ESMO BREAST CANCER
VIRTUAL MEETING

Final results of the double-blind placebo-controlled randomised phase 2 LOTUS trial of first-line ipatasertib plus paclitaxel for inoperable locally advanced/metastatic triple-negative breast cancer

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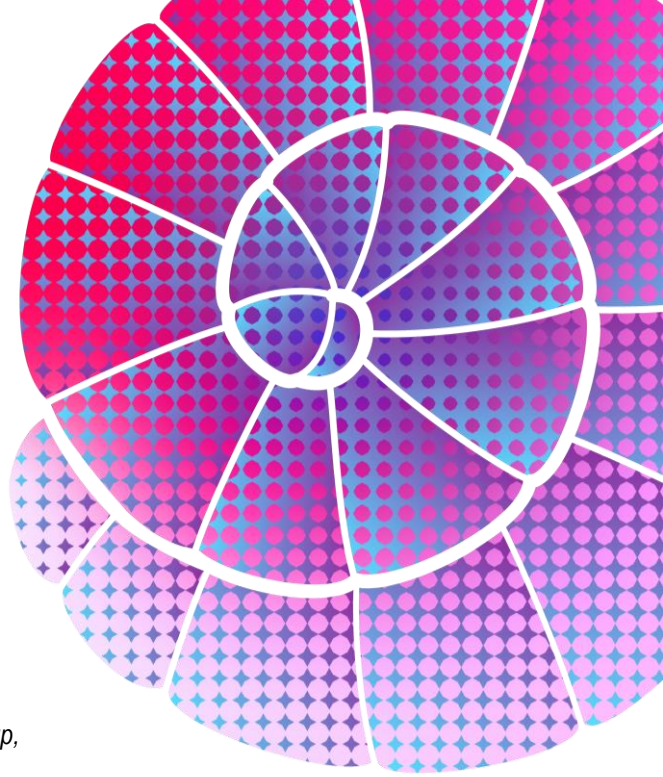

Disclosures

- R Dent discloses honoraria from Roche, Novartis, Lilly, Pfizer, Eisai, Merck and AstraZeneca
- The LOTUS trial was sponsored by Roche/Genentech
- Medical writing assistance for this presentation was provided by Jennifer Kelly, funded by F Hoffmann-La Roche Ltd

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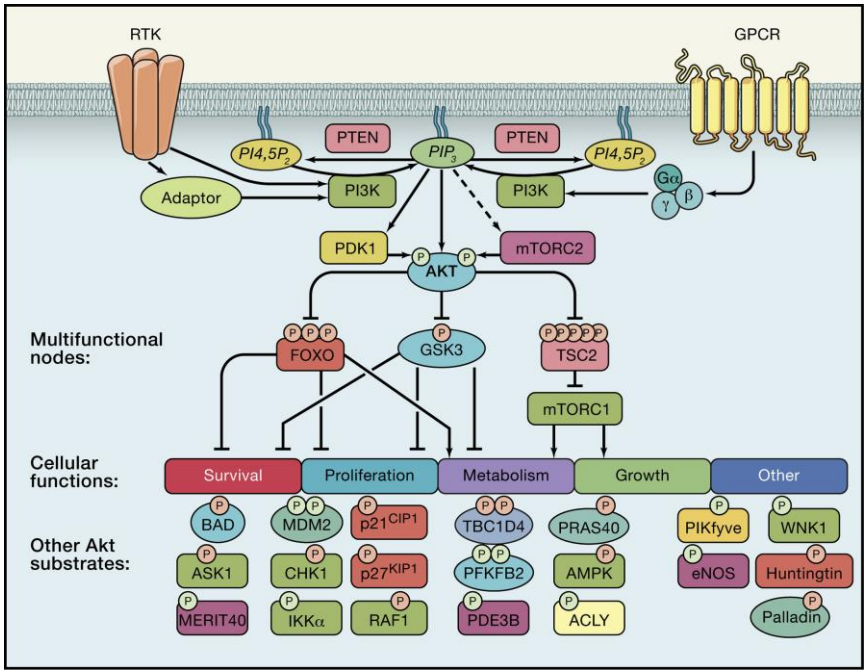
Breast cancer and the PI3K/AKT pathway



AKT can be activated by:

