ESMO VIRTUAL PLENARY

UNIRAD: A UCBG RANDOMIZED, DOUBLE BLIND, PHASE III INTERNATIONAL TRIAL EVALUATING THE ADDITION OF EVEROLIMUS TO ADJUVANT HORMONE THERAPY IN WOMEN WITH HIGH RISK HR+ AND HER2- PRIMARY BREAST CANCER

Thomas BACHELOT, Florence DALENC, Sylvie CHABAUD, Paul COTTU, Djelila ALLOUACHE, Etienne BRAIN, Jean-Philippe JACQUIN, Julien GRENIER, Laurence VENAT BOUVET, Murray BRUNT, Mario CAMPONE, Francesco DEL PIANO, Marc DEBLED, Anne-Claire HARDY BESSARD, Sylvie GIACCHETTI, Judith BLISS, Jean-Luc CANON, Jérôme LEMONNIER, David CAMERON, Fabrice ANDRE

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DECLARATION OF INTERESTS

Thomas Bachelot

- For the submitted work:

  Research grant / Funding (Institution) : Novartis

- Outside the submitted work:

  Honoraria (self) : Roche, Novartis, AstraZeneca, Pfizer, SeattleGenetics,

  Advisory / Consultancy : Roche, Novartis, AstraZeneca, Pfizer, SeattleGenetics

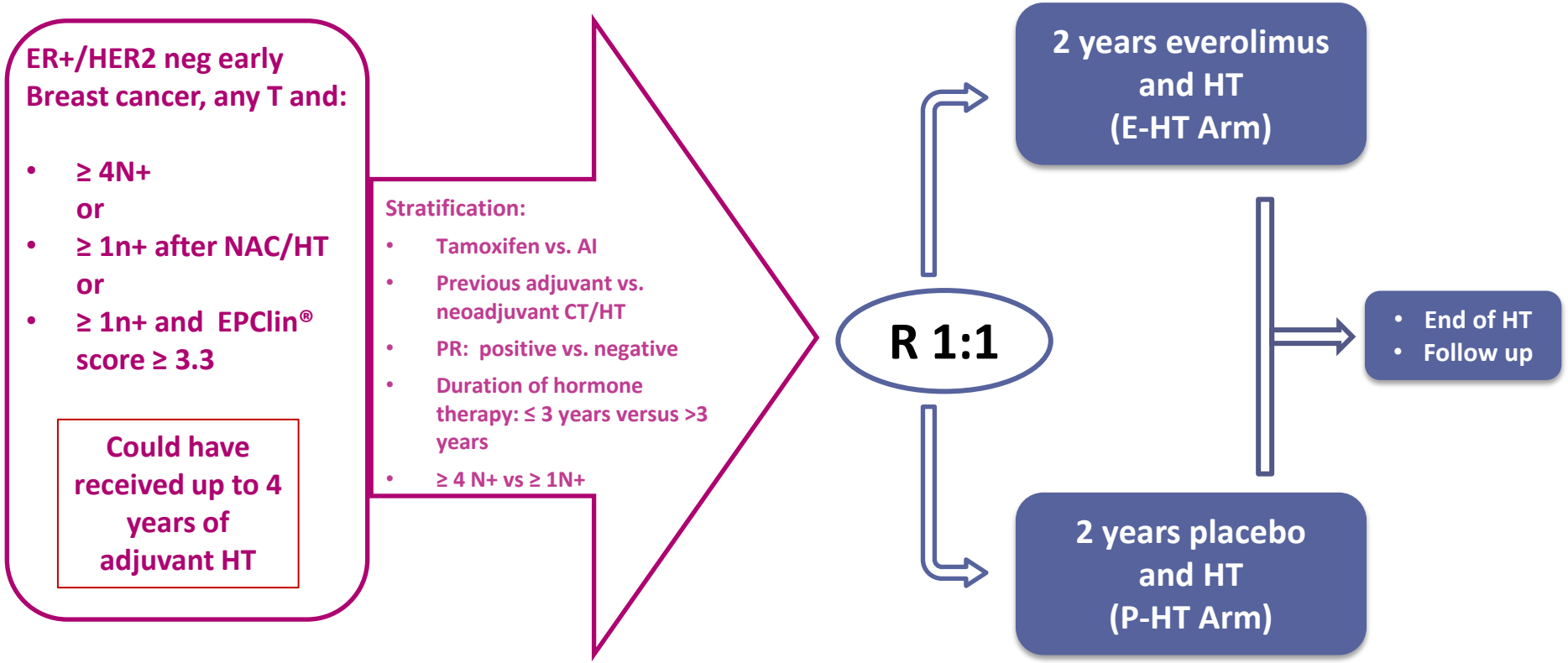
  Research grant / Funding (Institution) : Roche, AstraZeneca, Pfizer, SeattleGenetics

