Clinical Trial Statistical endpoints and their interpretation

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CANCER RESEARCH UK | UCL CENTRE

Agenda

- Clinical Trial Types
- Terminology in Clinical Trial Reporting
- Outcome measurements
- Interpretation of Outcome
- Biomarker- driven trials

What is a Clinical Trial and why are trials needed ?

*A scientific evaluation of a **clinical intervention***
*to find out the **effectiveness** of an intervention*
*measured by a **defined outcome** in a **specific population***

Intervention

- a **new drug** - therapeutic or prophylactic
- a **new diagnostic** technique – earlier or more accurate diagnosis
- a **new technology** e.g. laparoscopic surgery
- a **new management** policy e.g. clinics run by nurses

Outcome for cancer

- tumour response
- survival or disease-free survival
- time to progression
- palliation of symptoms, quality of life
- side effects profile
- laboratory or clinical measurement

Phases of Clinical Trials

- **Phase I**
  - is the drug usable- safe and any signs of activity?
  - escalating doses used
- **Phase II**
  - is the drug active at the selected dose?
  - this may be single arm but commonly randomised
  - endpoints such as tumour response, duration of response or progression-free survival used
- **Phase III**
  - is the drug better than what is currently available?
  - randomised trial

Clinical for licensing anti-cancer drugs

Mostly randomised phase III trials

Clear evidence of benefit

Survival increase

Progression-free survival with trend to overall survival benefit

Safety

Regulations more lenient for:

- orphan drug indication- rare conditions
- where randomised trials are difficult
- costs would make investment by pharma uneconomical

Terms used in Clinical Trial Reporting

- Outcomes
  - Response (RECIST- Response Evaluation Criteria In Solid Tumours)
  - Progression-Free Survival
  - Recurrence-Free Survival
  - Overall Survival
- Interim Analysis
- Subgroup analyses

RECIST

- There must be at least one tumour that can be measured
- Using
  - X-ray, CT, or MRI scans.
- The types of response are:
  - Complete response (CR)- disappearance of the target being measured
  - Partial response (PR)- a 30% or greater reduction in the size of the target lesion
  - Progressive disease (PD)- a greater than 20% increase in size or the appearance or new disease
  - Stable disease (SD)- Neither qualifying for PR or PD

Useful for the early evaluation of activity of a new therapy but gives no indication of the benefit to the patient

Progression-Free Survival

- The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse
- It takes account of patients who have either progressed or died since the trial started
- Measured from trial entry (usually randomisation) until the evaluation time

Why is progression-free survival often used at a primary endpoint (main endpoint) in clinical trials?

- Time to evaluation is shorter than overall survival
- Number of patients required are smaller
- It is cheaper to run, and for industry earlier licensing brings a return on investment sooner, with longer patent life
- Progression-Free Survival (PFS) is usually accepted by regulators for licensing particularly if:
  - There is a trend for overall survival benefit
  - Biomarker supporting its use
  - Surrogate endpoint for OS such as time to second progression (PFS2)

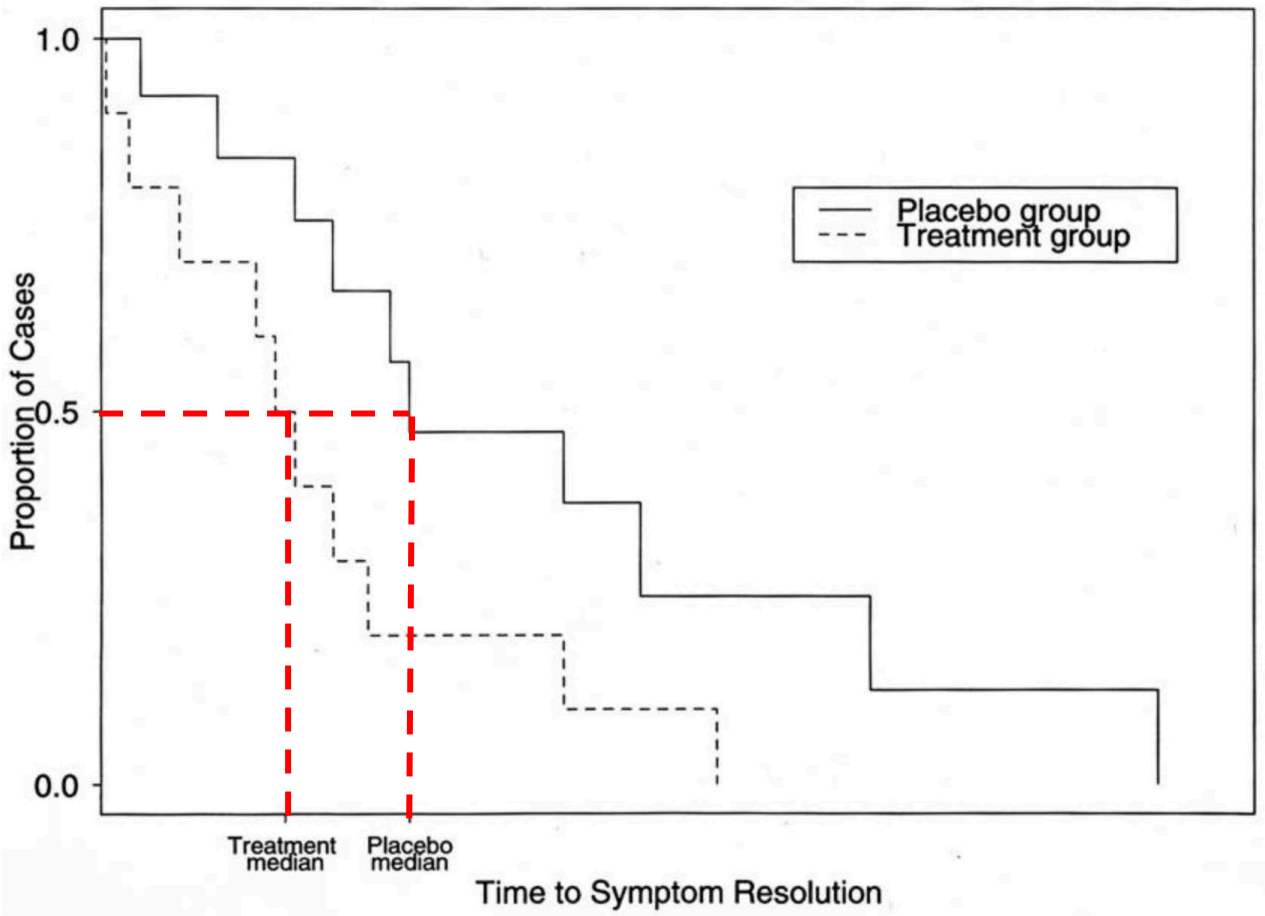
Are there disadvantages of using Overall Survival?

- For a curative therapy, eg first-line treatment of ovarian cancer, OS remains the most valuable measurable outcome
- For metastatic (or recurrent cancers) where the likelihood of cure is low, the problems demonstrating OS benefit are:
  - Patients may cross-over to the active drug after progression, diluting the benefit
  - Patients may have many treatments after progression and before death, making it harder to show that a PFS benefit holds up for OS

Measuring differences in outcome in randomised trials

- Median Progression Free Survival
- Hazard Ratio
- Confidence Interval
- ‘p value’

Median and Hazard Ratio



Median, time at which half the cases are resolved, and half are not resolved

It is a point estimate and does not take into account the shape of the curve

Hazard Ratio (HR) a measure of how often a particular event happens in one group compared to how often it happens in another group, over time

HR = treatment hazard rate/placebo hazard rate.
The hazard ratio is constant under the Cox proportional hazard model

HR < 1.0- there is an effect of treatment
HR > 1.0 there is no effect

Confidence Intervals

- The **confidence Interval** give an indication of how good is the estimate of the result
- The **confidence level** is the range of values that you expect your estimate to fall between, if the experiment is run again in the same way
- The 95% **confidence level** is the percentage of times you expect to reproduce an estimate between the upper and lower bounds of the confidence interval

If you have a small number of samples in each group there is likely to be greater variation each time you analyse the trial compared to a trial where there a very large number of patients in each group

Larger trial size means less 'wobble' around the results

P values

The assumption taken at the outset is that there is no difference between treatment ‘A’ and treatment ‘B’

