Patient-Reported Outcomes & Quality of Life

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Presenter Disclosures

Thanks to Felix Hilpert for sharing his slides!

Why?

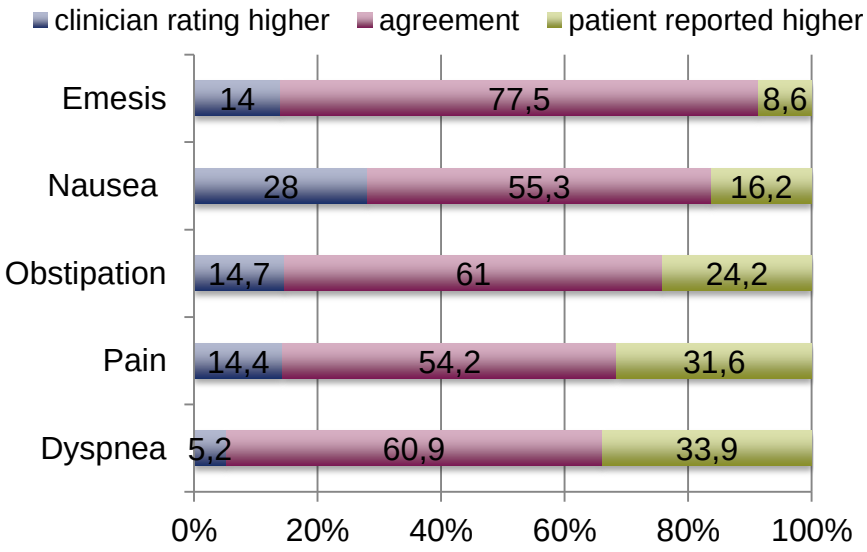
Correlation of toxicity according to NCI-CTC with EORTC QLQ-C30

2574 patients, ovarian cancer FIGO IIB-IV, 1st-line therapy

CTC- and QoL-Data after 6 cycles Carboplatin/Paclitaxel ± 3. drug

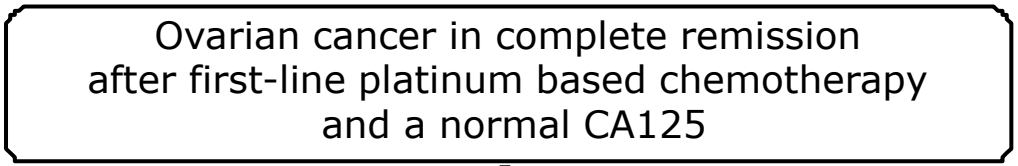
Spearman-rank correlation coefficients: < .30=low; .30-.50=moderate; >.50=high

	EORTC QLQ-C30 functional scales					
CTC	**Physical**	**Role**	**Emotion**	**Cognitive**	**Social**	**Global**
Hem-Tox. ≥3	Effect of Tox on QoL (experts' opinion)					
Leukopenia	-.01	.00	.00	-.05	-.05	-.03
Neutropenia	.02	.01	-.01	-.06	-.03	.01
Non-Hem. Tox. ≥2						
Alopecia	-.04	-.05	-.06	-.04	-.04	-.03
Nausea	-.14	-.16	-.10	-.10	-.07	-.20
Emesis	-.08	-.10	-.08	-.09	-.07	-.10
Obstipation	-.13	-.16	-.12	-.14	-.13	-.11
Neuropathy	-.24	-.19	-.09	-.09	-.12	-.15
Myalgia	-.06	-.12	-.11	-.11	-.11	-.13
Pain	-.11	-.15	-.12	-.12	-.12	-.15
Dyspnea	-.15	-.14	-.07	-.11	-.07	-.12



