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Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE

Masakazu Toi (Presenter)[1]; Nadia Harbeck[2]; Juan Manuel Puig[3]; Josefina Cruz[4]; Jae Hong Seo[5]; Masato Takahashi[6]; Maarten Hulstijn[7]; Elvis Asare Twum[7]; Arie Regev[7]; Belen San Antonio[7]; Dragos Mircea Median[8]; Mario Campone[9]

[1]Kyoto University Hospital, Kyoto, Japan; [2]Ludwig-Maximilians-Universität München, Munich, Germany; [3]Centro Polivalente de Asistencia e Investigación Clínica-CER, San Juan, Argentina; [4]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [5]Korea University Guro Hospital, Republic of Korea; [6]Hokkaido Cancer Center-Breast Surgery, Sapporo, Hokkaido, Japan; [7]Eli Lilly and Company, Indianapolis, IN, USA; [8]Spitalul Clinic Filantropia, Departamentul de Oncologie Medicala, București, România; [9]Institut de Cancérologie de l'Ouest, Centre René Gauducheau, Nantes / Saint-Herblain, France

on behalf of the monarchE investigators

Sponsored by Eli Lilly and Company

Disclosures

Masakazu Toi

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Background

Background – monarchE trial, a Phase 3 study

- *Abemaciclib:* oral, continuously dosed, CDK4 & 6 inhibitor, approved for HR+, HER2- advanced breast cancer in combination with endocrine therapy (ET)[1,2]
- *Abemaciclib in combination with ET as adjuvant treatment for HR+, HER2-, high-risk early breast cancer (EBC)*: first CDK4 & 6 inhibitor to demonstrate statistically significant improvement in invasive disease-free survival (IDFS), vs. ET alone[3,4]
- Overview of safety data previously presented[5]

Objective

- Here we focus on 3 clinically important adverse events (AEs) for abemaciclib:
  - Venous thromboembolic events (VTE)
  - Elevated aminotransferases (EAT)
  - Interstitial lung disease (ILD)

[1] Sledge GW, Jr., et al. J Clin Oncol 2017;35:2875-84; [2] Goetz et al. J Clin Oncol 2017;35:3638-46; [3]Rastogi P. et al. SABCS 2020; presentation number GS1-01; [4]Johnston SRD, et al. J Clin Oncol 38:3987-3998, 2020; [5]Rugo H. et al. SGBCC 2021; poster number 013

Methods

Trial oversight

- Study enrolment, design and key eligibility criteria previously reported[4]
- Median follow-up time in both arms: 19.1 months (data cut-off: 8-Jul-2020)
- Patients receiving at least one dose of study treatment were evaluated for safety
  - Asia subgroup population: patients located in mainland China, Hong Kong, Japan, Korea, Singapore, and Taiwan

AEs clinically important

- *VTE, EAT,* and *ILD:* comprehensive search of medical dictionary (MedDRA) terms falling under the category of Venous Thromboembolic Events, Hepatic events, and Interstitial Lung Disease was conducted
  - reported terms summarized under the composite terms of VTE, EAT, and ILD and described in the results
- Baseline risk factors for VTE evaluated for the safety population(Khorana risk score)
  - Known risk factors (increased age and BMI) were analyzed in patients experiencing VTE
- EAT and ILD are more frequently reported in Asia population ~~compared to the Safety population~~

Management guidelines

- Abemaciclib dose modifications (holds and reductions) mandated to manage study drug-related and clinically significant AEs. Max. 2 dose reductions allowed
  - VTE: Patients with prior history excluded. Management guidance includes holding abemaciclib for 1-2 weeks and starting anticoagulation therapy per local clinical practice; recommendation for patients treated with tamoxifen to change ET
  - EAT: Grade(G) 3 events require dose hold until toxicity resolves and dose reduction by 1 dose level; G4 events require discontinuation
  - ILD: During the study, ILD was identified as an adverse-drug reaction (ADR) and management evolved; G≥2 events require dose modifications