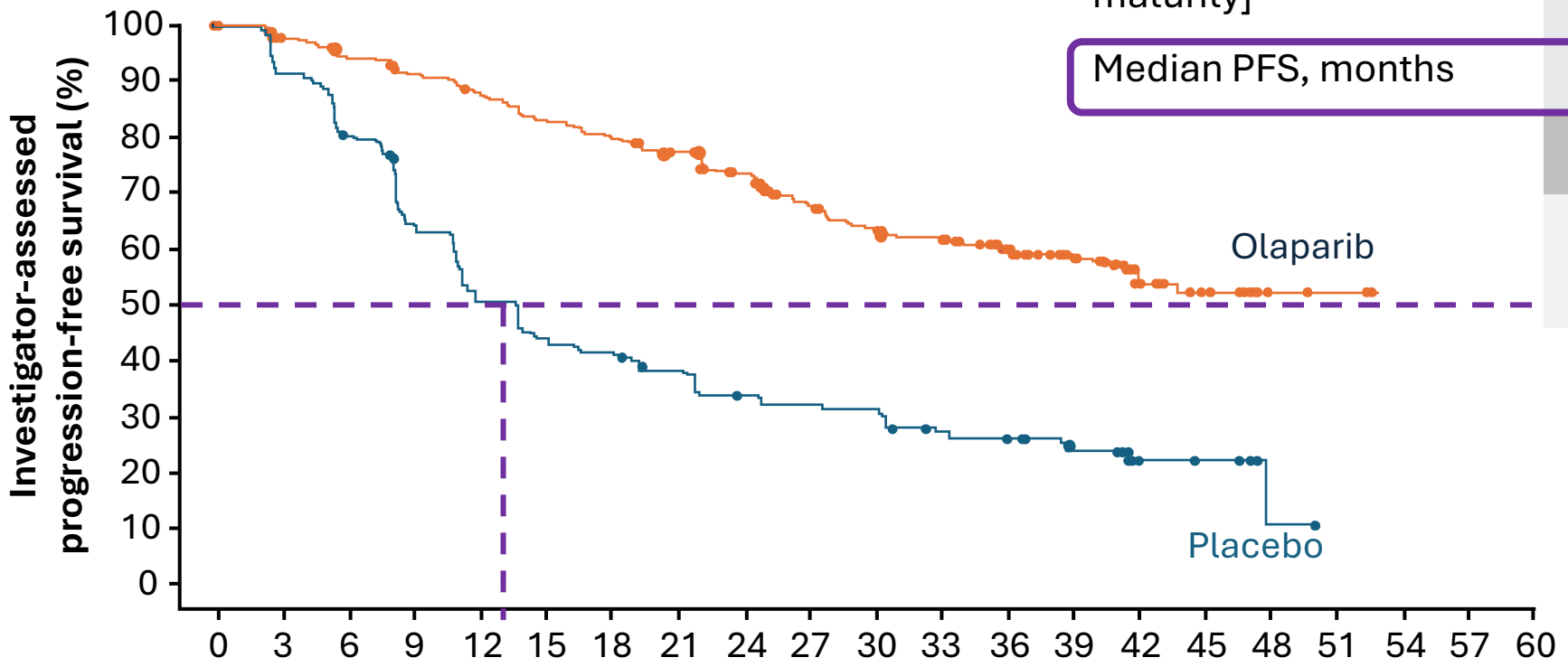
This is the **‘null hypothesis’** and with this the hazard ratio would equal 1.0

- So, if the HR is < 1.0 (say 0.70) what is the likelihood that this has occurred by chance?

- If the p value is <0.001, then there 0.1% probability, that is a 1 in a thousand chance, that the null hypothesis is correct and that this result occurred by chance
- This means that if you did the trial a thousand times, it is likely that one occasion there would be no difference
- So, you can conclude that actually there is a strong likelihood that the two results are really different!

SOLO1 trial of first-line olaparib maintenance in BRCAmut ovarian cancer

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23-0.41; *P*<0.0001		

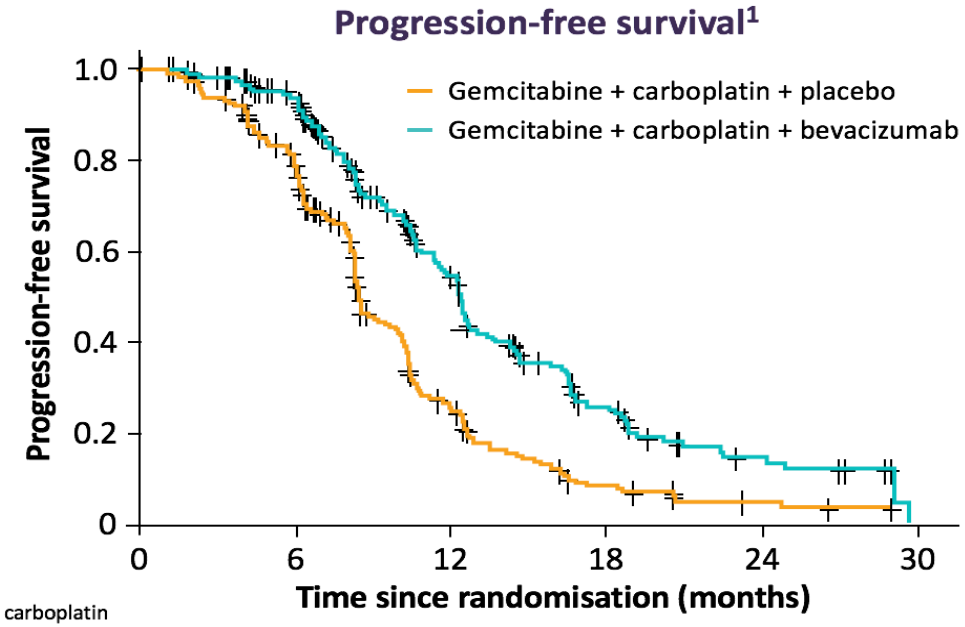


No. at risk																				
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

Moore et al ESMO 2018

CI, confidence interval; NR, not reached

OCEANS Trial Carboplatin and gemcitabine with bevacizumab or placebo in platinum-sensitive recurrent ovarian cancer



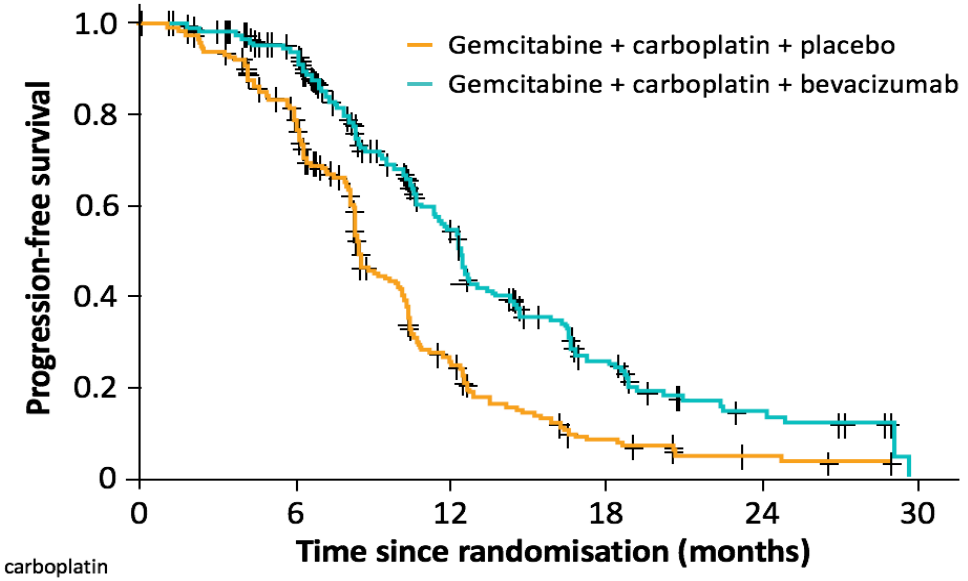
No. at risk						
Gemcitabine + carboplatin + placebo	242	177	45	11	3	0
Gemcitabine + carboplatin +bevacizumab	242	203	92	33	11	0

	Gemcitabine + carboplatin + placebo n=242*	Gemcitabine + carboplatin + bevacizumab n=242*
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Hazard ratio	0.484 (95% CI 0.388–0.605); log-rank *P*<0.0001	

An improvement in PFS does not always lead to an overall survival benefit!

OCEANS Trial Carboplatin and gemcitabine with bevacizumab or placebo in platinum-sensitive recurrent ovarian cancer

Progression-free survival[1]



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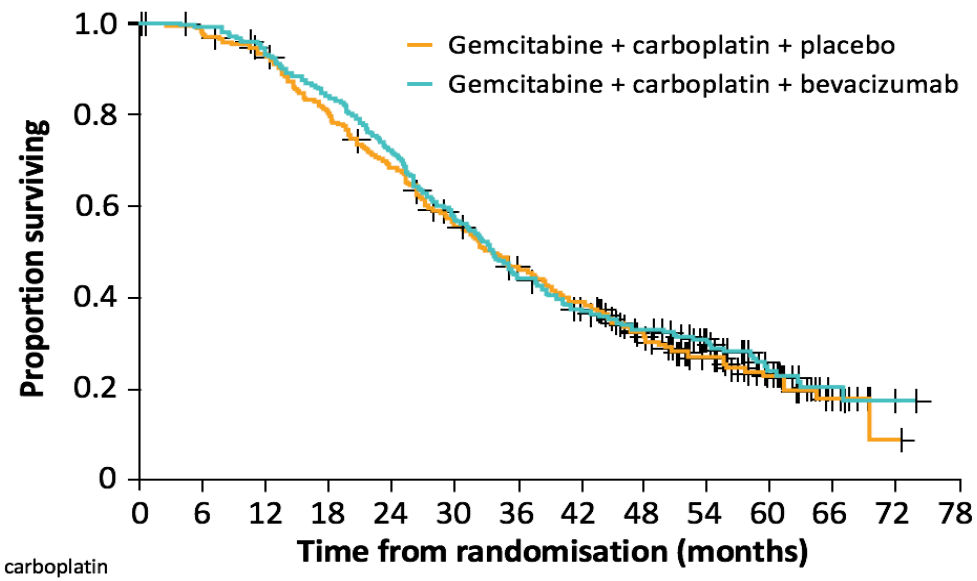
Overall survival[2]



No. at risk														
Gemcitabine + carboplatin + placebo	242	235	222	191	160	128	104	87	64	41	20	7	1	0
Gemcitabine + carboplatin +bevacizumab	242	239	226	201	172	138	105	87	68	47	25	7	1	0

	Gemcitabine + carboplatin + placebo n=242	Gemcitabine + carboplatin + bevacizumab n=242
Median OS, months	32.9	33.6
Hazard ratio	0.952 (95% CI 0.771–1.176); log-rank *P*=0.6479	