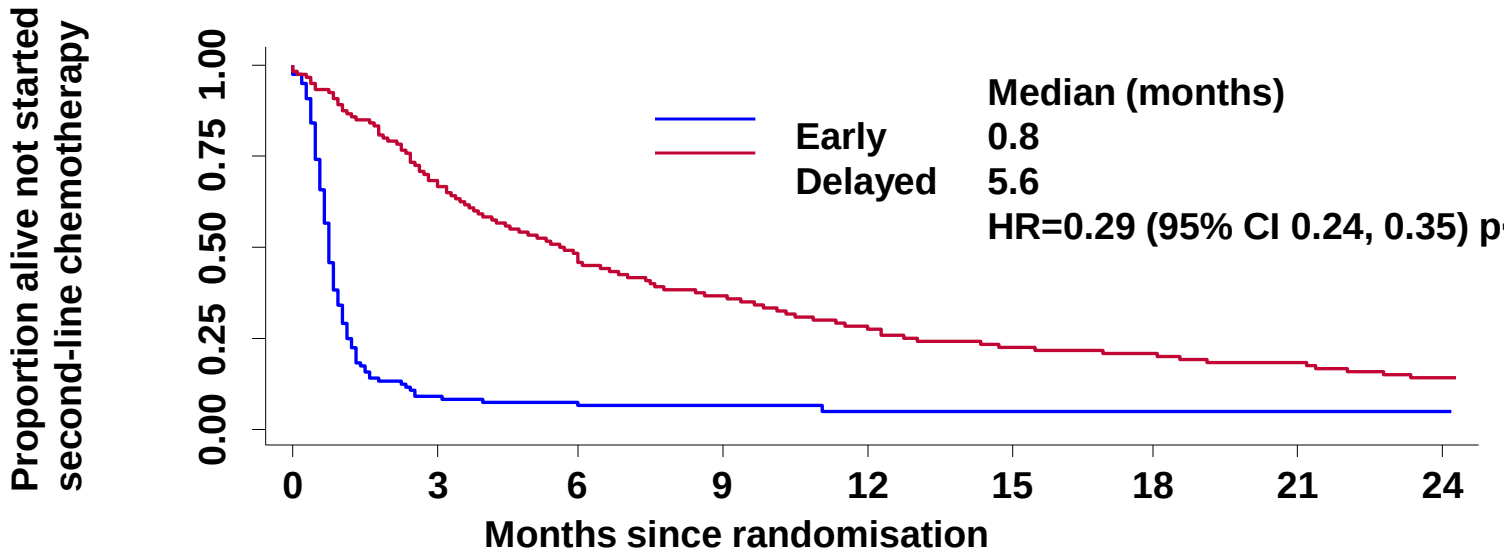
Greimel ER, Support Care Cancer 2011

Why? MRC OV05 / EORTC 55955



Rustin et al. Lancet. 2010; 376

Why? Time from randomisation to second-line chemotherapy

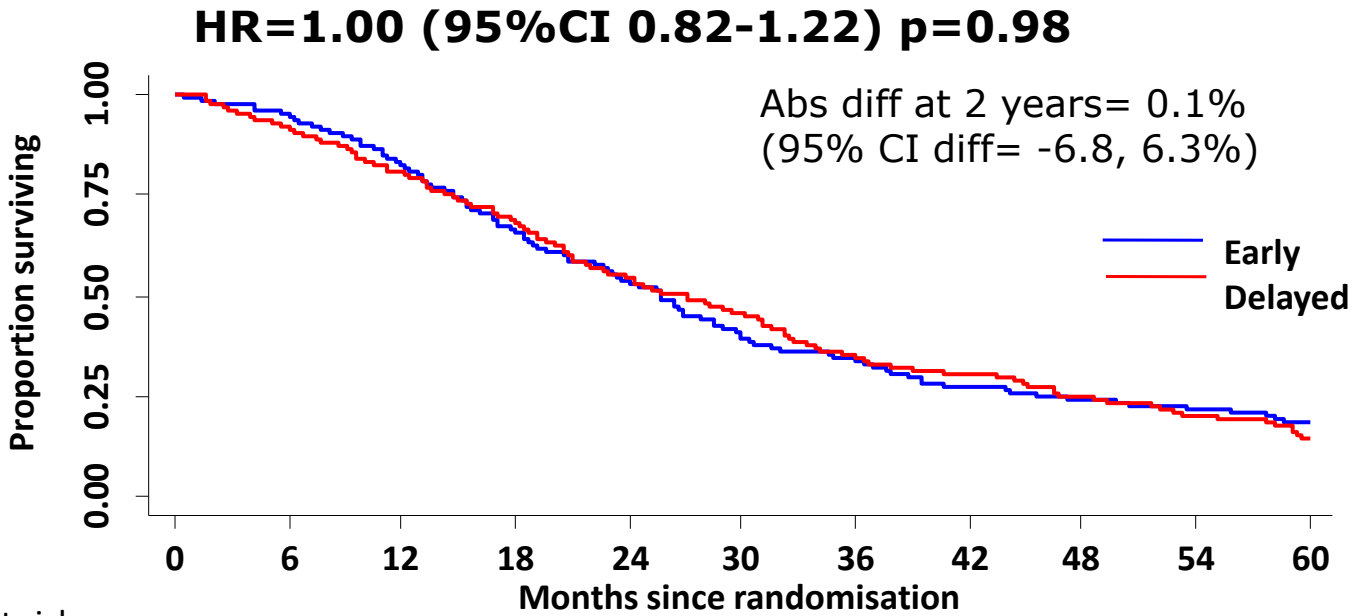


Number at risk

Early	265	23	16	14	11	11	10	10	9
