Pearls from ESMO

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Disclosure

- Honoraria, consulting and/or travel funds:
  - Roche, Novartis, Eli Lilly, Astrazeneca, Takeda, Ipsen, Eisai, Pfeizer, GE, MSD

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

N Engl J Med 2018;379:2108-21.

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IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

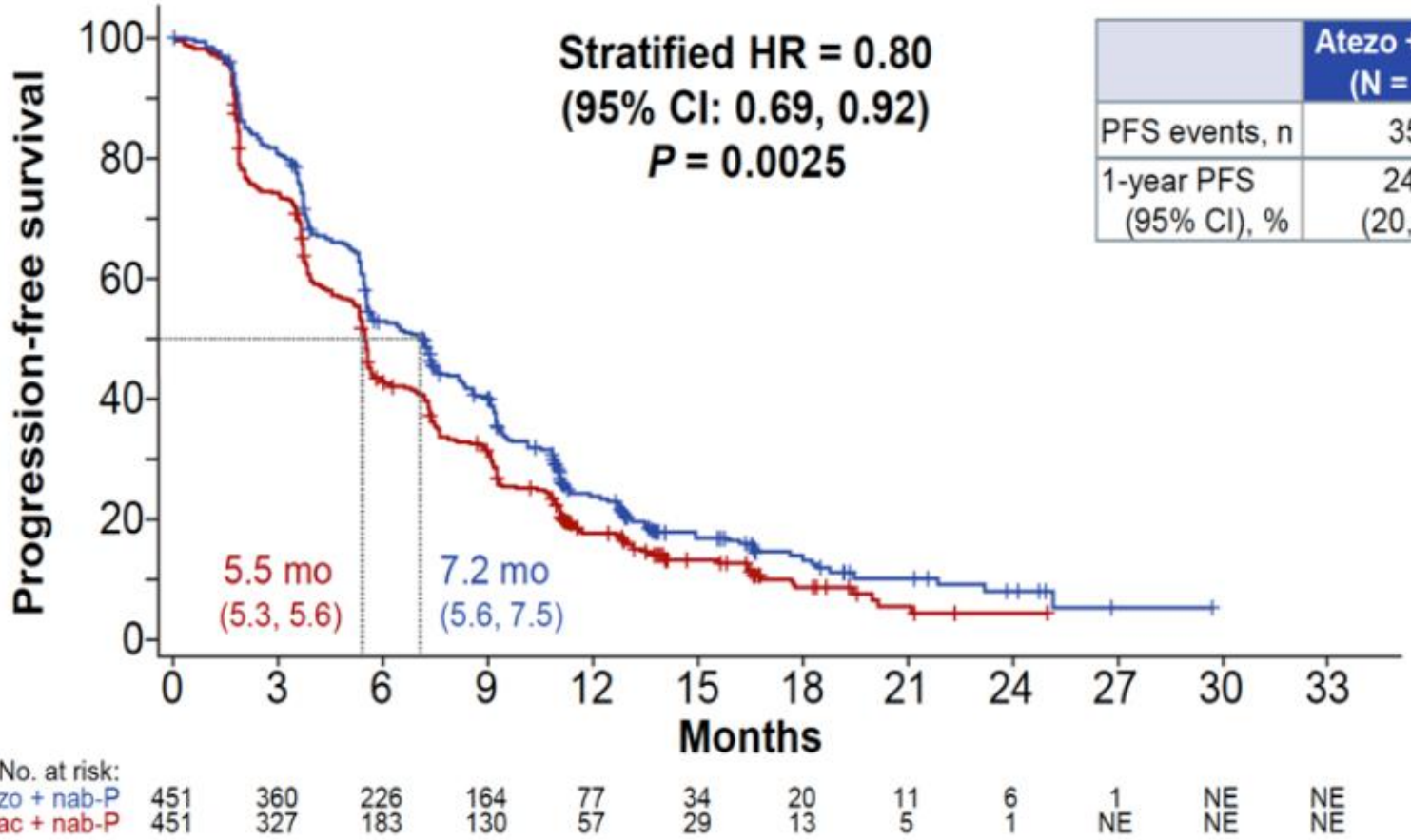
RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

Primary PFS analysis: ITT population



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

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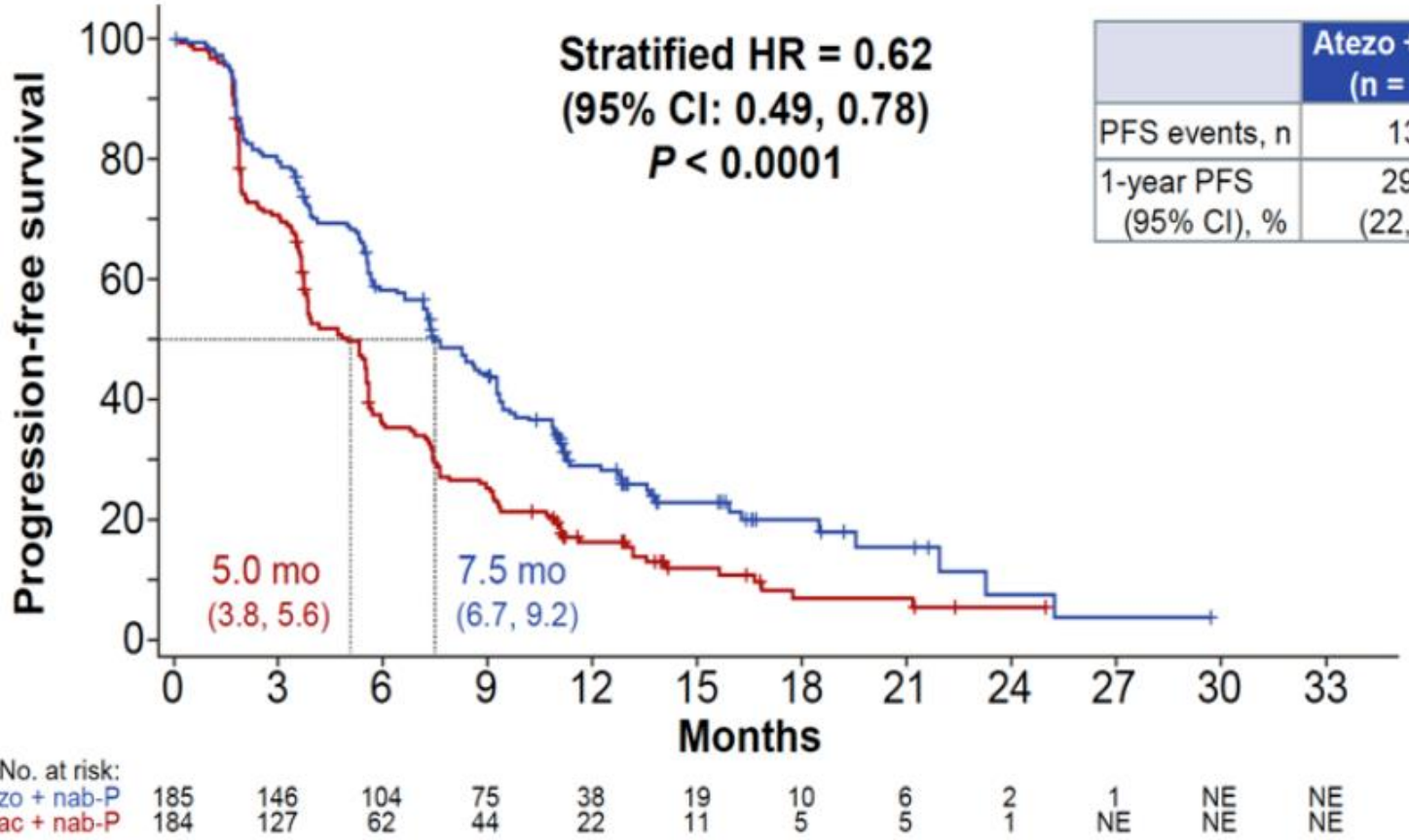
Primary PFS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Data cutoff: 17 April 2018.