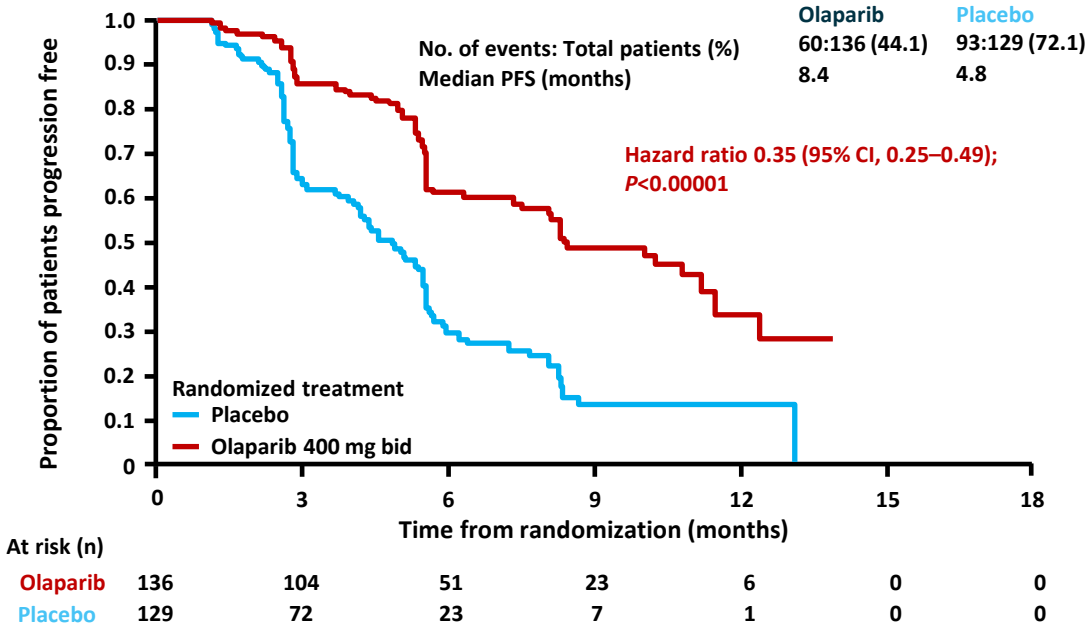
Interpreting PFS and OS results in ‘OCEANS’ trial

- **Cross-over 39%**
  (22 % had more bevacizumab on progression)

- ‘**Dilutional’ effect on OS due to multiple post progression therapies**
  post OCEANS
  - 69% (Placebo) & 68% (Beva) had **4** further lines
  - 26% (Placebo) & 36% (Beva) had **6** further lines

- **Long post progression survival** means detection of differences in OS is harder and requires a much larger sample size

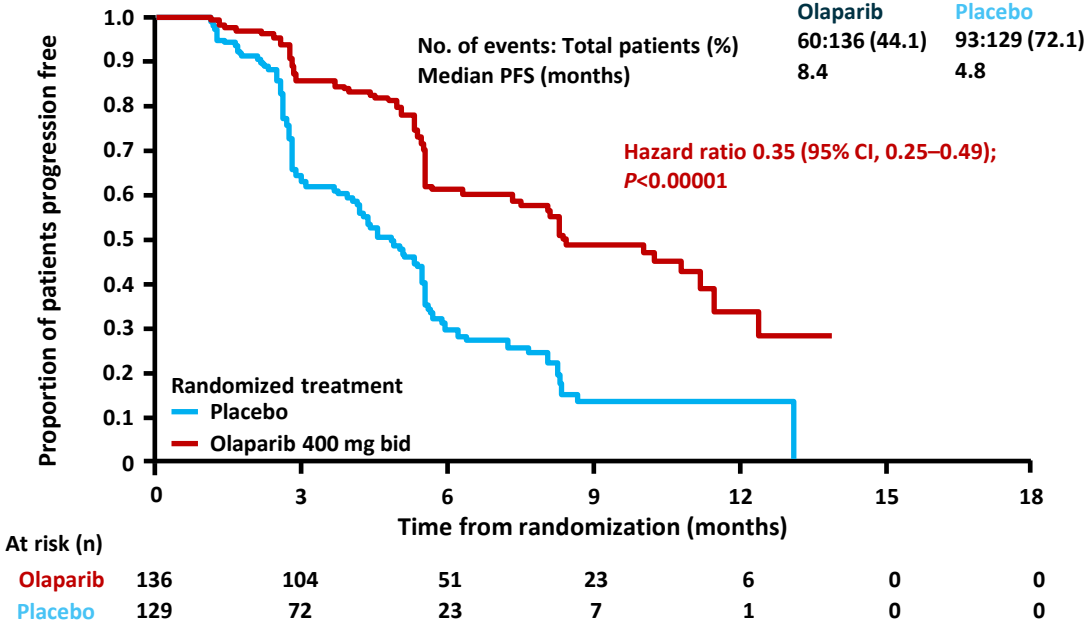
Study 19- Olaparib maintenance in patients responding to platinum-based chemotherapy for recurrent high grade serous ovarian cancer

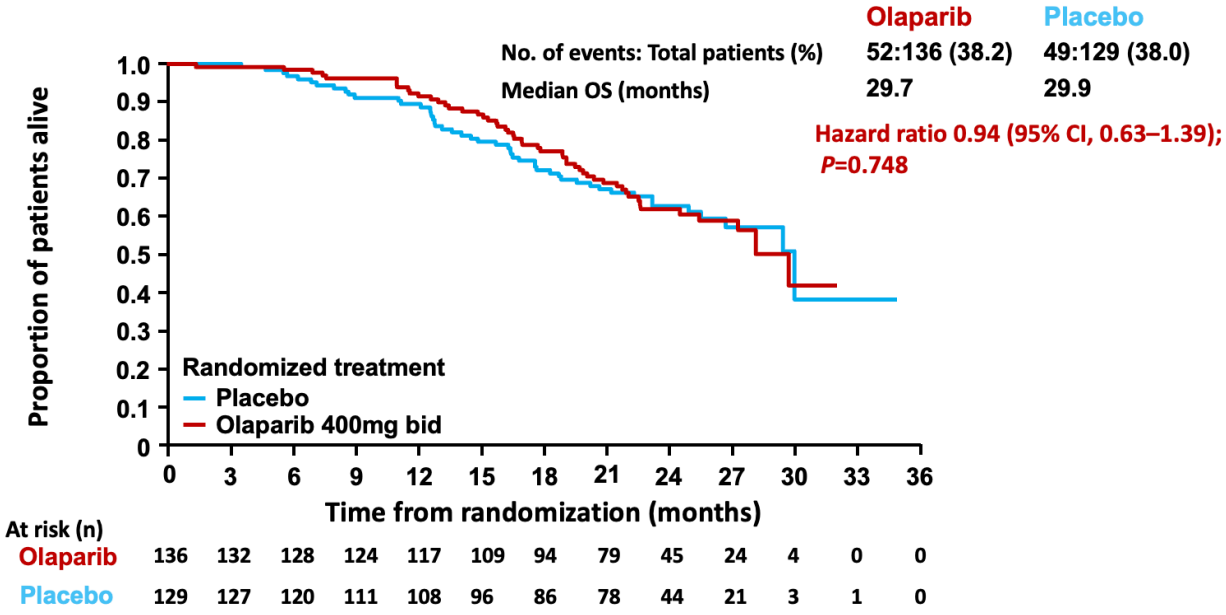


Ledermann J *et al*. *N Engl J Med* 2012;

Study 19- Olaparib maintenance in patients responding to platinum-based chemotherapy for recurrent high grade serous ovarian cancer

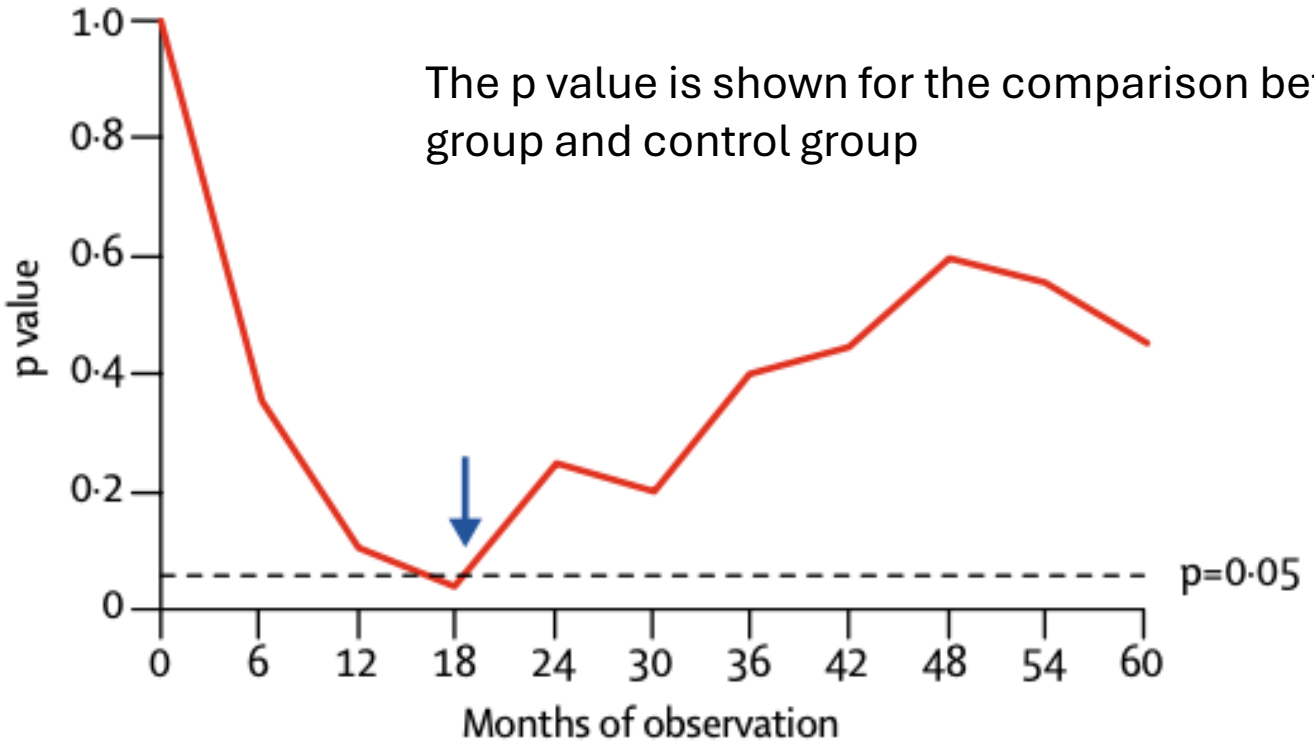
Interim overall survival performed at 38% maturity





