MADRID 2014 ESMO congress

RESILIENCE
A Phase III Randomized, Double-Blind Trial Comparing Sorafenib plus Capecitabine versus Placebo plus Capecitabine in the Treatment of Locally Advanced or Metastatic HER2-Negative Breast Cancer (RESILIENCE)

José Baselga [1]

Claudio Zamagni[2], Patricia Gomez[3], Begona Bermejo[4], Shigenori Nagai[5], Bohuslav Melichar[6], Arlene Chan[7], Laszlo Mangel[8], Jonas Bergh[9], Fredrico Costa[10], Henry L. Gomez[11], William Gradishar[12], Clifford Hudis[1], Bernardo Rapoport[13], Henri Roche[14], Patricia Maeda[15], Liping Huang[15], Joshua Zhang[15], Lee Schwartzberg[16]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]S. Orsola Malpighi Hospital, Bologna, Italy; [3]Hospital Vall d'Hebron, Barcelona, Spain; [4]Hospital Clinico Universitario de Valencia, Valencia, Spain; [5]Saitama Cancer Center, Saitama, Japan; [6]Lekarska fakulta UP a Fakultni nemocnice, Olomouc, Czech Republic; [7]Breast Cancer Research Centre - WA and Curtin University, Perth, Australia; [8]Pecsi Tudomanyegyetem OEKK, Pecs, Hungary; [9]Karolinska Institutet and University Hospital, Stockholm, Sweden; [10]Hospital Sirio Libanes, Sao Paulo, Brazil; [11]Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru; [12]Northwestern University, Chicago, IL, USA; [13]The Medical Oncology Center of Rosebank, Johannesburg, South Africa; [14]Institut Claudius Regaud, Toulouse, France; [15]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; [16]The West Clinic, Memphis, TN, USA.

Conflict of Interest Disclosure

José Baselga, MD

- None

Background

- Sorafenib is an oral multikinase inhibitor targeting Raf/MEK/ERK, VEGFR and PDGFR signaling pathways with antiproliferative and antiangiogenic effects[1]
- Sorafenib has demonstrated survival benefits in patients with advanced renal cell and hepatocellular carcinoma and has shown anti-tumor activity in other tumor types[2-4]
- Capecitabine, an oral prodrug of 5-fluorouracil, has been approved as monotherapy and in combination with docetaxel in patients with metastatic breast cancer resistant to anthracycline-based treatment[5-7]
- Angiogenesis is important in breast cancer growth and development, with angiogenic growth factors expressed early in tumorigenesis[8]
- In a phase II trial, the combination of sorafenib and capecitabine improved progression-free survival in patients with HER2-negative locally advanced or metastatic breast cancer[9]

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[3]Cheng AL, et al. *Lancet Oncol* 2009;10:25-34.
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[5]O'Shaughnessy J, et al. *J Clin Oncol* 2002;20:2812-2823.
[6]Fumoleau P, et al. *Eur J Cancer* 2004;40:536-542.
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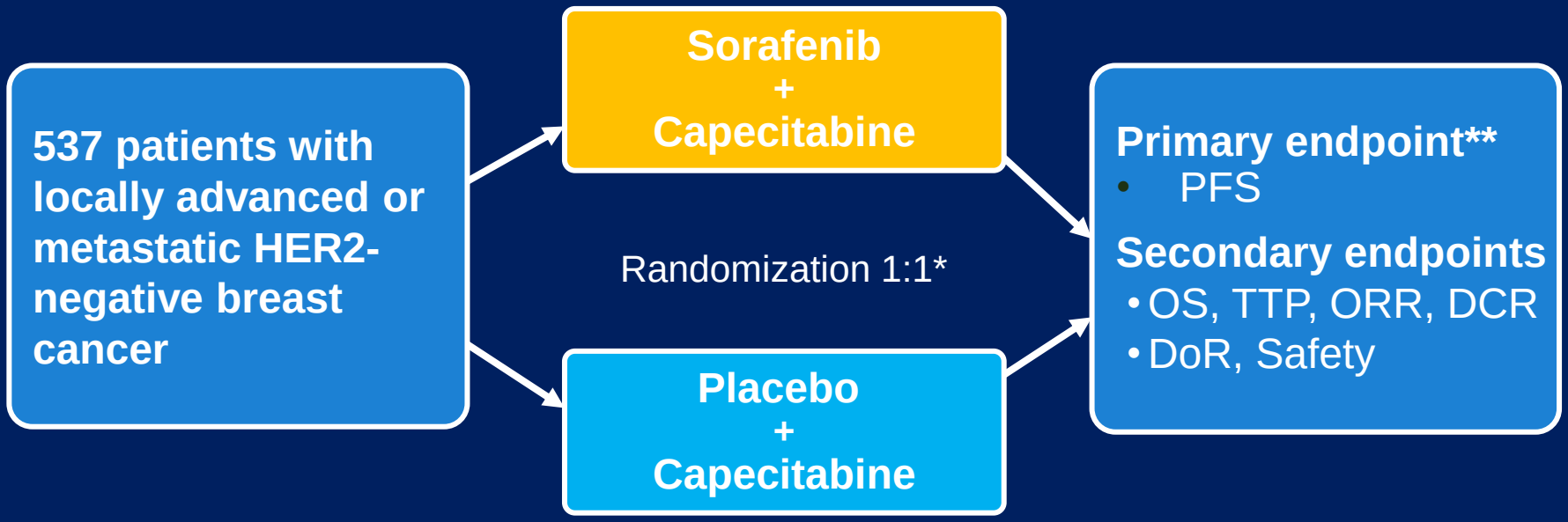
[9]Baselga J, et al. *J Clin Oncol* 2012;30:1484-1491.