  Travel / Accommodation / Expenses : Roche, Novartis, AstraZeneca, Pfizer

BACKGROUND

- mTOR pathway activation leads to hormone resistance
- The mTOR inhibitor everolimus (EVE) in combination with hormone therapy (HT) has been shown to improve progression free survival for advanced HR+/HER2- breast cancer (BC) previously treated by AI.
- The double blind randomized UNIRAD trial aimed to investigate the benefit of adjuvant EVE in combination with standard adjuvant HT versus HT alone for women with high-risk HR+/HER2- early BC.

UNIRAD* : STUDY DESIGN



*NCT018505271

UNIRAD : STUDY DESIGN

Main amendments:

- June 2013: Inclusion criteria limited to patients with ≥ 4N+ (or ≥ 1N+ after NAC) **and 3 years of adjuvant HT**
- May 2014: Possibility to include patients having received **at least 1 year and a maximum of 4 years of hormone therapy**
- May 2015: Expansion of the UNIRAD clinical trial to all patients with 1 to 3 lymph nodes positive at initial surgery and for whom the **Endopredict® test** indicates a high risk of relapse (EPClin® score ≥ 3.3)
- October 2015: Possibility to begin study treatment at the **treatment dose of 5 mg with the possibility of increasing the dose up to 10 mg between the first month and the third month** depending on the toxicity of the patient and **possibility to initiate the study treatment at the same time than hormone therapy**

STATISTICAL CONSIDERATION

- Primary end-point: Invasive disease free survival rate (iDFS) after randomization

- Secondary end-point: Overall survival (OS), Event free survival (EFS), Distant Metastasis Free Survival (DMFS). Toxicity (CTC-AE v4.0), Quality Of Life (QLQ-C30). Tumor collection.

- Hypothesis :
  - To show a gain of 3 % in the 2-year iDFS (90 % vs. 93 %, HR: 0.7)
  - Two side log-rank test, α=5%, β=15% => 286 events, 1984 patients
  - Two interim analysis at 95 and 191 events

STUDY STATUS

- **1278 patients were include from June 2013 to Mars 2020 in France, UK and Belgium** (35% started EVE/placebo at 10 mg; 64% started EVE/placebo at 5 mg)
- **August 2019: 95 iDFS events were recorded => First efficacy and futility analysis**
- **19 February 2020: IDMC meeting => recommendations to stop inclusions and experimental treatment for futility**
- **2 March 2020 : Steering committee => validation of IDMC's recommendations**
- **Communication of these decisions to the centers on 4 March 2020**
- **The database for this analysis was locked on 16th of November 2020** => Median follow-up 35.7 months, range 0.7 to 85 months (IQR= 19.9-47.4). => 143 progressions and 49 deaths (147 iDFS events)