Ledermann J *et al*. *N Engl J Med* 2012;

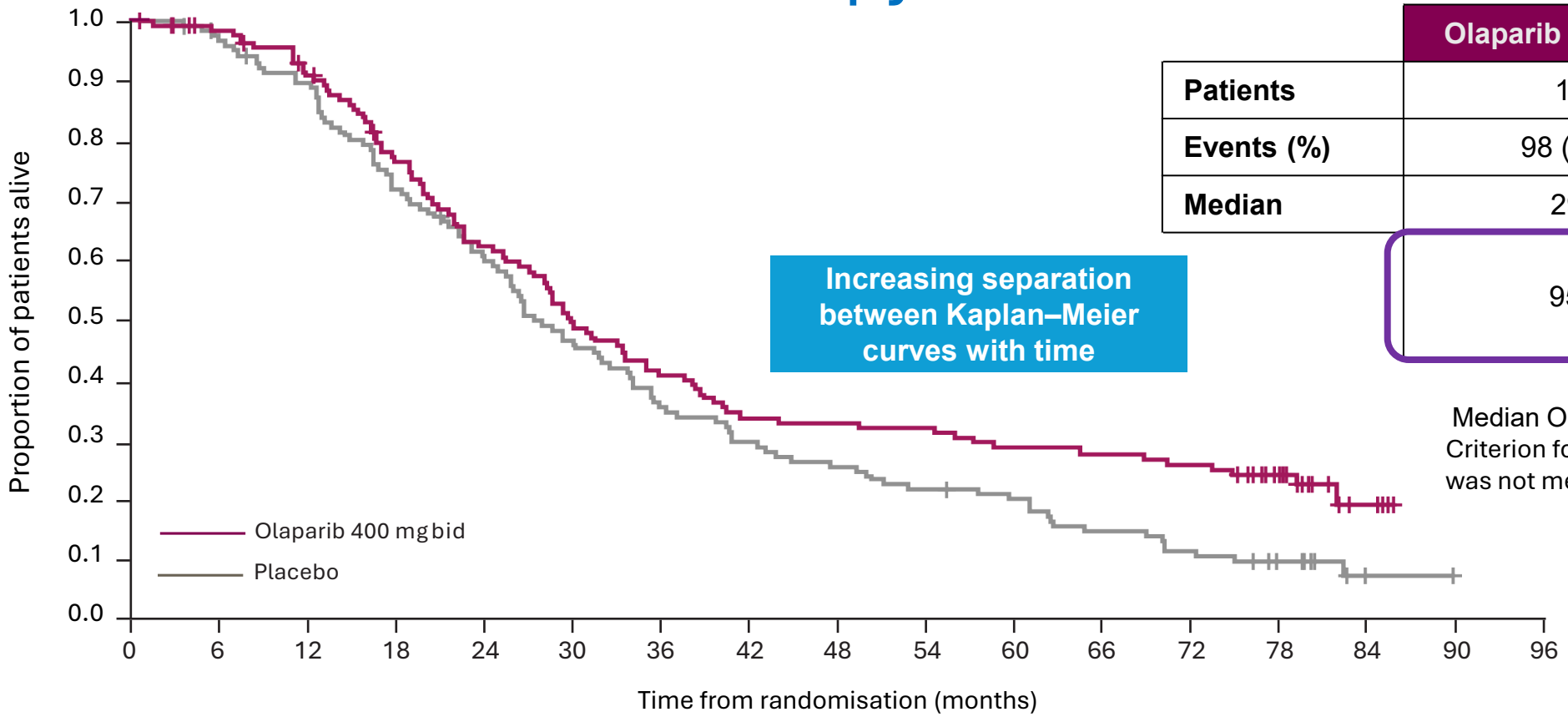
Interim Trial Analysis



The p value is shown for the comparison between the treatment group and control group

What can happen if you perform an interim analysis every 6 months for 5 years?

Final Overall survival in Study 19: Olaparib maintenance in recurrent high grade serous ovarian cancer after response to platinum-based chemotherapy



Increasing separation between Kaplan–Meier curves with time

	Olaparib 400 mg bd	Placebo
Patients	136	129
Events (%)	98 (72.1)	112 (86.8)
Median	29.8	27.8
	HR = 0.73 95% CI: (0.55–0.95); p=0.02138	

Median OS follow-up: 78.0 months
Criterion for statistical significance (*P*<0.0095) was not met.

Number of patients at risk:

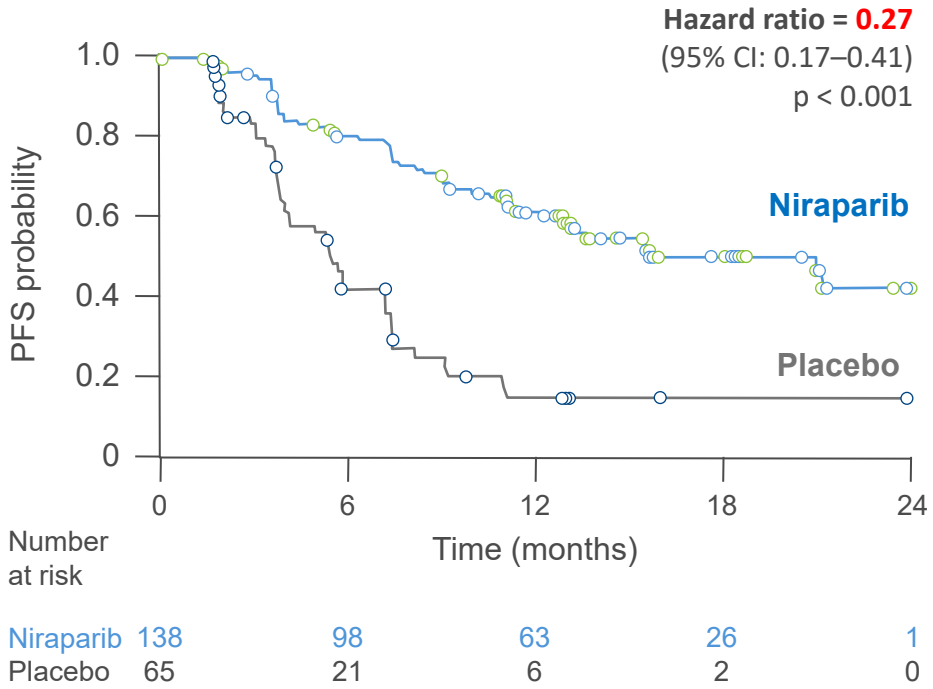
Olaparib	136	129	117	97	79	62	52	43	42	41	37	35	33	21	4	0	0
Placebo	129	122	112	90	75	57	44	37	32	27	24	18	14	9	1	0	0

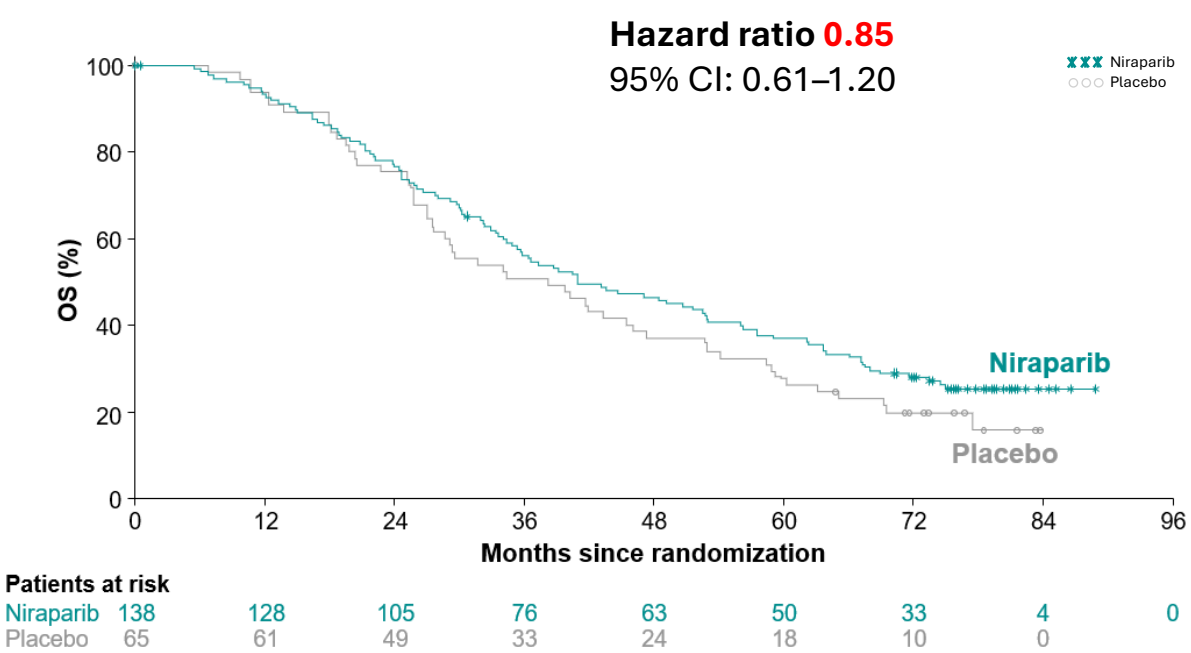
13% of placebo-receiving patients received post-discontinuation PARP inhibitor treatment in other studies

bid, twice daily. DCO: May 2016; data maturity 79%; Median FU: 78.0 months[1].

