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96MO A risk analysis of alpelisib (ALP)-induced hyperglycemia (HG) using baseline factors in patients (pts) with advanced solid tumours and breast cancer (BC): A pooled analysis of X2101 and SOLAR-1

J. Rodon[1], D. Demanse[2], H.S. Rugo[3], F. André[4], F. Janku[5], I. Mayer[6], H. Burris[7], R. Simo[8], A. Farooki[9], H. Hu[10], I. Lorenzo[11], C. Quadt[12], D. Juric[13]

[1]Drug Development Department, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [2]Oncology, Novartis Pharma AG, Basel, Switzerland; [3]Breast Department, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]Breast Cancer Unit, Medical Oncology Department, Gustave Roussy - Cancer Campus, Villejuif, France; [5]Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [6]Medical Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [7]Drug Development Department, Sarah Cannon Research Institute, Nashville, TN, USA; [8]Vall d'Hebron Research Institute, Autonomous University of Barcelona, Barcelona, Spain; [9]Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [11]Oncology, Novartis Farmacéutica SA, Madrid, Spain; [12]Translational Clinical Oncology, Novartis International AG - Basel, Basel, Switzerland; [13]Medical Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Background: ALP + fulvestrant is approved for PIK3CA-mutated, HR+/HER2− advanced BC in the US and EU. HG is an on-target adverse event (AE) of ALP and the most common all grade (G) and G3/4 AE in the phase III SOLAR-1 trial. Antihyperglycemic agents (AHAs) and ALP dose modifications (mods) and discontinuations (discs) were used to manage this AE (Table). We present a pooled risk factor model using safety sets of the phase I X2101 (NCT01219699) and SOLAR-1 (NCT02437318) trials and its application to SOLAR-1 data.

Methods: Pts (505) were randomly divided into training (405 pts) and testing sets (100 pts). Baseline factors for HG were identified, multiple models tested, and a random forest model was used to categorize pts as high or low risk for G3/4 HG based on 5 baseline factors (fasting plasma glucose [FPG], BMI, HbA1c, monocyte counts, and age). Performance metrics will be presented.

Results: The training set identified G3/4 HG in 126/131 high (96.2%) vs 3/274 low risk (1.09%) pts, and was validated in the testing set with 20/33 high (60.6%) vs 12/67 low risk (17.9%) pts. A 2-month (mo) analysis of G3/4 HG risk confirmed decreased probability at lower risk scores (area under the curve: training set = 0.991, testing set = 0.767). In all pts in the ALP arm of SOLAR-1, the model found a higher incidence of all-G and G3/4 HG, use of multiple AHAs, and more dose mods and discs in the high vs low risk pts (Table). There was no difference in median PFS in high (11.0 mo) vs low risk (10.9 mo) pts in the ALP arm with PIK3CA mutations.

Table: 96MO

HG incidence and management, n (%)	All Pts N = 284	High Risk N = 106	Low Risk N = 178
All-G HG	187 (65.8)	101 (95.3)	86 (48.3)
G3/4 HG	108 (38.0)	96 (90.6)	12 (6.7)
Patients who received AHAs	163 (57.4)	94 (88.7)	70 (39.3)
1 AHA	67 (41.1)	24 (25.5)	43 (61.4)
2 AHA	49 (30.1)	31 (33.0)	18 (25.7)
≥3 AHA	47 (28.8)	39 (41.5)	9 (12.9)
Dose mods for any reason (reductions and/or interruption of ALP)	213 (75.0)	92 (86.8)	122 (68.5)
Permanent discs for any reason	244 (85.9)	90 (84.9)	154 (86.5)
Discs due to HG	19 (6.7)	15 (14.2)	4 (2.2)

Conclusions: Risk modeling identified 5 baseline factors (FPG, BMI, HbA1c, monocyte counts, and age) associated with a higher probability of ALP-induced G3/4 HG. High risk pts had higher rates of AHAs and ALP mods. This model could be used clinically to identify pts at high risk for ALP-induced HG. Regardless of risk, pts with PIK3CA mutations derived a similar PFS benefit from ALP.

Clinical trial identification: NCT02437318, NCT01219699.

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97P Is continuing CDK4-6 inhibitor therapy safe during the COVID-19 pandemic? A UK cancer centre experience

V. Angelis, P. McFarlane, N. Cunningham, S. Gennatas, S.R.D. Johnston, A. Okines, S. McGrath

Medical Oncology, The Royal Marsden Hospital (Chelsea) - NHS Foundation Trust, London, UK

Background: CDK4-6 inhibitors are now considered the standard of care for advanced ER-positive HER2-negative advanced breast cancer (ABC) in combination with endocrine therapy (ET). During the first wave of the COVID-19 pandemic, clinicians were uncertain what impact CDK4-6 inhibitor-induced immunosuppression may have on the risk of contracting COVID-19 or the severity of infection. Some clinicians preemptively reduced doses, altered schedules, or even withheld treatment, continuing ET alone. There is currently no evidence that CDK4-6 inhibitors increase the risk or severity of COVID-19 infection, although there have reports of protracted illness. We describe our experience of 203 patients receiving CDK4-6 inhibitors during the first wave and demonstrate the safety of continuing treatment during this period.