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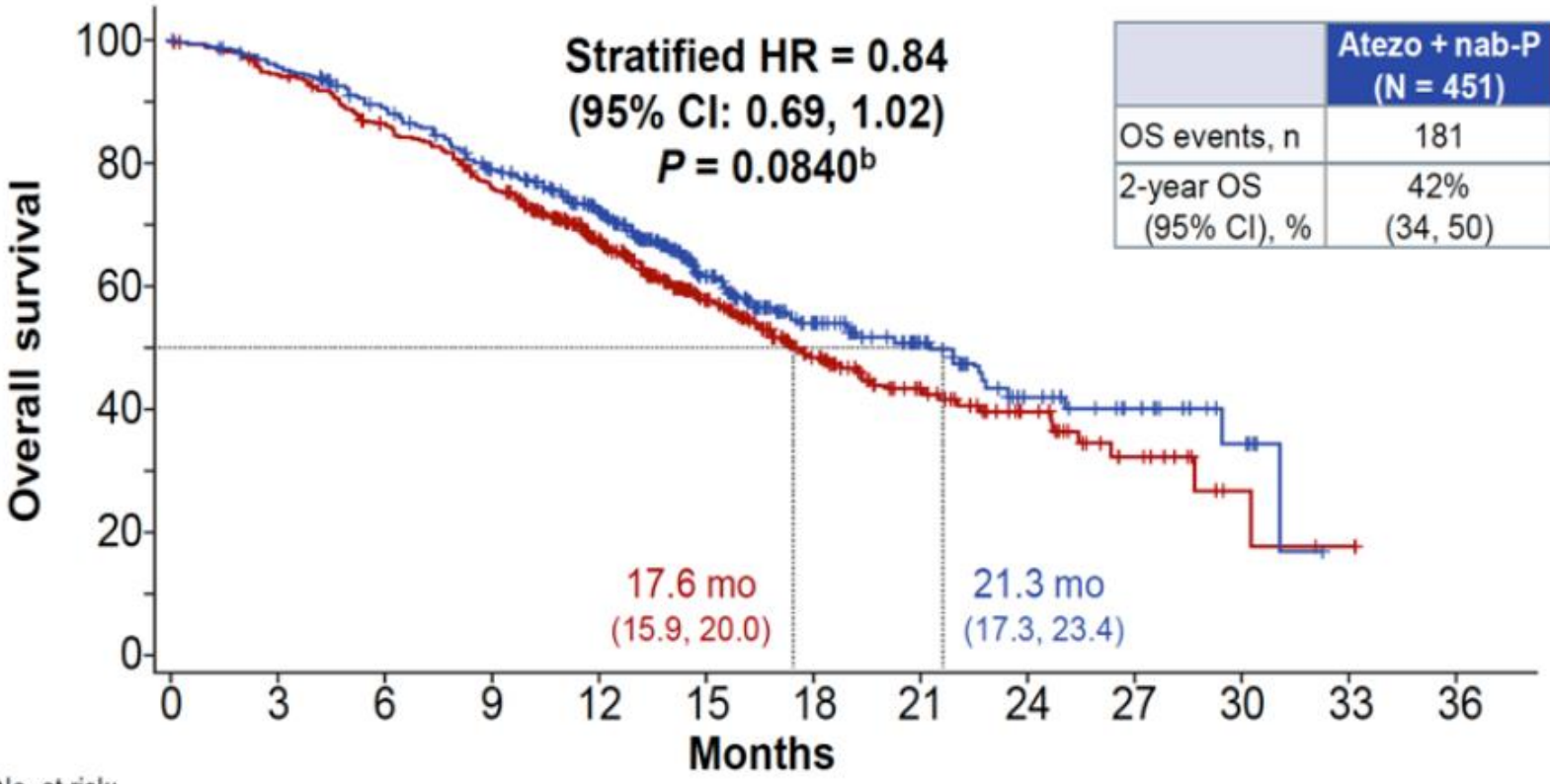
Interim OS analysis: ITT population[a]

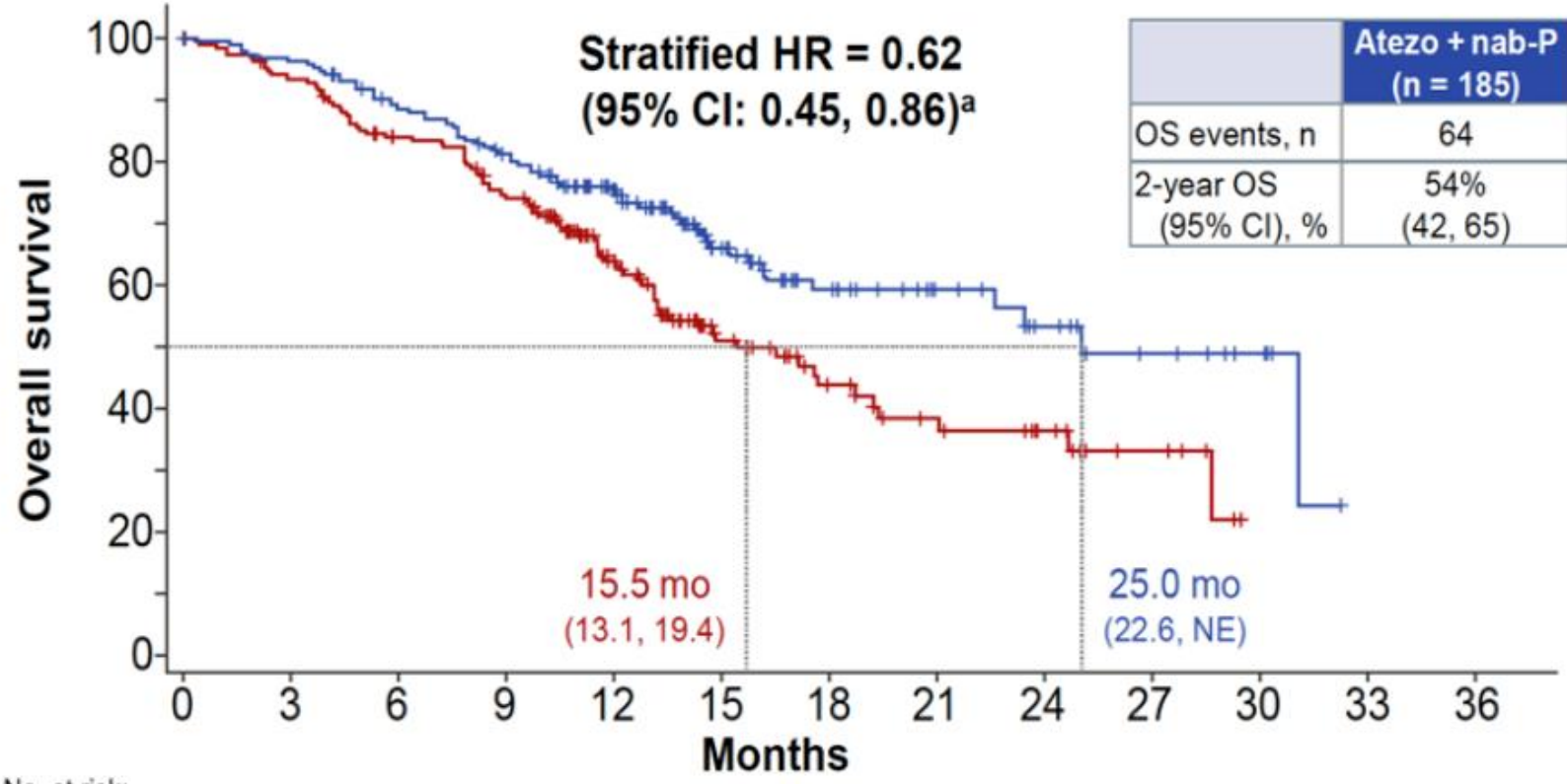


	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.
[a] For the interim OS analysis, 59% of death events had occurred. [b] Significance boundary was not crossed.