Study Objective

- Objective
  - To compare the efficacy and safety of sorafenib plus capecitabine with placebo plus capecitabine in patients with advanced/metastatic HER2-negative breast cancer
- Primary endpoint – progression-free survival (PFS)
  - Independent central review
  - Scans every 6 weeks for the first 36 weeks; every 9 weeks thereafter
- Secondary endpoints
  - Overall survival (OS)
  - Time to tumor progression (TTP)
  - Objective response rate (ORR)
  - Disease control rate (DCR)
  - Duration of response (DoR)
  - Safety

RESILIENCE study design



***Stratification**:

- Hormone receptor status (ER+ and/or PR+ vs. ER- and PR-)
- Number of prior therapy received for metastatic breast cancer (0 vs. 1)
- Geographic region (North America vs. Europe vs. Other #)

Dosing:

- Sorafenib or placebo: 600 mg (200 mg in am, 400 mg pm) orally, daily continuously
- Capecitabine: 1,000 mg/m2, orally, twice daily, 14 days on/7 days off

** Primary analysis by independent central review; database cut-off May 12, 2014

Other = Israel, South Africa, South America, Japan, China and Australia

Inclusion/Exclusion Criteria

- Inclusion criteria
  - HER2-negative locally advanced or metastatic breast cancer
  - Treatment with 0-1 prior chemotherapy regimen for metastatic disease
  - Resistant to or failed prior taxane and anthracycline or for whom further anthracycline therapy is not indicated
  - Prior adjuvant or neoadjuvant therapy allowed
  - Measurable or non-measurable disease allowed
  - Prior hormonal therapy for locally advanced or metastatic disease allowed
  - ECOG PS 0 or 1
- Exclusion criteria
  - Previous treatment with a VEGF inhibitor
  - Symptomatic brain metastases
  - Grade 3 or higher hemorrhage/bleeding event within previous 4 weeks
  - Thrombotic, embolic, venous, or arterial events within previous 6 months
  - Major surgery <4 weeks before study entry

Baseline Patient Characteristics*

	Placebo/Capecitabine N=271, (%)	Sorafenib/Capecitabine N=266, (%)
Median age, yr	55.0	53.0
Female	98.9	99.6
Europe / North America / Others	62.0 / 9.6 / 28.4	62.4 / 8.6 / 28.9
Prior chemotherapies for metastatic disease 0 / 1**	43.5 / 56.5	42.9 / 57.1
Hormone receptor status, negative / positive**	31.0 / 69.0	31.2 / 68.8
ECOG PS 0 / 1	59.4 / 40.6	57.1 / 41.9
Visceral disease, no / yes	21.0 / 78.6	24.8 / 74.8
Number of organs involved		
1 / 2 / 3	25.1 / 38.7 / 22.5	25.9 / 35.3 / 18.8
> 3	13.3	19.5

*ITT Population (all randomized patients)
** Per interactive voice response system (IVRS)