[4]Johnston SRD, et al. J Clin Oncol 38:3987-3998, 2020

VTE – Characterization and Management

Characterization and management of VTE

- Incidence of VTE higher in abemaciclib arm:
  - most VTEs were G≥3 (1.3%, incl. 0.9% pulmonary embolism [PE]) and resulted in a serious outcome
  - one third of PEs were not serious and thus did not require hospitalization; there were no fatal cases
  - most VTE were single occurrences (88.1%)
    - 8 patients reported 2 episodes of VTE, incl. 5 patients with simultaneous DVT and PE; only 1 patient had recurrent VTE after resuming abemaciclib
  - most patients continued abemaciclib after a VTE
    - 57% after dose hold
    - 19.4% discontinued (mainly due to G≥3)
  - VTEs were well managed with anti-coagulation (used in 94% of patients)
- Tamoxifen was associated with numerically higher incidence of VTE compared to AIs administered as initial ET

	Abemaciclib + ET N=2791		ET N=2800	
n (%)	Any Grade	G≥3	Any Grade	G≥3
Patients with ≥1 VTE TEAE	67 (2.4)	37 (1.3)	16 (0.6)	7 (0.3)
DVT[a]	45 (1.6)	12 (0.4)	13 (0.5)	3 (0.1)
PE[b]	27 (1.0)	27 (1.0)	4 (0.1)	4 (0.1)
Pulmonary embolism	26 (0.9)	26 (0.9)	4 (0.1)	4 (0.1)
Patients with SAE of VTE	33 (1.2)		8 (0.3)	
SAE of pulmonary embolism[c]	17 (0.6)		4 (0.1)	
Discontinuation	13 (0.5)		2 (0.1)	
VTE by first ET = tamoxifen (Nx=857 [Arm A] / 898 [Arm B])	35 (4.1)	19 (2.2)	6 (0.7)	4 (0.4)
DVT	23 (2.7)	5 (0.6)	5 (0.6)	3 (0.3)
PE	14 (1.6)	14 (1.6)	1 (0.1)	1 (0.1)
VTE by first ET = aromatase inhibitors (Nx=1929 [Arm A] / 1892 [Arm B]	32 (1.7)	18 (0.9)	10 (0.5)	3 (0.2)
DVT	22 (1.1)	7 (0.4)	8 (0.4)	0
PE	13 (0.7)	13 (0.7)	3 (0.2)	3 (0.2)

[a]*DVT* is a composite terms: abemaciclib arm (n) – deep vein thrombosis (33), device related thrombosis (3), jugular vein thrombosis (2), cerebral vein thrombosis (2), subclavian vein thrombosis (2), portal vein thrombosis (1), venous thrombosis limb (1), catheter site thrombosis (1), ET arm (n) - deep vein thrombosis (7), device related thrombosis (1), jugular vein thrombosis (2), hepatic vein thrombosis (1), ovarian vein thrombosis (1), jugular vein occlusion (1)
[b]*PE* is a composite term including embolism (n= 1 abemaciclib arm only, not confirmed by imaging) and pulmonary embolism (n=26); minimum severity grade per CTCAE for PE is Grade 3 for uncomplicated events
[c]1 fatal event in ET arm only, 0 in abemaciclib arm

VTE – Timing of Events and Risk Factors

Risk factors were well balanced between the 2 treatment arms

- Baseline Khorana risk score well balanced across arms
- Risk factor for patients reporting a VTE (abemaciclib vs. ET only):
  - central catheter: 22% vs. 50%
  - recent flight or recent period of immobility: 25.4% vs. 18.8%
  - 1 patient in abemaciclib arm had prior history of VTE

Approximately half of the *VTE* events occurred early on treatment in both arms

- Median time to onset of first *VTE*: ~6 months
- abemaciclib-treated patients: 47% experienced *VTE* within first 180 days
  - 48% of PE events occurred within first 180 days
  - the same trend was seen for patients treated with tamoxifen as first ET (51%)