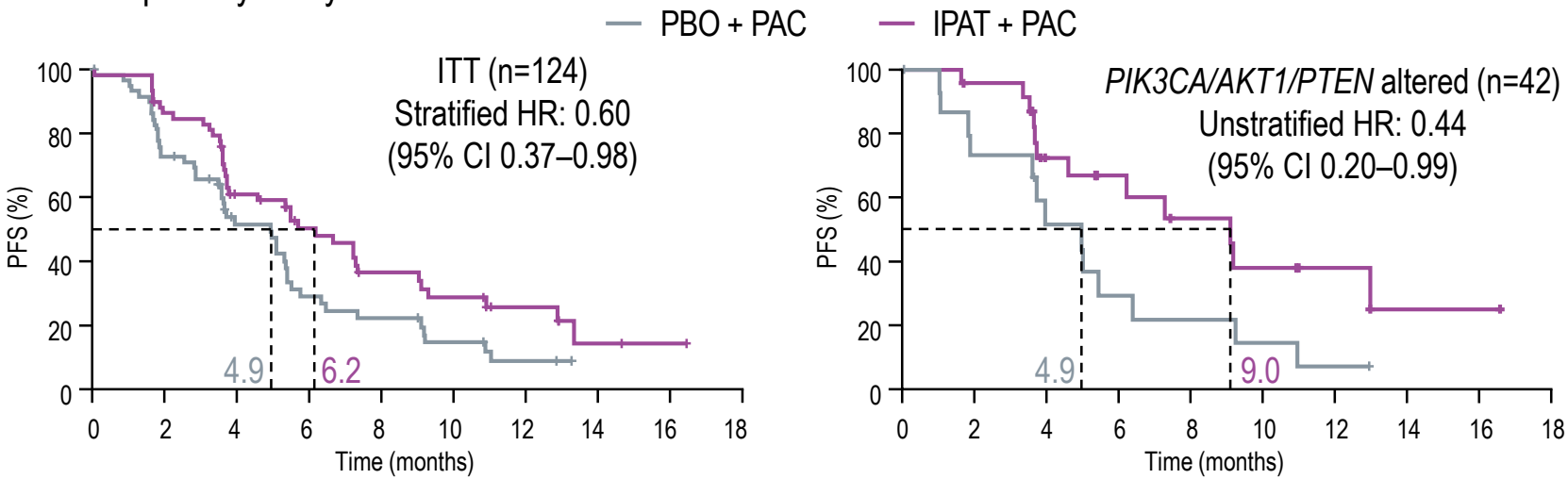
- Loss of function of negative regulators (PTEN, INPP4B, PHLPP, PP2A)
- Gain of function of positive regulators (PI3K, AKT, receptor tyrosine kinases [HER2])
- Therapy-induced survival response (chemotherapy, endocrine therapy)

PTEN = phosphatase and tensin homolog

Yap TA, et al. Curr Opin Pharmacol 2008; Manning BD and Toker A. Cell 2017

PI3K/AKT pathway inhibition in metastatic TNBC

- The oral AKT inhibitor ipatasertib (IPAT) is under evaluation in cancers with a high prevalence of PI3K/AKT pathway activation
- In the LOTUS trial in locally advanced/metastatic TNBC, treatment benefit from IPAT on PFS was observed in the ITT population and was more pronounced in the *PIK3CA/AKT1/PTEN*-altered subgroup at the primary analysis[1]



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; TNBC = triple-negative breast cancer

[1]Kim et al. Lancet Oncol 2017

LOTUS double-blinded placebo-controlled randomised phase 2 trial

- Measurable locally advanced/metastatic TNBC not amenable to curative resection
- No prior systemic therapy for advanced/metastatic disease
- Chemotherapy-free interval ≥6 months
- ECOG performance status 0/1
- Archival or newly obtained tumour tissue for central PTEN assessment

R 1:1

PAC 80 mg/m^2 days 1, 8 & 15 + IPAT 400 mg qd days 1–21 q28d

PAC 80 mg/m^2 days 1, 8 & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity or withdrawal of consent

124 patients from 44 sites in Europe, USA and Asia
Last patient last visit: 31 Jul 2019; study closure: 3 Sep 2019

Stratification factors:

- (Neo)adjuvant chemotherapy
- Chemotherapy-free interval
- Tumour IHC PTEN status

Endpoints:

- Co-primary: PFS in ITT and PTEN-low populations
- Secondary: OS, ORR, DoR (ITT, PTEN-low and PI3K/AKT pathway-activated populations), PFS in PI3K/AKT pathway-activated population, safety

DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; ORR = objective response rate; OS = overall survival; q28d = every 28 days; qd = every day; R = randomisation