Schmid P, et al. IMpassio
ESMO 2018 (LBA1
http://bit.ly/2DM

Interim OS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. [a] Not formally tested.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

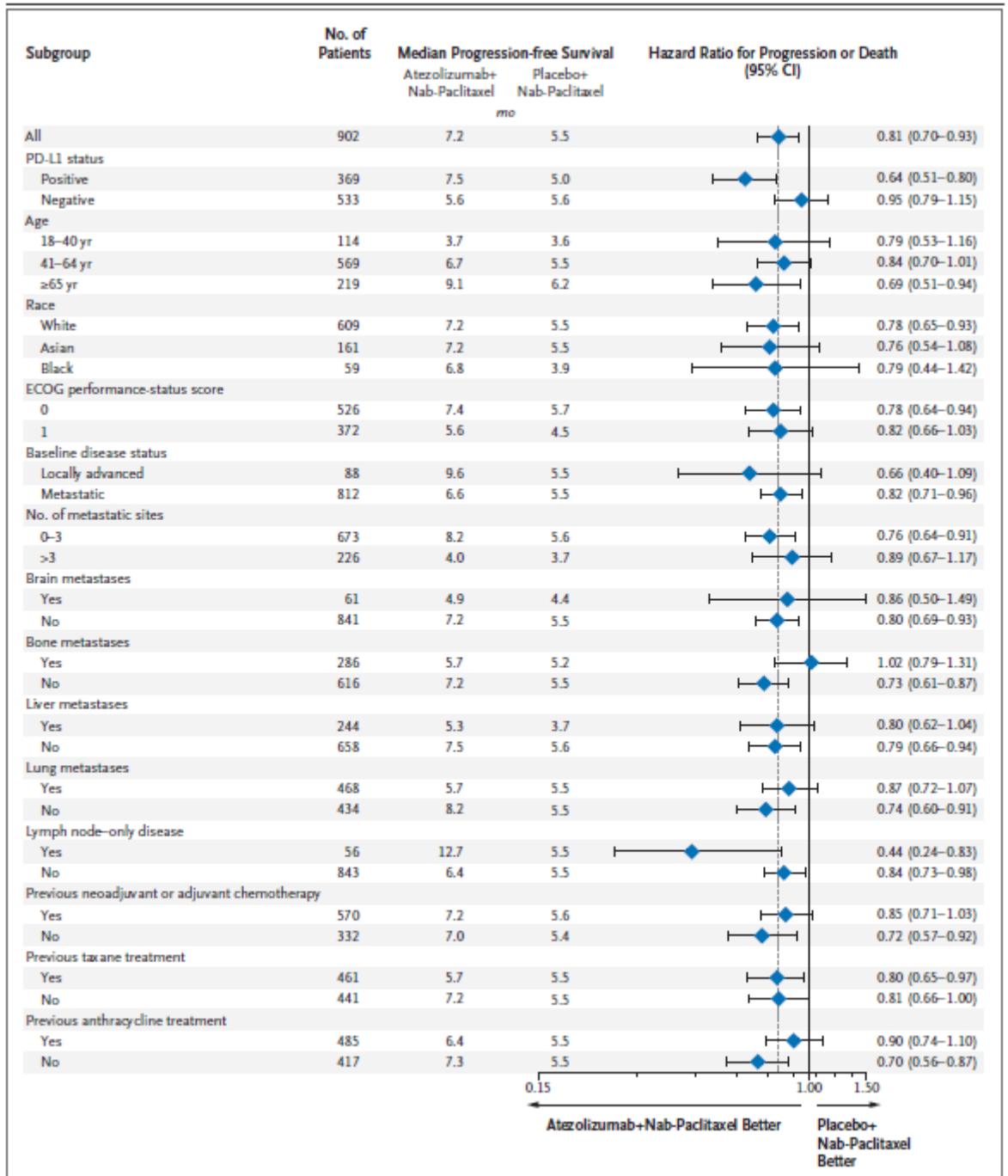
AESIs suggestive of potential immune-related aetiology

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- 1 grade 5 AESI per arm (both treatment related):
  - Atezo + nab-P: autoimmune hepatitis
  - Plac + nab-P: hepatic failure
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - Atezo + nab-P: 17%
  - Plac + nab-P: 4%
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - Atezo + nab-P: 3%
  - Plac + nab-P: < 1%
- Hepatitis rates were balanced

AESI, adverse event of special interest. Data cutoff: 17 April 2018. [a] Baskets of preferred terms according to medical concepts. [b] All events of photophobia. [c] Includes all AESIs occurring in ≥ 1% of patients in either arm.

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg


Subgroup
No. of Patients
Median Progression-free Survival
Atezolizumab+ Nab-Paclitaxel
Placebo+ Nab-Paclitaxel
mo
Hazard Ratio for Progression or Death (95% CI)
All 902 7.2 5.5 0.81 (0.70–0.93)
PD-L1 status
Positive 369 7.5 5.0 0.64 (0.51–0.80)
Negative 533 5.6 5.6 0.95 (0.79–1.15)
Age
18–40 yr 114 3.7 3.6 0.79 (0.53–1.16)
41–64 yr 569 6.7 5.5 0.84 (0.70–1.01)
≥65 yr 219 9.1 6.2 0.69 (0.51–0.94)
Race
White 609 7.2 5.5 0.78 (0.65–0.93)
Asian 161 7.2 5.5 0.76 (0.54–1.08)
Black 59 6.8 3.9 0.79 (0.44–1.42)
ECOG performance-status score
0 526 7.4 5.7 0.78 (0.64–0.94)
1 372 5.6 4.5 0.82 (0.66–1.03)
Baseline disease status
Locally advanced 88 9.6 5.5 0.66 (0.40–1.09)
Metastatic 812 6.6 5.5 0.82 (0.71–0.96)
No. of metastatic sites
0–3 673 8.2 5.6 0.76 (0.64–0.91)
>3 226 4.0 3.7 0.89 (0.67–1.17)
Brain metastases
Yes 61 4.9 4.4 0.86 (0.50–1.49)
No 841 7.2 5.5 0.80 (0.69–0.93)
Bone metastases
Yes 286 5.7 5.2 1.02 (0.79–1.31)
No 616 7.2 5.5 0.73 (0.61–0.87)
Liver metastases
Yes 244 5.3 3.7 0.80 (0.62–1.04)
No 658 7.5 5.6 0.79 (0.66–0.94)
Lung metastases
Yes 468 5.7 5.5 0.87 (0.72–1.07)
No 434 8.2 5.5 0.74 (0.60–0.91)
Lymph node–only disease
Yes 56 12.7 5.5 0.44 (0.24–0.83)
No 843 6.4 5.5 0.84 (0.73–0.98)
Previous neoadjuvant or adjuvant chemotherapy
Yes 570 7.2 5.6 0.85 (0.71–1.03)
No 332 7.0 5.4 0.72 (0.57–0.92)
Previous taxane treatment
Yes 461 5.7 5.5 0.80 (0.65–0.97)
No 441 7.2 5.5 0.81 (0.66–1.00)
Previous anthracycline treatment
Yes 485 6.4 5.5 0.90 (0.74–1.10)
No 417 7.3 5.5 0.70 (0.56–0.87)
0.15
1.00
1.50
Atezolizumab+Nab-Paclitaxel Better
Placebo+ Nab-Paclitaxel Better

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ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

CONCLUSIONS

Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. Adverse events were consistent with the known safety profiles of each agent. (Funded by F. Hoffmann–La Roche/Genentech; IMpassion130 ClinicalTrials.gov number, NCT02425891.)