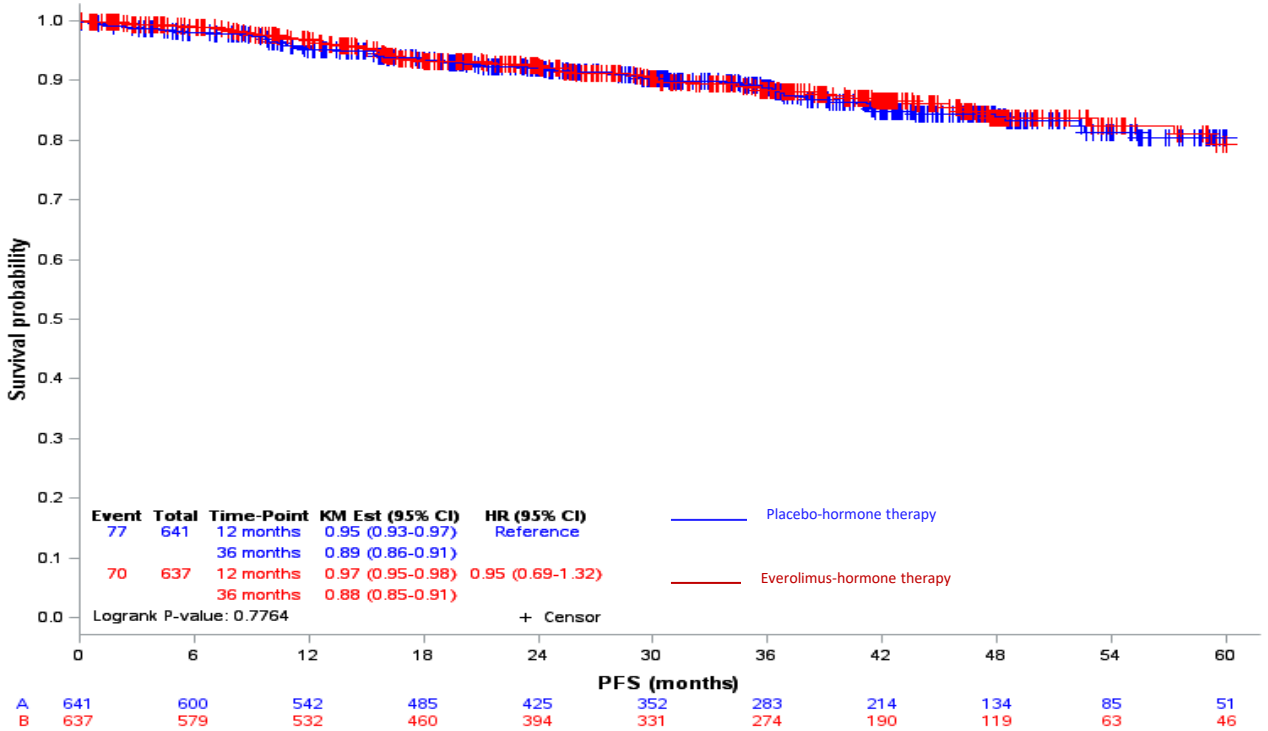
PATIENT CHARACTERISTICS

Characteristics	All (n=1278)	Placebo arm (n=641)	Everolimus arm (n=637)
Median age (IQR)	54 (48 - 63)	53.5 (48 -63)	54 (48-63))
Post Menopausal	838 (65.8%)	419 (65.6%)	419 (66%)
Pathologicat tumor size			
pT1	362 (28.6%)	171 (26.9%)	185 (30.1%)
pT2	632 (49.9%)	308 (48.6%)	324 (51.2%)
pT3	239 (18.3%)	137 21.3%)	102 (16%)
pT4	28 (2.1%)	15 (2.3%)	13 (2%)
≥ 4 N+	663 (52.7%)	328 (52%)	335 (53,3%)
1-3 N+ after neo-adjuvant treatment	170 (13.3%)	85 (13.2%)	85 (13.3%)
1-3 N+ and EPClin® score ≥ 3.3	412 (32.2%)	208 (32.4%)	204 (32%)
Histological grade			
Grade I	93 (7.3%)	43 (6.8%)	50 (7.9%)
Grade II	745 (58.7%)	375 (59.1%)	370 (58.3%)
Grade III	380 (29.9%)	191 (30.1%)	189 (29.8%)
IHC subtypes			
ER+/PR+	1066 (85%)	537 (85.6%)	529 (84.4%)
HR+/PR-	188 (15%)	90 (14.4%)	98 (15.6%)