Study Drug Administration*

	Placebo / Capecitabine		Sorafenib / Capecitabine	
	Placebo	**Capecitabine**	**Sorafenib**	**Capecitabine**
Daily dose	(mg)	(mg/m^2)	(mg)	(mg/m^2)
Mean	654	1913.5	566	1734.1
Mean % planned	92.9	87.4	79.9	75.5
Overall Tx Duration, wks				
Median	24.0	22.9	18.1	18.1
Mean	30.7	30.2	26.8	26.6
Cycles				
Mean	10.0	10.0	8.7	8.9
Median	8.0	8.0	6.0	6.0
Tx Modification, (%)				
Dose Interruption	47.6	28.8	68.1	46.5
Dose Reduction	20.6	44.6	42.7	67.3

*ITT Population

Overview of Treatment-Emergent AEs*

	Placebo/Capecitabine n (%)	Sorafenib/Capecitabine n (%)
Any AE	257 (96.3)	260 (100)
Grade 3	105 (39.3)	152 (58.5)
Grade 4	12 (4.5)	15 (5.8)
Grade 5	12 (4.5)	16 (6.2)
SAEs	67 (25.1)	80 (30.8)
AEs Leading to dose modification	160 (59.9)	225 (86.5)
AEs leading to permanent discontinuation of study drug	28 (10.5)	61 (23.5)
Study drug related treatment-emergent deaths	0 (0.0)	1 (0.4)**

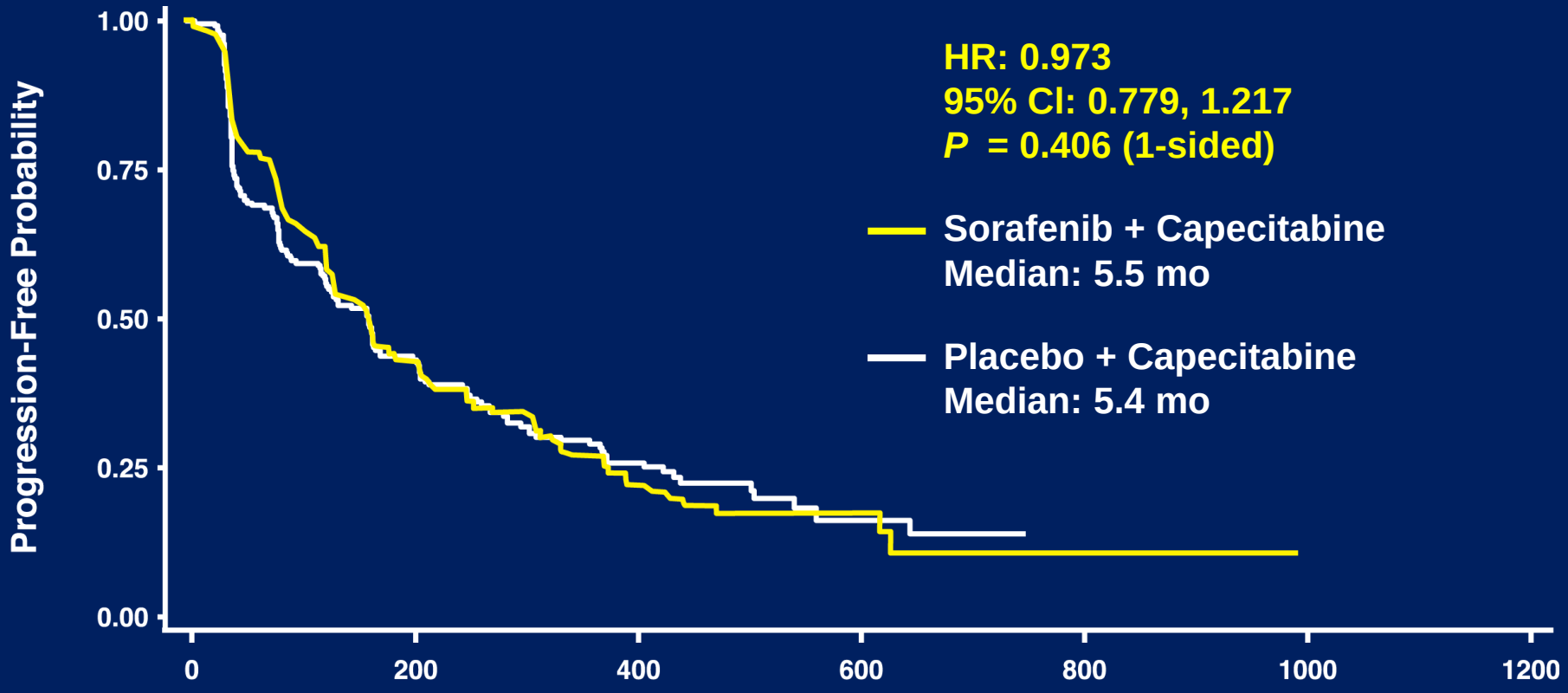
AE= Adverse Event; SAE= Serious Adverse Event
*Safety Population (all patients receiving ≥1 dose of study drug)
** Hepatic failure