Delayed	264	177	116	91	69	56	49	42	33

Rustin et al. Lancet. 2010; 376

Why? Overall Survival

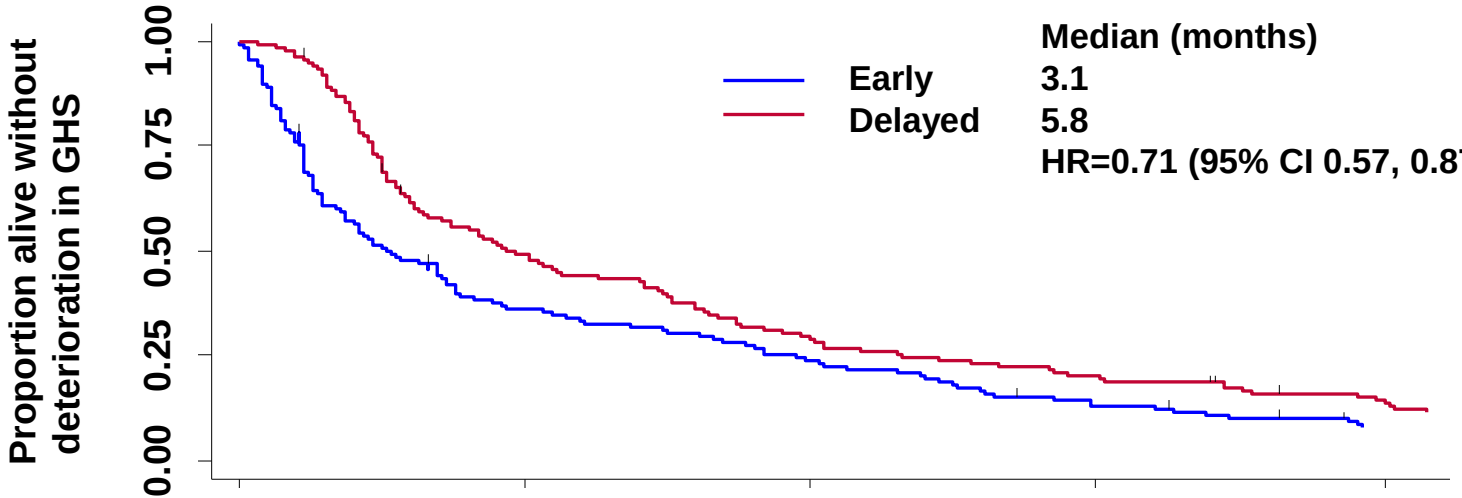


Number at risk

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

Rustin et al. Lancet. 2010; 376

Time from randomisation to first deterioration in Global Health Score (or death)

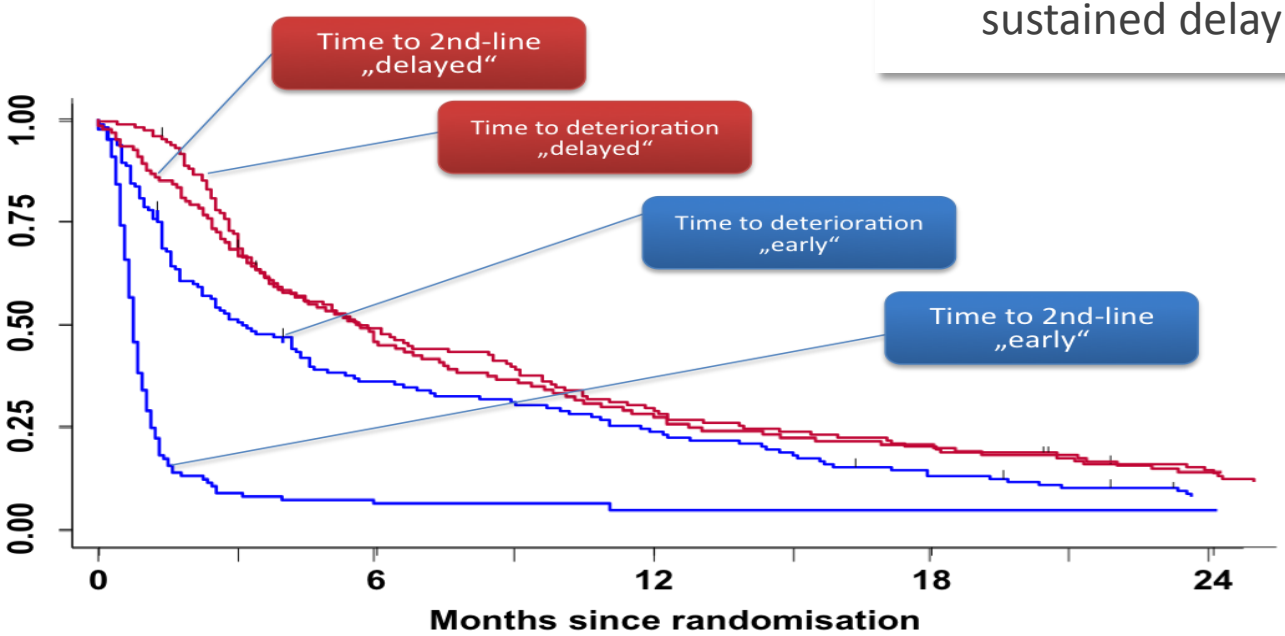


Number at risk

Early	190	68	44	23	12
Delayed	194	93	55	38	25

Matched: Time from randomisation to second-line chemotherapy and time to deterioration of QoL (memo: the numbers differ)

Delay of subsequent therapy results in a sustained delay of QoL deterioration?



When should PROs be incorporated into Clinical Trials?

When it enables investigators to address a decision-relevant question!

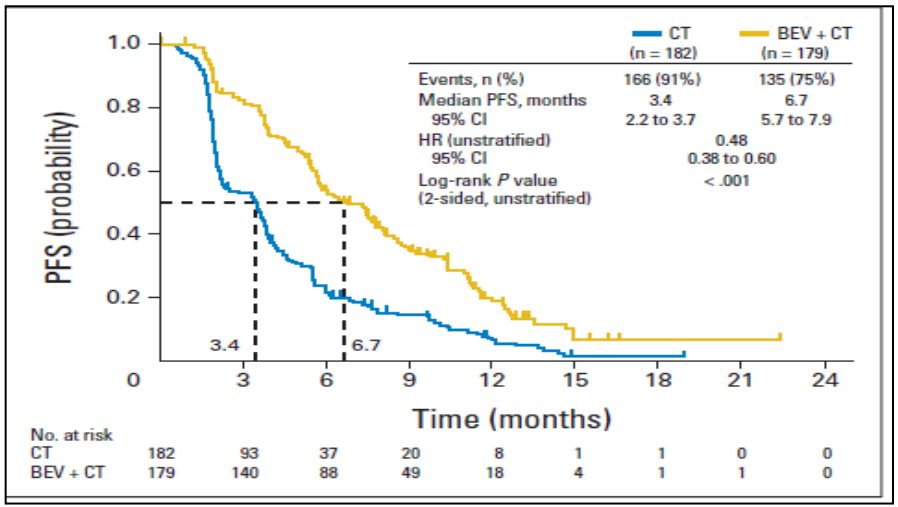
- When treatment results are expected to be equivalent in terms of survival
- When QoL benefits are anticipated
- When minimal benefits in survival might not outweigh QoL impairments
- *When treatment differ in short term efficacy but the overall failure rate is high*

What? PRO endpoints in Ovarian Cancer
to support convention efficacy end-points

- HRQoL Global
- Symptom Benefit
- Patient Reported Adverse Effects
- Time to Deteriorate
- Compliance / Drop Outs
- …….

Example: Definitive Treatment
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Resistant Relapse*

Improved PFS by adding bevacizumab to non-platinum based chemo + QoL benefit in symptomatic pts.



AURELIA: PFS NonPlat +/- Bev
HR 0.48; 95% CI 0.38-0.60, p< 0.001

Pujade-Lauraine E.... Mirza MR et al. J Clin Oncol 2014

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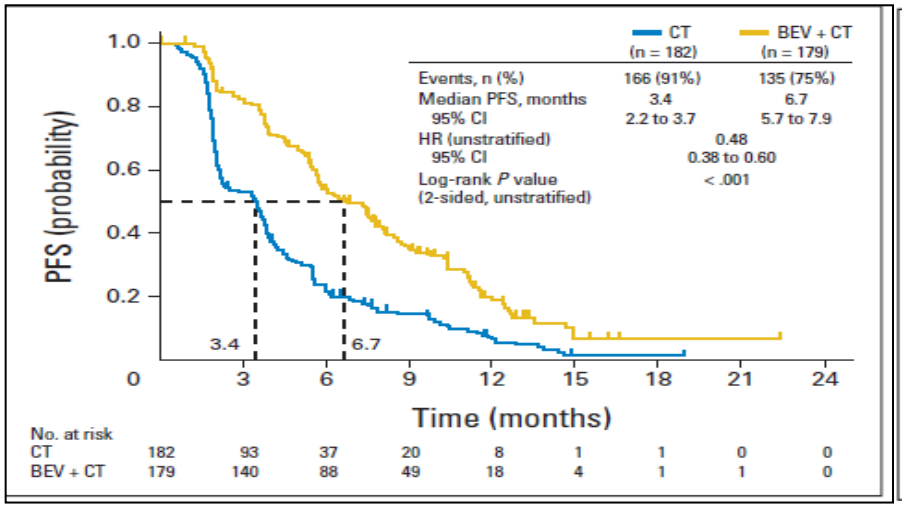

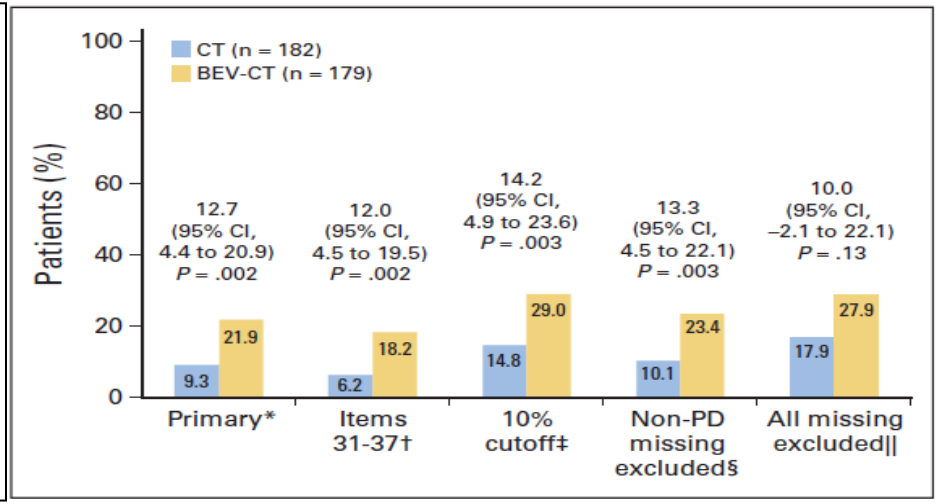

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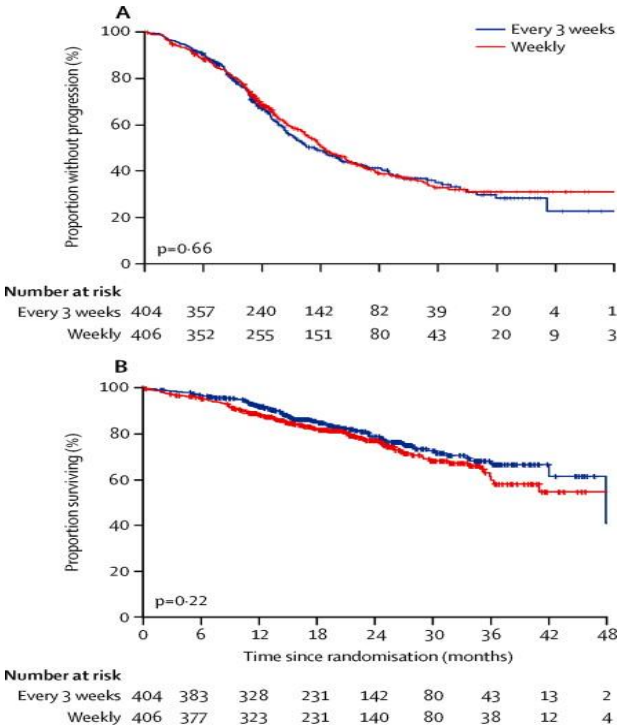
AURELIA: Primary and sensitivity analysis of the primary hypothesis (≥ 15% improvement in symptomatic pts)

Pujade-Lauraine E.... Mirza MR et al. J Clin Oncol 2014

Stockler MR.... Mirza MR et al. J Clin Oncol 2014

Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial



- **No difference in PFS and OS**

Pignata et al, Lancet Oncol 2014

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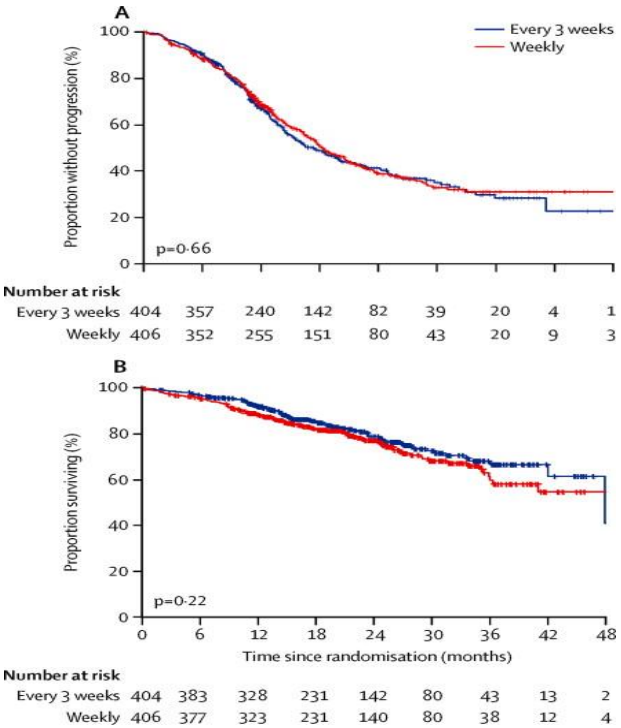

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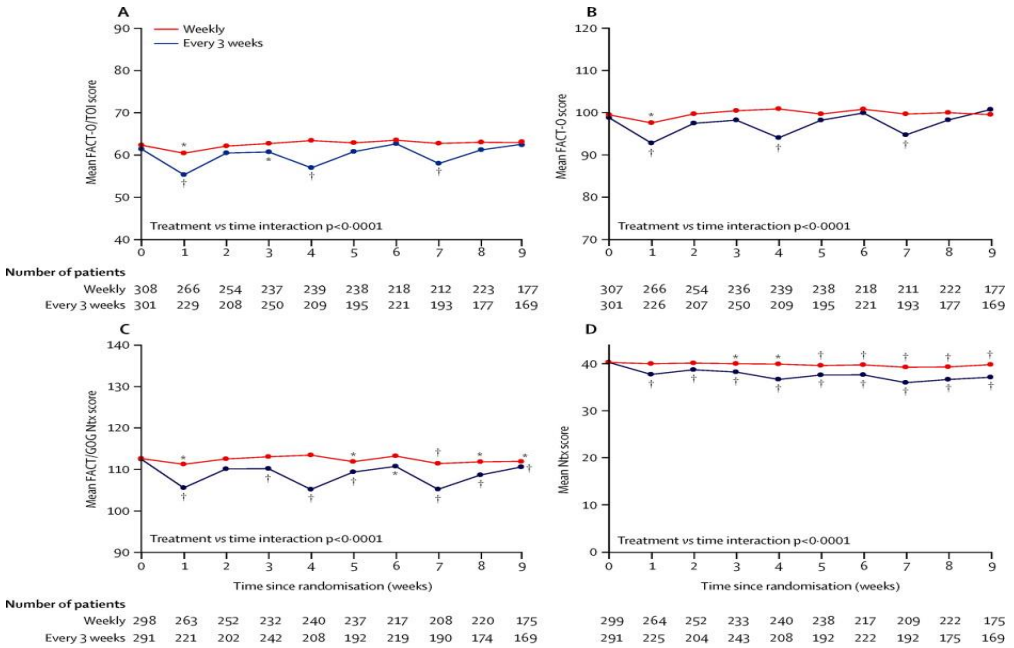


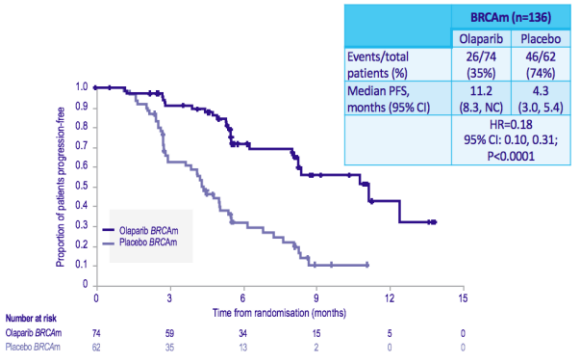
- QoL, Co-primary endpoint, EVALUATED EVERY WEEK for the first 9 weeks
- **PRO's favor the weekly schedule**

Pignata et al, Lancet Oncol 2014

Examples: Maintenance Therapy!