NCT02162719

Baseline characteristics

Characteristic, n (%)	PBO + PAC (n=62)	IPAT + PAC (n=62)
Median age, years (range)	53 (45–63)	54 (44–63)
ECOG performance status[a]		
0	36 (58)	44 (71)
1	22 (35)	18 (29)
Prior (neo)adjuvant therapy[b]	40 (65)	41 (66)
Prior taxane	34 (55)	31 (50)
Chemotherapy-free interval[b]		
6–12 months	16 (26)	18 (29)
>12 months	24 (39)	23 (37)
No prior chemotherapy	22 (35)	21 (34)
Targos PTEN H-score[b]		
0	11 (18)	10 (16)
1–150	27 (44)	27 (44)
>150	24 (39)	25 (40)
Metastatic sites[c]		
Lung	32 (52)	27 (44)
Liver	17 (27)	19 (31)
Lymph nodes	38 (61)	36 (58)
Bone	17 (27)	16 (26)

[a]Missing in 4 patients (6%) in the PBO + PAC arm. [b]Stratification factor, reported according to interactive web-response system (except prior taxane). [c]More than one answer possible

Overview of OS analyses

	Primary analysis[1]		Updated OS analysis[2,a]		Final analysis	
	PBO + PAC (n=62)	IPAT + PAC (n=62)	PBO + PAC (n=62)	IPAT + PAC (n=62)	PBO + PAC (n=62)	IPAT + PAC (n=62)
Data cut-off	7 June 2016		26 July 2017		3 September 2019	
Median duration of follow-up, months (IQR)	10.2 (6.0–13.6)	10.4 (6.5–14.1)	16.1 (8.7–22.2)	18.1 (11.4–23.8)	16.0 (8.7–33.5)	19.0 (11.4–29.4)
Deaths, n (%)	17 (27)	9 (15)	35 (56)	33 (53)	46 (74)	41 (66)

