Hormone therapy in metastatic ER+/HER2- breast cancer

Which sequence in 2017?

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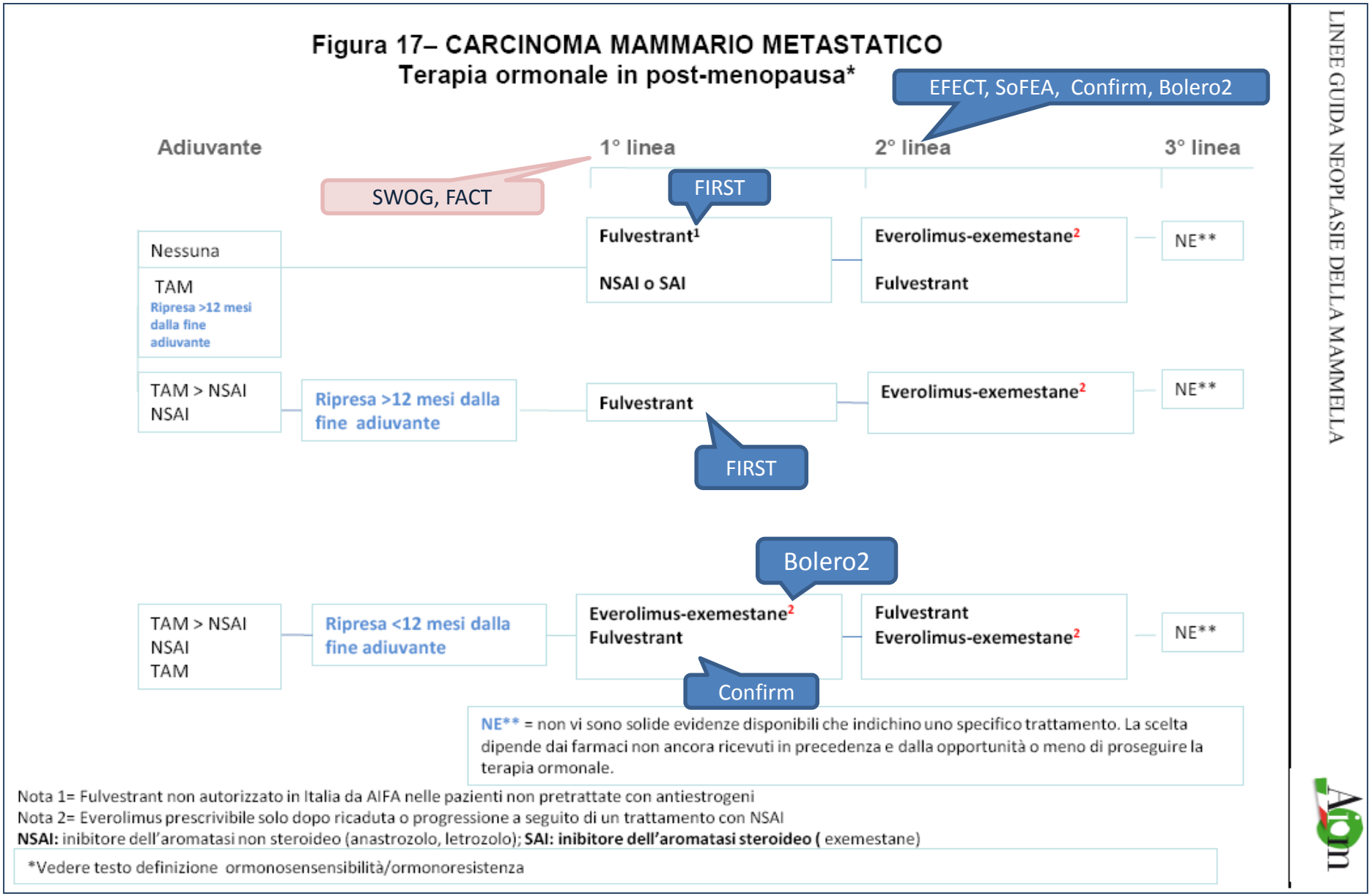
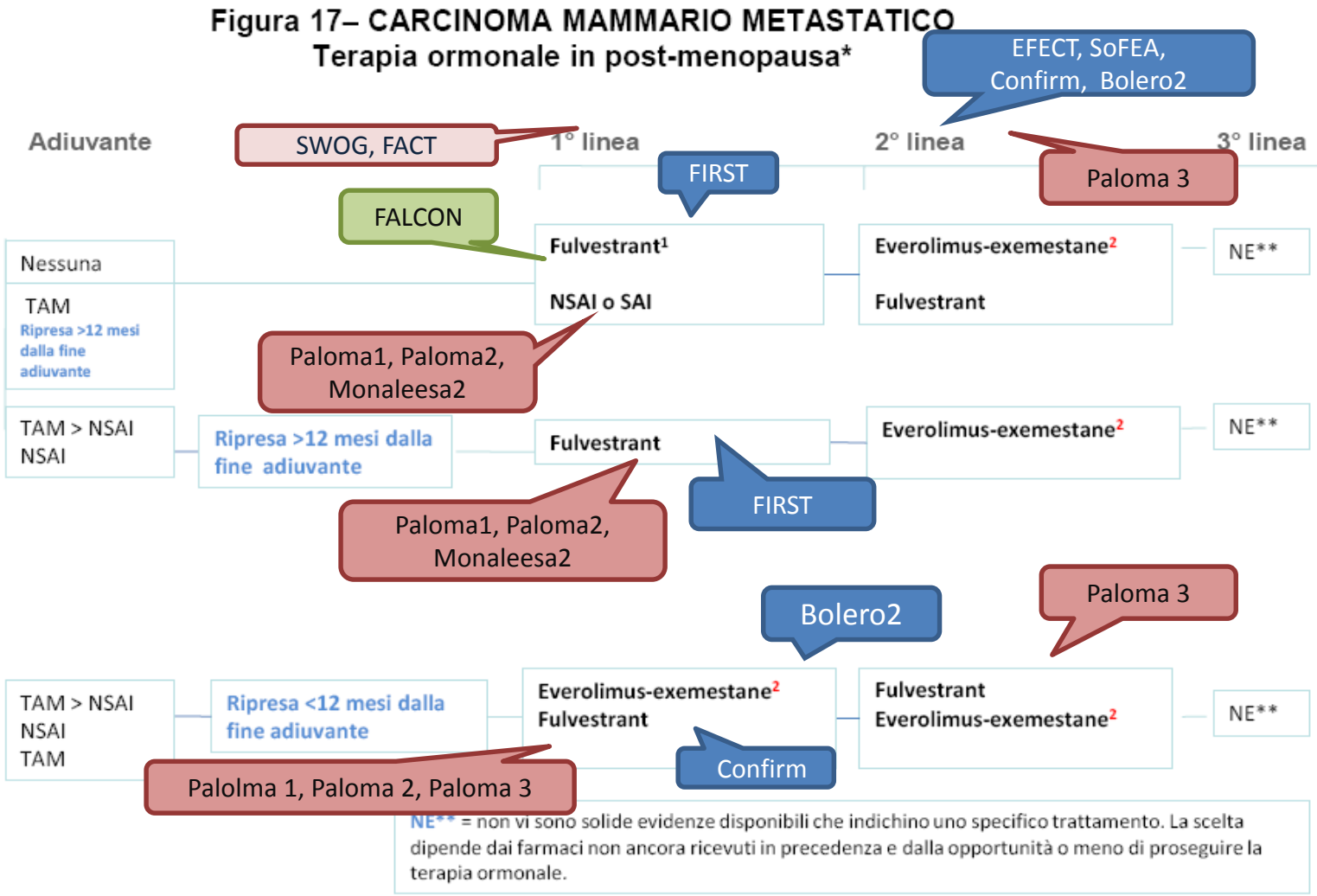
DA SEICENTO ANNI GUARDIAMO AVANTI.

