiosarcoma?

69-year-old woman with a relapsing metastatic angiosarcoma treated with a combination of metronomic chemotherapy and propranolol. A complete response was quickly obtained and lasted for 20 months.

ecancermedicalscience

Targeted therapy with propranolol and metronomic chemotherapy combination: sustained complete response of a relapsing metastatic angiosarcoma

Shripad Banavali[1,2], Eddy Pasquier[2,3] and Nicolas Andre[2,3,4]

Banavali S et al. 2015. Targeted therapy with propranolol and metronomic chemotherapy combination. *Ecancermedicalscience* 9:499.

Chow W et al . 2015. Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated β-Blockade. *JAMA dermatology*:1–4.

Progressive images of the patient during and following combination therapy with propranolol hydrochloride, paclitaxel poliglumex, and radiotherapy.

Case Report/Case Series

Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated β-Blockade

William Chow, DO; Clarissa N. Amaya, MS; Steven Rains, MS; Michael Chow, BS; Erin B. Dickerson, PhD

IMPORTANCE Patients with stage T2 multilesion angiosarcomas of the scalp and face that are larger than 10 cm demonstrate a 2-year survival rate of 0%. To our knowledge, major therapeutic advances against this disease have not been reported for decades. Preclinical data indicate that blocking β-adrenergic signaling with propranolol hydrochloride disrupts angiosarcoma cell survival and xenograft angiosarcoma progression.

OBSERVATIONS A patient presented with a β-adrenergic–positive multifocal stage T2 cutaneous angiosarcoma (≥20 cm) involving 80% of the scalp, left forehead, and left cheek, with no evidence of metastasis. The patient was immediately administered propranolol hydrochloride, 40 mg twice a day, as his workup progressed and treatment options were elucidated. Evaluation of the proliferative index of the tumor before and after only 1 week of propranolol monotherapy revealed a reduction in the proliferative index of the tumor by approximately 34%. A combination of propranolol hydrochloride, 40 mg 3 times a day, paclitaxel poliglumex, 2 mg/m^2 infused weekly, and radiotherapy during the subsequent 8 months resulted in extensive tumor regression with no detectable metastases.

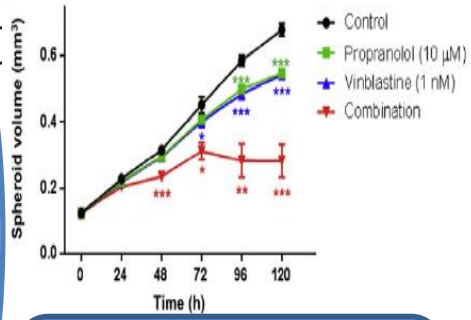
More human data

Pasquier E et al. 2016. Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study. *EBioMedicine* 6:87–95.

Seven additional patients treated in India. 100% response rate. PFS and OS superior to standard treatments

Treatment duration and responses.

Patient no.	Duration of Rx A*	Best response to Rx A*	Duration oral maintenance**	PFS	Additional treatment	Status as of Feb. 2016	OS
1	3 months (stopped on request)	Very good partial response (VGPR)	5 months	7 months	EBRT to eye; doxorubicin; gemcitabine + cisplatin	Died of PD Oct. 2012	14 months
2	12 months	Complete clinical response. MRI still showed some diffuse scalp thickening: VGPR.	12 months	24 months	EBRT to scalp	Died of PD Oct. 2014	30 months
3	12 months	Complete clinical & metabolic response	2 months	14 months	EBRT to scalp, bones; paclitaxel; thalidomide	Died of PD Mar. 2015	19 months
4	4 months (could not continue due to low platelet counts)	Bone marrow complete morphological response	Could not take much chemo due to autoimmune thrombo-cytopenia	5 months	EBRT to bones; thalidomide	Died of PD Aug. 2014	10 months
5	11 months	Complete response of residual lung nodules	3 months	11 months	Palliative care	Died of progresive disease Apr. 2015	16 months
6	12 months	Very good partial response (VGPR)	3 months	19+ months	N/A	Alive on Rx with VGPR	19+ months
7	5 months (stopped due to logistics)	Partial response	Not started	14+ months	Presently on thalidomide/oral etoposide	Alive on Rx with stable disease	14+ months