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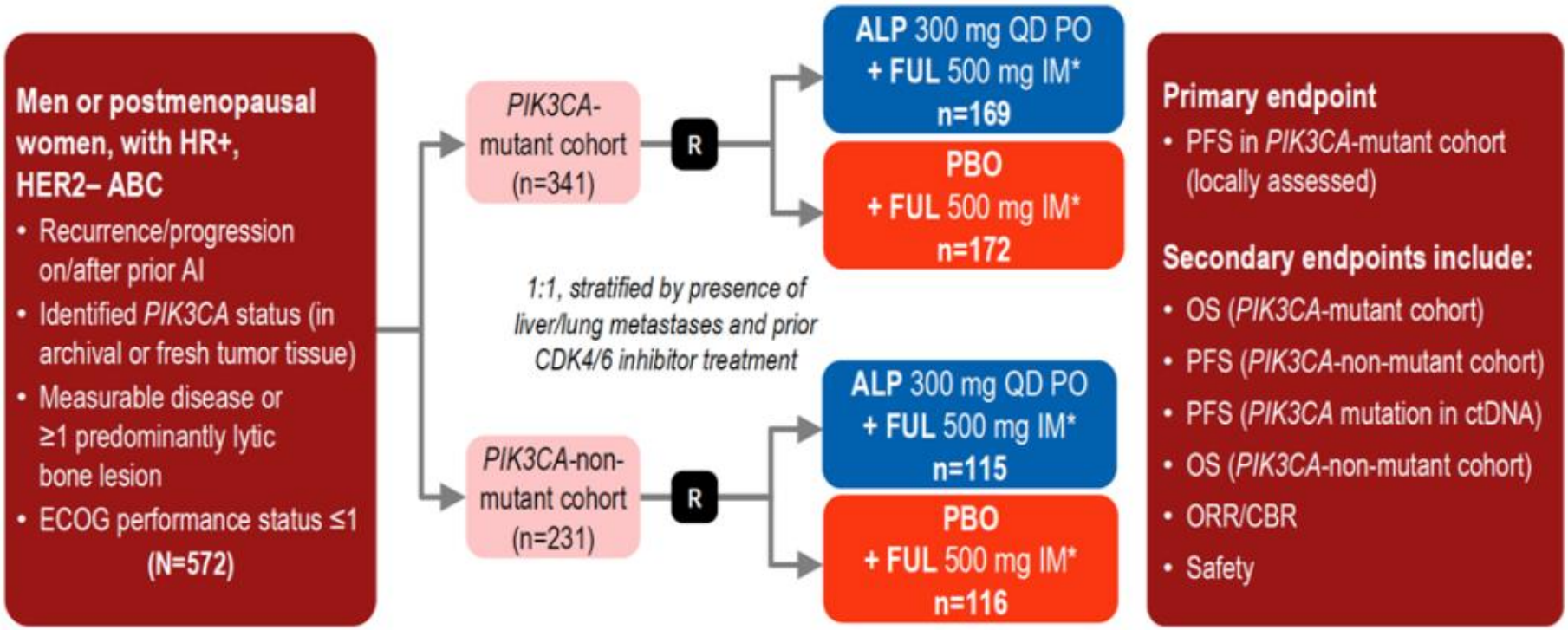
ALPELISIB + FULVESTRANT FOR HR+, HER2– ADVANCED BREAST CANCER: RESULTS OF THE PHASE III SOLAR-1 TRIAL

Fabrice André,[1] Eva Maria Ciruelos,[2] Gabor Rubovszky,[3] Mario Campone,[4] Sibylle Loibl,[5] Hope S Rugo,[6] Hiroji Iwata,[7] Pierfranco Conte,[8] Ingrid A Mayer,[9] Bella Kaufman,[10] Toshinari Yamashita,[11] Yen-Shen Lu,[12] Kenichi Inoue,[13] Masato Takahashi,[14] Zsuzsanna Pápai,[15] Anne-Sophie Longin,[16] David Mills,[17] Celine Wilke,[17] Samit Hirawat,[18] Dejan Juric[19]

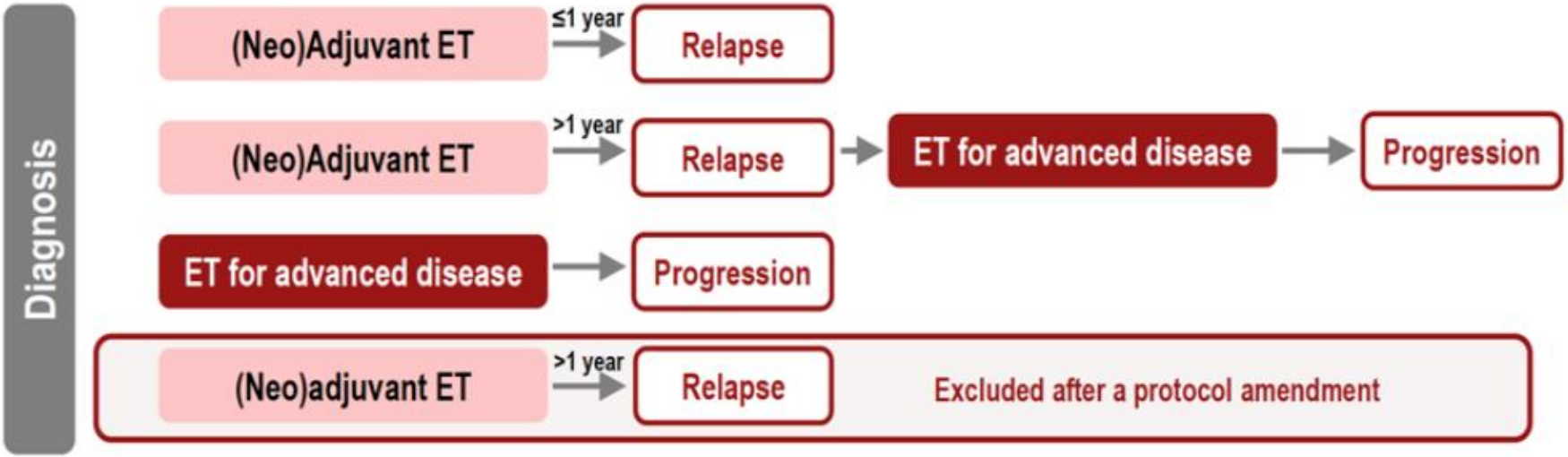
[1]Gustave Roussy, INSERM U981, Université Paris-Sud, Villejuif, France; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]National Institute of Oncology, Budapest, Hungary; [4]Institut de Cancérologie de l'Ouest, St Herblain, France; [5]German Breast Group, Neu-Isenburg, Germany and Centre for Haematology and Oncology Bethanien, Frankfurt, Germany; [6]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [7]Aichi Cancer Center, Nagoya, Japan; [8]Istituto Oncologico Veneto, Padua, Italy and Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy; [9]Vanderbilt University, Nashville, TN, USA; [10]Chaim Sheba Medical Center, Tel Hashomer, Israel; [11]Kanagawa Cancer Center, Yokohama, Japan; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]Saitama Cancer Center, Saitama, Japan; [14]NHO Hokkaido Cancer Center, Sapporo, Japan; [15]Duna Medical Center, Budapest, Hungary; [16]Novartis Pharma S.A.S, Paris, France; [17]Novartis Pharma AG, Basel, Switzerland; [18]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [19]Massachusetts General Hospital, Boston, MA, USA

SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



*Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28 day cycles.

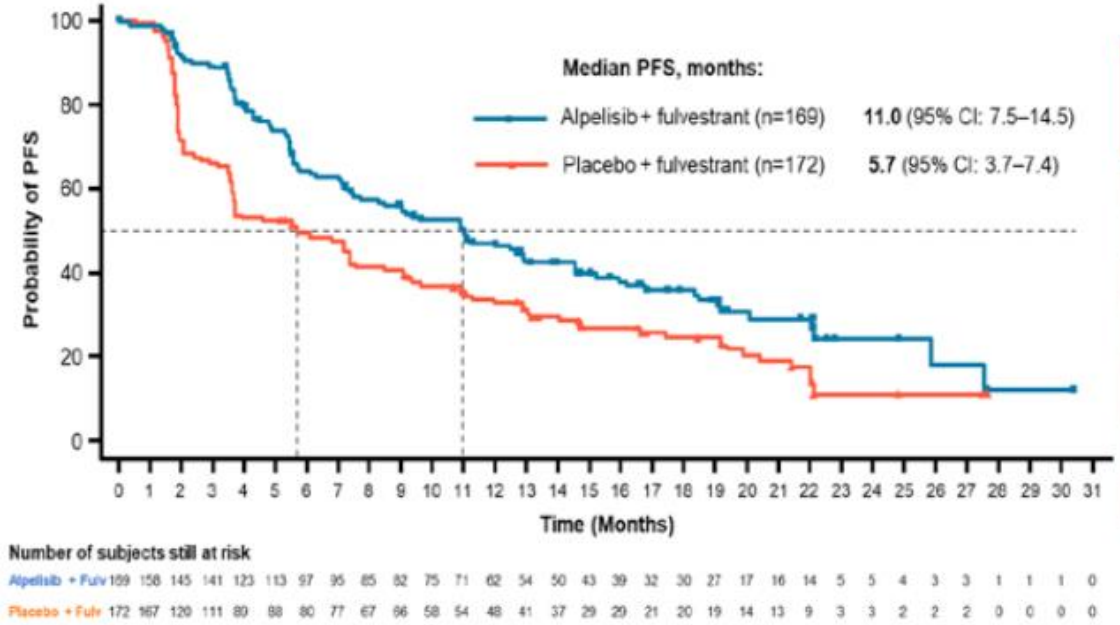
Inclusion criteria: Prior exposure to AI