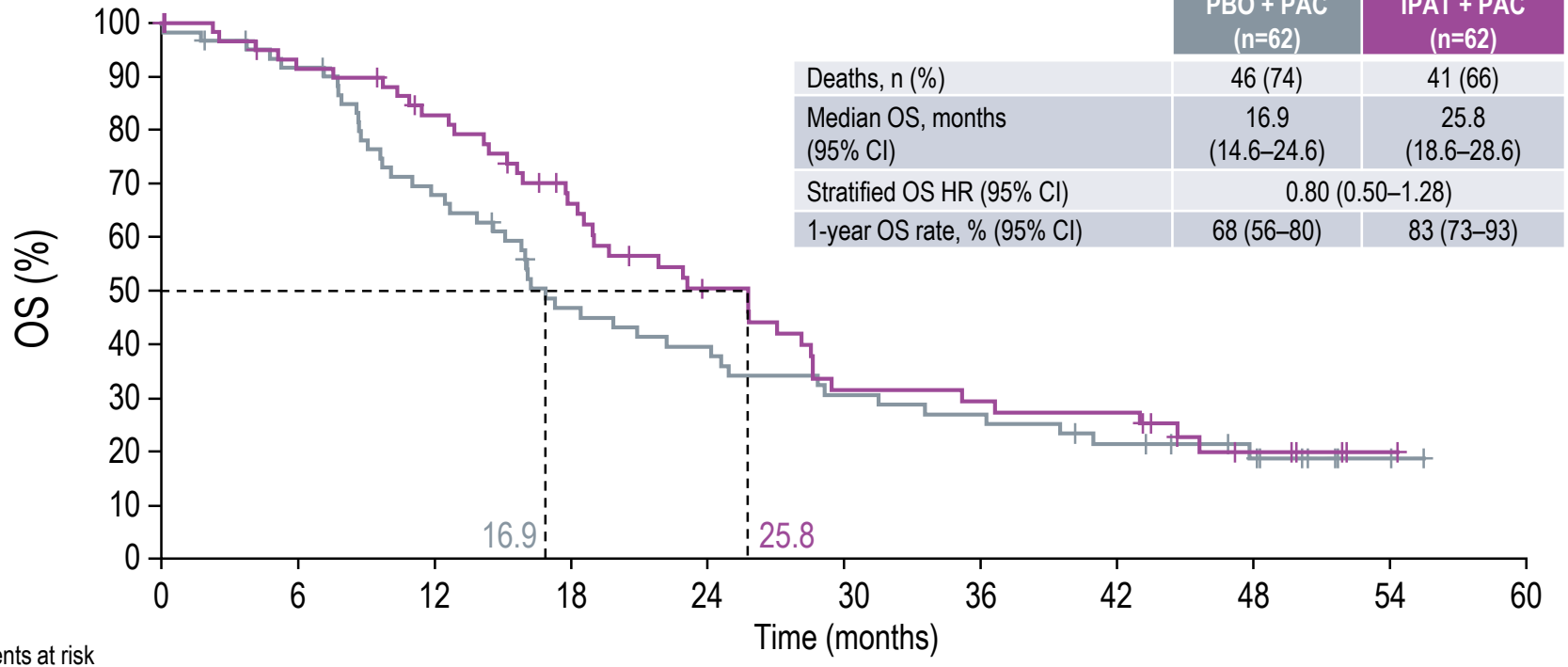
[a]Not prespecified

IQR = interquartile range

[1]Kim et al. Lancet Oncol 2017; [2]Dent et al. ASCO 2018

Final OS in the ITT population

	PBO + PAC (n=62)	IPAT + PAC (n=62)
Deaths, n (%)	46 (74)	41 (66)
Median OS, months (95% CI)	16.9 (14.6–24.6)	25.8 (18.6–28.6)
Stratified OS HR (95% CI)	0.80 (0.50–1.28)	
1-year OS rate, % (95% CI)	68 (56–80)	83 (73–93)



Patients at risk

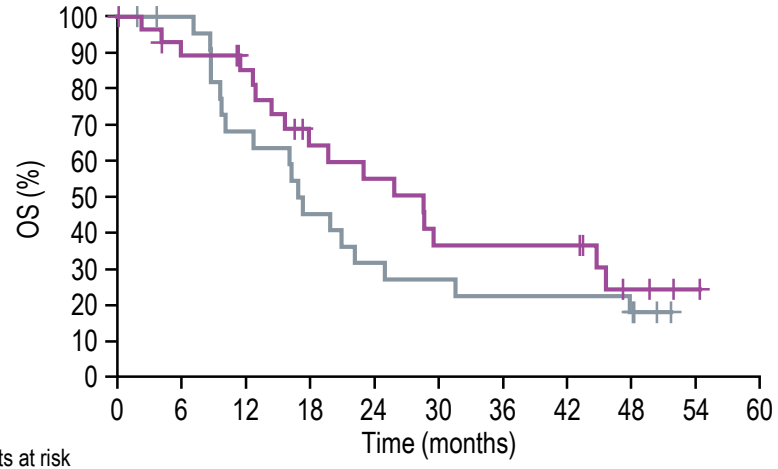
IPAT + PAC	62	54	46	34	24	15	14	13	5	1
PBO + PAC	62	55	40	26	22	17	15	11	7	1

Data cut-off: 3 September 2019

OS according to IHC PTEN status (Ventana)

PTEN normal

	PBO + PAC (n=24)	IPAT + PAC (n=29)
Deaths, n (%)	18 (75)	17 (59)
Median OS, months (95% CI)	17.1 (10.1–24.9)	28.5 (17.8–45.6)
Unstratified OS HR (95% CI)	0.70 (0.36–1.36)	
1-year OS rate, % (95% CI)	68 (49–88)	85 (72–99)

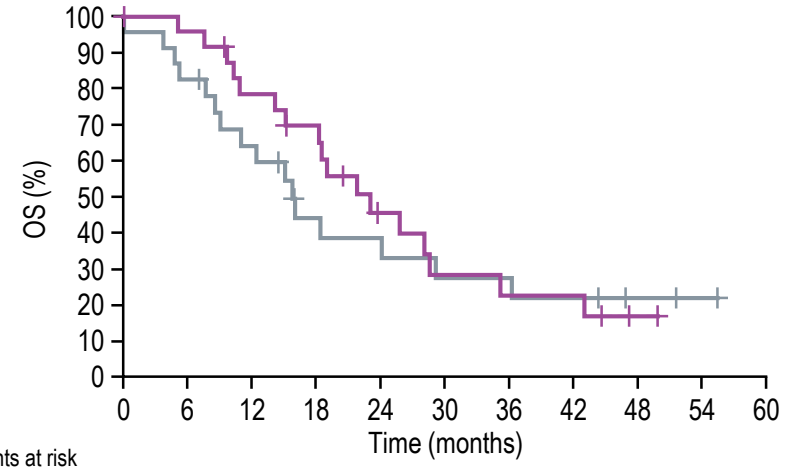


Patients at risk

IPAT + PAC	29	24	21	14	12	8	8	8	3	1
PBO + PAC	24	22	15	10	7	6	5	5	4	

PTEN low[a]