Evidences for treatment sequences for 2016 GL



Evidences for treatment sequences for **2017** GL

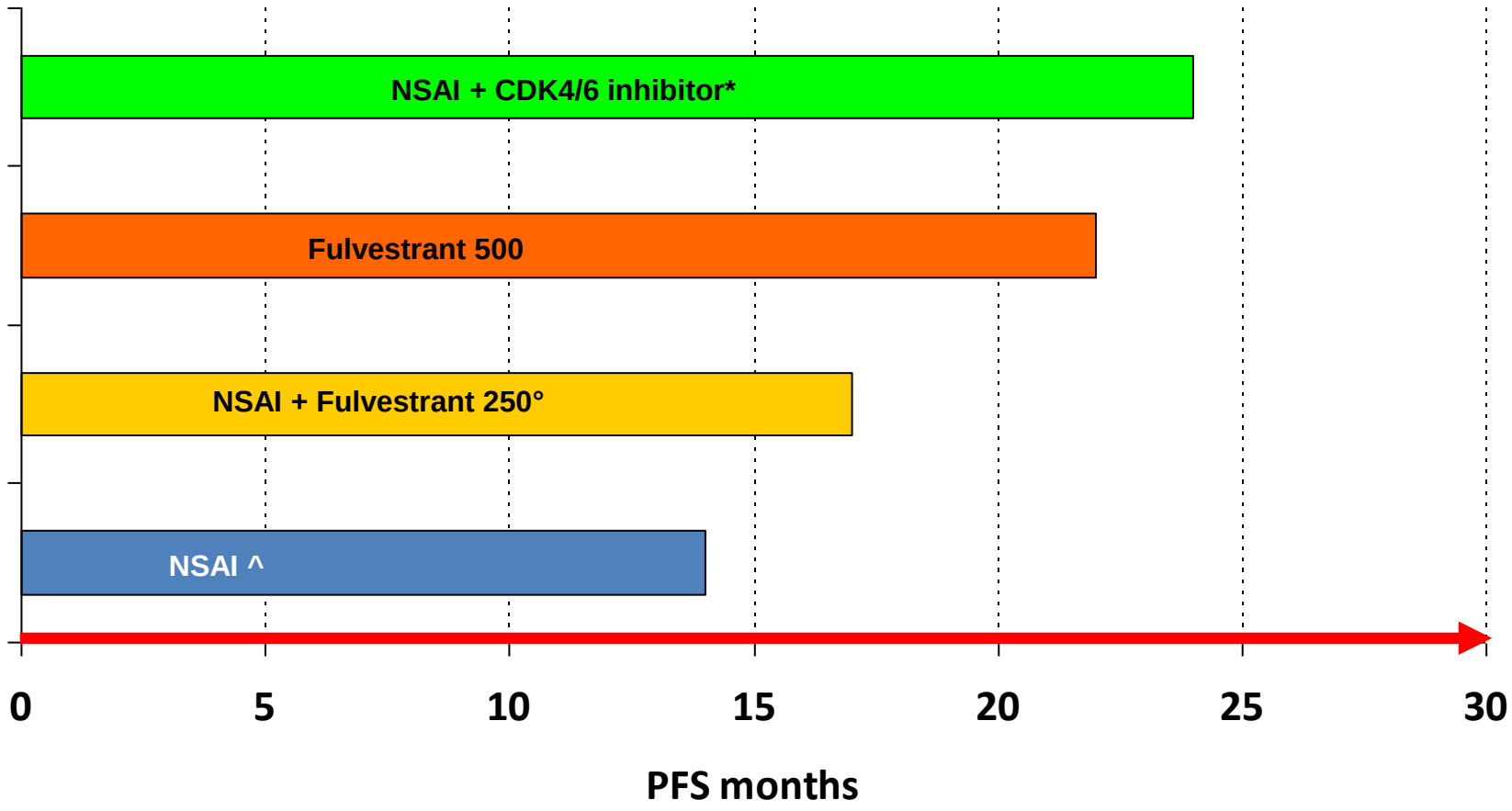


Trials in first line hormone-sensitive ABC

Trial	Design	Pts (Rand)	Treatments	Effect on PFS (primary endpoint)	Effect on OS
First	PhII	205 (1:1)	Ful500 vs Ana	**23.4 vs 13.1** **HR 0.66**	54.1 vs 48.4 HR 0.70
Falcon	Ph III	462 (1:1)	Ful500 vs Ana	**16.6 vs 13.9** **HR 0.79**	N.A. (31% maturity)
FACT	PhIII	514 (1:1)	Ful250+Ana vs Ana	**10.8 vs 10.2 *** **HR 0.99**	37.8 vs 38.2 HR 1.0
Swog0226	PhIII	694 (1:1)	Ful250+Ana vs Ana	**15 vs 13.5** **HR 0.80**	47.7 vs 41.3 HR 0.81
Paloma 1	Ph II	165 (1.1)	Let+Palb vs Let	**20.2 vs 10.2** **HR 0.48**	37.5 vs 33.3 HR 0.81
Paloma 2	Ph III	666 (2:1)	Let+Palb vs Let	**24.8 vs 14.5** **HR 0.58**	N.A. (immature data)
Monaleesa 2	Ph III	668 (1:1)	Let+Ribo vs Let	**NR vs 14.7** **HR 0.56**	N.A. (immature data)

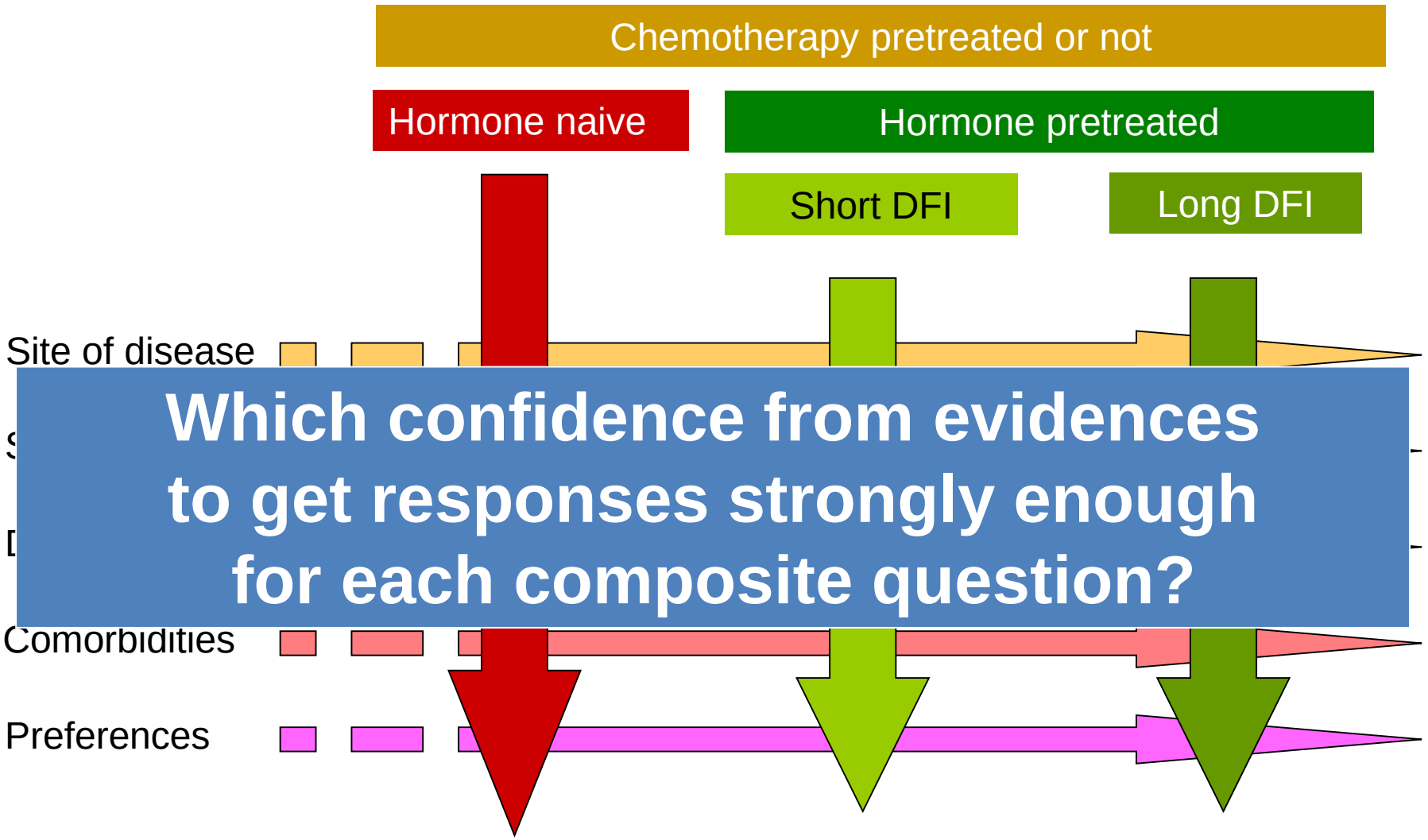
* TTP

Which effect, as a mean, can we expect from therapies in first line H-sensitive ABC



* Bar refers to Letro+Palbociclib; for ribociclib, median PFS not reached at 15.3 mos median FU; ° bar refers to the cohort untreated with tamoxifen; ^ bar refers to median results of control arm from different trials

What would we get from evidences to support clinical decision in first and subsequent lines?



Which confidence from evidences to get responses strongly enough for each composite question?