- Patients who had received one prior line of endocrine therapy were enrolled
  - Endocrine resistance and endocrine sensitivity were defined according to the ESMO guidelines[1]
  - Patients who had not received ET for ABC were considered "first line"

1. Cardoso F, et al. *Ann Oncol* 2018;29:1634–57.

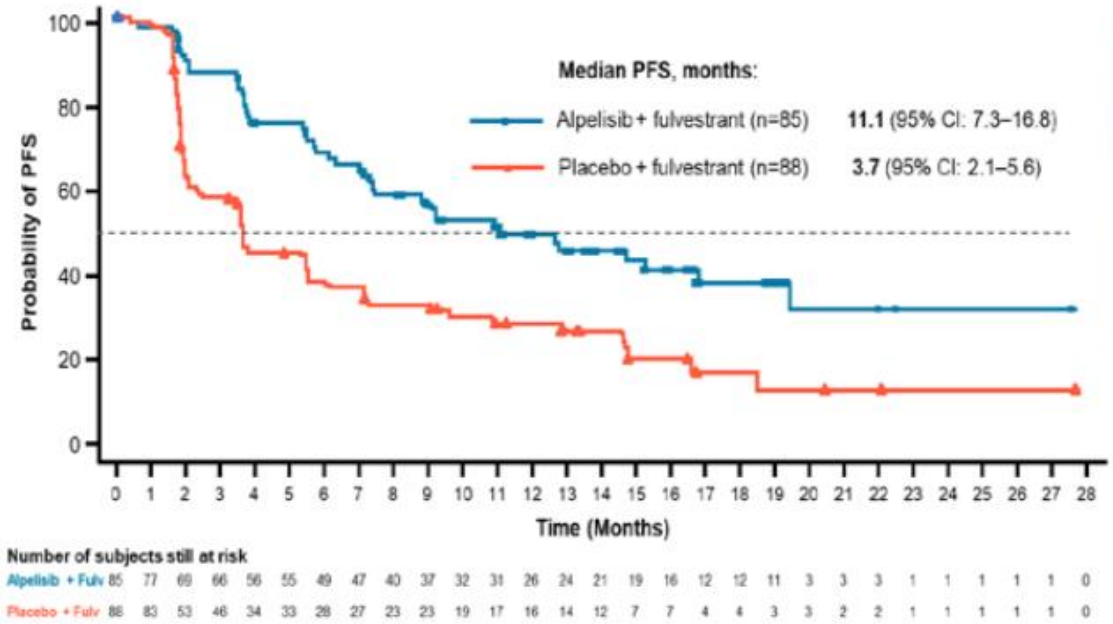
Primary endpoint: Locally assessed PFS in the *PIK3CA*-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

- The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

BIRC audit: Centrally assessed PFS in the *PIK3CA*-mutant cohort

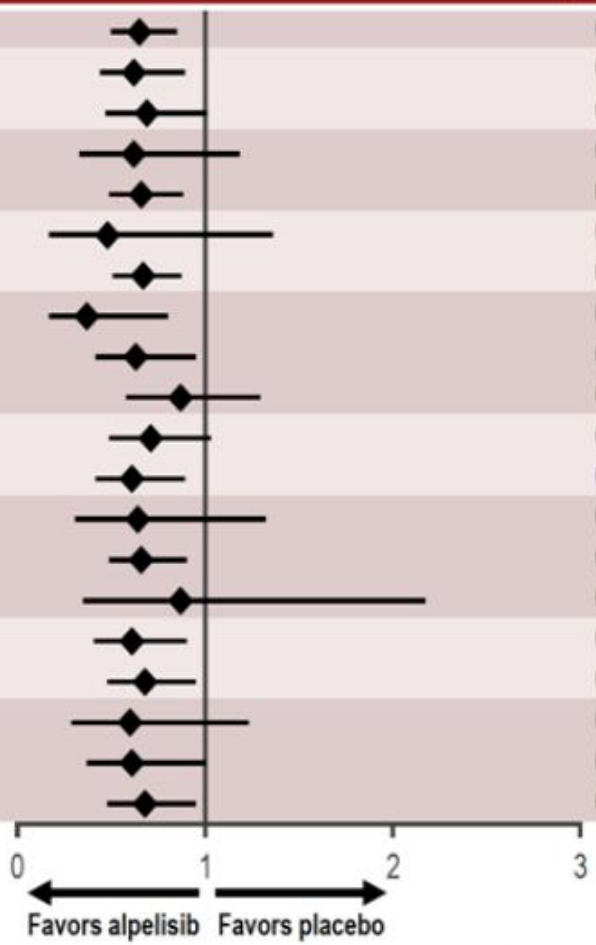


Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=85)	Placebo + fulvestrant (N=88)
Number of PFS events, n (%)	43 (50.6)	63 (71.6)
Median PFS (95% CI)	11.1 (7.3–16.8)	3.7 (2.1–5.6)
HR (95% CI)	0.48 (0.32–0.71)	

- Blinded independent review committee audit of 50% of randomized patients in the *PIK3CA*-mutant cohort (n=173)
- A full BIRC review of all patient data in the *PIK3CA*-mutant cohort was not required, based on prespecified thresholds

PFS by subgroup (*PIK3CA*-mutant cohort)

Subgroup		No. of patients	Hazard Ratio (95% CI)
All subjects		341	0.65 (0.50–0.85)
Lung/liver metastases	Yes	170	0.62 (0.44–0.89)
	No	171	0.69 (0.47–1.01)
Bone-only disease	Yes	77	0.62 (0.33–1.18)
	No	264	0.66 (0.49–0.88)
Prior CDK4/6 inhibitor treatment	Yes	20	0.48 (0.17–1.36)
	No	321	0.67 (0.51–0.87)
Prior chemotherapy	Neoadjuvant	46	0.37 (0.17–0.80)
	Adjuvant	161	0.63 (0.42–0.95)
	None	133	0.87 (0.58–1.29)
Line of advanced anti-cancer treatment	First line	177	0.71 (0.49–1.03)
	Second line	161	0.61 (0.42–0.89)
Endocrine status	Primary resistance	45	0.64 (0.31–1.32)
	Secondary resistance	247	0.66 (0.49–0.90)
	Sensitive	39	0.87 (0.35–2.17)
PIK3CA mutation exon	Exon 9	165	0.61 (0.41–0.90)
	Exon 20	193	0.68 (0.48–0.95)
PIK3CA mutation subtype*	*E542K*	60	0.60 (0.29–1.23)
	E545X†	105	0.61 (0.37–1.00)
	H1047X†	193	0.68 (0.48–0.95)



*Mutations detected in tissue. Patients may have had more than one *PIK3CA* mutation; †Includes multiple subtypes of *E545* and *H1047*.