In vitro and in vivo evidence in addition to patient data

CASE REPORT

Visceral metastatic angiosarcoma treated effectively with oral cyclophosphamide combined with propranolol

CrossMark

Justine Daguzé, MD,[a] M
Gaëlle Quéreux, M

Daguzé J et al. 2016. Visceral metastatic angiosarcoma treated effectively with oral cyclophosphamide combined with propranolol. *JAAD case reports* 2:497–499.

To date we have more than 10 published cases – and know of other unpublished cases with good responses.

Next steps…

Clinical trial initiated in France (PROPAN trial)

Propranolol as

Anticance
drug des

Propranc
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Propranolol and breast cancer—a work in progress

Pan Pantziarka[1,2], Brad A Bryan[3], Sergio Crispino[1] and Erin B Dickerson[4,5]

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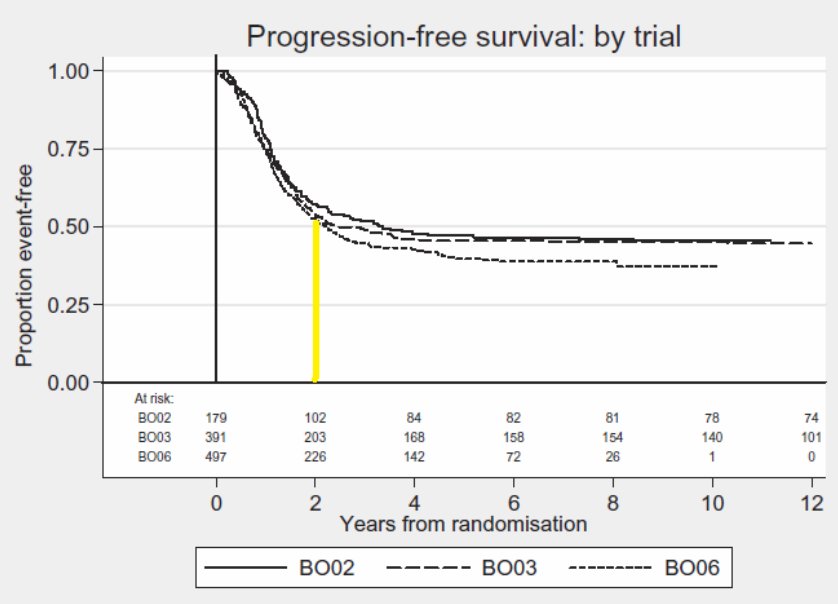
[2]The George Pantziarka TP53 Trust, London, UK
[3]Department of Biomedical Sciences, Texas Tech University Health Sciences Center, El Paso, Texas, USA
[4]Department of Veterinary Clinical Sciences, University of Minnesota, Saint Paul, Minnesota, USA
[5]Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota, USA

Scientific Advice meeting with MHRA

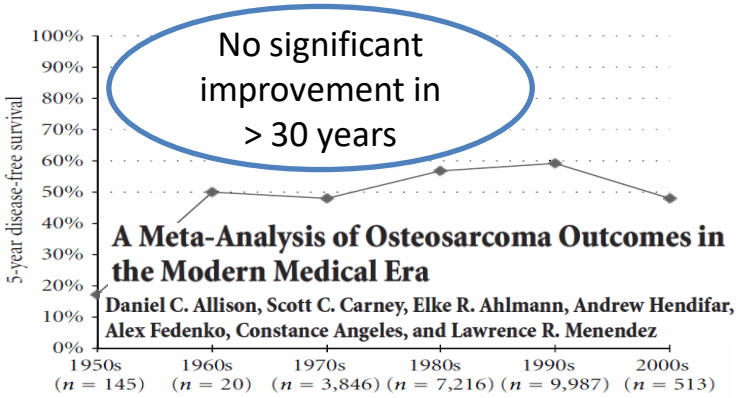
Additional clinical trial(s)

