INSTITUT
JULES BORDET
INSTITUUT

ONCO DISTINCT NETWORK

Therapeutic Strategies Changing Clinical Practice and Emerging in Breast Cancer

Ahmad Awada, MD, PhD
Head of Oncology Medicine Department
Institut Jules Bordet
Université Libre de Bruxelles (U.L.B.)
Brussels - Belgium

December 2021

ULB iris

Disclosures

Advisory role, research grants to my Institute, Speaker fees:

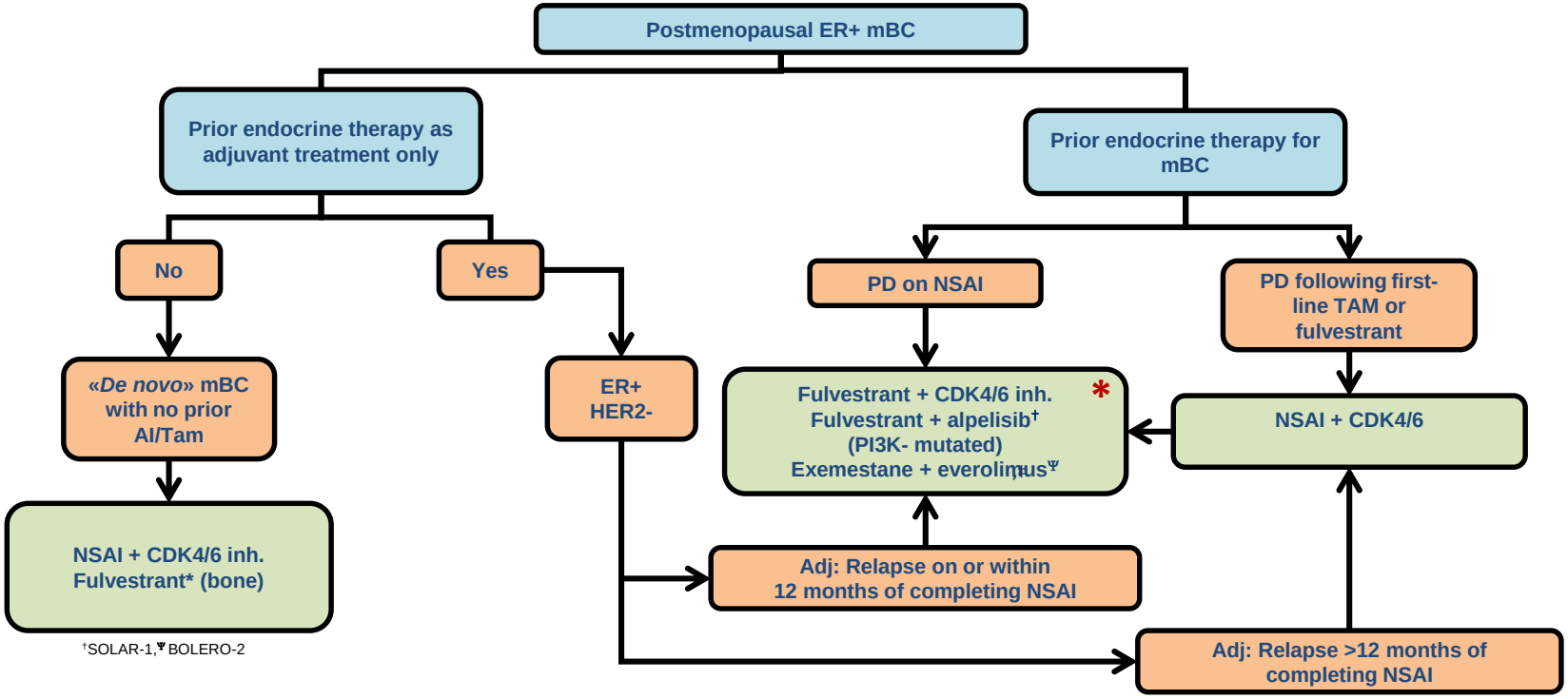
Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma, Merck, Daiichi, Seattle Genetics, Pierre Fabre

Content of the talk: Studies changing practice in early and MBC + therapeutic algorithms

- Luminal Breast Cancer
- HER2 positive BC
- TNBC
- Precision Oncology in MBC

I. Luminal Breast Cancer

Therapeutic algorithm for luminal subtype MBC in 2021: CDK4/6 inhibitors as early as possible



* Individualisation based on prior therapy and PI3K status

MONALEESA2 (ET ±Ribo;1L) : ↑ OS(med 0S>5Y!)