Adverse events in the total population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

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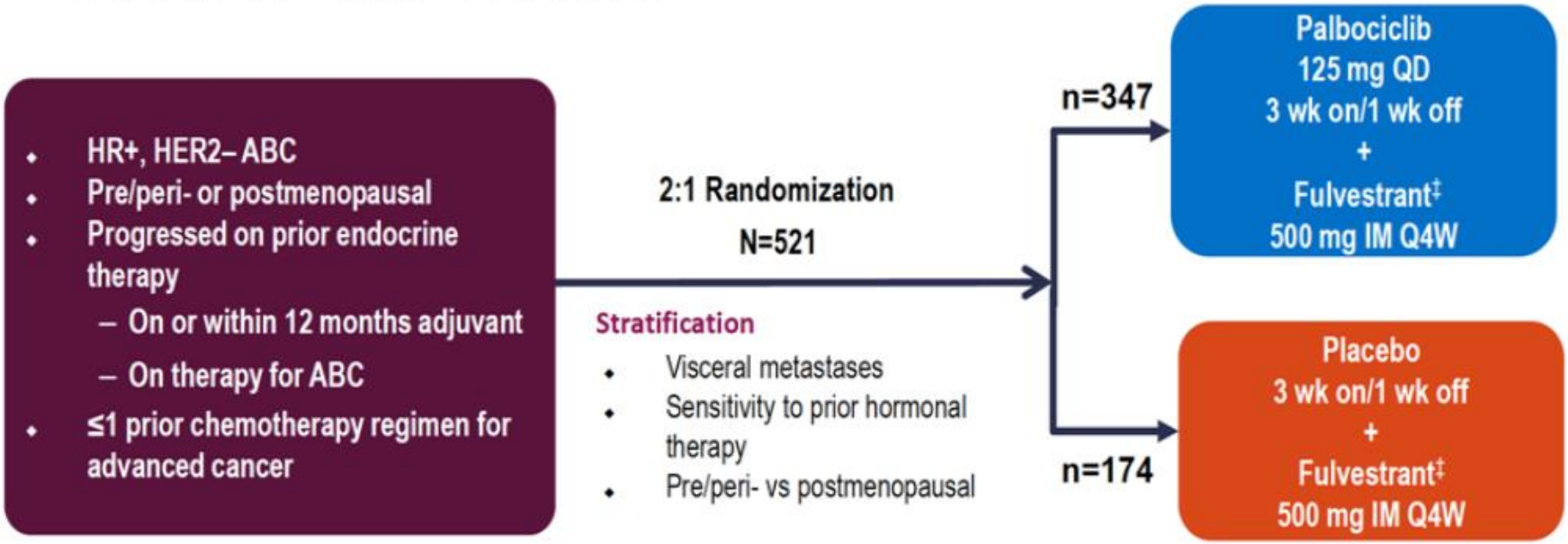
OVERALL SURVIVAL WITH PALBOCICLIB + FULVESTRANT IN WOMEN WITH HORMONE RECEPTOR–POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2–NEGATIVE ADVANCED BREAST CANCER: ANALYSES FROM PALOMA-3

Massimo Cristofanilli,[1] Dennis J. Slamon,[2] Jungsil Ro,[3] Igor Bondarenko,[4] Seock-Ah Im,[5] Norikazu Masuda,[6] Marco Colleoni,[7] Angela DeMichele,[8] Sherene Loi,[9] Sunil Verma,[10] Hiroji Iwata,[11] Nadia Harbeck,[12] Sibylle Loibl,[13] Fabrice André,[14] Kathy Puyana Theall,[15] Xin Huang,[16] Carla Giorgetti,[17] Cynthia Huang Bartlett,[18] Nicholas C. Turner[19]

[1]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [2]David Geffen School of Medicine at University of California Los Angeles, Santa Monica, CA, USA; [3]National Cancer Center, Goyang-si, South Korea; [4]Dnipropetrovsk Medical Academy, City Multiple-Discipline Clinical Hospital #4, Dnipropetrovsk, Ukraine; [5]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [6]NHO Osaka National Hospital, Osaka, Japan; [7]Istituto Europeo di Oncologia, Milan, Italy; [8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [9]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC, Australia; [10]Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [11]Aichi Cancer Center Hospital, Nagoya, Japan; [12]Brustzentrum der Universität Muenchen (LMU), Munich, Germany; [13]German Breast Group, Neu-Isenburg, Germany; [14]Institut Gustave Roussy, Villejuif, France; [15]Pfizer Oncology, Cambridge, MA, USA; [16]Pfizer Oncology, San Diego, CA, USA; [17]Pfizer Oncology, Milan, Italy; [18]Pfizer Oncology, Collegeville, PA, USA; [19]Royal Marsden Hospital and Institute of Cancer Research, London, UK

PALOMA-3* STUDY DESIGN[1]



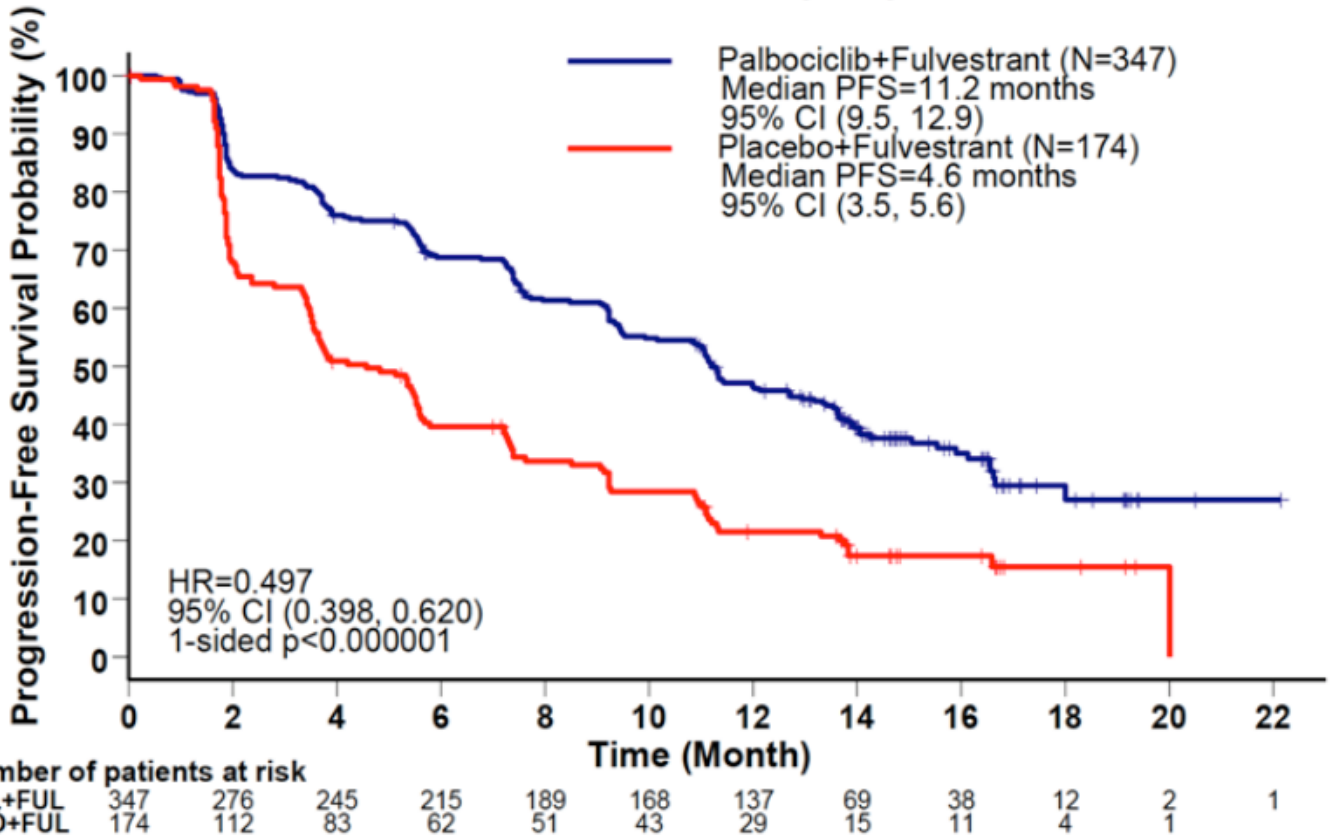
- Sensitivity to prior hormonal therapy was defined as documented clinical benefit (CR, PR, or SD ≥24 weeks) to ≥1 prior hormonal therapy regimen in the metastatic setting or ≥24 months of adjuvant hormonal therapy before recurrence.

AI=aromatase inhibitor; CR=complete response; IM=intramuscular; PR=partial response; Q4W=once every 4 wk; QD=once daily; SD=stable disease.

*Clinicaltrials.gov, NCT01942135; ‡Administered on days 1 and 15 of cycle 1, then on day 1 of every cycle thereafter.