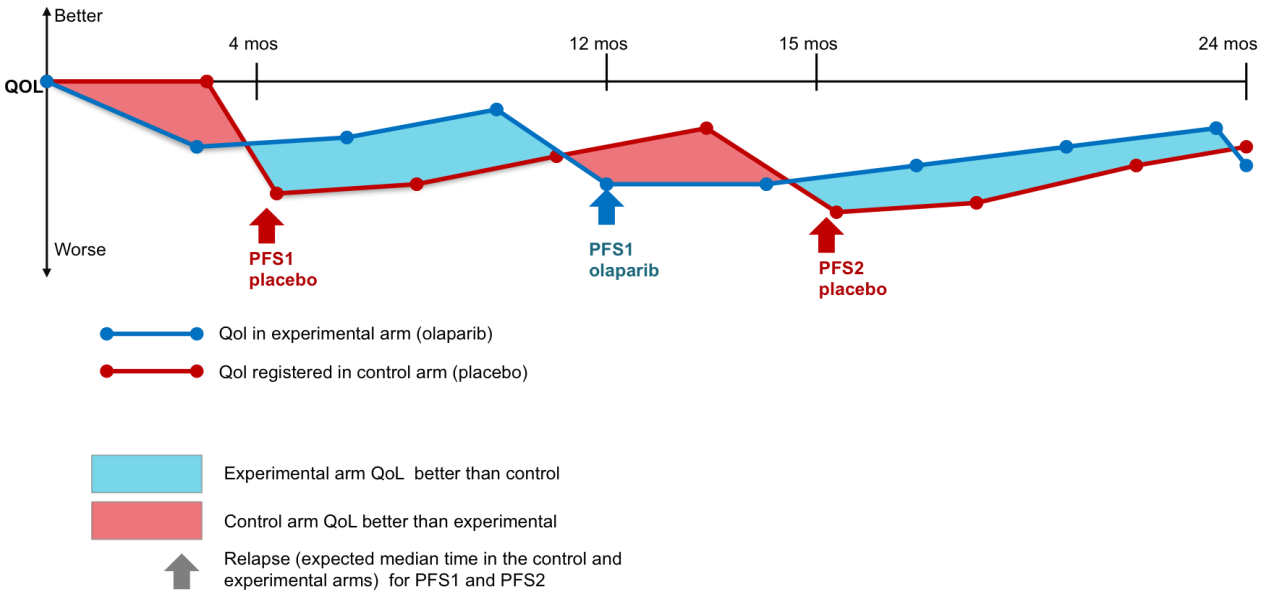
AZ Study 19: PFS vs PROs

Phase 2 randomised trial of maintenance olaparib in platinum-sensitive high-grade serous relapse OC



	BRCAm (n=136)	
	Olaparib	Placebo
Events/total patients (%)	26/74 (35%)	46/62 (74%)
Median PFS, months (95% CI)	11.2 (8.3, NC)	4.3 (3.0, 5.4)
	HR=0.18 95% CI: 0.10, 0.31; P<0.0001	

Subpopulation with a BRCA mutation



Ledermann J et al. Lancet Oncol 2014

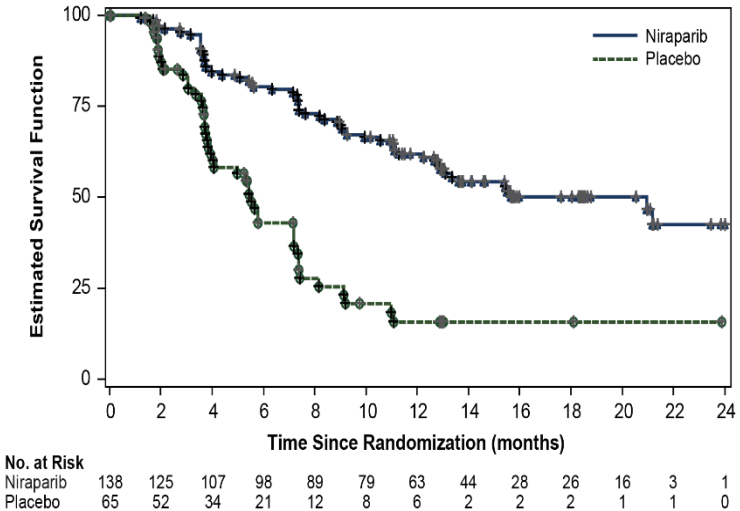
Ledermann J et al. Br J Cancer 2016

ENGOT-OV16 / NOVA: PFS

Phase 3 randomised trial of maintenance niraparib in platinum-sensitive high-grade serous relapse OC

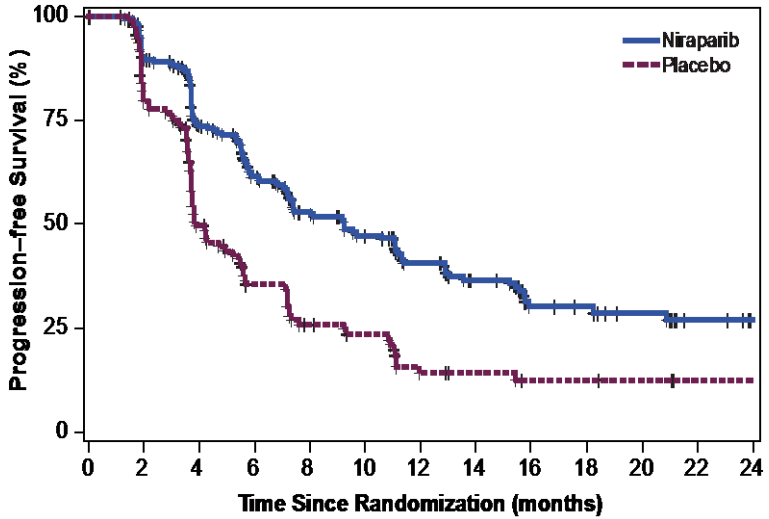
PFS: gBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NE)	**0.27** (0.173, 0.410) p<0.0001	62%	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16%	16%