Methods: Epidemiological and clinical data were collected prospectively for patients at the Royal Marsden Hospital (RMH) and one network hospital with a ER-positive HER2-negative ABC that were receiving a CDK4-6 inhibitor between April 1st and June 30th 2020.

Results: 200 patients received a CDK4-6 inhibitor in combination with ET, of which of 65/200 fulfilled local criteria to be screened with COVID-19 PCR testing and 6/65 were swab-positive. Two patients required hospital admission but there were no ICU admissions or COVID-19-associated deaths. Only 12 patients (6%) had treatment adjustments in the form of dose reduction (3/12), regime adjustment (2/12), or temporary interruption (7/12). In 9/12 cases this was a prophylactic measure due to additional risk factors; age (n=1), co-morbidities(n=3), patient choice (n=1) or overall concerns (n=4) to reduce the risk of contracting COVID-19. Results on dispensing >2 cycles at a time, telephone clinics, deferred CT scans and complications relating due to remote monitoring will also be reported.

Conclusions: Based on this snapshot during the first wave of the COVID-19 pandemic, we conclude that continuation of CDK4-6 inhibitors appears safe. This project is helping to drive a UK-wide review of CDK4-6 inhibitor treatment continuation, adjustment during the pandemic, assessing the risk of acquiring clinically severe COVID-19 infection, and subsequent cancer-related outcomes for these patients.

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98P Final results from AVANTI, a multicentre German observational study of first-line bevacizumab (BEV) + chemotherapy (CT) in >2000 patients (pts) with advanced breast cancer (aBC)

V. Mueller[1], M. Ruhnke[2], O. Hoffmann[3], A. Grafe[4], O. Tomé[5], W. Fett[6], H-R. Bruch[7], A-K. Sommer[8], A. Schneeweiss[9]

[1]Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Paracelsus-Klinik Osnabrück, Osnabrück, and Helios Klinikum Aue, Aue (Current Affiliation), Germany; [3]Gynecology and Obstetrics, Universitätsklinikum Essen, Essen, Germany; [4]MVZ Nordhausen gGmbh, Praxis Dr Grafe/Brustzentrum der Frauenklinik, Südharz-Klinikum Nordhausen gGmbh, Nordhausen, Germany; [5]Gynaecological Cancer Centre and Cooperative Breast Centre, St. Vincentius-Kliniken gAG, Karlsruhe, Germany; [6]Oncology, Onkologische Praxis, Wuppertal, Germany; [7]Oncology, Schwerpunktpraxis Bonn, Bonn, Germany; [8]Pharma Medical Affairs, Roche Pharma AG, Grenzach-Wyhlen, Germany; [9]Nationales Centrum für Tumorerkrankungen, Universitätsklinikum und Deutsches Krebsforschungszentrum, Heidelberg, Germany

Background: In Europe, BEV is approved in combination with paclitaxel (PAC) or capecitabine (CAP) as 1st-line therapy for HER2-negative aBC. AVANTI (ML22452) assessed safety, effectiveness and pt-reported outcomes (EORTC QLQ-C30) with these regimens in German routine oncology practice.

Methods: Eligible pts had HER2-negative aBC, no BEV contraindications and had received no prior CT for aBC. CT schedule, diagnostics and follow-up visits were at the physician's discretion. Data were collected for 1 y after starting BEV, then every 6 mo for 1.5 y (max follow-up: 2.5 y). Treatment satisfaction was rated by pts and physicians. Subgroup analysis was prespecified in clinically relevant subgroups, including triple-negative breast cancer (TNBC).

Results: Between 1 Nov 2009 and 30 Apr 2016, 2065 eligible pts at 346 centres received ≥1 dose of BEV with PAC (n=1821) or CAP (n=295); 51 switched CT and were analysed in both subgroups. Data cut-off for the final analysis was 3 Feb 2020. Median age was 60 y, 21% had TNBC, 56% prior (neo)adjuvant CT and 29% de novo metastatic disease. Pts receiving BEV + CAP were less likely to have de novo disease and more likely to have TNBC, age ≥60 y and prior CT and endocrine therapy (ET). The median treatment duration was 6.0 mo (95% CI 5.6—6.3) for BEV and 4.2 mo (4.0—4.2) for CT. Overall (complete or partial) response rate was 49% (95% CI 46—51%). Median PFS was 12.6 (95% CI 11.9—13.2) mo (12.8 with BEV + PAC, 10.5 with BEV + CAP); median OS was 23.9 (22.2—25.1) mo. PFS and OS were worse in pts with TNBC, prior CT or prior ET (Table). Grade 3/4 AEs were reported in 27% of pts and led to treatment discontinuation in 15%. Treatment satisfaction was rated as good or better by 304/394 (77%) responding pts at week 54 and in 1393/2065 pts (67%) by physicians across the study.