INSTITUT JULES BORDET INSTITUUT

Adapted from Awada A, et al. ESMO Open. 2019.

ULB iris

ALPELISIB + Fulvestrant in HR+, HER2- MBC
Results of the phase III SOLAR-1 Trial

André F. et al
ESMO 2018 - NEJM 2019

Men or postmenopausal women, with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

(N=572)

PIK3CA-mutant cohort (n=341)

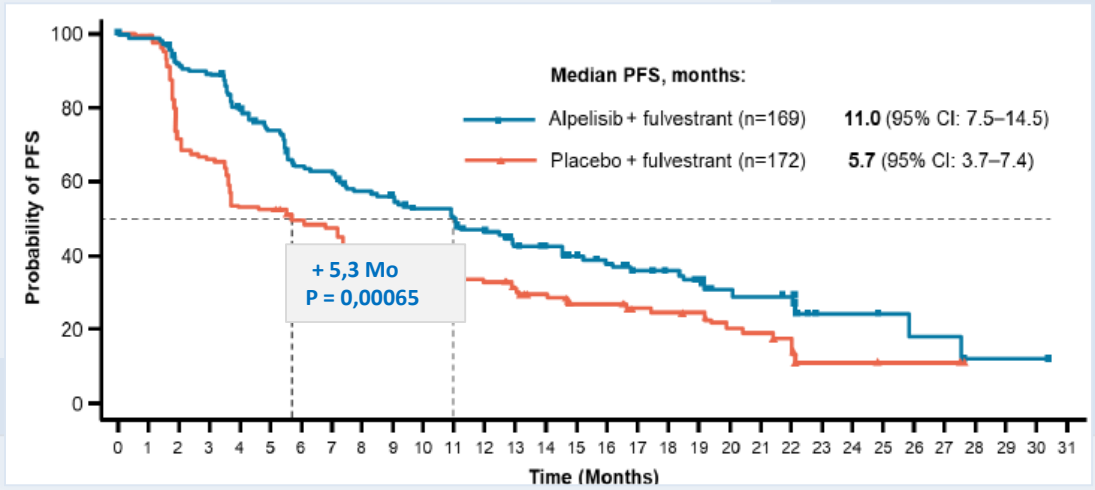
R

ALP 300 mg QD PO + FUL 500 mg IM* n=169

PBO + FUL 500 mg IM* n=172

Primary endpoint

- PFS in *PIK3CA*-mutant cohort



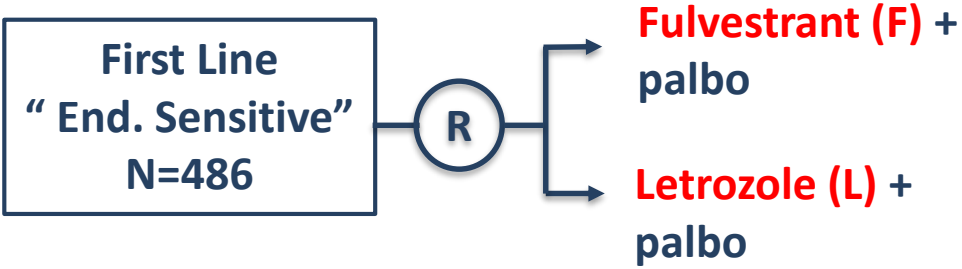
INSTITUT JULES BORDET INSTITUUT

CHL KRIIBSZENTRUM

Trials in luminal MBC of interest for clinical practice

Aim: Best endocrine partner with CDK4-6 inhibitor?