Treatment-Emergent AEs*

	Placebo/Capecitabine (n=267), %			Sorafenib/Capecitabine (n=260), %		
	All grade	G3	G4	All grade	G3	G4
Dermatology/Skin						
Alopecia	2.6	0	0	16.9	0	0
Skin disorders, other	4.9	0	0	11.9	0	0
Hand-Foot skin reaction	61.8	7.5	0	80.4	15.8	0
Rash maculo-papular	9.4	0.4	0	23.1	1.2	0
Gastrointestinal						
Abdominal pain	12.4	3.4	0	18.1	2.3	0
Constipation	12.0	0	0	20.8	0	0
Diarrhea	38.6	6.4	0	48.1	3.8	0.4
Mucositis (oral cavity)	17.6	1.1	0	34.6	1.5	0.4
Vomiting	20.2	0.7	0	25.8	3.5	0
Metabolism / nutrition						
Anorexia	14.2	0	0	20.4	1.2	0
Musculoskeletal						
Arthralgia	4.9	0	0	10.8	0.8	0
Other						
Weight loss	4.5	0.4	0	10.8	1.5	0
Hypertension	5.6	2.2	0	26.5	14.2	0

*Frequency ≥10% in either group (Safety population) differing ≥5% in the two groups, and corresponding grade 3/4 AEs

Progression-Free Survival
(by independent central review)

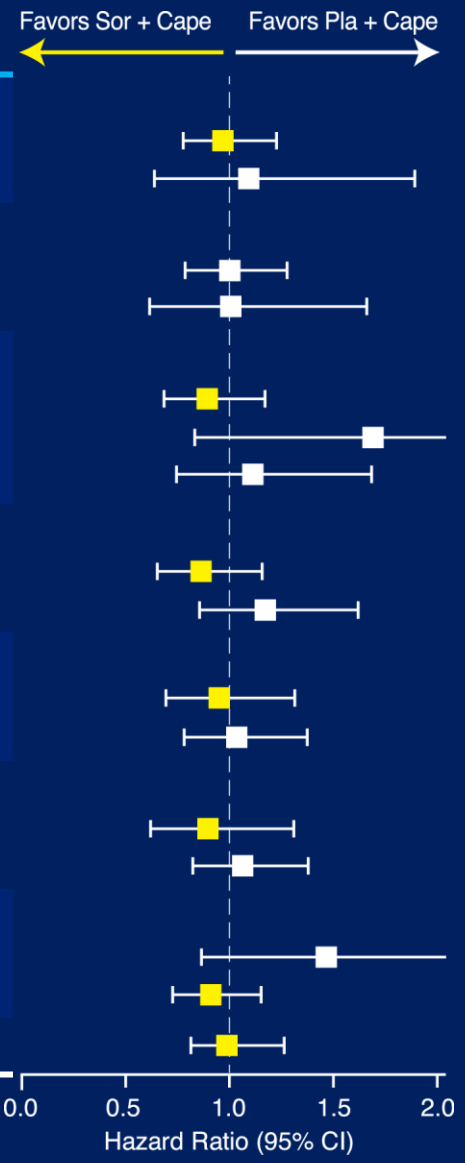


Patients at Risk:						
Sor+Cape	266	66	22	7	2	1
Pla+Cape	271	84	35	8	0	0

Note: 1-sided p-value from log-rank test stratified per randomization

PFS Subgroup Analyses

Subgroup (n)	Median PFS (months)		HR
	Pla + Cape	Sor + Cape	
Age, yrs			
<65 (447)	5.4	5.4	0.955
≥65 (90)	5.5	8.3	1.074
Race			
White (417)	5.4	5.4	1.000
Asian (100)	5.4	5.5	0.986
Region			
Europe (334)	4.5	5.5	0.875
North America (49)	5.5	3.1	1.666
Other (154)	5.5	5.9	1.097
ECOG PS			
0 (313)	5.5	6.1	0.849
1 (224)	5.4	4.1	1.155
Number of Prior Treatments			
0 (232)	4.5	4.6	0.934
1 (305)	5.5	5.5	1.015
Hormone Receptor Status			
Negative (167)	2.7	3.0	0.879
Positive (370)	6.9	6.8	1.043
Visceral Disease at baseline			
No (123)	21.4	5.5	1.443
Yes (412)	4.5	5.4	0.894
Overall ITT (537)	5.4	5.5	0.973