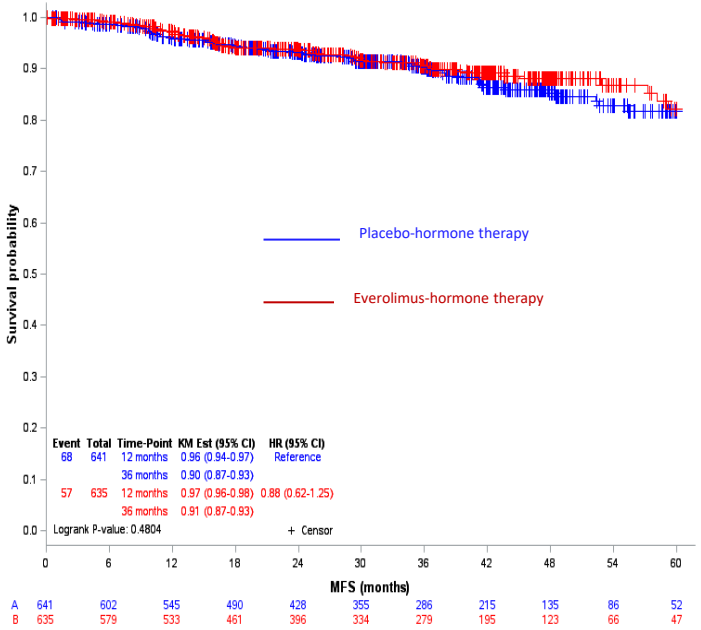
PATIENT CHARACTERISTICS

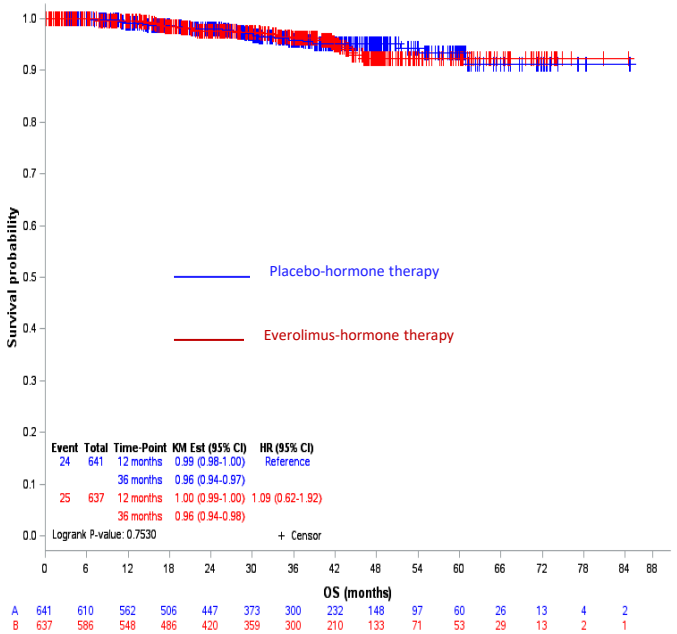
Characteristics	All (n=1278)	Placebo arm (n=641)	Everolimus arm (n=637)
Adjuvant or neo-adjuvant treatment			
Adjuvant	948 (74.1%)	474 (73.9%)	474 (74.4%)
Neo-adjuvant chemo/HT	330 (25.8%)	167 (26%)	163 (25.5%)
Hormonal treatment before inclusion			
0-1 years of hormonal therapy	540 (43.1)	278 (44%)	262 (43.1)
2-3 years of hormonal therapy	526 (42%)	261 (41.3%)	265 (42.7%)
More than 3 years	186 (14.9%)	92 (14.5%)	94 (15.1%)
Hormone therapy			
Aromatase inhibitor	773 (60.4%)	388 (60.5%)	385 (60.4%)
Tamoxifen	505 (39.5%)	253 (39.4%)	252(39.5%)

PRIMARY END-POINT: IDFS



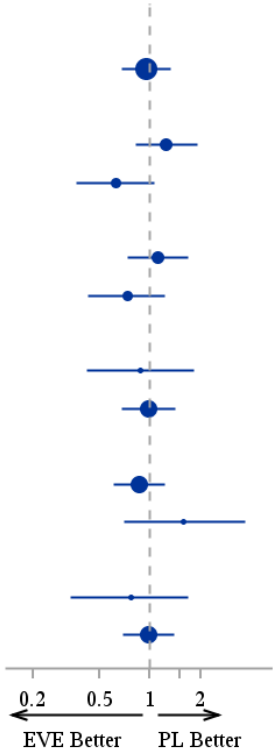
SECONDARY END-POINT: MFS AND OS





PREPLANNED IDFS SUB GROUP ANALYSIS

Subgroup	PL *no. of patients with disease progression or death/total no. (%)*	EVE *no. of patients with disease progression or death/total no. (%)*	Hazard Ratio for Disease Progression or Death (95% CI)
All	77/641 (12%)	70/637 (11%)	0.94 [0.68- 1.31]
Tamoxifen vs. Aromatase inhibitor			.....
Aromatase inhibitor	41/388 (10.6%)	48/385 (12.5%)	1.25 [0.82- 1.90]
Tamoxifen	36/253 (14.2%)	22/252 (8.7%)	0.63 [0.36- 1.05]
Previous adjuvant vs. neoadjuvant CT/HT			.....
Adjuvant CT/HT	44/474 (9.3%)	45/474 (9.5%)	1.11 [0.73- 1.68]
Neoadjuvant CT/HT	33/167 (19.8%)	25/163 (15.3%)	0.73 [0.43- 1.22]
PR: positive vs. negative			.....
PR : Negative	16/92 (17.4%)	13/89 (14.6%)	0.88 [0.42- 1.83]
PR : Positive	61/549 (11.1%)	57/548 (10.4%)	0.98 [0.68- 1.40]
Duration of hormone therapy before inclusion			.....
<=3 years	67/540 (12.4%)	57/543 (10.5%)	0.86 [0.60- 1.23]
>3 years	10/101 (9.9%)	13/94 (13.8%)	1.58 [0.69- 3.69]
>=4N+ or >=1N+ after neoadjuvant setting vs 1-3N+ and EPClin score high			.....
1-3N+ and EPClin score high	15/208 (7.2%)	10/204 (4.9%)	0.77 [0.33- 1.69]
>=4N+ or >=1N+ after neoadjuvant setting	62/433 (14.3%)	60/433 (13.9%)	0.98 [0.69- 1.40]



EXPERIMENTAL TREATMENT: DRUG REDUCTION

Characteristics	Placebo arm	Everolimus arm
Dose reduction: whole population	75/641 (11.7%)	218/637 (34.2%)
Dose reduction: When started at 10mg (439 patient)	24/219 (11.0%)	103/220 (46.8%)
Dose reduction: When started at 5 mg (812 patient)	51/411 (12.4%)	114/401 (28.4%)

EXPERIMENTAL TREATMENT: DRUG DISCONTINUATION

Characteristics	Placebo arm (n=641)	Everolimus arm (n=637)
All patients **Median Treatment duration (Q1-Q3)**	**22.5 (9.7 – 23.9)**	**9.2 (2.1-23.4)**
Patients stopping early (n, %)	**143/641 (22.3%)**	**340/637 (53.4%)**
Med. treatment duration before stopping	6.3 (2.3-11.7)	3.1 (1.1-7.8)
Reason to stop		
Adverse Event	64 (10.0%)	225 (35.3%)
Withdrawal by subject	46 (7.2%)	97 (15.2%)
Progressive	33 (5.1%)	18 (2.8%)
Patients stopping early when dose was initiated at 10mg (439 patients)		
Patients stopping early	**41/219 (18.7%)**	**128/220 (58.2%)**
Med. treatment duration before stopping	6.3 (2.5-11.2)	2.5 (0.8-7.7)
Adverse Event	15 (6.8%)	90 (40.9%)
Withdrawal by subject	14 (6.4%)	32 (14.5%)
Progressive	12 (5.5%)	6 (2.7%)
Patients stopping early when dose was initiated at 5mg (812 patients)		
Patients stopping early	**96/411 (23.3%)**	**204/401 (50.9%)**
Med.treatment duration before stopping	6.9 (2.7-11.9)	3.4 (1.3-8.0)
Adverse Event	48 (11.7%)	134 (33.4%)
Withdrawal by subject	28 (6.8%)	58 (14.5%)
Progressive	20 (4.9%)	12 (3.0%)

SAFETY (1)

Characteristics	Placebo arm (n=641)	Everolimus arm (n=637)
Grade >=3 AE	101 (15.9%)	187 (29.9%)
When initial dose = 10 mg	34 (15.5%)	84 (38.2%)
When initial dose = 5mg	66 (16.1%)	102 (25.4%)
Serious adverse event	59 (9.3%)	74 (11.8%)
Grade Max		
1	215 (33.9%)	72 (11.5%)
2	296 (46.7%)	354 (56.6%)
3	90 (14.2%)	174 (27.8%)
4	10 (1.6%)	11 (1.8%)

One toxic death was considered related to everolimus (Sceptic shock due to streptococcus septicemia)

SAFETY (2)