Trials in first line hormone sensitive ABC have been not created equally

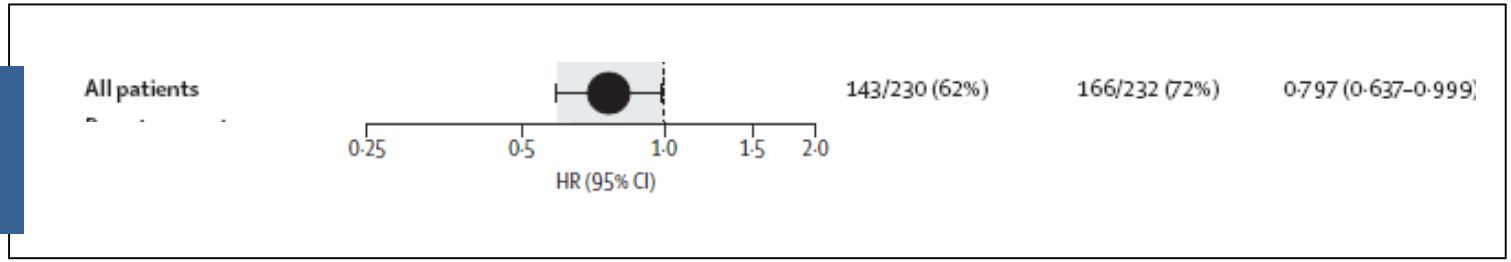
Trial	Treatments	Pts (Rand)	Hormone Naive %	Early relapse % (<12 mos*)	Late relapse % (>12 mos)	% Visceral vs bone only
First	Ful500 vs Ana	205 (1:1)	**74**	**0**	**28**	**48 vs 10**
Falcon	Ful500 vs Ana	462 (1:1)	**100**	**0**	**0**	**55 vs 10**
FACT	Ful250+Ana vs Ana	514 (1:1)	**32**	**31**	**31**	**50 vs 25**
Swog0226	Ful250+Ana vs Ana	694 (1:1)	**60**	**n.r.**	**n.r.**	**48 vs 22**
Paloma 1	Let+Palb vs Let	165 (1.1)	**52**	**17**	**31**	**49 vs 18**
Paloma 2	Let+Palb vs Let	666 (2:1)	**44**	**0**	**56**	**49 vs 22**
Monaleesa 2	Let+Ribo vs Let	668 (1:1)	**48**	**1**	**51**	**59 vs 22**

NR: not reported; * during or within 12 months from the end of adjuvant hormones

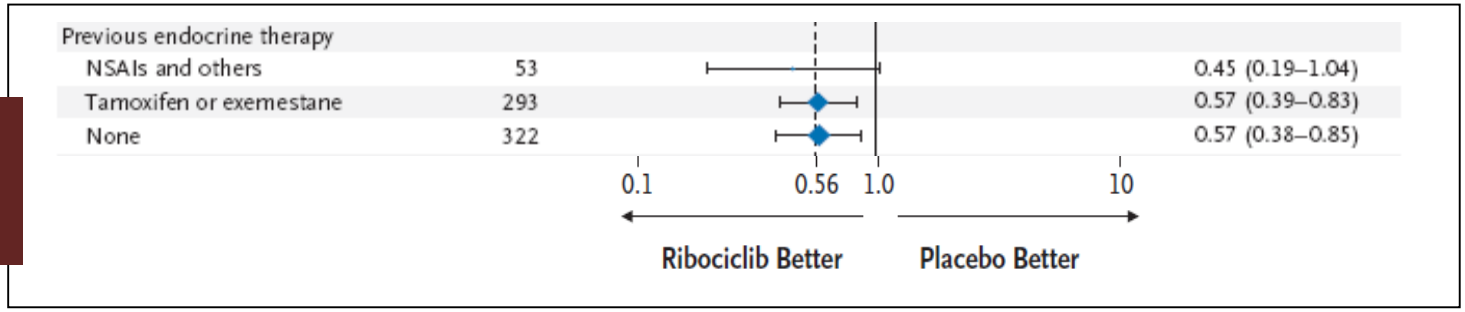
Hormone-naive

- Overall, Fulv500 (± ANA) is superior to ANA, and CDK4/6 inhibitors + LET are superior to LET

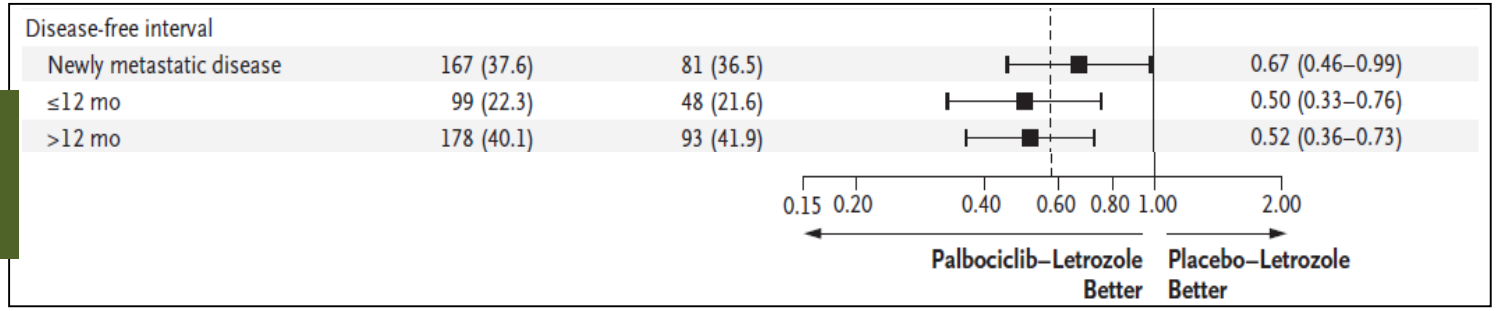
Falcon
(99% of the trial population)



Monaleesa 2
(48% of the trial population)



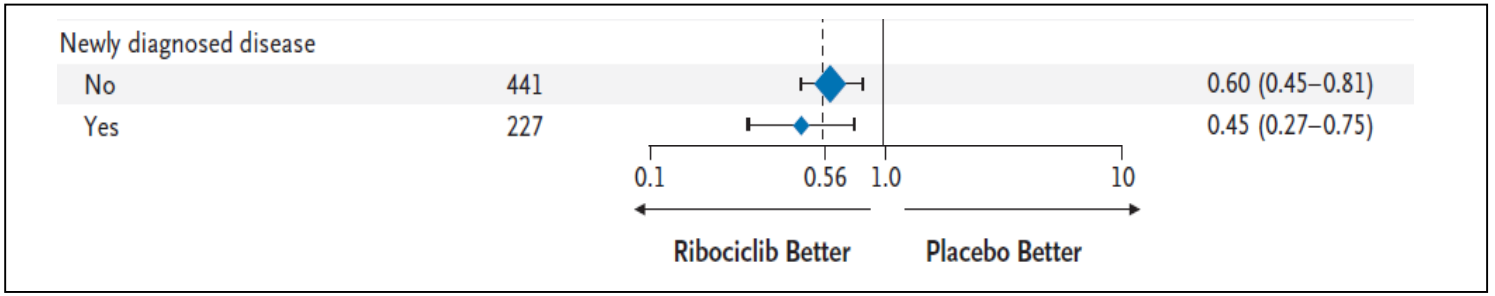
Paloma2
(44% of the trial population)



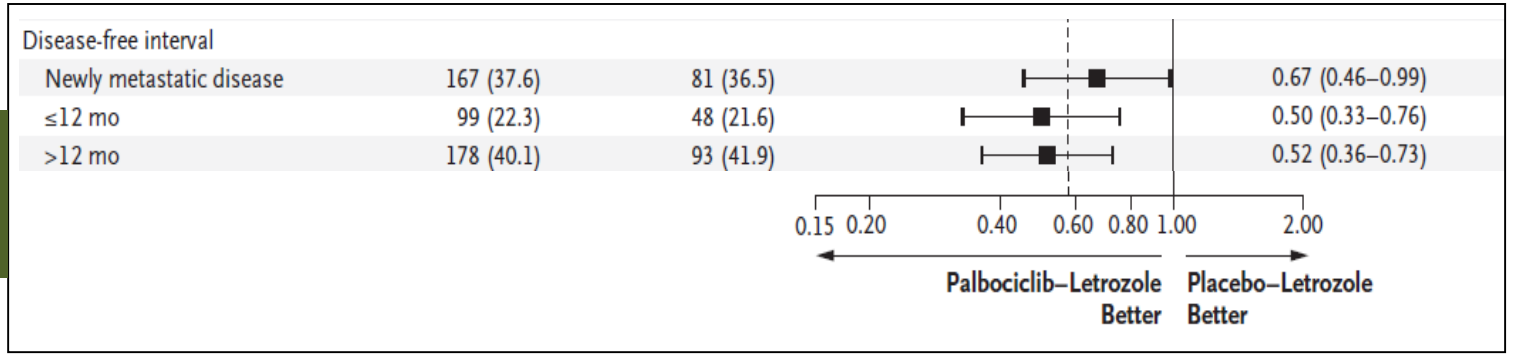
Late relapse (DFI >12 months)(?)