Osteosarcoma - Roadblocked



Status	N	%
Local recurrence	67	6%
Metastases	497	47%
No recurrence	503	47%
Total	*1067*	*100%*

Annals of Oncology 23: 1607–1616, 2012
doi:10.1093/annonc/mdr491
Published online 19 October 2011



A Meta-Analysis of Osteosarcoma Outcomes in the Modern Medical Era

Daniel C. Allison, Scott C. Carney, Elke R. Ahlmann, Andrew Hendifar, Sant Chawla, Alex Fedenko, Constance Angeles, and Lawrence R. Menendez

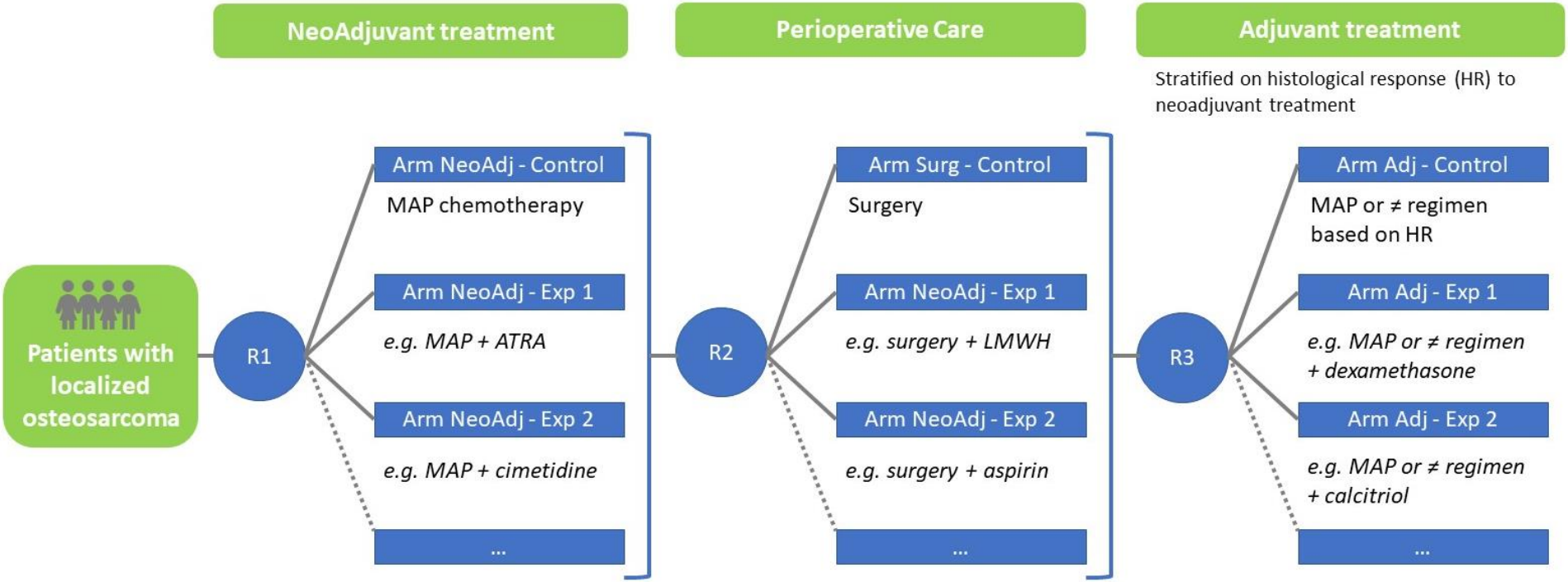
Survival from high-grade localised extremity osteosarcoma: combined results and prognostic factors from three European Osteosarcoma Intergroup randomised controlled trials

J. S. Whelan[1]*, R. C. Jinks[2], A. McTiernan[1], M. R. Sydes[2], J. M. Hook[2], L. Trani[1], B. Uscinska[2], V. Bramwell[3], I. J. Lewis[4], M. A. Nooij[5], M. van Glabbeke[6], R. J. Grimer[7], P. C. W. Hogendoorn[8], A. H. M. Taminiau[9] & H. Gelderblom[5]