	PBO + PAC (n=23)	IPAT + PAC (n=25)
Deaths, n (%)	16 (70)	17 (68)
Median OS, months (95% CI)	15.8 (9.0–29.1)	23.1 (18.3–28.6)
Unstratified OS HR (95% CI)	0.83 (0.42–1.64)	
1-year OS rate, % (95% CI)	64 (44–84)	79 (62–95)



Patients at risk

IPAT + PAC	25	23	18	15	8	5	4	4	1	
PBO + PAC	23	19	14	8	7	5	5	4	2	1

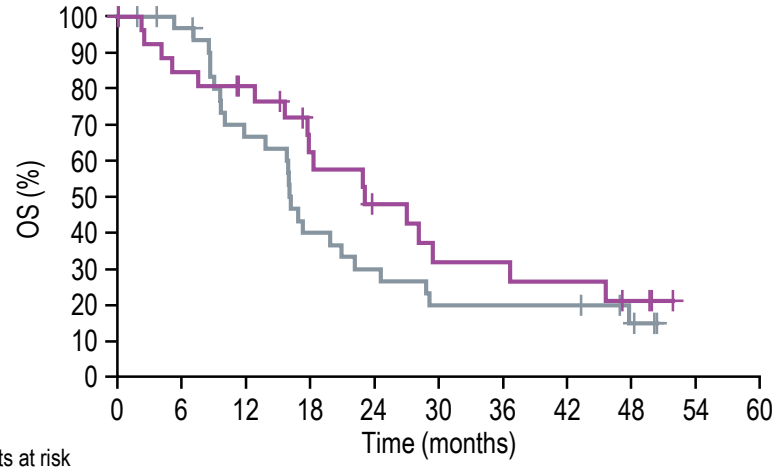
[a]IHC 0 in ≥50% of tumour cells (Ventana IHC).

Data cut-off: 3 September 2019

OS according to *PIK3CA/AKT1/PTEN* status by NGS

Non altered

	PBO + PAC (n=33)	IPAT + PAC (n=28)
Deaths, n (%)	25 (76)	17 (61)
Median OS, months (95% CI)	16.2 (11.8–22.2)	23.1 (17.7–36.6)
Unstratified OS HR (95% CI)	0.72 (0.39–1.33)	
1-year OS rate, % (95% CI)	67 (50–84)	81 (66–96)

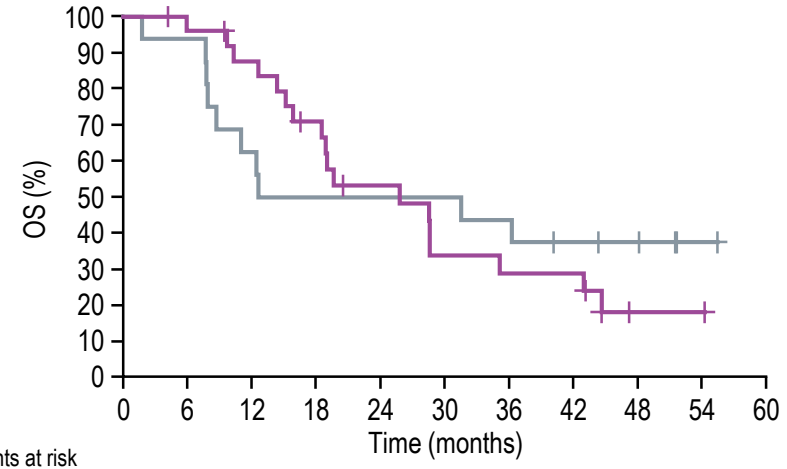


Patients at risk

IPAT + PAC	28	22	19	13	9	6	6	5	3
PBO + PAC	33	30	20	12	9	6	6	6	3

Altered

	PBO + PAC (n=16)	IPAT + PAC (n=26)
Deaths, n (%)	10 (63)	18 (69)
Median OS, months (95% CI)	22.1 (8.7–NE)	25.8 (18.6–35.2)
Unstratified OS HR (95% CI)	1.13 (0.52–2.47)	
1-year OS rate, % (95% CI)	63 (39–86)	88 (75–100)