Conclusions: Final results from AVANTI show median PFS of 12.6 mo and a safety profile consistent with phase III experience.

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Table: 98P

Subgroup		PFS		OS	
		Median, mo	HR (95% CI)	Median, mo	HR (95% CI)
Baseline hypertension	Hypertensive v normotensive	13.6 v 11.9	0.88 (0.77 −1.00)	25.1 v 23.2	0.88 (0.76 −1.01)
TNBC[a]	Yes v no	10.3 v 12.9	1.44 (1.24 −1.67)	16.8 v 25.2	1.53 (1.30 −1.80)
Age	≥60 v <60 y	12.8 v 12.3	1.09 (0.96 −1.23)	21.9 v 25.4	1.26 (1.11 −1.44)
Metastatic sites	≥3 v <3	11.6 v 12.8	1.06 (0.88 −1.28)	19.3 v 24.9	1.15 (0.96 −1.39)
Prior anthracycline/taxane	Yes v no	11.5 v 14.3	1.32 (1.16 −1.50)	20.8 v 27.4	1.25 (1.09 −1.43)
Prior ET	Yes v no	10.7 v 13.2	1.56 (1.33 −1.82)	17.6 v 25.1	1.56 (1.33 −1.82)

[a]Unknown in 127 pts. CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

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99P Analysis of ctDNA in advanced breast cancer reveals polyclonal disease associated with adverse outcome

B. Kingston[1], R. Cutts[1], M. Beaney[1], G. Walsh-Crestani[1], S. Hrebien[1], L. Kilburn[2], S. Kernaghan[2], L. Moretti[2], K. Wilkinson[2], I. MacPherson[3], R.D. Baird[4], R. Roylance[5], J.S. Reis-Filho[6], M. Hubank[7], I. Faull[8], K. Banks[8], I. Garcia-Murillas[1], J. Bliss[2], A. Ring[9], N. Turner[1]

[1]Breast Cancer Research, The Institute of Cancer Research, London, London, UK; [2]Clinical Trials & Statistics Unit, ICR - Institute of Cancer Research, London, UK; [3]Medical Oncology, BWSCC - Beatson West of Scotland Cancer Centre - NHS Greater Glasgow and Clyde, Glasgow, UK; [4]Oncology, Addenbrooke's Hospital - Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [5]Oncology, University College London Hospitals NHS Foundation Trust, London, UK; [6]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Clinical Genomics, The Royal Marsden Hospital - NHS Foundation Trust, London, UK; [8]Medical Affairs, Guardant Health, Inc., Redwood City, CA, USA; [9]Breast Unit, The Royal Marsden Hospital - NHS Foundation Trust, London, UK

Background: Tumour biopsy studies demonstrate that metastatic breast cancers often acquire alterations, such as ESR1 and MAP kinase (MAPK) pathway mutations, which may confer treatment resistance. Tumour biopsy series have found ESR1 and MAPK mutations to be mutually exclusive. Single-site tumour biopsies may not fully sample tumour heterogeneity. Circulating tumour DNA (ctDNA) analysis samples spatially distinct tumour sites and may identify polyclonal cancers. Here we leverage ctDNA analysis in the plasmaMATCH trial to assess the relationship between ctDNA-described polyclonal cancer and patient outcome.

Methods: The plasmaMATCH trial enrolled patients with advanced breast cancer for ctDNA testing. Patients with selected mutations were enrolled into targeted treatment cohorts, including cohort A patients with ESR1 mutations for treatment with extended-dose fulvestrant. Baseline plasma was sequenced with the Guardant360 panel (Guardant Health, USA). Mutations in ESR1, MAPK, and PIK3CA defined patient groups. Survival data were analysed with log-rank test with hazard ratios calculated using Cox-regression.

Results: Of 1051 patients enrolled, 800 had ctDNA sequencing results. MAPK alterations were more frequent in patients with ESR1 mutations (77/265, 29.1% vs 100/535, 18.7%, p=0.001), and further enriched in patients with polyclonal versus single ESR1 mutations (50/127, 39.4% vs 27/138, 19.6%, p=0.0004). Patients with HR+HER2- disease (n=515) and concurrent MAPK and ESR1 alterations (n=32) had a shorter overall survival than patients wildtype for both (n=26) (p=0.0092). In PIK3CA-mutant