Further analysis on abemaciclib-treated patients reporting VTE

- No correlation was observed with incidence of VTE/PE and increasing age[1]
- Trend for higher incidence of PE and Grade 3/4 VTE with increasing BMI

n (%)	Abemaciclib + ET N=2791				
BMI categories	<18.5 n=49	18.5-24.9 n=1070	25.0-29.9 n=890	30+ n=721	Not Reported n=78
VTE, Any Grade	1 (2.0)	16 (1.5)	23 (2.6)	25 (3.5)	2 (2.6)
VTE, Grade 3 and 4	0	7 (0.7)	10 (1.1)	19 (2.6)	1 (1.3)
PE, Any Grade	0	5 (0.5)	8 (0.9)	12 (1.7)	1 (1.3)
PE, Grade 3 and 4	0	5 (0.5)	8 (0.9)	12 (1.7)	1 (1.3)

[1] Age 40 was utilized as an appropriate cut-off for assessing VTE risk by age as per: Anderson FA and Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107:I9-16. https://doi.org/10.1161/01.cir.0000078469.07362.e6.

Elevated aminotransferases – Characterization and Management

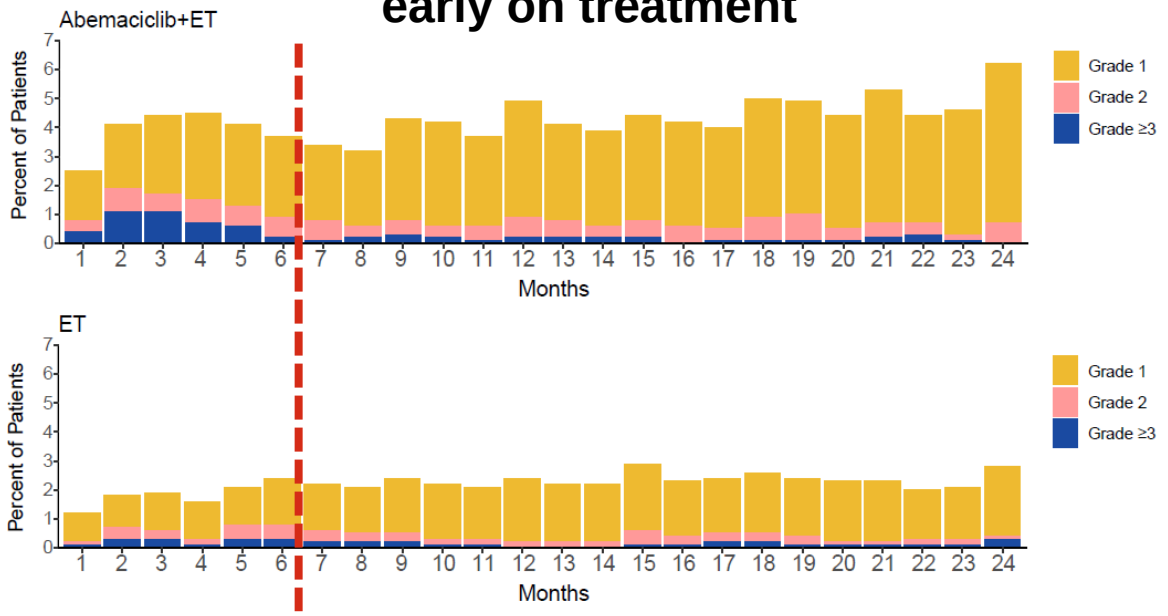
Characterization and management of G≥3 EAT events in abemaciclib arm

- Incidence of EAT higher in abemaciclib arm:
  - most G≥3 (85%) were single occurrences
    - 13 (15%) patients had a recurrent G≥3 event
  - most patients could continue treatment after G≥3 EAT
    - 71.3% after dose hold and/or reduction
    - 16% patients discontinued