Patients at risk

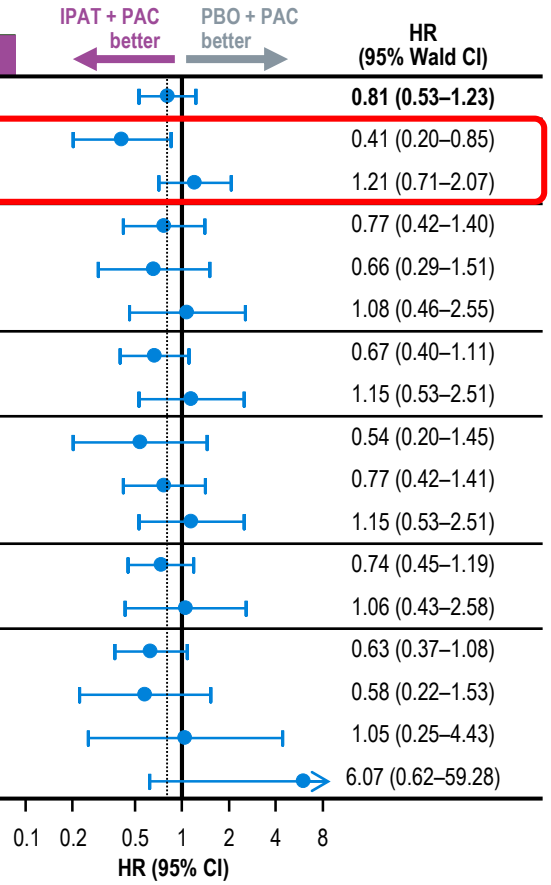
IPAT + PAC	26	24	21	16	11	7	6	6	1	1
PBO + PAC	16	15	10	8	8	8	7	5	4	1

NGS = next-generation sequencing

Data cut-off: 3 September 2019

OS in clinically relevant subgroups

Factor	Subgroup	No. of events/No. of patients (%)		Median OS, months		HR (95% Wald CI)
		PBO + PAC	IPAT + PAC	PBO + PAC	IPAT + PAC	
All	–	**46/62 (74)**	**41/62 (66)**	**16.9**	**25.8**	**0.81 (0.53–1.23)**
Age, years	<50	20/24 (83)	12/22 (54)	15.1	35.2	0.41 (0.20–0.85)
	≥50	26/38 (68)	29/40 (73)	20.9	21.8	1.21 (0.71–2.07)
Region	Asia	23/30 (77)	20/29 (69)	18.4	25.8	0.77 (0.42–1.40)
	EU	12/16 (75)	11/18 (61)	16.2	25.8	0.66 (0.29–1.51)
	USA	11/16 (69)	10/15 (67)	15.8	19.7	1.08 (0.46–2.55)
Prior (neo)adjuvant chemotherapy (eCRF)	Yes	33/42 (79)	28/42 (67)	15.8	23.1	0.67 (0.40–1.11)
	No	13/20 (65)	13/20 (65)	18.4	25.8	1.15 (0.53–2.51)
DFI since last chemotherapy, months (eCRF)	≤12	11/14 (79)	8/11 (73)	11.3	14.4	0.54 (0.20–1.45)
	>12	22/28 (79)	20/31 (65)	22.2	25.8	0.77 (0.42–1.41)
	No prior chemotherapy	13/20 (65)	13/20 (65)	18.4	25.8	1.15 (0.53–2.51)
Stage at initial diagnosis	0–III	35/45 (78)	32/48 (67)	15.8	22.9	0.74 (0.45–1.19)
	IV	11/17 (65)	9/14 (64)	20.9	27.0	1.06 (0.43–2.58)
Time from initial to metastatic diagnosis	≤3 years	29/35 (83)	26/36 (72)	14.6	19.0	0.63 (0.37–1.08)
	>3 years	10/15 (67)	7/16 (44)	36.2	45.6	0.58 (0.22–1.53)
	de novo metastatic	3/5 (60)	5/6 (83)	16.0	24.1	1.05 (0.25–4.43)
	Unknown	4/7 (57)	3/4 (75)	41.0	16.5	6.07 (0.62–59.28)



DFI = disease-free interval; eCRF = electronic case report form

Subsequent anti-cancer therapy

Therapy, n (%)	PBO + PAC (n=62)	IPAT + PAC (n=62)
Any systemic anti-cancer therapy[a]	56 (90)	48 (77)
Any chemotherapy	55 (89)	48 (77)
Platinum containing	32 (52)	33 (53)
Non-platinum containing	55 (89)	48 (77)
Immunotherapy	11 (18)	7 (11)