	Placebo arm (n=641)		Everolimus arm (n=637)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Mucositis oral	204 (32.2%)	2 (0.3%)	370 (59.2%)	46 (7.4%)
Hypertriglyceridemia	99 (15.6%)	1 (0.2%)	176 (28.2%)	19 (3.0%)
Hepatic ALAT/ASAT/GGT increase	111 (17.5%)	11 (1.7%)	165 (26.4%)	14 (2.2%)
Fatigue	296 (46.7%)	8 (1.3%)	327 (52.3%)	12 (1.9%)
Hyperglycemia	67 (10.6%)	1 (0.2%)	103 (16.5%)	9 (1.4%)
Venous Thrombotic Event	1 (0.2%)	1 (0.2%)	8 (1.3%)	8 (1.3%)
Pneumonitis	5 (0.8%)	1 (0.2%)	20 (3.2%)	5 (0.8%)
Rash	71 (11.2%)	0 (0.0%)	180 (28.8%)	3 (0.5%)

CONCLUSION

- In the UNIRAD study, after 3 years median follow-up of 1278 patients with high risk early BC, everolimus given in combination with adjuvant HT did not improve DFS compared with HT alone (HR 0.95; 95% CI 0.69-1.32)
- Acceptability was a concern, with 50% of the patients stopping everolimus before study completion for toxicities or personal decision.
- Subgroup analysis showed a trend for higher efficacy in patients treated with tamoxifen
- Follow-up will continue to evaluate long-term outcomes.

Thanks!

The 1278 patients who participated to UNIRAD

Sponsor: unicancer

Protocol writting committe:
Fabrice ANDRE (GR, France)
Thomas BACHELOT (CLB, France)
Hervé BONNEFOI (IB, France),
Sylvie CHABAUD (CLB, France)
Jerome LEMONNIER (Unicancer, France)
Anne-Laure MARTIN (Unicancer, France)
David PEROL (CLB, France)

IDMC Members:
Prof. Kathy PRITCHARD (UCL, UK)
Prof. Alain RAVAUD (CHU Bordeaux, France)
Dr Meredith REGAN (Dana Farber, USA)

70 Investigational sites: UCBG unicancer ICR The Institute of Cancer Research

Gustave Roussy (GR), Centre L. Bérard (CLB), Centre F. Baclesse, Western Gen., IUCT, Institut Curie, IC Lucien Neuwirth, I. Ste Catherine, Royal Stoke Hospital, CHU Dupuytren, ICO, Hôp. du Léman, I. Bergonié (IB), CARIO HPCA Plérin, Hôp. St Louis, Hôp. Civil, CH de Cotentin, Centre O. Lambret, Centre Oncogard, Centre J. Perrin, Cl. Pasteur_Toulouse, Musgrove Park Hospital, Hôp. Diaconnesses, Hop. Laennec_Quimper, Ninewells Hosp., CH Annecy, CH Montélimar, Weston Park Hosp., Centre Hospitalier Fleyriat, Royal Alb. Ed. Infirmary, Macclesfield District GH, CH Blois, Peterborough City Hosp., Hôp. L. Pasteur_Chartres, CHU Nîmes, Univ. College London Hospital, Royal Free, CH Lorient, Centre J. Bernard, Weston General Hosp., Royal Cornwall Hosp., CHU Dinant-Mont Godinne, Huddersfield R. Infirmery, CH A. Paré_Marseille, Cl St-J. de Languedoc, Hop. De Sens, County Hospital, CHIC Creteil, CH Ambroise Paré, I. J. Godinot, Velindre Cancer Centre, CHR Verviers, Centre G. F. Leclerc, Hôp. P. Drôme Ardèche, Gd Hôp. de Charleroi, Cl. du Sud Luxembourg, Cl. C. Bernard, Centre A. Vautrin, CU St-Luc_Bruxelles, Nottingham Hospital, CHC Saint-Joseph, Hôp. Tenon, Maidstone Hospital, Hôp. Américain , CH Leman, CH de l'Ardenne, CH Cahors, Cl. Sauvegarde, Calderdale Royal hospital, CH d'A. Méridionale

EndoPredict platform:
Ludovic

Statistics:
Sylvie CHABAUD (CLB, France)

Data Center:
Lise ROCA (ICM, France)

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ESMO VIRTUAL PLENARY

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org