- Overall, Let + CDK4/6 inhibitors are superior to Let alone

Monaleesa 2
(65% of the trial population)



Paloma 2
(40% of the trial population)

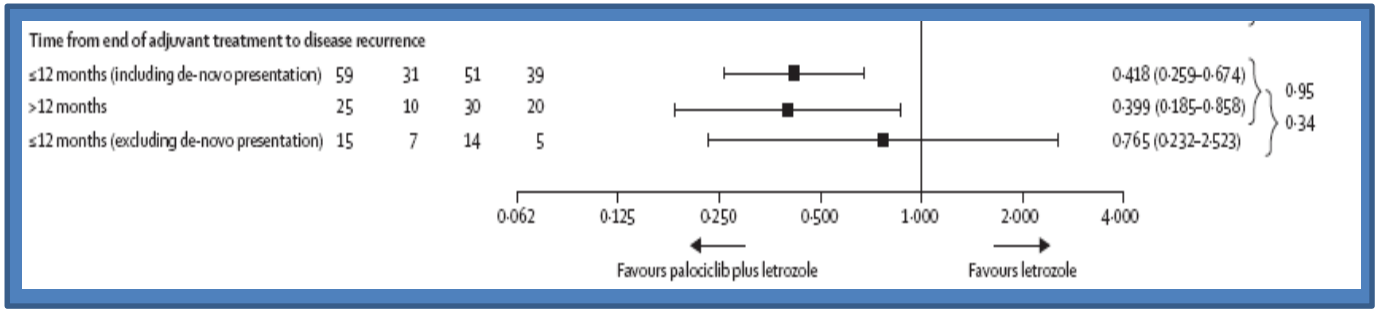


Results form Falcon might be also considered for (very) late relapse, if we would consider this condition biologically similar to hormone-naive state

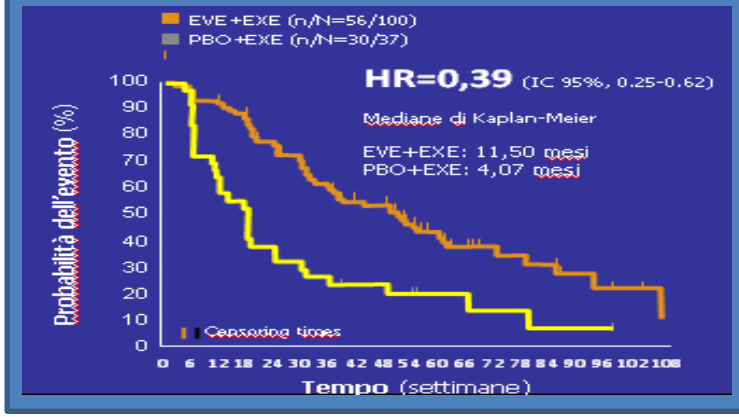
Early relapse (DFI < 12 months)(?)

- Hormone-sensitivity doubtful
- Limited number of patiens from 1° line RCTs

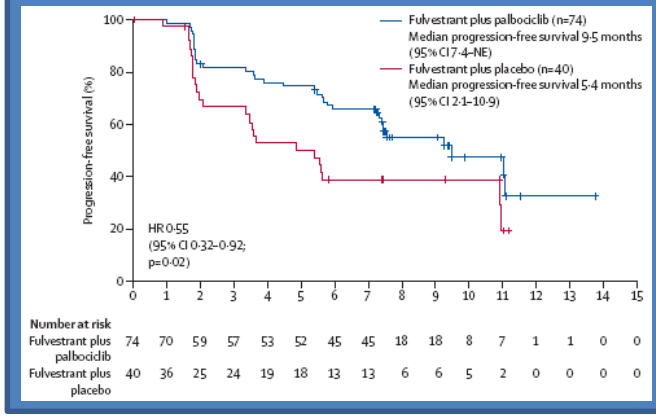
Paloma1
(17% of trial population)



- Some data derived from 2° line RCTs



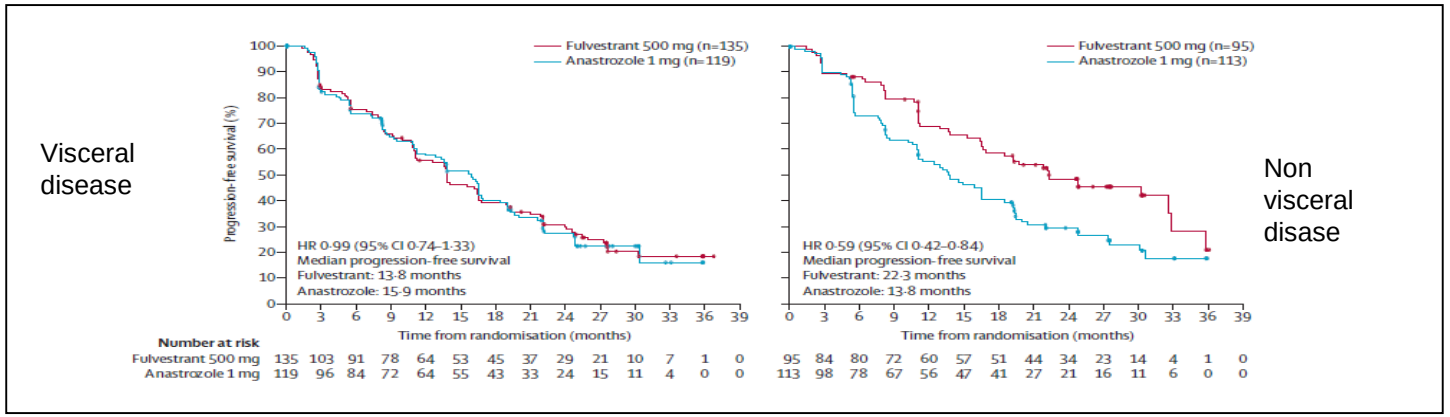
Bolero 2
(19% of trial population in first line)



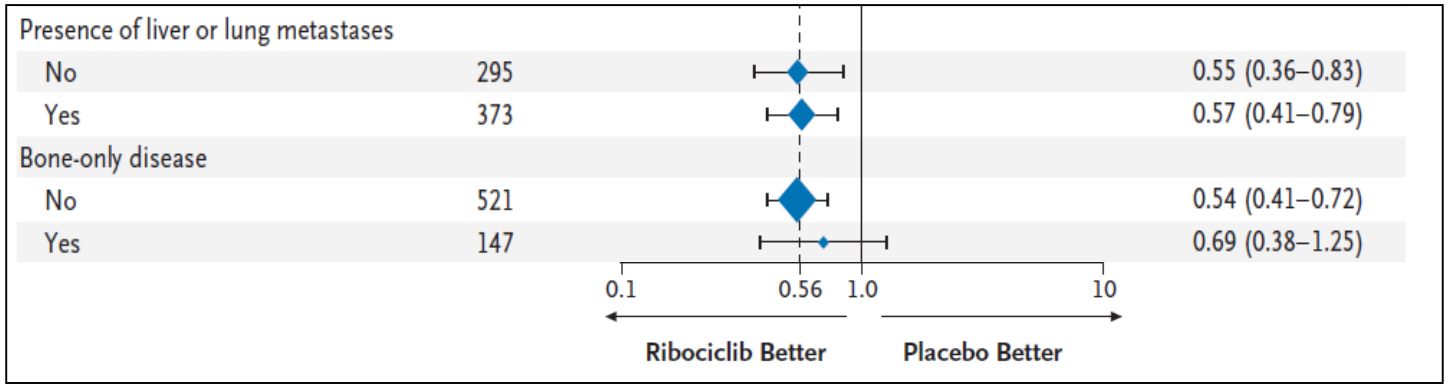
Paloma 3
(21% of trial population in first line)