PRESTO

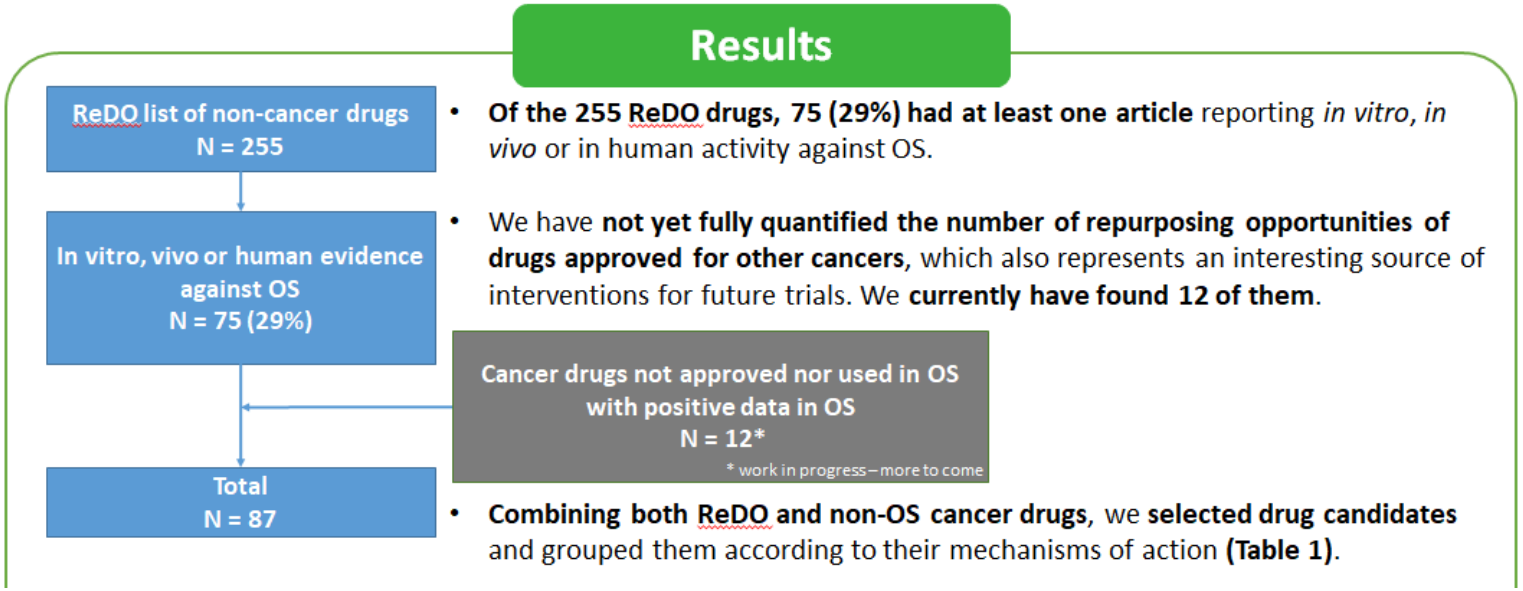
Currently there are NO trials in localised osteosarcoma with a survival end-point in Europe and North America. Only a series of independent early phase trials looking at other end-points….

PRESTO: Platform for the Rapid Evaluation of Several Treatments in Osteosarcoma



Next steps…

- Idea for PRESTO being presented at major cancer conferences…
- Meetings and discussions on-going with clinicians across Europe and North America…
- Researching for possible drugs to test…



A UK LFS Registry?

- A central registry of people with LFS would be extremely valuable
  - We can have an idea about total numbers diagnosed
  - A data source for further study
  - Easy to contact people for clinical trials or more research
- To date initiatives to create a register have stalled
- The national screening program will record data for people eligible for screening
- This opens the door to create a centralised LFS registry for the UK as a whole
- Given the possible increase in the numbers of people with LFS – based on the results from Dundee – this may become even more important