EAT – Safety population	Abemaciclib + ET N=2791		ET N=2800	
	Any Grade	G≥3	Any Grade	G≥3
Patients with ≥1 TEAE; n(%)	356 (12.8)[c]	87 (3.1)	181 (6.5)	24 (0.9)
SAEs	11 (0.4)		2 (0.1)	
Discontinuations	22 (0.8)		0	
Time to onset Grade ≥3 event; median (range), days	91.0 (1.0-670.0)		131.5 (16.0-719.0)	

SAE: serious adverse event; Grade 4: 6 events in abemaciclib arm, 1 events in ET arm; No fatal AEs reported in either arm
EAT includes the following preferred terms (n in abemaciclib arm): ALT increased (291), AST increased (281), transaminase increased (10), hepatic function abnormal (8), hepatic enzyme increased (2), drug-induced injury (3), liver function test increased (3), hepatotoxicity (1), hypertransaminasemia (1), and liver function test abnormal (2)

Most clinically important (G≥3) EAT events occur early on treatment



- G≥3 events mainly occurred during early months of treatment
  - median time to onset ~3 and 4 months in abemaciclib and ET only arm, respectively
- After 6 months, G≥3 events per month were rare
  - ≤0.5% of treated patients and similar in both arms

ALT/AST Characterization: Safety and Asia population

ALT and AST characterization

- Reversibility of all G≥3 ALT central laboratory elevations with dose modifications or abemaciclib discontinuation
- No cases of drug-induced liver injury

	Safety population				Asia population			
	Abemaciclib + ET N=2791		ET N=2800		Abemaciclib + ET N=572		ET N=572	
	Any Grade	G≥3	Any Grade	G≥3	Any Grade	G≥3	Any Grade	G≥3
Patients with ≥1 TEAE; n(%)								
ALT increased	291 (10.4)	68 (2.4)	136 (4.9)	16 (0.6)	108 (18.9)	24 (4.2)	53 (9.3)	4 (0.7)
SAEs	5 (0.2)		1 (0.0)		2 (0.3)		0	
Discontinuation	16 (0.6)		0		9 (1.6)		0	
AST increased	281 (10.1)	49 (1.8)	120 (4.3)	14 (0.5)	108 (18.9)	18 (3.1)	40 (7.0)	4 (0.7)
SAEs	5 (0.2)		1 (0.0)		2 (0.3)		0	
Discontinuation	4 (0.1)		0		2 (0.3)		0	

SAE: serious adverse event; CTCAE v4.03

Safety population: G≥3 ALT/AST

- Events were short-lived (≤13 days)
- Low number of discontinuations (<1%)

Asia vs. Safety populations – abemaciclib arm

- Higher incidence of G≥3 ALT and AST
- Similar median time to onset and event duration
- Slightly higher discontinuation rate (<2%)

ILD – Management and Timing

Characterization and management of ILD

- Incidence of ILD higher in abemaciclib arm:
  - most ILD events were asymptomatic (G1:1.4%)
  - low number of serious ILDs (0.5%); 1 fatal case
  - most patients continued abemaciclib after ILD
    - 19 (23%) pts discontinued abemaciclib, primarily due to G≥2 events
- Most ILD events in both arms were single occurrences (>97%)
- ILD events were treated with steroids/antibiotics
  - 52% and 35% of patients in the abemaciclib arm and ET only, consistent with symptomatic events (G≥2) incidence
- Prior radiation therapy, a risk factor for ILD, was balanced across arms (>95%)

Approximately half of the events occur early on treatment

- Among abemaciclib-treated patients experiencing clinically significant events (G≥2)
  - 47% started within first 180 days

	Abemaciclib + ET N=2791		ET N=2800	
n (%)	Any Grade	G≥3	Any Grade	G≥3
Patients with ≥1 *ILD/pneumonitis* event using SMQ	82 (2.9)	11 (0.4)[a]	34 (1.2)	1 (0.0)
Pneumonitis	43 (1.5)	7 (0.3)	10 (0.4)	0
Radiation pneumonitis	25 (0.9)	2 (0.1)	14 (0.5)	1 (0.0)
Interstitial lung disease	5 (0.2)	1 (0.0)	1 (0.0)	0
Pulmonary fibrosis	4 (0.1)	0	3 (0.1)	0
Organizing pneumonia	2 (0.1)	1 (0.0)	2 (0.1)	0
Radiation fibrosis lung	2 (0.1)	0	2 (0.1)	0
Lung opacity	3 (0.1)	0	2 (0.1)	0
Sarcoidosis	0	0	1 (0.0)	0
Serious ILD Events	14 (0.5)		1 (0.0)	
time to onset of first event; median (range), days	190.0 (23.0 – 517.0)		158.0 (29.0-539.0)	

[a]1 grade 5 event; SAE: serious adverse event

ILD in Asia population and SAEs

	Safety population						Asia population					
	Abemaciclib + ET N=2791			ET N=2800			Abemaciclib + ET N=572			ET N=572		
	G1	G2	G≥3	G1	G2	G≥3	G1	G2	G≥3	G1	G2	G≥3
Patients with ≥1 TEAE; n(%)	39 (1.4)	32 (1.1)	11 (0.4)[a]	23 (0.8)	10 (0.4)	1 (0.1)	28 (4.9)	8 (1.4)	2 (0.3)[a]	12 (2.1)	4 (0.7)	1 (0.2)
Pneumonitis	17 (0.6)	19 (0.7)	7 (0.3)[a]	7 (0.3)	3 (0.1)	0	15 (2.6)	5 (0.9)	1 (0.2)[a]	4 (0.7)	2 (0.3)	0
Radiation pneumonitis	13 (0.5)	10 (0.4)	2 (0.1)	8 (0.3)	5 (0.2)	1(0.1)	10 (1.7)	3 (0.5)	1 (0.2)	6 (1.0)	2 (0.3)	1 (0.2)
SAEs	14 (0.5)[b]			1 (0.1)			3 (0.5)			0		
Subjects discontinued due to AE	19 (0.7)			0			5 (0.9)			0		

SAE: serious adverse event; [a]1 grade 5 event; [b]1 patient was deemed to have pneumonia and not included in the SAE ILD description

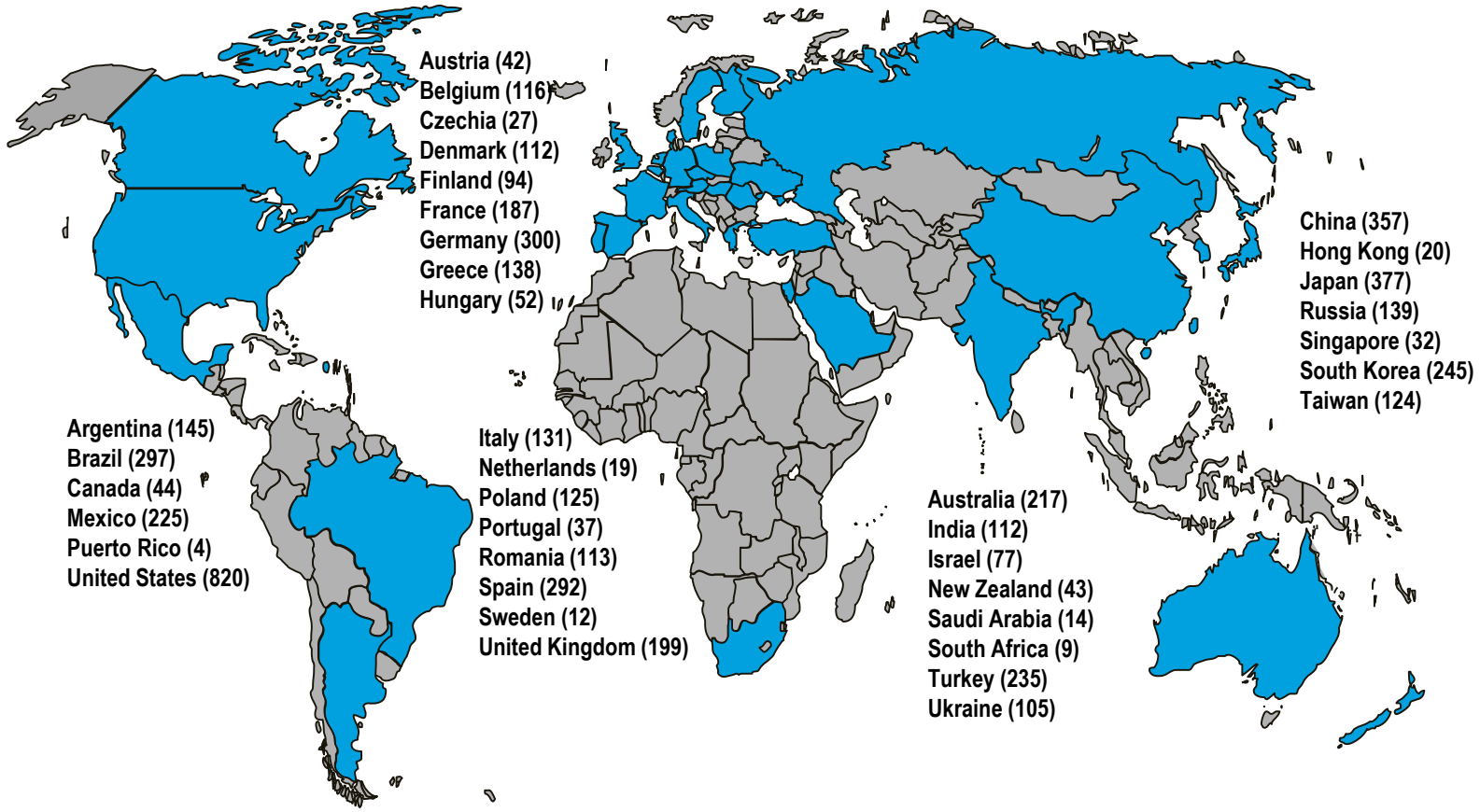
- **ILD in Asia vs. Safety populations – abemaciclib arm**
  - higher incidence of ILD in Asia population
  - most ILD events in the Asia population were asymptomatic (G1:4.9%)
  - clinically significant AEs (G≥2), SAEs, and discontinuations similar in both populations
- **Serious ILD events in safety population**
  - prior adjuvant radiotherapy: all patients
  - time to onset: 45 to 394 days
  - race: 9 Caucasian, 4 Asian (1 Indian), 1 other
    - 1 fatal event of pneumonitis in abemaciclib arm (Asian patient)
  - steroid treatment: 86%
  - discontinued abemaciclib: all abemaciclib-treated patients

Conclusions

- The majority of clinically significant EAT, VTE, and ILD occurred within the first 6 months; no cumulative effect or increased risk with longer treatment duration of abemaciclib was observed
  - EAT were well managed, reversible, and did not lead to liver injury
  - VTE and ILD were manageable per standard clinical practice
    - tamoxifen is associated with a numerically higher incidence of VTE compared to AIs
    - clinically significant ILD (G≥2) were similar in Asia and Safety populations (*see Poster#143 for additional safety analyses in Asia population*)
- Most patients experiencing EAT, VTE and ILD could continue abemaciclib treatment without further recurrences
- Findings related to EAT, VTE and ILD support the tolerability of abemaciclib in the EBC population

Safety data collection continues since >50% of patients are still on treatment

We thank the 5,637 patients and their families/caregivers from 603 sites in the following 38 countries for participating in this trial:



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