PFS: non-gBRCAmut

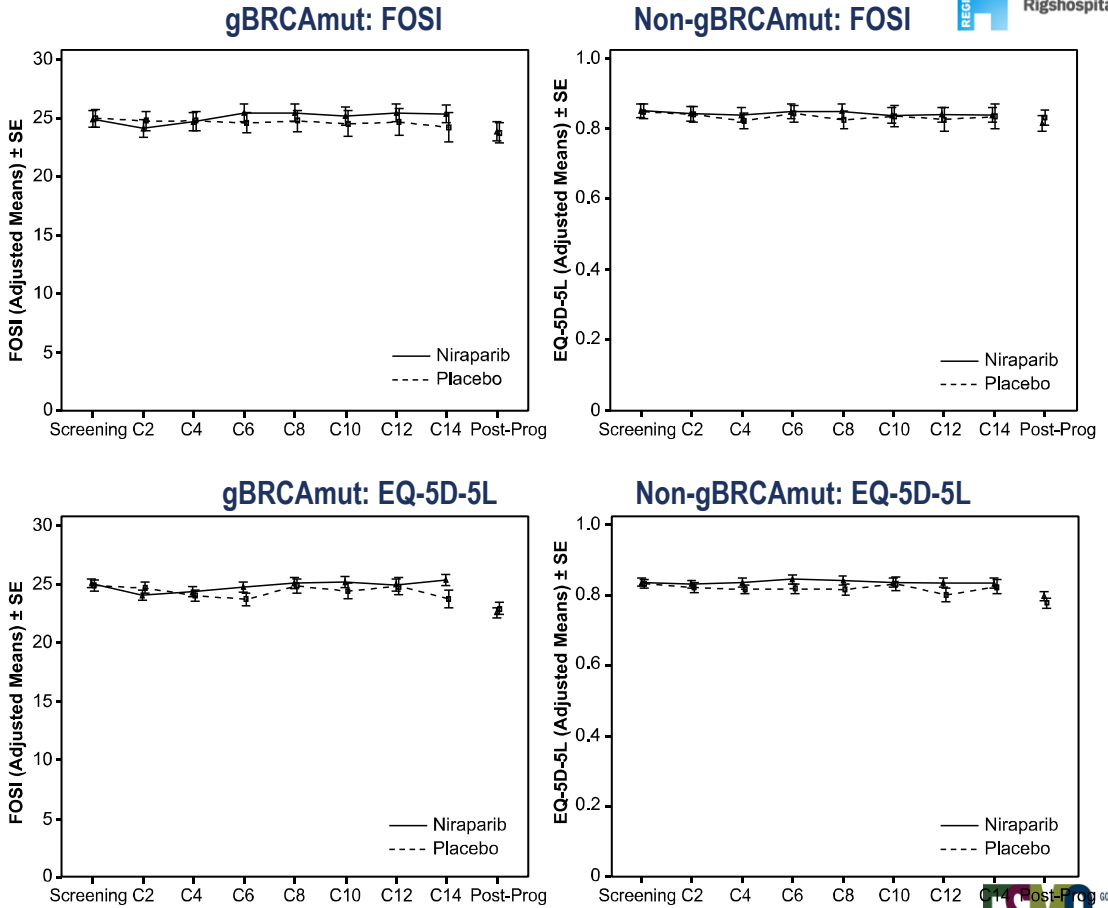
Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001	41%	**30%**
Placebo (N=116)	**3.9** (3.7, 5.5)		14%	12%



Mirza MR et al. N Engl J Med 2016

Examples: Maintenance Therapy!
ENGOT-OV16 NOVA

- **Measured using the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) and the EQ-5D-5L**
- **PRO surveys were collected at:**
  - Screening visit
  - Every other cycle through cycle 14
  - Post progression
- **Compliance rates were high, and similar between the two treatment arms**
  - Niraparib: FOSI completion rate ranged from 75.0% to 97.1%
  - Placebo: FOSI completion rate ranged from 77.6% to 97.4%
- **PROs were similar for niraparib compared with placebo**



Mirza MR et al. N Engl J Med 2016

Challenges!

- What are the most important PRO endpoints in clinical trials?
- Are we ready to make PRO's the primary endpoint or co-primary endpoint in Platinum Resistant Ovarian Cancer?
- Including PRO endpoints in trials with novel targeted therapies and immunotherapy- what's different – duration/new toxicities
- Special settings e.g survivorship / surgical trials – what are the PRO endpoints
- Are we ready to include patient reported adverse events and patient preferences in trials?