Friedlander M et al. Br J Cancer. 2018 Oct 24

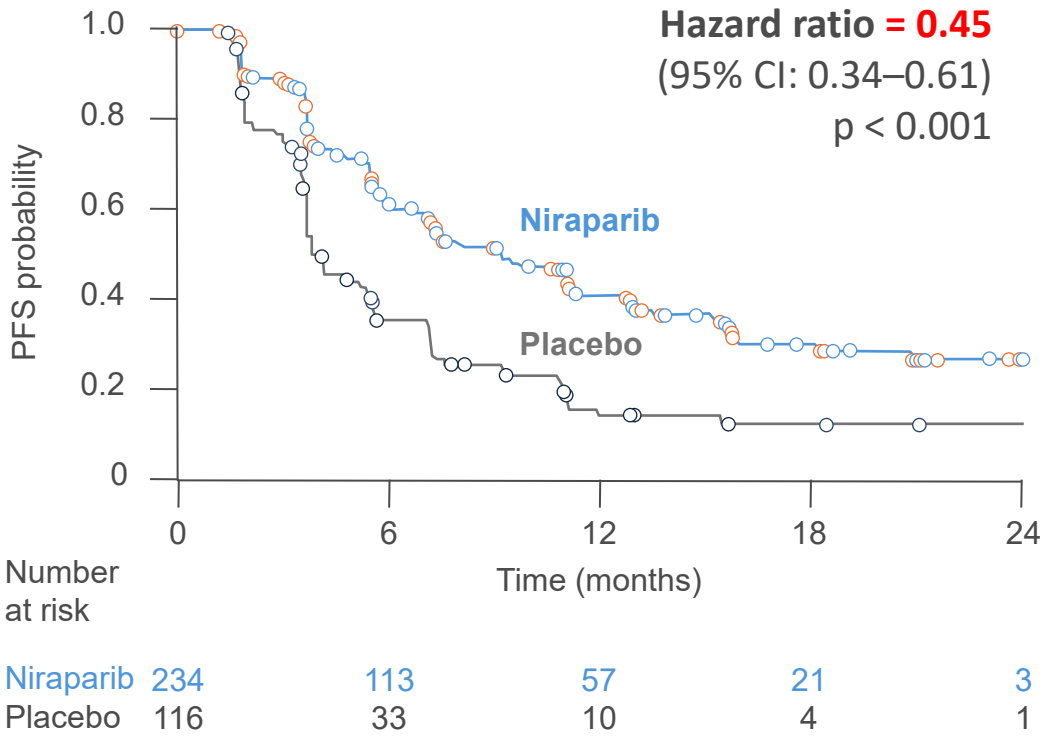
NOVA Trial Progression-Free Survival and Overall Survival in **gBRCA** Cohort

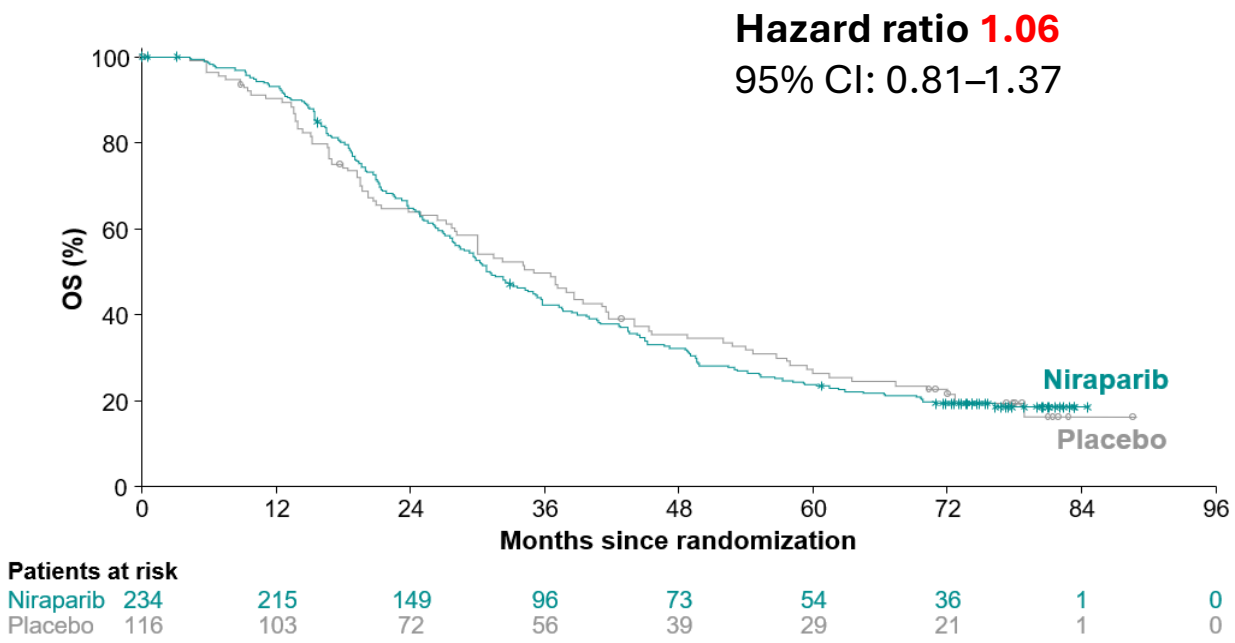




Mirza et al NEJM 2016; Matulonis et al SGO 2023

NOVA Trial Progression-Free Survival and Overall Survival in **non-gBRCA** Cohort





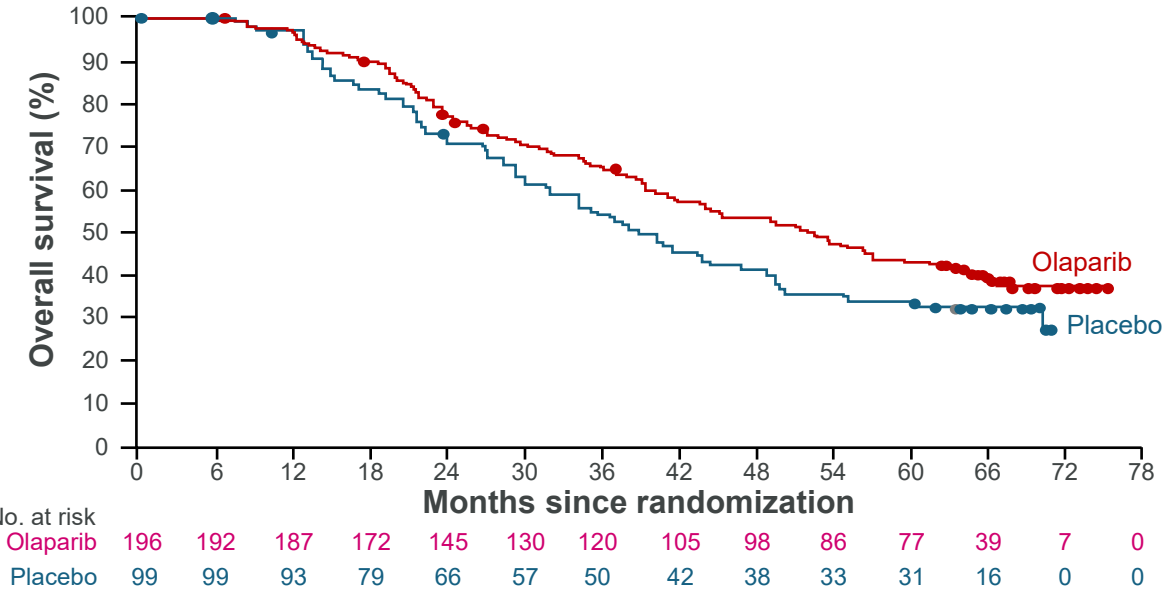
Mirza et al NEJM 2016; Matulonis et al SGO 2023

Why did this happen?

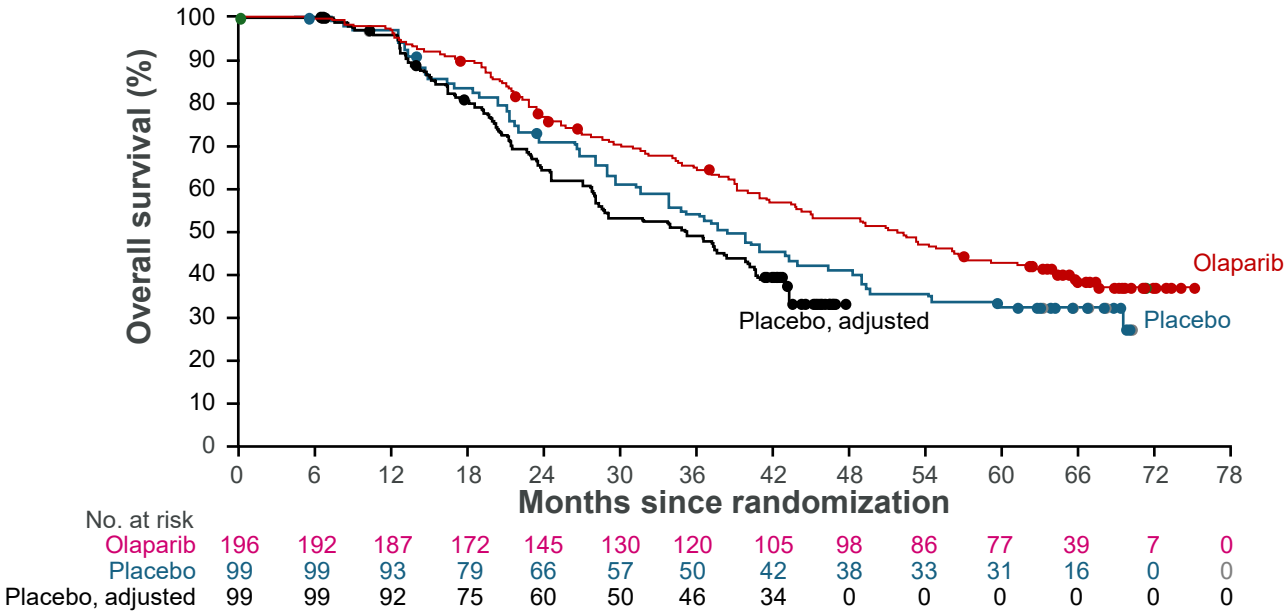
The following factors need to be considered:

1. Crossover to a PARP inhibitor in the control arm
2. Subsequent lines of treatment, often over many months, and often for a longer period than on the PARP inhibitor trial
3. Patients lost to follow up
4. Potential negative effect of a PARP inhibitor on subsequent therapy- late drug toxicity or drug resistance

Adjusting for PARP inhibitor crossover in SOLO-2- olaparib in BRCAm recurrent ovarian cancer



38% of placebo patients and 10% of olaparib patients in SOLO-2 received subsequent PARPi therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	**51.7**	**38.8**

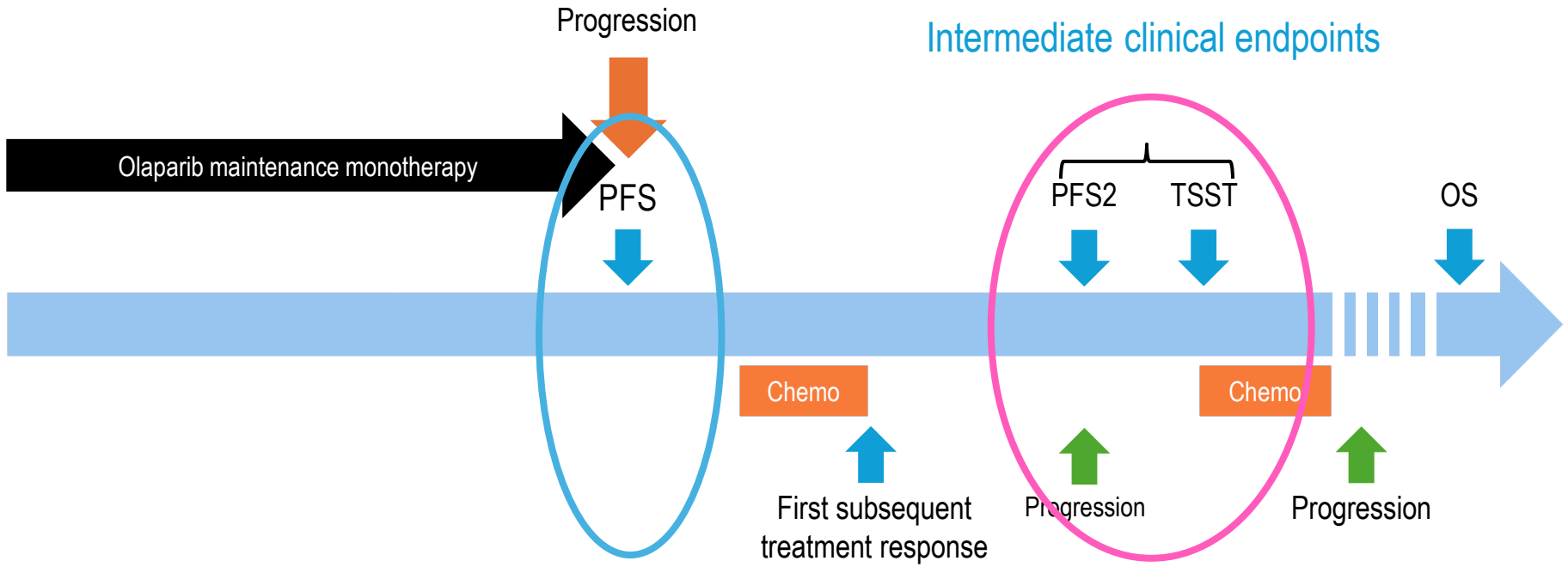
HR 0.74 (95% CI 0.54–1.00); *P*=0.0537

	Olaparib (N=196)	Placebo adjusted (N=99)
Events, n (%) [60% maturity]	116 (59)	61 (62)
Median OS, months	**51.7**	**35.4**

HR 0.56 (95% CI 0.35–0.97)

Poveda et al *Lancet Oncol* 2021;22(5):620–63

Intermediate Endpoints: **T**ime to **S**econd **S**ubsequent **T**herapy: a new exploratory endpoint

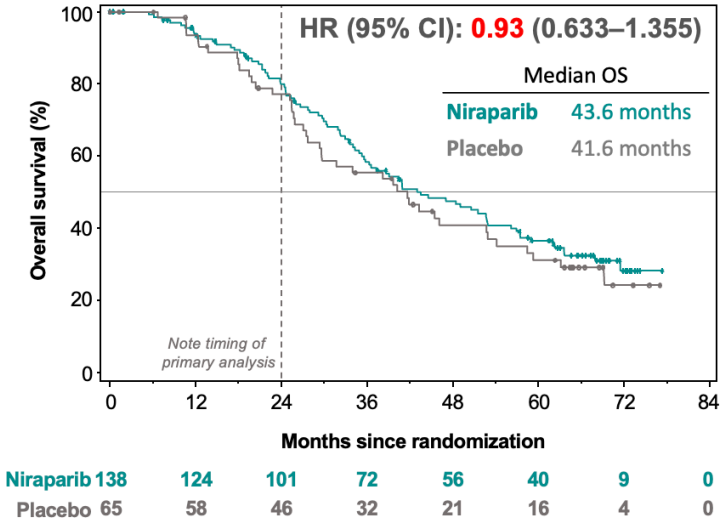


All patients who received treatment were included in exploratory endpoint analyses

*PFS2 is a surrogate for TSST

Ledermann J et al. Lancet Oncol 2014;15:852–861

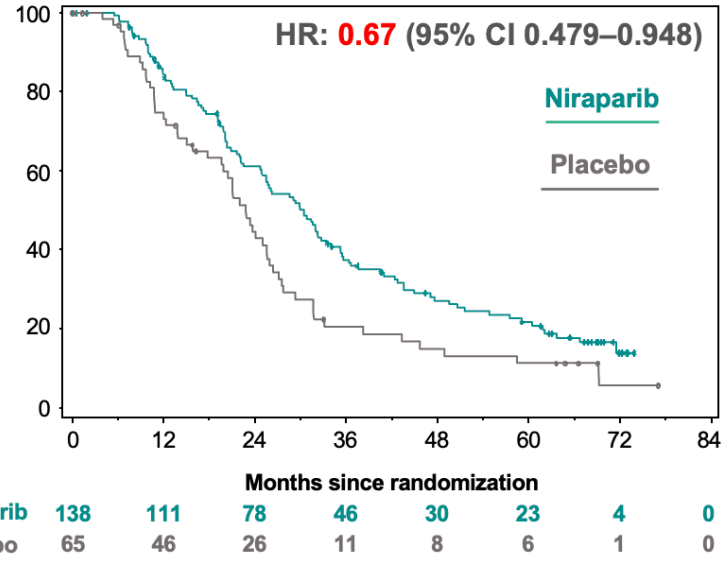
Overall Survival and Secondary Endpoint analysis (PFS2) in NOVA trial



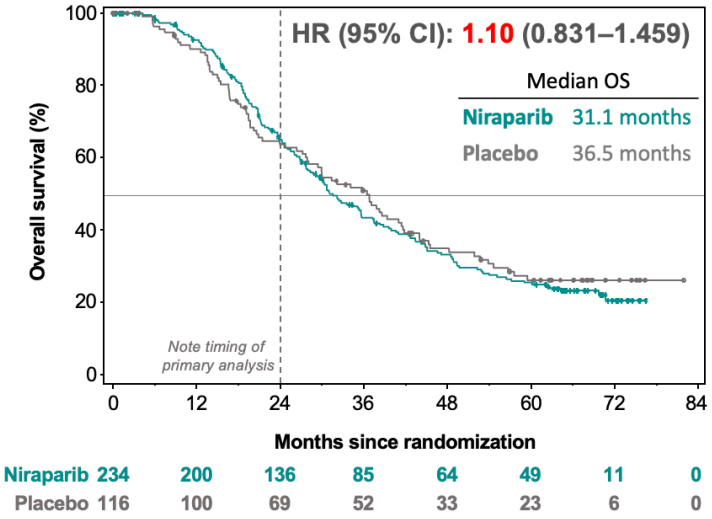
Final data cutoff date was October 1, 2020.

g*BRCA*m

OS → **PFS2**

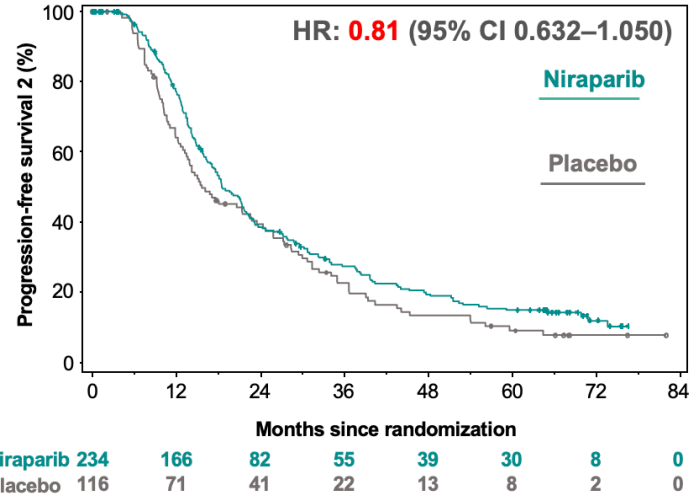


Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months).
PFS2 was measured from the time of randomization to progression on subsequent chemotherapy.



Non-g*BRCA*m

OS → **PFS2**



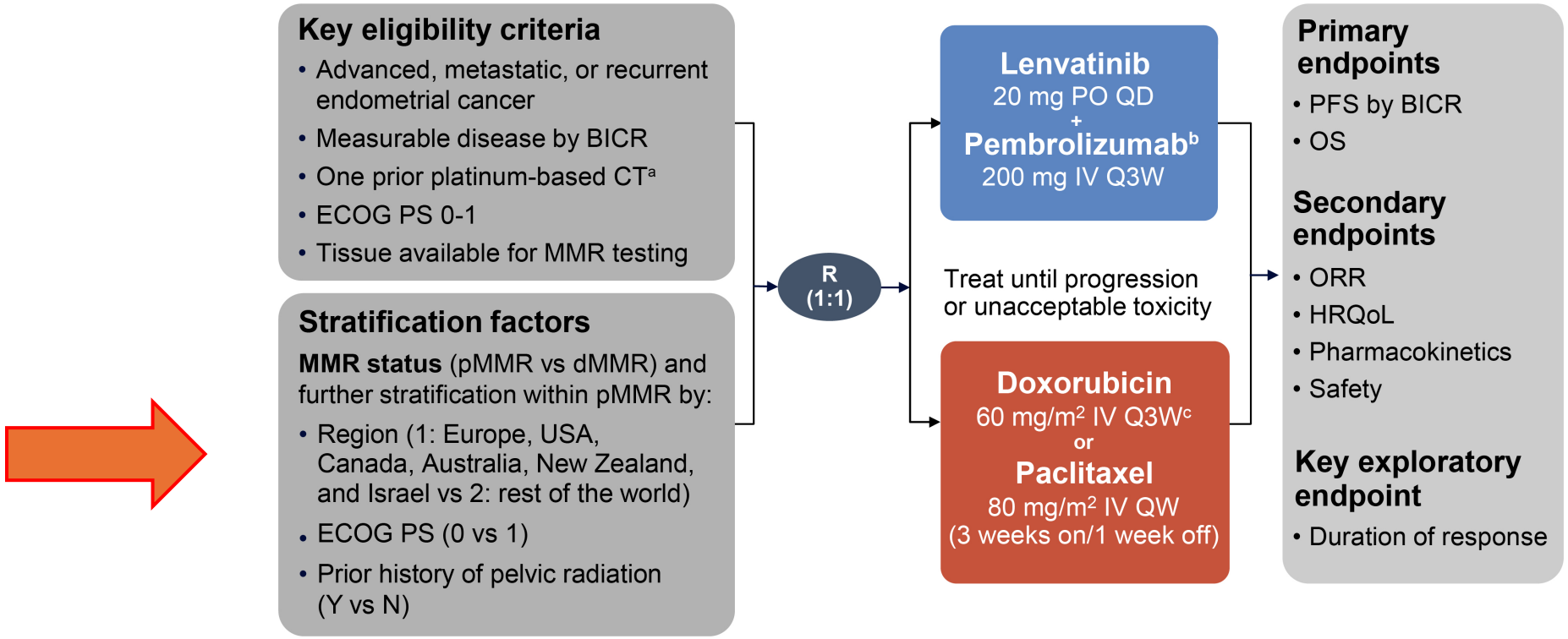
Matulonis et al SGO 2021

Stratification and Subgroup analysis

- Ensures balance between important variables
- Allows for **pre-planned** subgroup analysis. Examples include:
  - HRD +ve vs HRD -ve groups
  - Stage III v Stage IV
  - Complete vs partial responses to chemotherapy
  - MMRd v pMMR

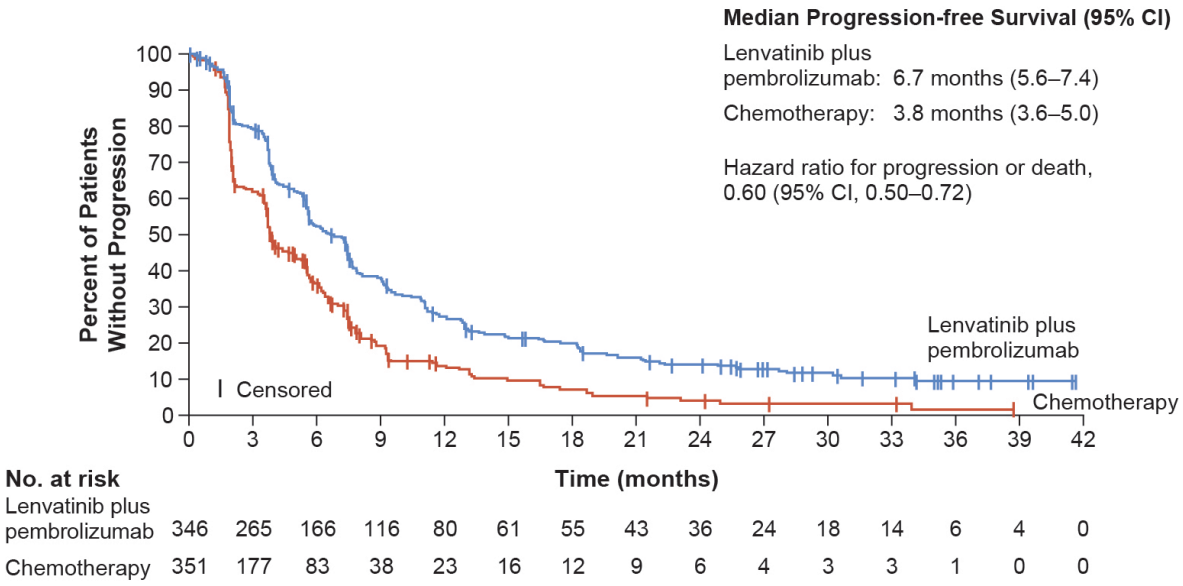
Subgroup analysis

KEYNOTE 775: Combining Lenvatinib and pembrolizumab in Endometrial Cancer after platinum failure

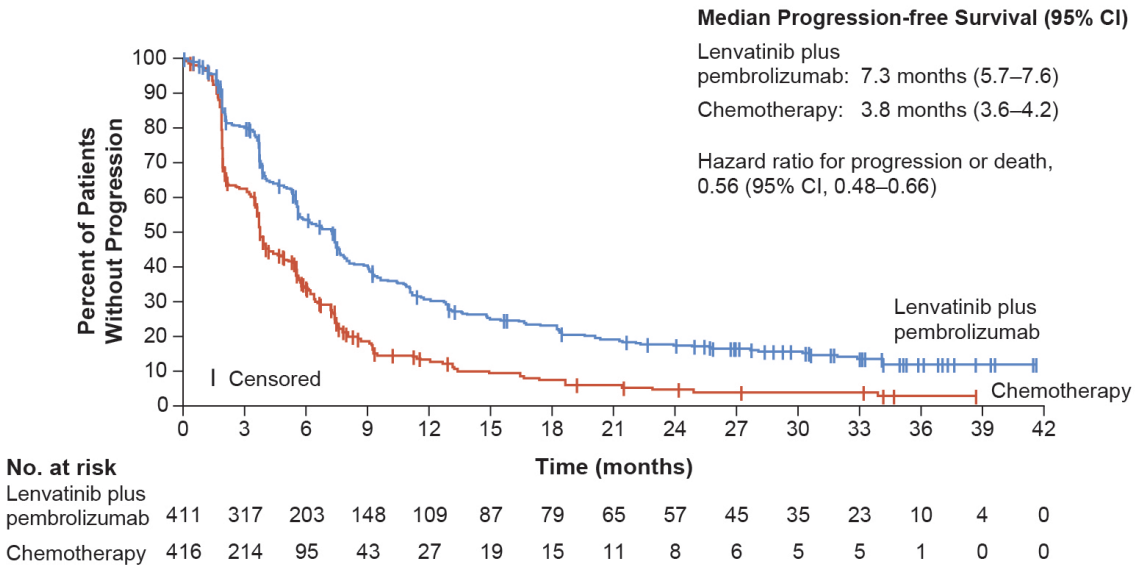


Continued PFS benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

pMMR Population



All-Comer Population



Makker et al ESMO 2022

Randomised trials are not always needed

- Pembrolizumab KEYNOTE 158
- Dostarlimab GARNET Trials

Two studies in recurrent Endometrial Cancer driven by biomarkers

KEYNOTE-158: Single-arm phase II trial of Pembrolizumab in MSI-H (dMMR) recurrent Endometrial Cancer

STUDY DESIGN[1]