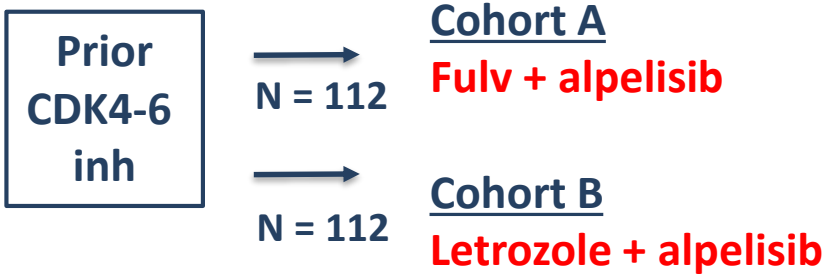
Parsifal



Median PFS 28m (F) vs 33m (L)
- Failed to show superiority or inferiority of F !
- Same dose intensity

Aim: Does Alpelisib work after CDK4-6 inhibitor?

BY-lieve



Cohort A
Median PFS 7.3m
Clinical benefit 45%
Discontinued for AE 20%
Benefit of prophyl antihistaminics (70% w/o rashh)

ASCO 2020 – abst 1007/1006

INSTITUT JULES BORDET INSTITUUT

ULB iris

BYLieve cohort B results into context

	SOLAR-1 Fulv + Alp	BYLieve cohort A Fulv + Alp	BYLieve cohort B Let + Alp
1st line 2nd line 3rd line	52% 47% -	11.8% 70.1% 16.5%	1.6% 52.4% 44.4%
Prior CDK4/6i	5.9%	100%	100%
mPFS (months)	11.0	7.3	5.7
ORR%	36%	21%	18%
CBR%	57%	42%	32%
Decrease in best % change from baseline	75.6%	70.1%	66.3%
AEs leading to discontinuation	25%	20.5%	14.3%

>80% progressed on prior AI

5.7 months mPFS compares favorably with available data on post-CDK4/6i tx

Improvement in toxicity management with increasing experience?

André F, NEJM 2019; Rugo H et al, ASCO 2020; Rugo H et al, SABCS 2020

INSTITUT JULES BORDET INSTITUUT

ULB iris

BYLieve: conclusions

- **BYLieve cohorts A and B** support Alpelisib + ET as a treatment option after CDK4/6i for *PIK3CA*-mut patients.

- **In cohort B**, efficacy of Alpelisib + Letrozole was demonstrated despite >80% of pts progressed on prior AI.
  - Reasonable to expect substantial rate of ESR1 mutations
  - Any role for combining Alpelisib with new SERDs in this context?

Luminal MBC : Perspectives

- CDK4/6i are SOC in patients with metastatic disease
- Drug activity of post CDK4/6i therapy is not good enough
- Agents under investigations:

SERDs

- EMERALD: Elacestrant vs choice ET
- AMEERA: SAR439859 vs let + Pal
- GDC9545 + Pal vs Let+ Pal
- SERENA-2: AZD9833vs Fulvestrant

AKT i

- CAPitello-291: Ful +- capivasertib
- IPATunity 150: Pal/Ful +/- ipatasertib

SER/SERM

- ELAINE: Lasofoxifene vs Fulvestrant
- Enobosarm mono

ADC's

- Sac Gov
- Tras Deruxtecan
- Ladiratuzumab vedotin (Liv1a)