Summary of Best Response by RECIST Criteria*

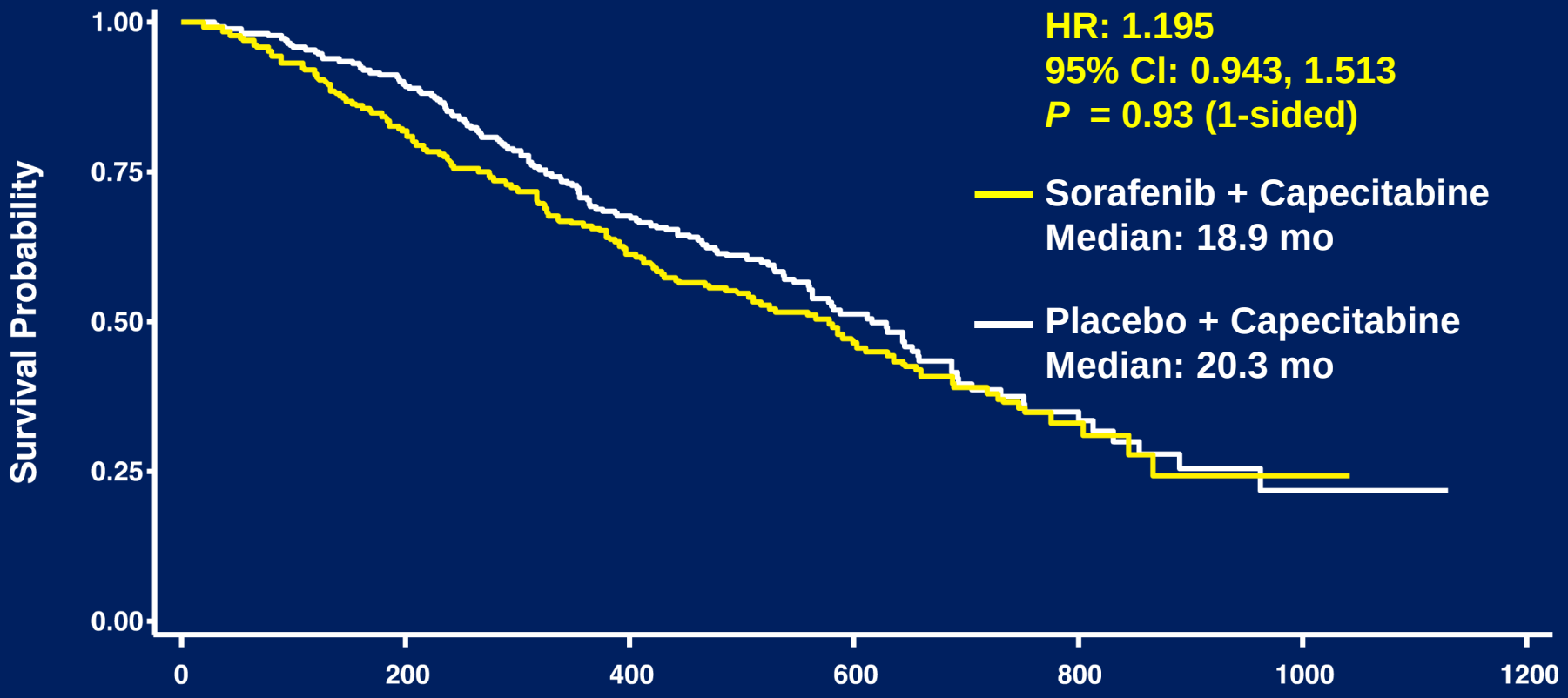
n (%)	Placebo + Capecitabine (n=271)	Sorafenib + Capecitabine (n=266)	P-value**
Overall Response Rate (ORR; CR + PR)	42 (15.5)	36 (13.5)	0.257
CR	4 (1.5)	0 (0.0)	
PR	38 (14.0)	36 (13.5)	
SD	65 (24.0)	80 (30.1)	
Non CR/Non PD	51 (18.8)	45 (16.9)	
PD	89 (32.8)	61 (22.9)	
Unable to evaluate	12 (4.4)	19 (7.1)	
Not assessed	12 (4.4)	25 (9.4)	
Disease Control Rate (DCR; CR + PR + SD + Non CR/Non PD)	158 (58.3)	161 (60.5)	0.285