[a]Patients may have received more than one therapy

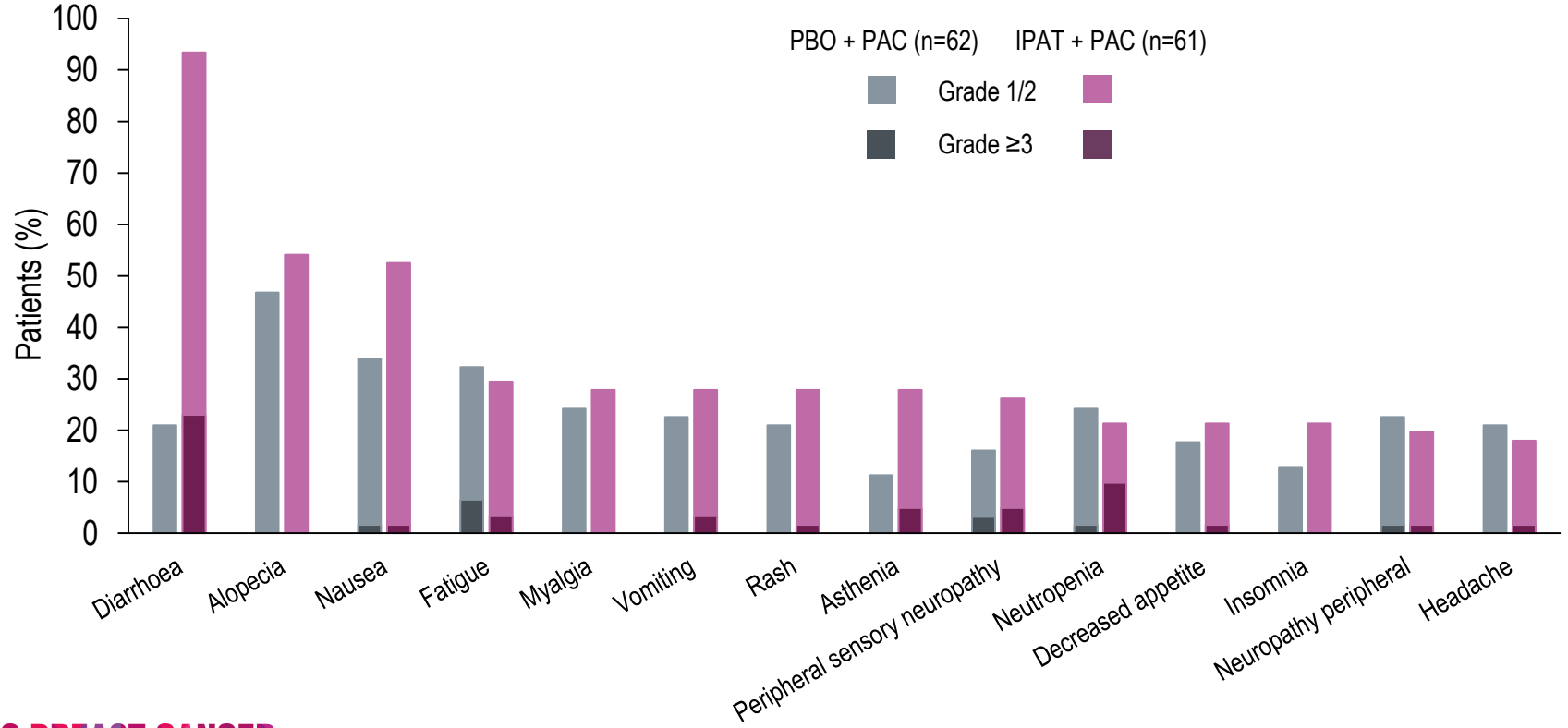
Updated safety results

AE, n (%)	Primary results[1]		Final results	
	PBO + PAC (n=62)	IPAT + PAC (n=61)	PBO + PAC (n=62)	IPAT + PAC (n=61)
Median (IQR) treatment duration, months				
IPAT/PBO	3.5 (1.6–5.4)	5.0 (3.5–7.8)	3.5 (1.6–6.0)	5.3 (3.4–9.2)
PAC	3.5 (1.5–5.1)	4.1 (3.2–7.2)	3.5 (1.4–5.6)	5.1 (3.2–8.8)
Grade ≥3 AE	26 (42)	33 (54)	28 (45)	34 (56)
AE leading to treatment discontinuation				
IPAT/PBO	1 (2)	4 (7)	1 (2)	4 (7)
PAC	5 (8)	5 (8)	6 (10)	8 (13)
AE leading to treatment interruption				
IPAT/PBO	12 (19)	22 (36)	14 (23)	22 (36)
PAC	30 (48)	31 (51)	32 (52)	32 (52)
AE leading to dose reduction				
IPAT/PBO	4 (6)	13 (21)	4 (6)	13 (21)
PAC	7 (11)	23 (38)	8 (13)	23 (38)

AE = adverse event

[1]Kim et al. Lancet Oncol 2017

Final safety: Most common[a] adverse events (all grades)



Primary prophylactic anti-diarrhoeal drugs were not specified as part of safety management guidelines in the protocol

[a]AEs in >20% of patients in either treatment arm

Conclusions

- At the final analysis after deaths in 70% of patients, OS was numerically longer with IPAT + PAC:
  - Median OS: 16.9 vs 25.8 months in the PBO + PAC vs IPAT + PAC arms, respectively
  - Hazard ratio: 0.81 (95% CI 0.53–1.23)
- In all biomarker-defined subgroups (PTEN normal or low, *PIK3CA/AKT1/PTEN* altered or non-altered), median OS favoured IPAT + PAC
  - However, the small sample sizes and heterogeneity of TNBC limit interpretation
- Median OS of >2 years represents a meaningful outcome in metastatic TNBC
- Safety results are consistent with previous reports[1,2]; no new safety signals were observed

[1]Kim et al. Lancet Oncol 2017; [2]Dent et al. ASCO 2018

Implications

- Now recognised that TNBC is a heterogenous disease with recognised subtypes
  - Why is blocking AKT so important?
  - Likely due to blocking a recognised driver of carcinogenesis

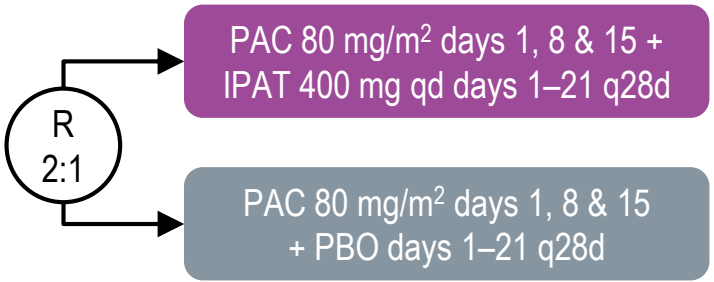
- Seems to do so with less toxicity than seen in other classes of drugs targeting this pathway

- The ongoing IPATunity130 phase 3 trial (NCT03337724) is evaluating IPAT + PAC in patients with *PIK3CA/AKT1/PTEN*-altered locally advanced or metastatic breast cancer

- IPATunity170 (NCT04177108) is evaluating first-line IPAT + PAC + atezolizumab in locally advanced or metastatic TNBC

IPATunity130: double-blinded placebo-controlled randomised phase 3 trial[a]

- Locally advanced or metastatic *PIK3CA/AKT1/PTEN*-altered TNBC
- Archival or newly obtained tumour tissue for central molecular evaluation
- Measurable disease according to RECIST v1.1
- Candidate for taxane therapy
- No prior chemotherapy for locally advanced/metastatic breast cancer



- Treatment until disease progression, intolerable toxicity[b] or elective withdrawal
- Crossover from PBO to IPAT is not permitted

[a]The trial includes two additional cohorts: Cohort B is comparing PAC + IPAT vs PAC + PBO in patients with *PIK3CA/AKT1/PTEN*-altered hormone receptor-positive HER2-negative breast cancer who have received no prior chemotherapy for LA/MBC; Cohort C (safety and efficacy signal seeking, open in 11 countries) is evaluating IPAT + PAC + atezolizumab in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours
[b]Patients discontinuing PAC or IPAT/PBO due to toxicity can continue on single-agent treatment

RECIST = Response Evaluation Criteria in Solid Tumours

NCT03337724

Acknowledgments

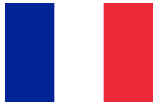
We are grateful to the patients who participated in the trial, their families, and the investigators and staff at the 44 participating centers:

South Korea

S-B Kim
KS Lee
S-A Im
JH Sohn
JH Kim
JH Seo
JS Kim
S Park

USA

S Blau
A Tan
M Velez
S Dakhil
S Hurvitz
V Valero
G Vidal
R Figlin
MAK Allison
D Chan
M Cobleigh
V Hansen
N Iannotti
SJ Isakoff
W Lawler
M Salkini
L Seigel



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