Visceral or non visceral disease

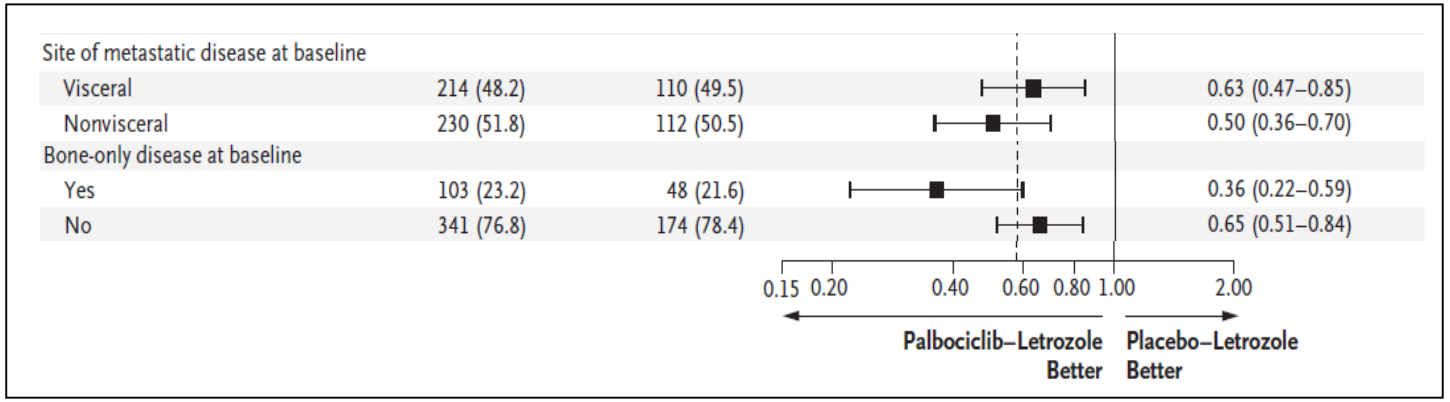
Falcon
(bone only 21% of non visceral)



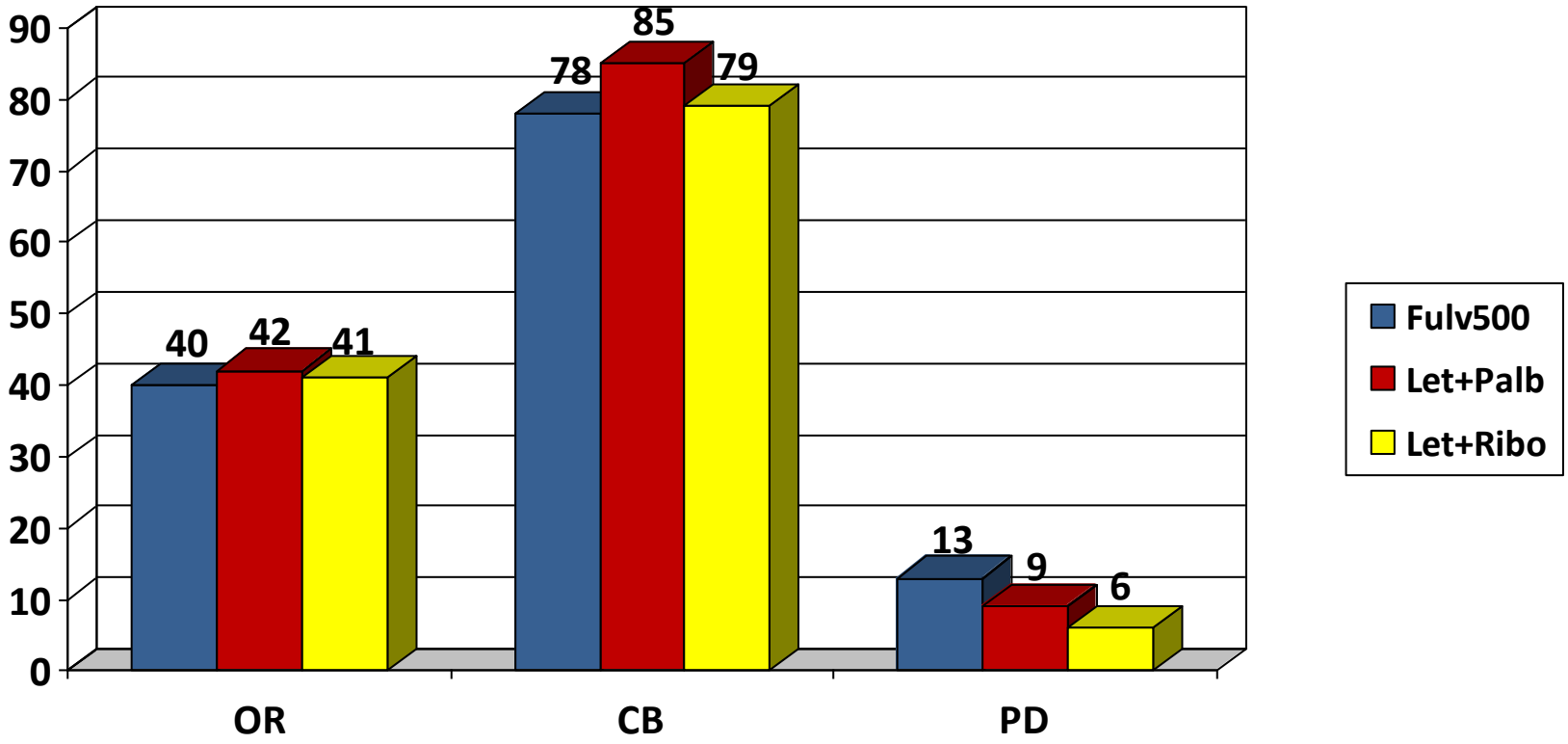
Monaleesa 2
(bone only 22% of trial population)



Paloma 2
(bone only 22% of trial population)



What can we expect form different treatments in terms of Response?

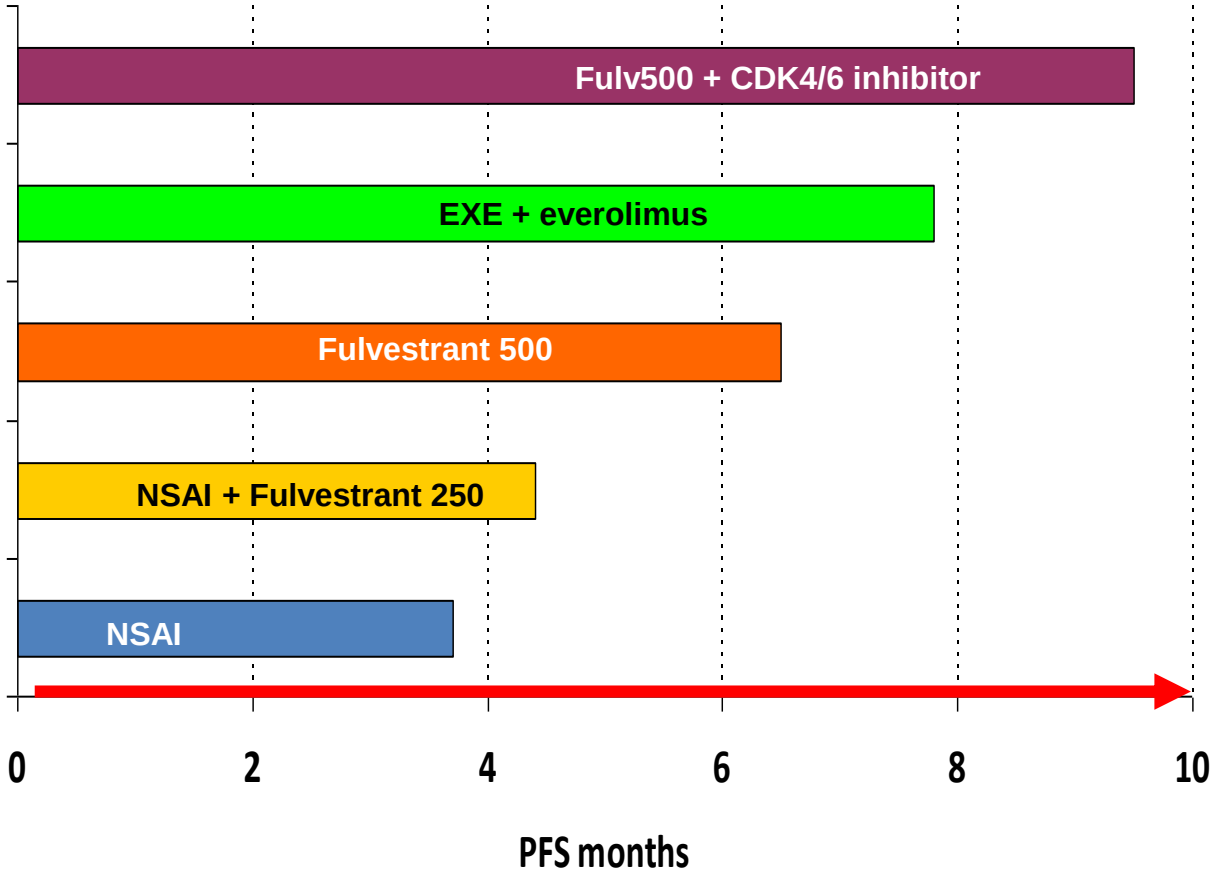


OR: Objective response (CR+PR); CB: clinical benefit (CR+PR+SD); PD: progressive disease