RECIST (v 1.1) = Response Evaluation Criteria in Solid Tumors; CR= Complete Response; PR= Partial Response; SD= Stable Disease; PD= Partial Disease

*By central assessment.

**By Cochran Mantel-Haenszel test (one-sided).

Overall Survival

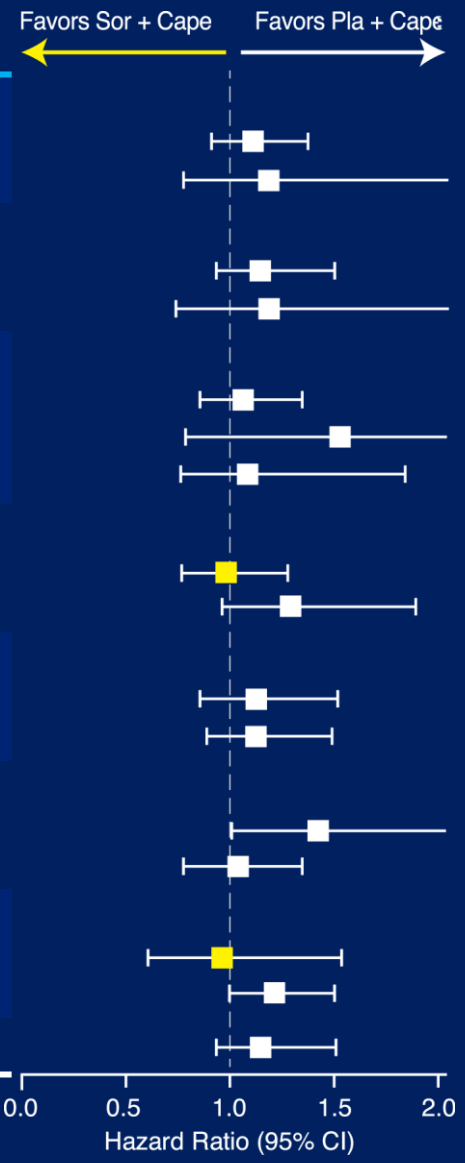


Patients at Risk:						
Sor+Cape	266	210	154	69	16	2
Pla+Cape	271	232	174	72	22	5

Note: 1-sided p-value from log-rank test stratified per randomization

OS Subgroup Analyses

Subgroup (n)	Median OS (months) Pla + Cape	Sor + Cape	HR
Age, yrs			
<65 (447)	20.7	18.9	1.135
≥65 (90)	20.1	19.1	1.215
Race			
White (417)	20.1	17.0	1.175
Asian (100)	21.4	19.3	1.227
Region			
Europe (334)	18.5	17.0	1.077
North America (49)	24.0	12.1	1.619
Other (154)	20.1	19.2	1.174
ECOG PS			
0 (313)	22.6	21.7	0.974
1 (224)	18.0	12.7	1.355
Number of Prior Treatments			
0 (232)	20.3	18.9	1.153
1 (305)	20.7	18.6	1.152
Hormone Receptor Status			
Negative (167)	11.7	9.1	1.468
Positive (370)	21.6	22.7	1.041
Visceral Disease at baseline			
No (123)	22.8	23.9	0.946
Yes (412)	18.5	15.5	1.250
Overall ITT (537)	20.3	18.9	1.195



Summary and Conclusions

- This trial did not meet its primary endpoint. The addition of sorafenib to capecitabine did not significantly prolong PFS (HR 0.973; 95% CI: 0.779, 1.217) or OS (HR 1.195; 95% CI: 0.943, 1.513) compared with capecitabine alone in the overall study population of patients with HER2-negative, locally advanced or metastatic breast cancer

- The average daily dose of capecitabine and the duration of capecitabine treatment were lower in the sorafenib plus capecitabine group than in the placebo plus capecitabine group