Open-label, multi-cohort (non-colorectal), Phase 2 basket trial

- Selected for MSI-H status

Patients with advanced endometrial cancer

- **MSI-H by PCR or IHC**
- Progression after ≥1 standard therapy
- Measurable disease
- ECOG PS of 0 or 1

(N=49)

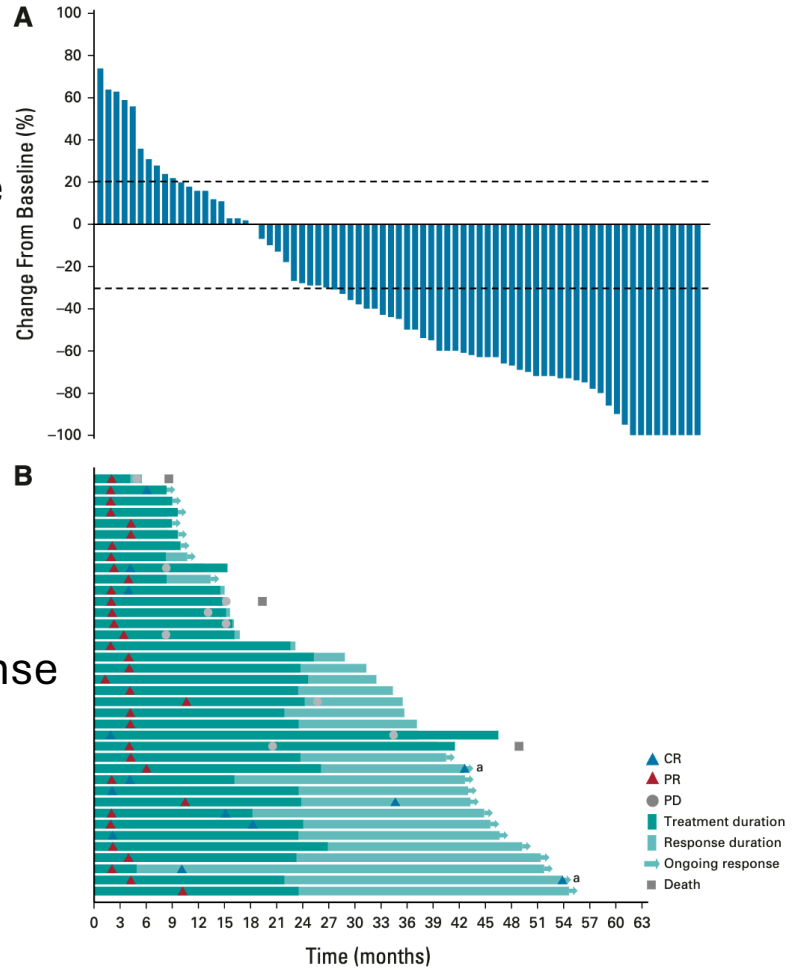
→ **Pembrolizumab** 200 mg every 3 weeks →

Up to 24 months (35 cycles), or until PD or unacceptable toxicity

Primary endpoint: ORR by ICR
Secondary endpoints: DoR, PFS, OS, safety

RECIST Response

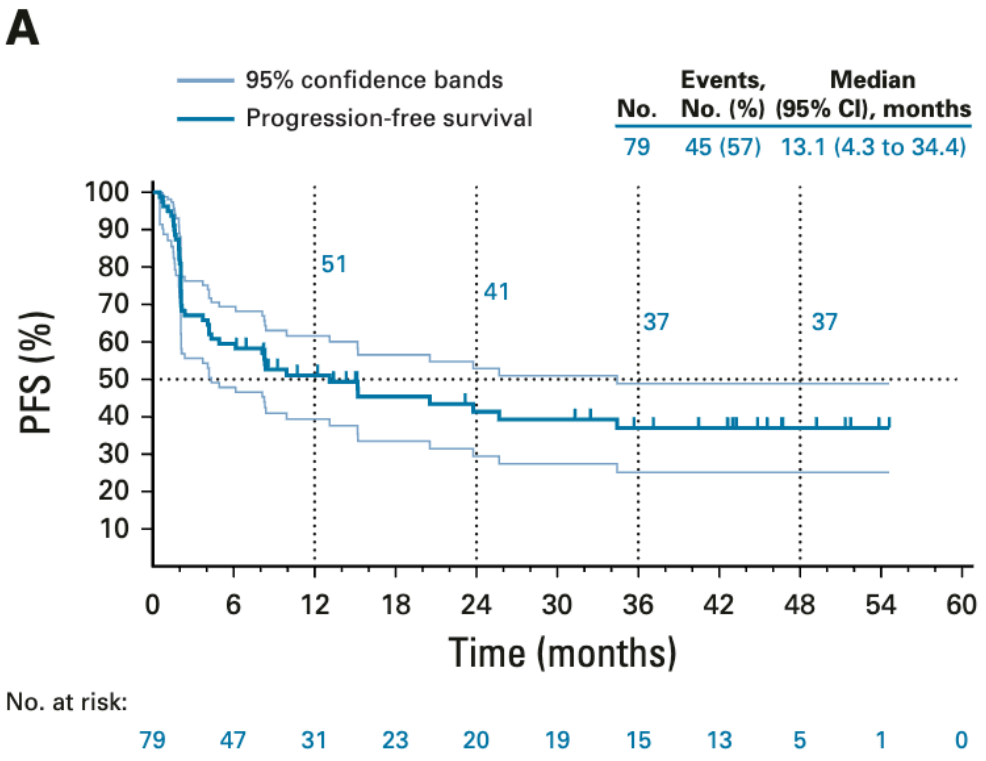
Duration of Response



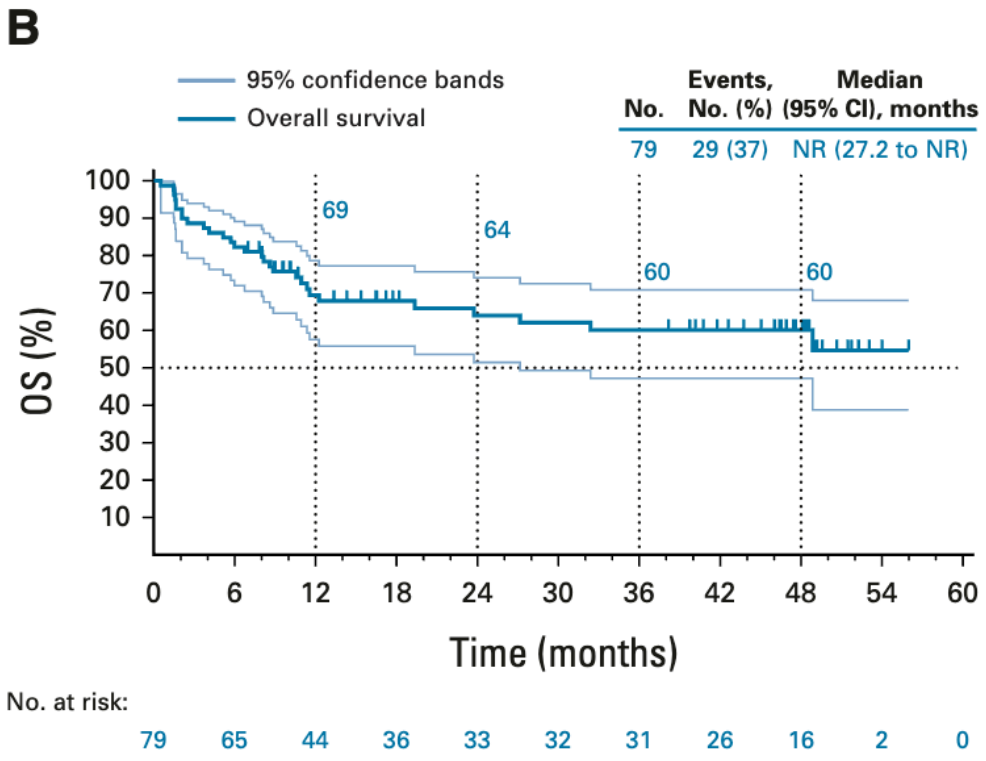
O'Malley et al J Clin Oncol 2022

Keynote 158: Final Results of Pembrolizumab in Recurrent MSI-H Endometrial Cancer- a single-arm phase II trial

Progression-Free Survival



Overall Survival



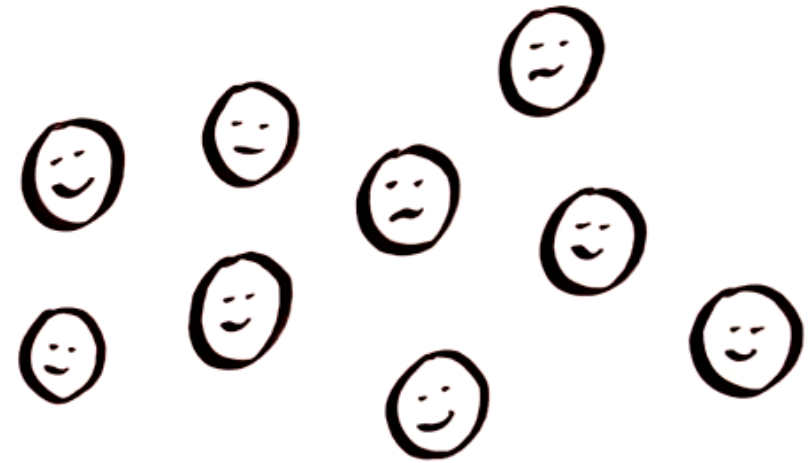
O'Malley et al J Clin Oncol 2022

CLINICAL TRIAL

"TREATMENT X"

SAFE?

EFFECTIVE?



APPROVED
REGULATED
EVALUATED

BY THE U.S.

FDA


Thank you