Trials in second line ER+/HER2- ABC

Trial	Design	N Patients (Random)	Treatments	Effect on PFS (primary endpoint	Effect on OS
Efect	PhIII	693 (1:1)	Ful250 vs Exe	3.7 vs 3.7 (TTP) HR 0.96	N.A.
Sofea	PhIII	723 (1:1:1)	Ful250+Ana vs Ful250 vs Exe	4.4 vs 4.8 vs 3.4 HR 1,0; 0,95	20.2 vs 19.4 vs 21.6 HR 0.95; 1.05
Confirm	Ph III	736 (1.1)	Ful 500 vs Ful250	6.5 vs 5.5 HR 0.80	26.4 vs 22.3 HR 0.81
Bolero 2	Ph III	724 (2.1)	Exe/Eve vs Exe	7.8 vs 3.2 HR **0.45**	31.0 vs 26.6 HR 0.89
Paloma 3	Ph III	521 (2:1)	Ful/Palb vs Ful500	9.5 vs 4.6 HR **0.46**	N.R. (immature data)

Expected mean effect of therapies in second line hormone-resistant ABC



% HT-sens patients
79
84
17
65
63

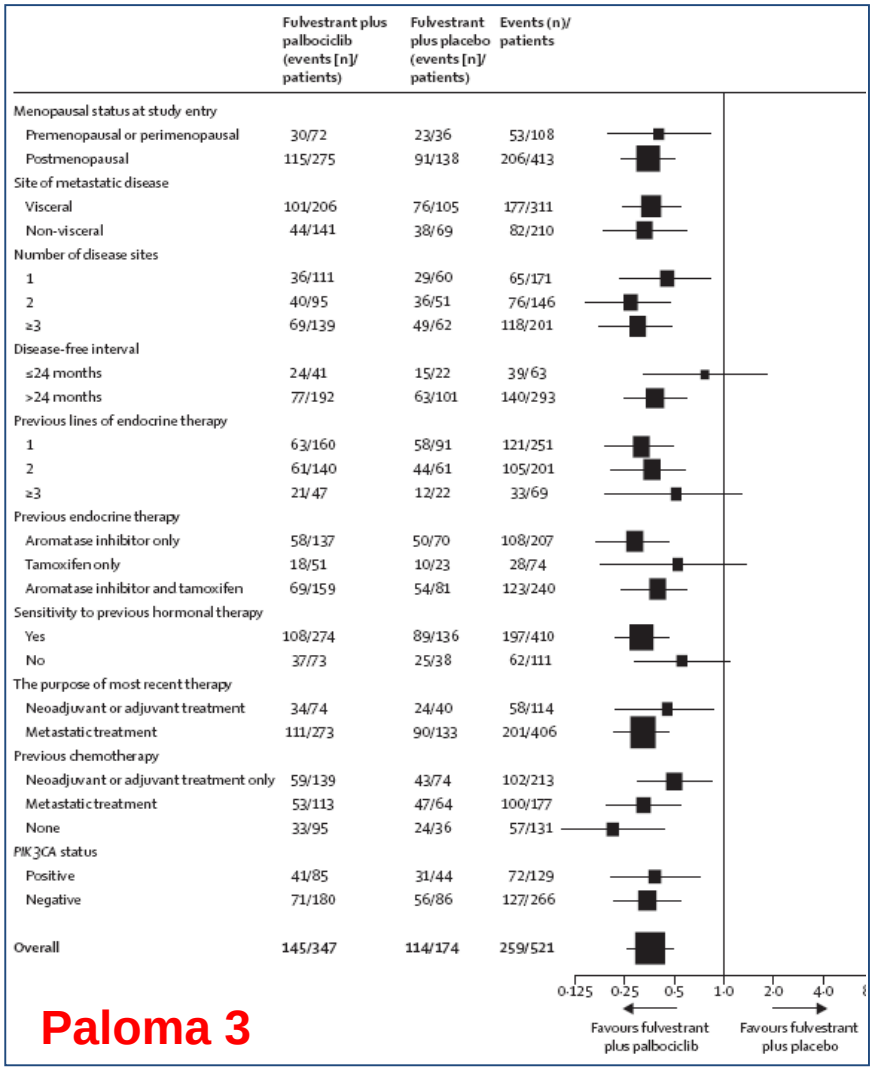
Trials in second line ER+/HER2- ABC

Also these trials have not been created equally

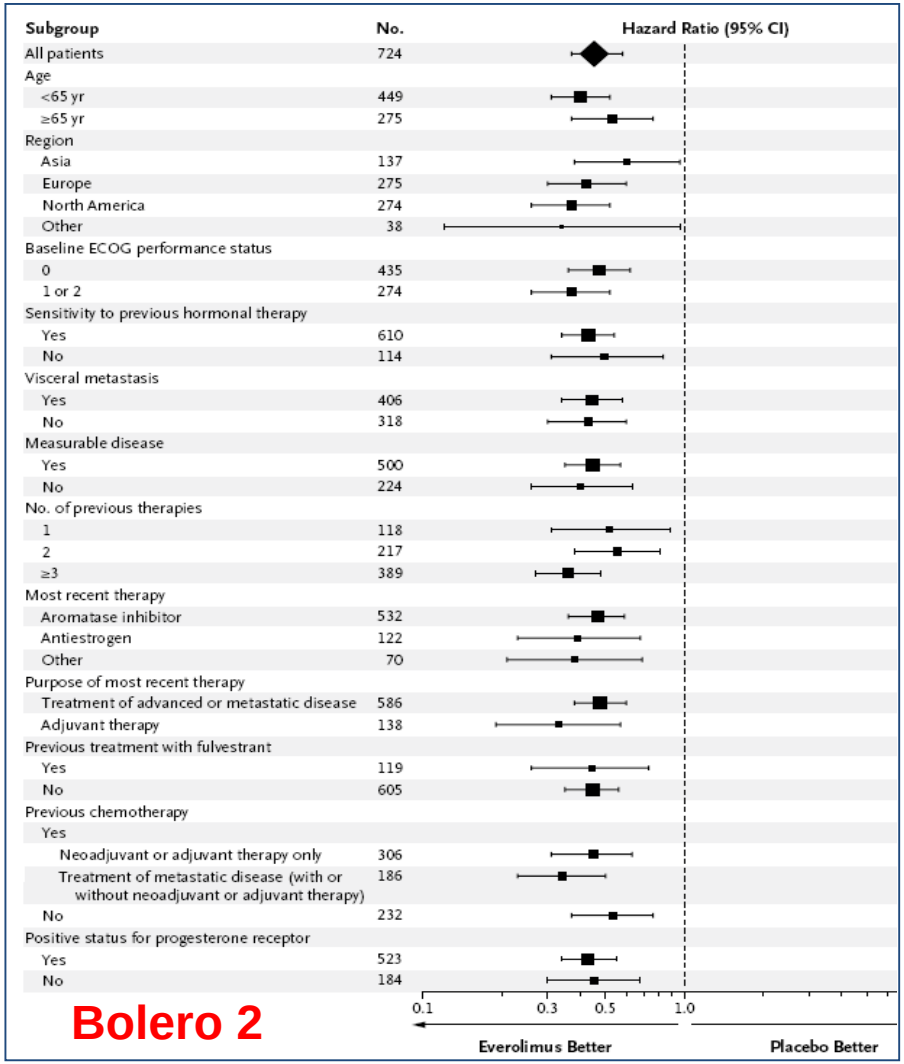
Trial	Treatments	% Previous HT sensitivity	% Previous Rx for ABC	n. lines of previous Rx (%)	% Visceral vs bone disease
Efect	Ful250 vs Exe	62	98	1 = 40	56 vs 66*
Sofea	Ful250+Ana vs Ful250 vs Exe	65	80	n.r.	60 vs 15°
Confirm	Ful 500 vs Ful250	17	**45**	1 = 90 2 = 10	66 vs n.r.
Bolero 2	Exe/Eve vs Exe	84	82	1 = 17 **≥ 3 = 53**	56 vs 76*
Paloma 3	Ful/Palb vs Ful500	79	**78**	1 = 49 **≥ 3 = 14**	60 vs 20°

* Not as only disease site; °As only site

Subgroup analyses of two trials using multiple agents



Paloma 3



Bolero 2

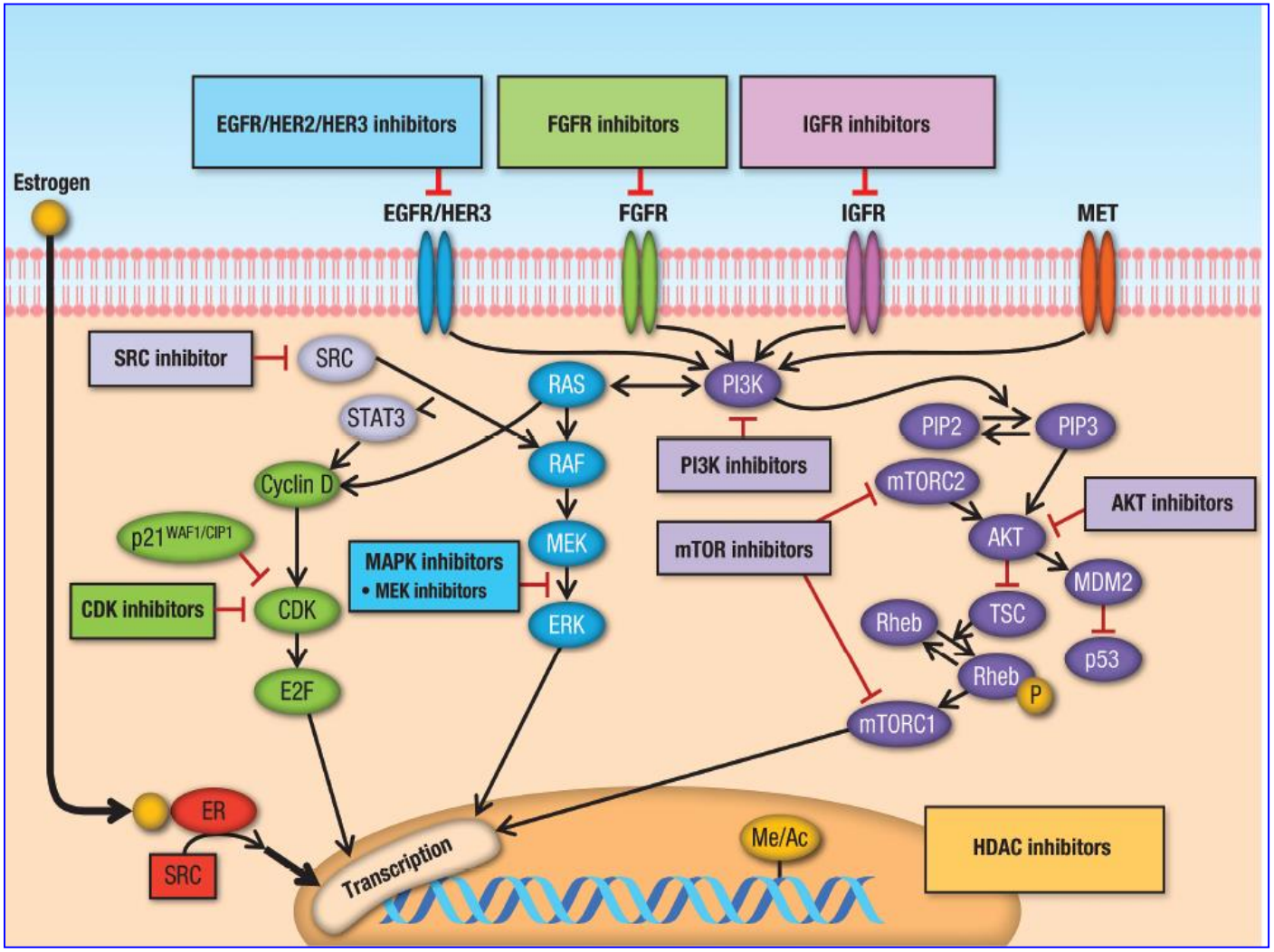
What could be also considered ?
(even if not evidence-based)

- **Tumor biology**
  - Degree of ER and PR expression
  - Proliferative activity
  - Luminal subtype
  - Gene alterations

Network of signalling possibly involved in hormone-resistance

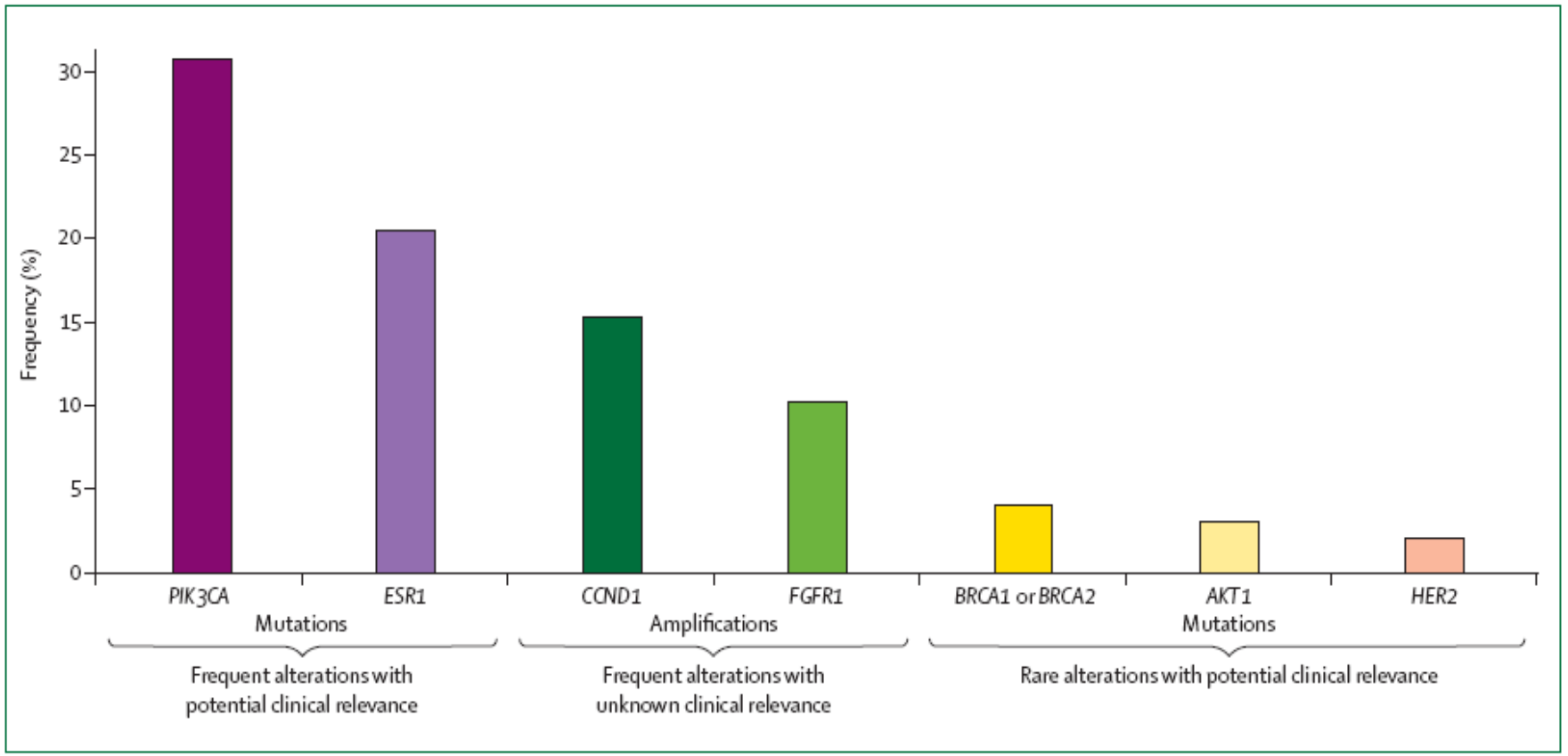
Four main targets

- **Estrogen receptor**
- **Growth-factor receptors**
- **Cell-cycle**
- **PIK3CA-AKT-mTOR axis**



Johnston, JNCI 2015

Frequency of potentially relevant gene alterations in ER+/HER2- ABC



Turner, Lancet 2016

ESR1 alterations could predict drug/s effectiveness

ESR1mut

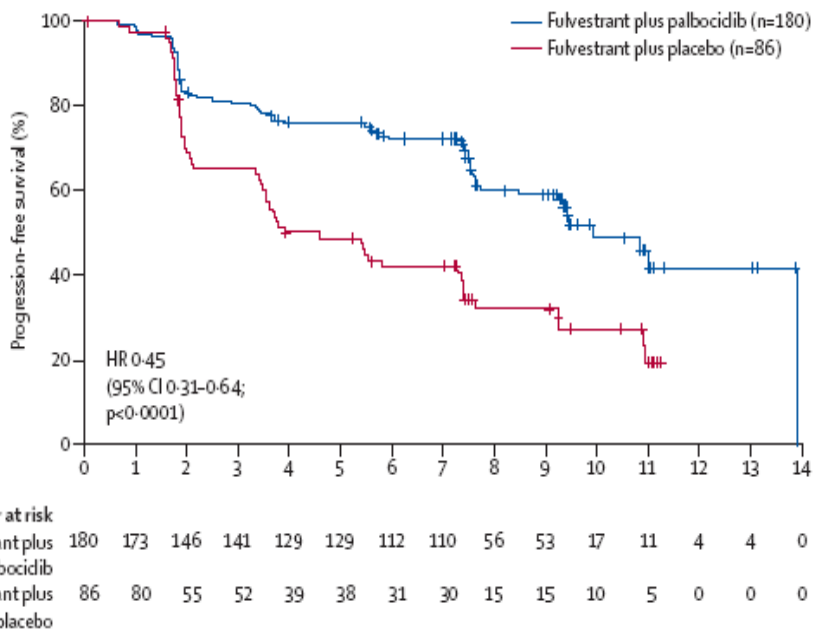
- **Ful** > Exe[1]
- **Ful+Palb** > Ful[2]
- **Eve+Exe** > Exe (D538)[3]
- Eve+Exe = Exe (Y537)[3]

ESR1wt

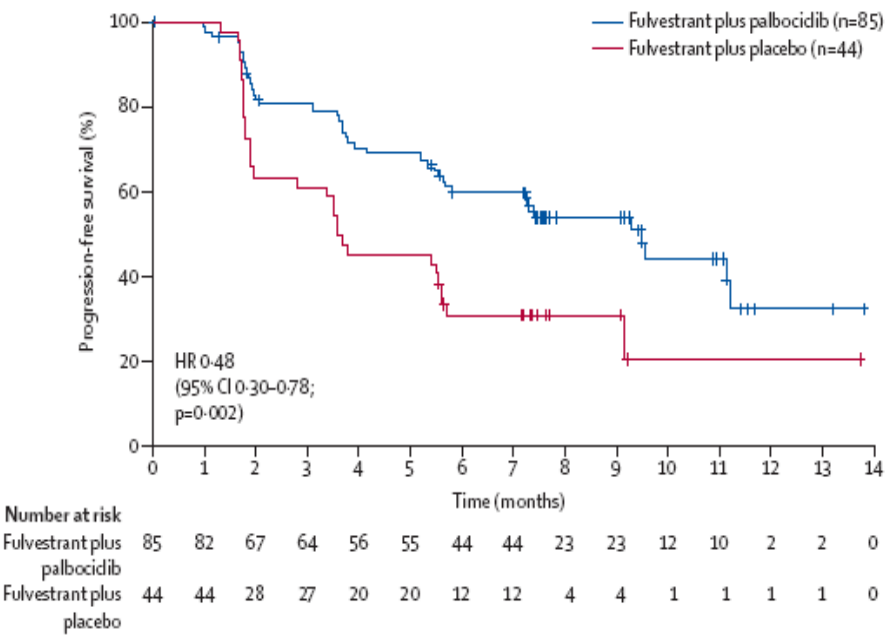
- Ful = Exe
- **Eve+Exe** > Exe (D538)[3]
- **Eve+Exe** > Exe (Y537)[3]
- **Ful+Palb** > Ful[2]

1: Fribbens, JCO 2016 – SoFEA cohort; 2:Chandarlapaty, Jama Oncol 2016; 3: Fribbens, JCO 2016, Paloma 3 cohort

Effect of fulv + palbo vs fulv on PFS, by ctDNA PIK3ca mut



Patients *with PIK3CA wild type*



Patients *with PIK3CA* mutated

Effect of palbociclib is irrespective of PIK3CA status

Cristofanilli, Lancet Oncol 2016

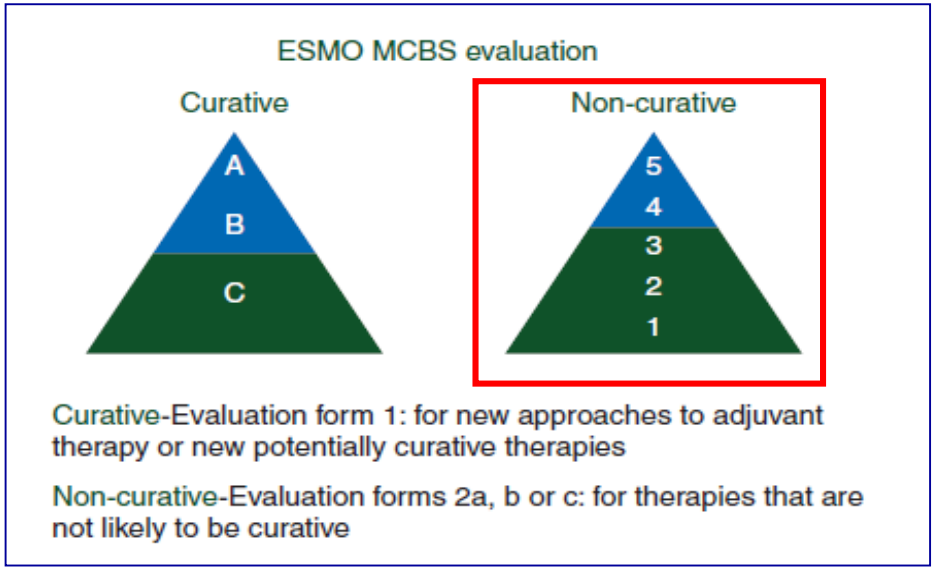
A look at side effects of treatments

	Absolute Increase in any grade side effects versus control			
	Fulv500	Eve+Exe	Palbo+Letro	Ribo+Letro
Stomatitis	NR	**45**	9	NR
Nausea	1	0	9	**23**
Vomiting	NR	3	-1	**14**
Diarrhea	0	**14**	7	**13**
Fatigue	4	7	**10**	6
Neutropenia	NR	NR	**73**	**69**
Infections	NR	8	2	8
Arthralgia	7	0	0	-1
Hot flash	1	NR	-10	-2
Rash	NR	**30**	7	9
Alopecia	NR	NR	**17**	**18**
ALT increase	4	7	NR	11
Any adverse effect	-2	11 (SAEs)	3	1

The fourth dimension – the value
Medical oncology Magnitude of Clinical benefit

Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months



Drug	Trial	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS
Ful500	Falcon	M 1°line	PFS	13.9 m	2.7m	0.79 (0.63-0.99)	NR	NR	NR	No impr	Similar	2
Palb +Let	Paloma 2	M 1°line	PFS	14.5 m	10.3 m	0.58 (0.46-0.72)	NR	NR	NR	NR	Higher	3
Ribo +Let	Monaleesa 2	M 1°line	PFS	14.7 m	Not. Reached	0.58 (0.43-0.72)	NR	NR	NR	NR	Higher	4
EVE-Exa	Bolero 2	M 2°line	PFS	3.2 m	4.6 m	0.45 (0.35-0.54)	26.6 m	4.4 m	0.89 (0.73-1.1)	No impr	higher	2*
Palb +Ful	Paloma 3	M 2°line	PFS	4.6 m	4.9 m	0.46 (0.36-0.59)	NR	NR	NR	Improv	higher	3

* Chemy, Ann Oncol 2015; other evaluations are personal estimate

Few data on response to different combination after some drugs

	% Previous hormones		
	Tamoxifen	**NSAIs**	**Fulvestrant**
Fulvestrant ***(Confirm)***	58	42	0
Fulvestrant ***(Falcon)***	0	0	0
Letro+ Palbo ***(Paloma 2)***	49	27	0
Letro + Ribo ***(Monaleesa 2)***	42	30	0
Ful + Palb ***(Paloma 3)***	15	85*	0
Eve+Exe ***(Bolero 2)***	47	57	17

* +/-Tam

CARCINOMA MAMMARIO METASTATICO
a terapia ormonale in post-menopausa

Consider possibility to use the highest number of hormone lines, based on prediction of prolonged hormone sensitivity

Adiuvante | 1° linea | 2° linea | 3° linea

Nota 1= Fulvestrant non ancora autorizzato in Italia da AIFA nelle pazienti non pretrattate con antiestrogeni
Nota 2= Everolimus prescrivibile solo dopo ricaduta o progressione a seguito di un trattamento con NSAI
Nota 3 = In base a registrazione EMA

NSAI: inibitore dell'aromatasi non steroideo (anastrozolo, letrozolo); SAI: inibitore dell'aromatasi steroideo **(** exemestane)

Conclusions

- Several options available for ER+/HER2- MBC
- Disease behavior, DFI, site of disease, previous therapies are variables influencing the choice of treatment
- Biology of disease (gene mutation and type) might be useful in the next future for fine tuning the strategy
- NHS regulatory rules limit our choices and may dictate the sequence strategy