- The AEs observed were consistent with the known safety profiles of sorafenib and capecitabine, although the rates of grade 3 AEs, dose modifications and discontinuations due to AEs were higher in the sorafenib plus capecitabine arm

- The trend for lower median OS in patients treated with sorafenib plus capecitabine was not readily explainable by study treatment-related toxicity

RESILIENCE Trial Investigators

Argentina: Ibarguren Beltran, Ernesto Korbnfeld

Australia: Arlene Chan, Paul Craft, Vinod Ganju, Kelly Mok, Ina Nordman, Say Ng, Sudarsha Selva-Nayagam

Austria: Christian Dittrich, Ernst Rechberger

Belgium: Sevilay Altintas, Alain Bols, Andreas Gombos, Guy Jerusalem, Eric Joosens

Canada: Jean-Pierre Ayoub, Michael Thirlwell

China: Zefei Jiang, Wenchao Liu, Yunpeng Liu, Zhimin Shao, Zhongsheng Tong, Weimin Xie, Binghe Xu

Czech Republic: Martina Kubecova, Bohuslav Melichar, Lubos Petruzelka, Petra Pokorná, Petr Rychlik, Martin Safanda, Jan Vydra, Martina Zimovjanova

France: Etienne Brain, Mario Campone, Florence Dalenc, Jean-Marc Nabholtz, Laurence Vanlemmens

Germany: Susanne Briest, Christian Loehberg, Peter Mallmann, Jochem Potenberg, Marcus Schmidt, Andrea Stefek, Hans Tesch, Mathias Warm

Great Britain: Anne Armstrong, Stephen Chan, Alison Jones, David Miles, Duncan Wheatley

Greece: Evangelos Eleutherakis-Papaiakovou, Maria Kalogeropoulou, Eleftherios Kambletsas, Athanasios Kotsakis, Georgios Papatsimpas

Hungary: Katalin Boer, Tibor Csoszi, Jozsef Erfan, Mihaly Kispal, Laszlo Mangel

Ireland: John Crown, Brian Hennessy, Maccon Keane, Catherlne Kelly, John Kennedy, Conleth Murphy

Israel: Georgeta Fried, David Geffen, Rut Isacson, Bella Kaufman, Mariana Steiner, Salomon Stemmer, Beatrice Uziely

Italy: Dino Amadori, Paolo Nidoli, Stefano Cascinu, Enrico Cortesi, Giorgio Cruciani, PierFranco Conte, Alfredo Fancone, Sergio Palmeri, Armando Santoro, Claudo Zamagni

Japan: Hiroji Iwata, Yoshinori Ito, Seung Jin Kim, Katsumasa Kuroi, Norikazu, Masuda, Shigenori Nagai, Shinji Ohno, Yoshiaki Rai, Toshiaki Saeki, Seiki Takashima, Naohito Yamamoto

Poland: Jacek Jassem, Krzysztof Lesniewski-Kmak Elzbieta Wojcik

Russia: Oleg Gladkov, Guzel Mukhametshina

South Africa: Antonia Coccia-Portugal, Graham Cohen, John Crockett, Lydia Dreosti, Bernardo Rapoport

Spain: Antonio Avella, Begona Bermejo, Lourdes Calvo, Miguel Angel Climent Duran, Luis Garcia Estevez, Isabel Garau, Jose Angel Garcia Saenz, Patricia Gomez, Sonia Gonzalez, Xavier Gonzalez, Antonio Gonzalez Martin, Vega Iranzo, Rafael Loez Lopez, Luis Manso, Eduardo Martinez, Maria Martinez, Noelia Martinez Jañez, Alvaro Montaño Periañez, Serafin Morales, Belen Ojeda, Miguel Angel Segui, Sara Serrano Solares, Juan Antonio Virizuela

Sweden: Jonas Bergh, Hanjing Xie, Thomas Hatschek, Elisabet Lidbrink

United States: Maqbool Ahmed, Francis Arena, Mark Burkard, Fernando Cabanillas-Escabaño Marc Citron, Peter Eisenberg, Nancy Feldman, Viran Holden Steven Isakoff, Farrah Khan, Sue Prill, Marilyn Raymond, Melani Royce, Grace Shumaker Lee Schwartzberg, Kulumani Sivarajan, Neil Spector, Joseph Udaya

We thank the patients for their contribution to this study

Supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals