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Ipatasertib + paclitaxel for *PIK3CA/AKT1/PTEN*-altered hormone receptor-positive HER2-negative advanced breast cancer: Primary results from Cohort B of the IPATunity130 randomised trial

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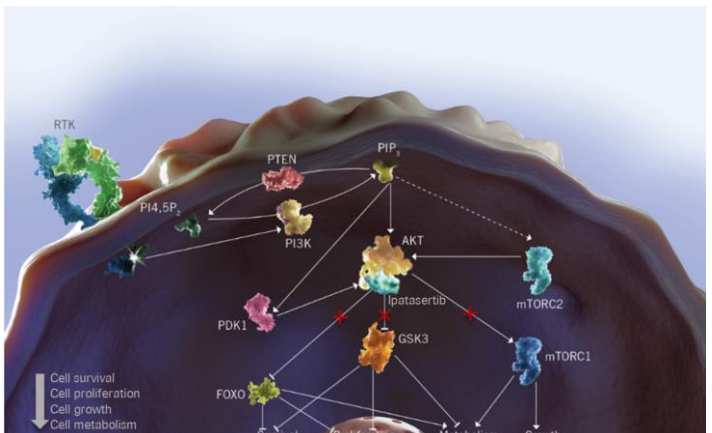
Slides are available at: https://bit.ly/30Vd8xf

Rationale: Preclinical and phase 1b data support evaluation of ipatasertib (IPAT) in HR+ HER2-negative aBC



- The PI3K/AKT pathway plays a critical role in HR+ HER2-negative breast cancer; AKT activation is implicated in resistance to endocrine therapy[1]
- IPAT is an oral ATP-competitive selective inhibitor of AKT1–3, the central node of the PI3K/AKT pathway[2–6]
- Several HR+ cell lines with *PIK3CA* mutations or PTEN loss are sensitive to single-agent IPAT[7]
- Phase 1b data suggest clinical activity of IPAT + taxane in HR+ mBC[8]

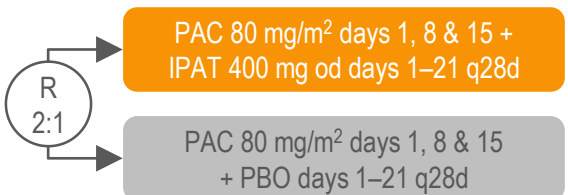
[1]El Sayed R, et al. Front Oncol 2019. [2]Lin J, et al. Clin Cancer Res 2013. [3]Tan SX, et al. Biochem J 2010. [4]Testa JR & Tsichlis PN. Oncogene 2005. [5]Huang WC & Hung MC. J Formos Med Assoc 2009. [6]Manning BD & Toker A. Cell 2017. [7]Saura C, et al. Cancer Discov 2017. [8]Isakoff SJ, et al. Ann Oncol 2020

aBC = locally advanced/metastatic breast cancer; HR+ = hormone receptor positive

IPATunity130 Cohort B (NCT03337724): Double-blinded placebo-controlled randomised trial[a]

- HR+ (≥1%) HER2-negative measurable aBC
- *PIK3CA/AKT1/PTEN* alteration[b]
- Not considered appropriate for endocrine-based therapy
- No prior chemotherapy for aBC
- Prior CDK4/6 inhibitor and/or mTOR inhibitor permitted
- Candidate for taxane therapy
- ECOG performance status 0/1

222 patients enrolled between 6 Jan 2018 and 29 Mar 2019 (50% Europe, 26% Asia-Pacific)



Treatment until disease progression, intolerable toxicity[c] or elective withdrawal

Crossover from PBO to IPAT is not permitted

Analysis of primary endpoint (investigator-assessed PFS) planned after ~150 PFS events

- 80% power to detect an increase in median PFS from 8.5 → 13.8 months with the addition of IPAT to PAC
- Target hazard ratio = 0.62 at 2-sided 5% significance level

[a]Cohort A comparing the same two regimens in triple-negative breast cancer will be analysed independently. Cohort C (safety and efficacy signal seeking) is evaluating IPAT + PAC + atezolizumab in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours. [b]Centrally or locally tested archival or newly obtained tumour tissue; activating alterations in *PIK3CA* and/or *AKT1* and/or inactivating alterations in *PTEN*.[1] [c]Patients discontinuing PAC or IPAT/PBO due to toxicity can continue single-agent treatment

CDK = cyclin-dependent kinase; ECOG = Eastern Cooperative Oncology Group; mTOR = mammalian target of rapamycin; od = once daily; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; q28d = once every 28 days; R = randomisation

[1]Wongchenko M, et al. AMP 2019

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Baseline characteristics

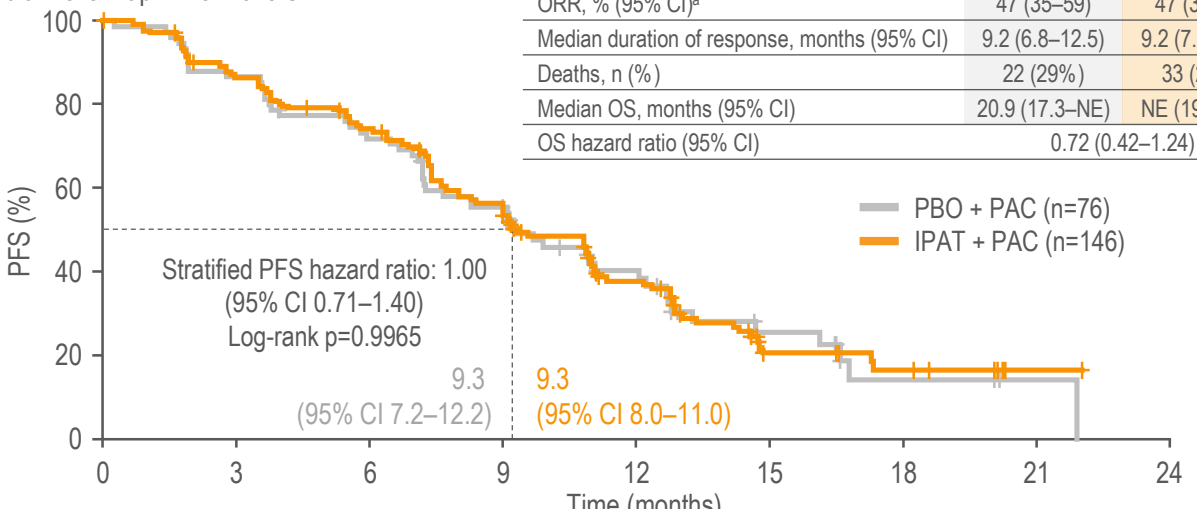
Characteristic, n (%)		PBO + PAC (N=76)	IPAT + PAC (N=146)
Post-menopausal[a]		59 (78%)	113 (78%)
Prior therapy	(Neo)adjuvant chemotherapy[b]	43 (57%)	80 (55%)
	PI3K/mTOR inhibitor[b]	17 (22%)	36 (25%)
	CDK4/6 inhibitor	21 (28%)	36 (25%)
Chemotherapy-free interval, years[c]	1–3	18 (24%)	29 (20%)
	>3	18 (24%)	45 (31%)
	No prior chemotherapy	36 (47%)	65 (45%)
Metastatic sites[d]	Lung	35 (46%)	52 (36%)
	Liver	43 (57%)	70 (48%)
	Bone	54 (71%)	95 (65%)
	Lymph node	36 (47%)	76 (52%)
No. of lines of prior endocrine treatment for aBC	0	39 (51%)	81 (55%)
	1	17 (22%)	34 (23%)
	2	9 (12%)	15 (10%)
	3+	11 (14%)	16 (11%)
Endocrine resistance status[e]	Primary	14 (18%)	26 (18%)
	Secondary	32 (42%)	67 (46%)
	Visceral crisis without endocrine resistance	10 (13%)	29 (20%)
PIK3CA/AKT1/PTEN alteration status[f]	*PIK3CA/AKT1*-activating mutation	60 (81%)	127 (88%)
	PTEN alteration without *PIK3CA/AKT1*-activating mutation	14 (19%)	17 (12%)

[a]Not applicable in 2 male IPAT + PAC patients. [b]As recorded in interactive web-response system. [c]Not available in 4 PBO + PAC and 7 IPAT + PAC patients. [d]Missing in 3 PBO + PAC and 5 IPAT + PAC patients. [e]Categories are mutually exclusive. [f]Missing in 2 patients in each arm.

Summary of efficacy

Primary endpoint: investigator-assessed PFS

Median follow-up: 12.9 months



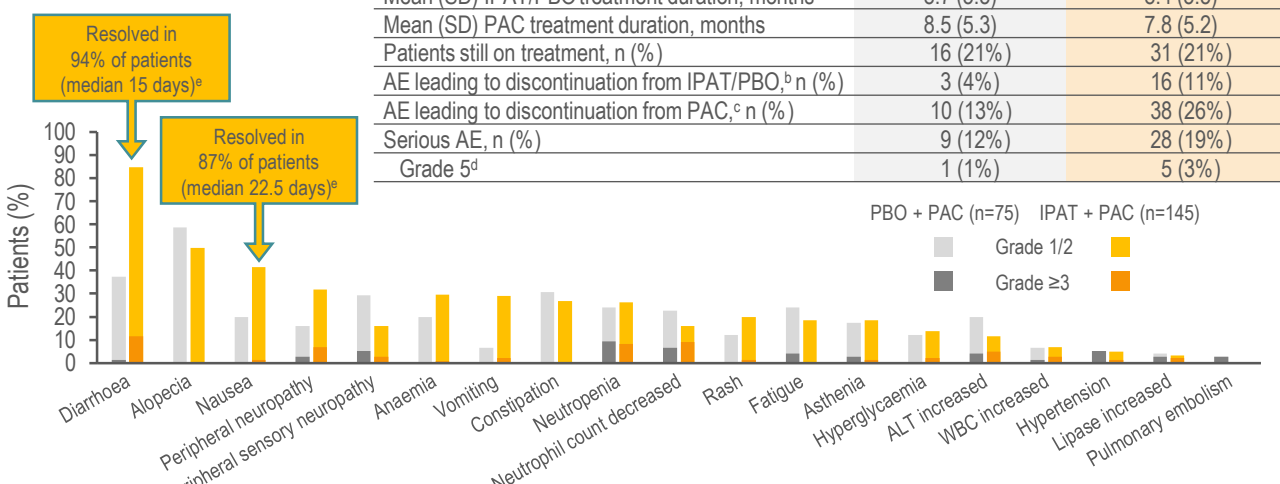
Secondary endpoints	PBO + PAC (n=76)	IPAT + PAC (n=146)
ORR, % (95% CI)[a]	47 (35–59)	47 (38–55)
Median duration of response, months (95% CI)	9.2 (6.8–12.5)	9.2 (7.2–11.3)
Deaths, n (%)	22 (29%)	33 (23%)
Median OS, months (95% CI)	20.9 (17.3–NE)	NE (19.2–NE)
OS hazard ratio (95% CI)	0.72 (0.42–1.24)	

Clinical cut-off date: 17 January 2020. [a]Patients with measurable disease (n=75 PBO + PAC, n=144 IPAT + PAC)

ORR = objective response rate; NE = not estimable

Treatment exposure and safety[a]

	PBO + PAC (N=75)	IPAT + PAC (N=145)
Mean (SD) IPAT/PBO treatment duration, months	8.7 (5.5)	8.4 (5.5)
Mean (SD) PAC treatment duration, months	8.5 (5.3)	7.8 (5.2)
Patients still on treatment, n (%)	16 (21%)	31 (21%)
AE leading to discontinuation from IPAT/PBO,[b] n (%)	3 (4%)	16 (11%)
AE leading to discontinuation from PAC,[c] n (%)	10 (13%)	38 (26%)
Serious AE, n (%)	9 (12%)	28 (19%)
Grade 5[d]	1 (1%)	5 (3%)



[a]≥20% any grade or ≥5% grade ≥3 in either arm. [b]Including diarrhoea in 1.3% vs 2.8%, neutropenia/febrile neutropenia in 0% vs 2.1% and hyperglycaemia in 0 vs 1.4%, respectively. [c]Nervous system disorders in 8.0% vs 15.2%. [d]Sepsis in the PBO + PAC arm; one case each of pneumonia, febrile neutropenia, respiratory distress, death and road traffic accident/general physical health deterioration in the IPAT + PAC arm. [e]Time to resolution of first episode

ALT = alanine aminotransferase; WBC = white blood cell

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Conclusions and next steps

- Adding the AKT inhibitor ipatasertib to paclitaxel in *PIK3CA/AKT1/PTEN*-altered HR+ HER2-negative aBC did not improve PFS or ORR
  - Overall survival follow-up is ongoing
- Safety was consistent with previously reported results for this combination[1]
- Results are consistent with findings from the phase 1/2 BEECH trial (paclitaxel ± the AKT inhibitor capivasertib in HR+ mBC)[2]
  - In contrast, combining an AKT inhibitor with fulvestrant improved PFS in the phase 2 FAKTION trial,[3] suggesting that endocrine blockade may be critical for the activity of AKT inhibitors in the HR+ setting
- Ongoing and planned studies in HR+ HER2-negative aBC are evaluating ipatasertib combined with endocrine-based regimens

[1]Kim S-B, et al. Lancet Oncol 2017; [2]Turner N, et al. Ann Oncol 2019; [3]Jones RH, et al. Lancet Oncol 2020