1. Turner et al. *New Engl J Med*. 2015.

FINAL PROGRESSION-FREE SURVIVAL (ITT)[1]



- **Absolute improvement in median PFS in the palbociclib arm vs the placebo arm was 6.6 months.**

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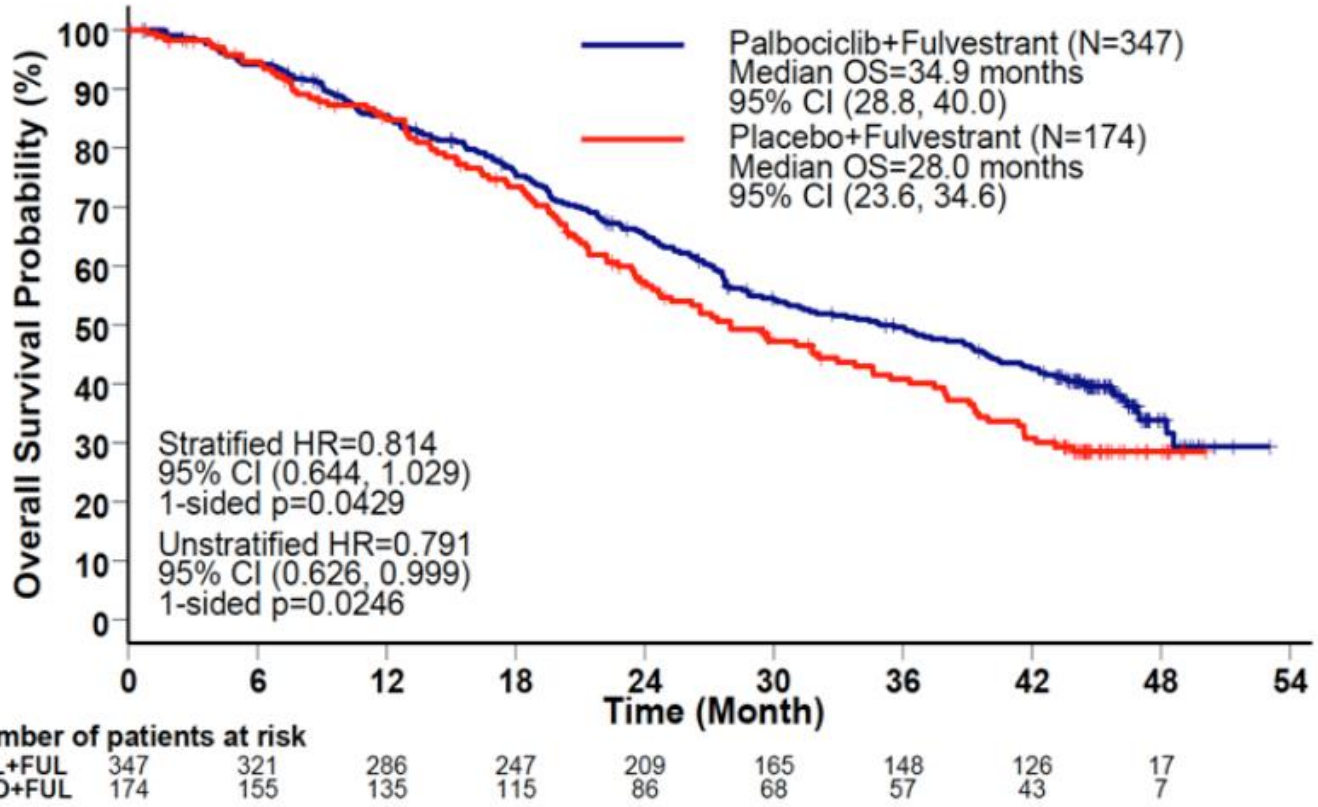
FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; PAL=palbociclib; PBO=placebo.

1. Ibrance Summary of Product Characteristics; Pfizer Ltd; Kent, UK; 2018. Data cutoff date: 23 October 2015.

OVERALL SURVIVAL (ITT)



Number of patients at risk

PAL+FUL	347	321	286	247	209	165	148	126	17
PBO+FUL	174	155	135	115	86	68	57	43	7

- **Absolute improvement in median OS in the palbociclib arm vs the placebo arm was 6.9 months.**

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Back From Monaco

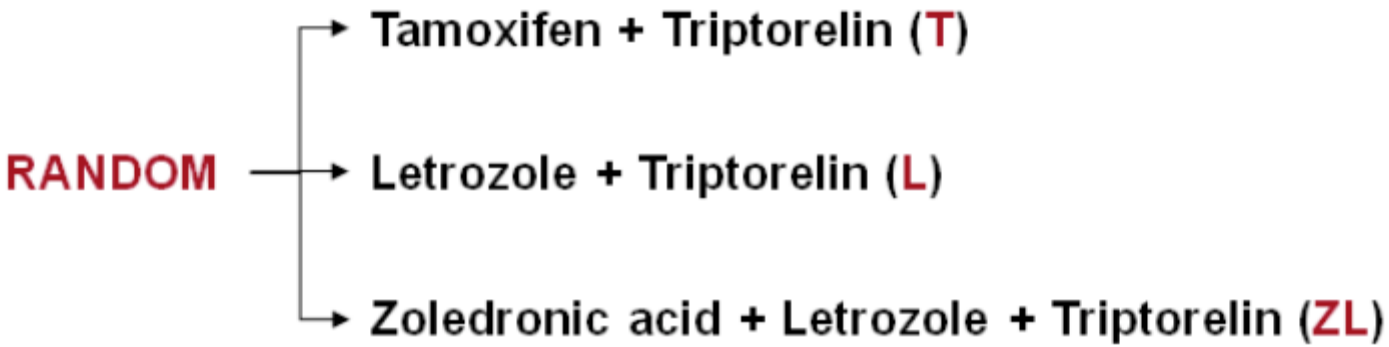
Impassion 130
Solar-1
Paloma-3
HOBOE-2

The HOBOE-2 multicenter randomized phase 3 trial in premenopausal patients with hormone-receptor positive early breast cancer comparing Triptorelin plus either Tamoxifen or Letrozole or Letrozole + Zoledronic acid.

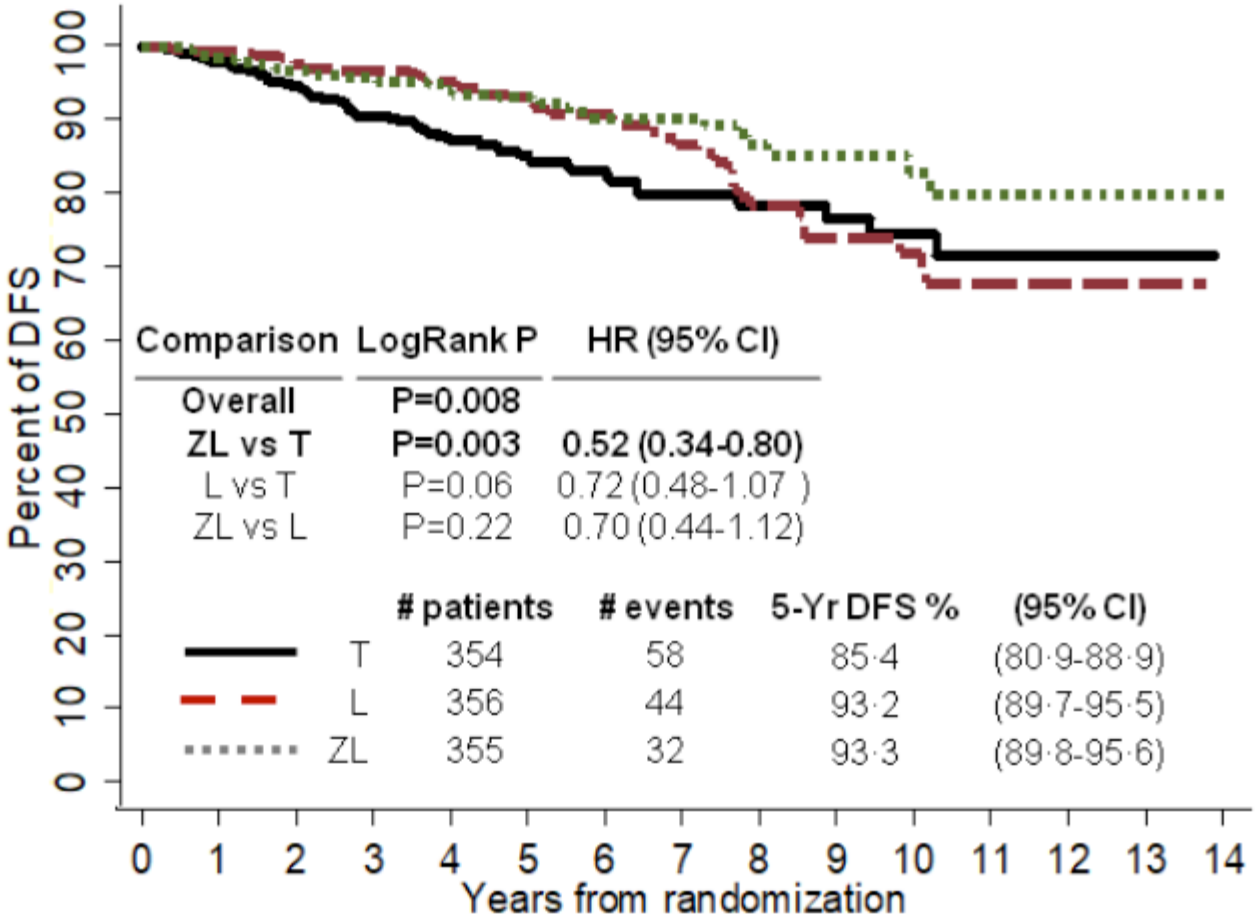
F. Perrone, M. De Laurentiis, S. De Placido, M. Orditura, S. Cinieri, F. Riccardi, A.S. Ribecco, C. Putzu, L. Del Mastro, E. Rossi, B. Daniele, A.M. Mosconi, F. Di Rella, G. Landi, F. Nuzzo, C. Pacilio, R. Lauria, L. Arenare, M.C. Piccirillo, C. Gallo

Aim of the study

- To compare Letrozole and Zoledronic acid + Letrozole to Tamoxifen (always associated with Triptorelina) in terms of disease-free survival in premenopausal patients with early breast cancer



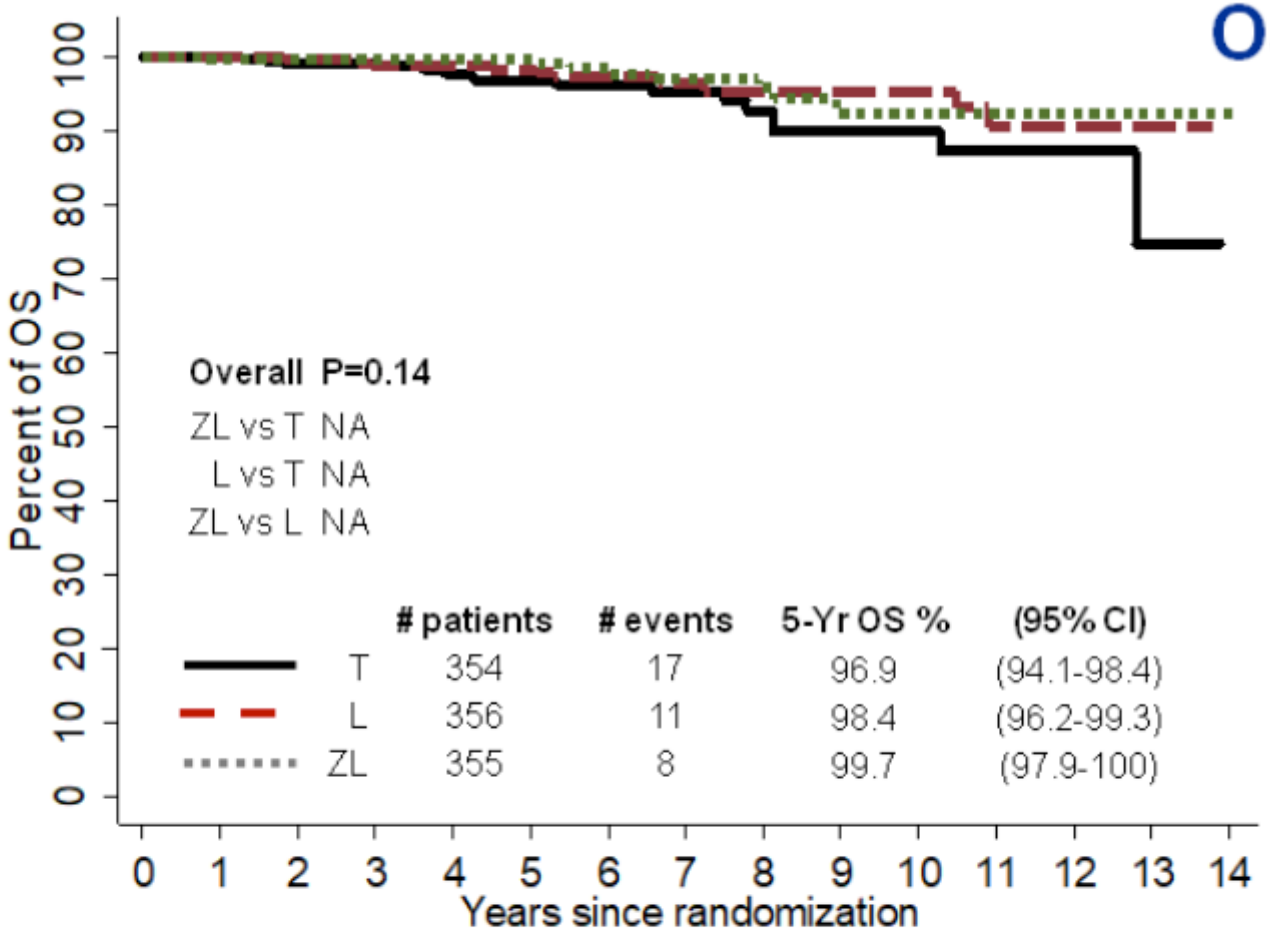
DFS



Number at risk

T	354	346	326	288	226	189	113	73	56	39	27	18	12	4	0
L	356	348	340	311	259	218	132	89	60	47	35	26	15	4	0
ZL	355	333	323	298	252	210	131	90	65	43	31	25	14	5	1

OS



Number at risk

T	354	353	341	312	252	214	131	90	69	50	35	25	18	5	0
L	356	350	346	314	267	228	140	99	71	58	46	34	21	6	0
ZL	355	337	333	307	265	220	142	98	73	48	34	29	15	5	1

Rate of selected adverse events

CTC term	T (N=351) Any (≥1)	T (N=351) Severe (≥3)	L (N=362) Any (≥1)	L (N=362) Severe (≥3)	ZL (N=328) Any (≥1)	ZL (N=328) Severe (≥3)	P*
Fever	-	-	0.8	-	**13.7**	**0.6**	<0.0001
Hypercholesterolemia	20.2	-	**30.4**	**-**	**25.6**	**0.3**	0.006
Arthralgia	21.9	-	**45.0**	**3.0**	**45.7**	**2.7**	<0.0001
Bone pain	15.4	-	**29.0**	**0.3**	**26.8**	**2.4**	0.0001
Osteonecrosis	-	-	-	-	**1.2**	**1.2**	0.01
Neuropathy – sensory	7.7	-	**13.0**	**0.3**	**14.3**	**0.3**	0.02
Endometrial abnormalities	**6.8**	**0.3**	3.0	-	2.4	-	0.005
Vaginal dryness	11.7	-	**20.7**	**-**	**19.8**	**-**	0.002

* exact Kruskal Wallis non-parametric analysis of variance of the worst reported grade

Novità nel Carcinoma Mammario

- IMPASSION130: Atezolizumab+Nab-Pacitaxel ↑ la PFS e OS nei PDL1+
- SOLAR-1: Fulvestrant+Alpelisib ↑ la PFS nei PIK3CA-mut
- PALOMA-3: Palbo+Fulvestrant ↑ OS (non-statisticamente significativo)
- HOBOE-2: Zolendronato+Letrozolo vs Tam ↑ la DFS in premenop (vs letrozolo???)