CDK4/6 inhibitors: Adjuvant setting

MonarchE and PALLAS : Study characteristics

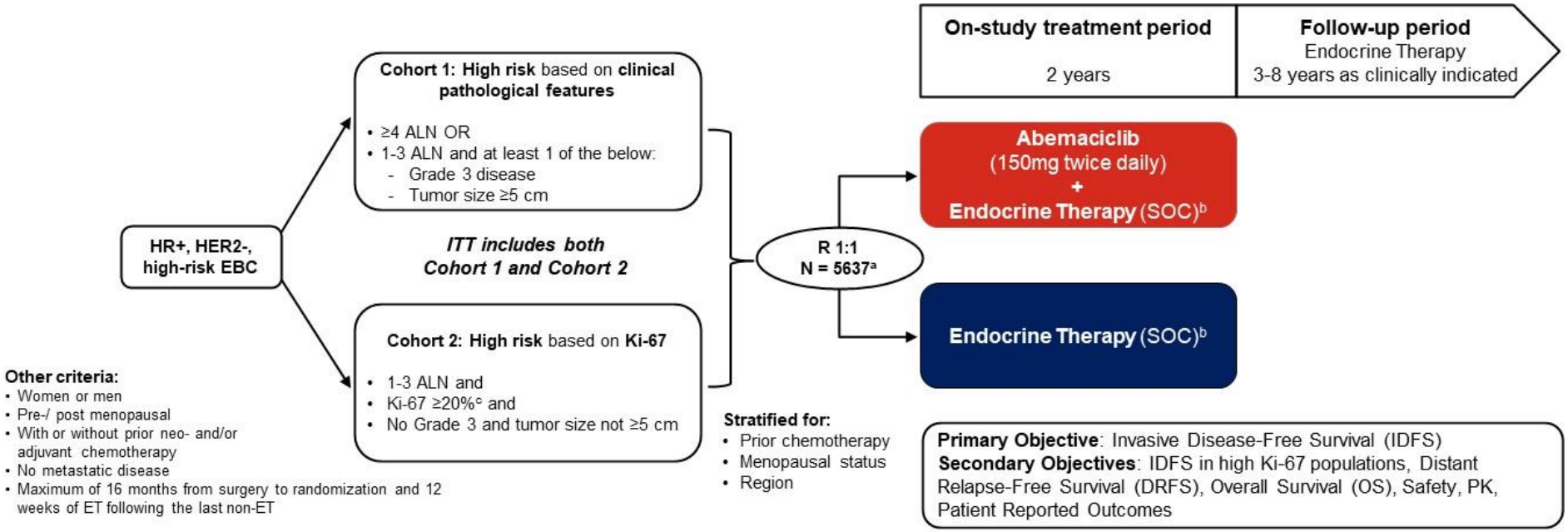
CHARACTERISTICS	MONARCHE	PALLAS
Study drug (2y) Inclusion period	Abemaciclib 07/17 – 08/19	Palbociclib 09/15 – 11/18
Stratification factors	Previous chemo Menopausal status Region	Stage II A vs IIB/III Chemo yes/no Age (50), Region
Pts eligibility	LN + (≥4) or LN + (1-3) + T≥5cm or gr3 or ki67 ≥ 20%	Stage II – III
Statistics	85% power for HR 0.73 5y IDFS 82,5% in control Arm (390 IDFS events)	85% power for HR 0.75 (IDFS)
Interim analysis	50% of required events → Updated results	1st futility (167 events) 2d futility (313 events) 69 IDFS for final analysis → Negative results

INSTITUT JULES BORDET INSTITUUT

Johnston et al, JCO, 38, 2020
Mayer et al, ESMO 2020

ULB iris

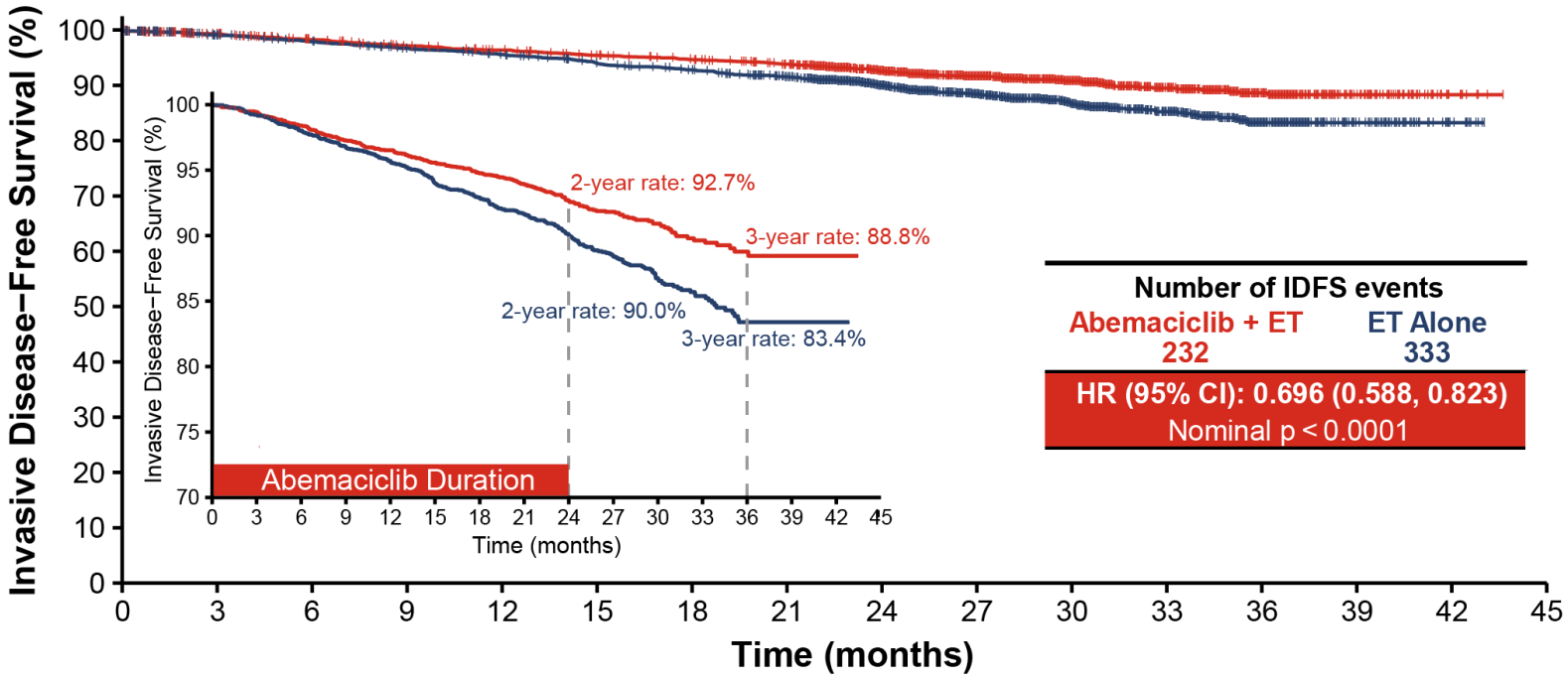
MonarchE Study Design



[a]Recruitment from July 2017 to August 2019; [b]Endocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; [c]Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent

Abbreviations: ALN = positive axillary lymph nodes; CPF = clinicopathological features; HER2 = human epidermal receptor 2; HR = hormone receptor; ITT = intent-to-treat population; N = number of patients in the ITT population; R = randomized; SOC = standard of care

IDFS Benefit Maintained with Additional Follow-up in ITT population



Number at risk																
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET Alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

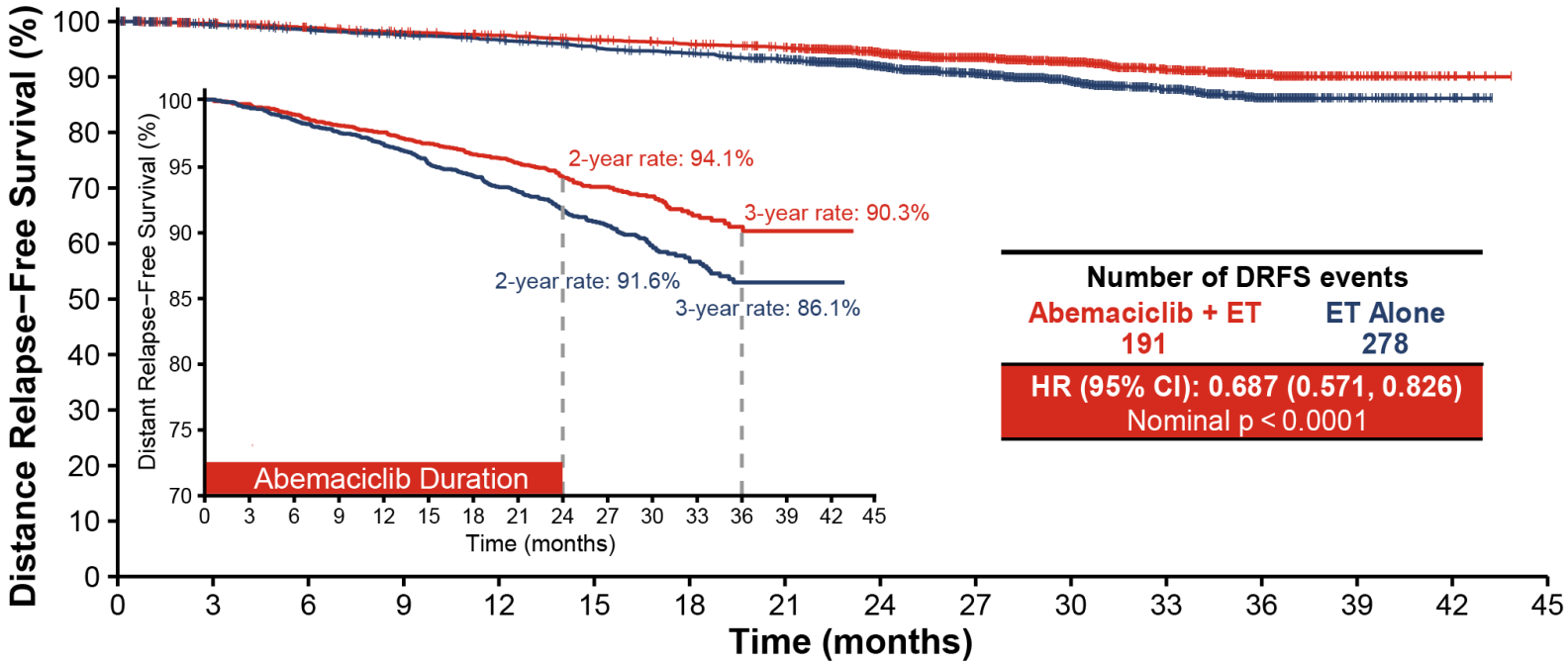
30.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 5.4% at 3 years.

INSTITUT JULES BORDET INSTITUUT

Joyce O'Shaughnessy ESMO 2021

ULB iris

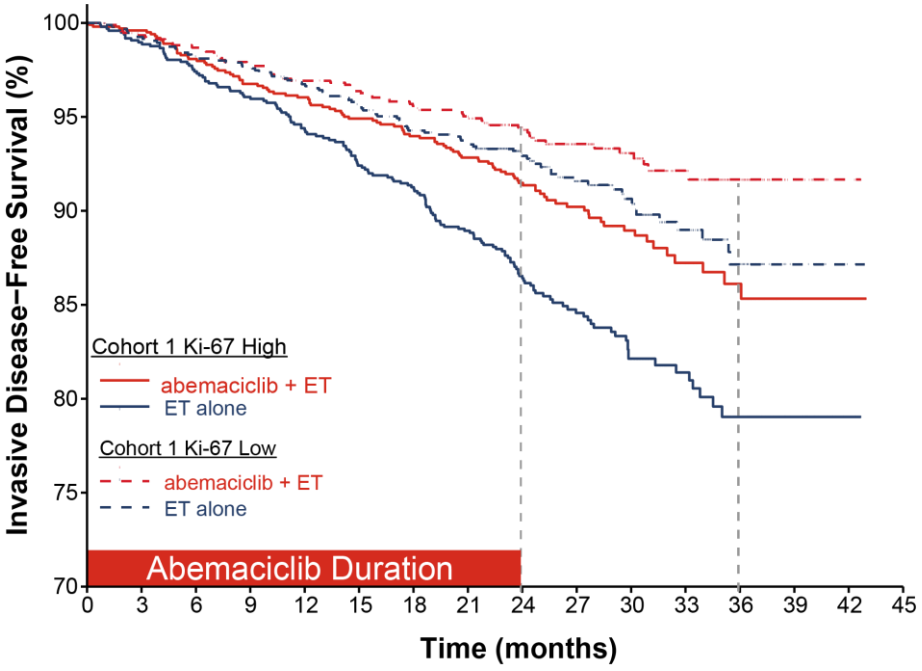
Benefit of DRFS Maintained with Additional Follow-up in ITT population



Number at risk																
Abemaciclib + ET	2808	2684	2629	2595	2566	2529	2497	2455	1990	1300	930	530	281	68	8	0
ET Alone	2829	2704	2660	2622	2591	2535	2499	2427	1955	1287	924	537	287	66	10	0

31.3% reduction in the risk of developing a DRFS event.
The absolute difference in DRFS rates between arms was 4.2% at 3 years.

Ki-67 as a prognostic marker in Cohort 1



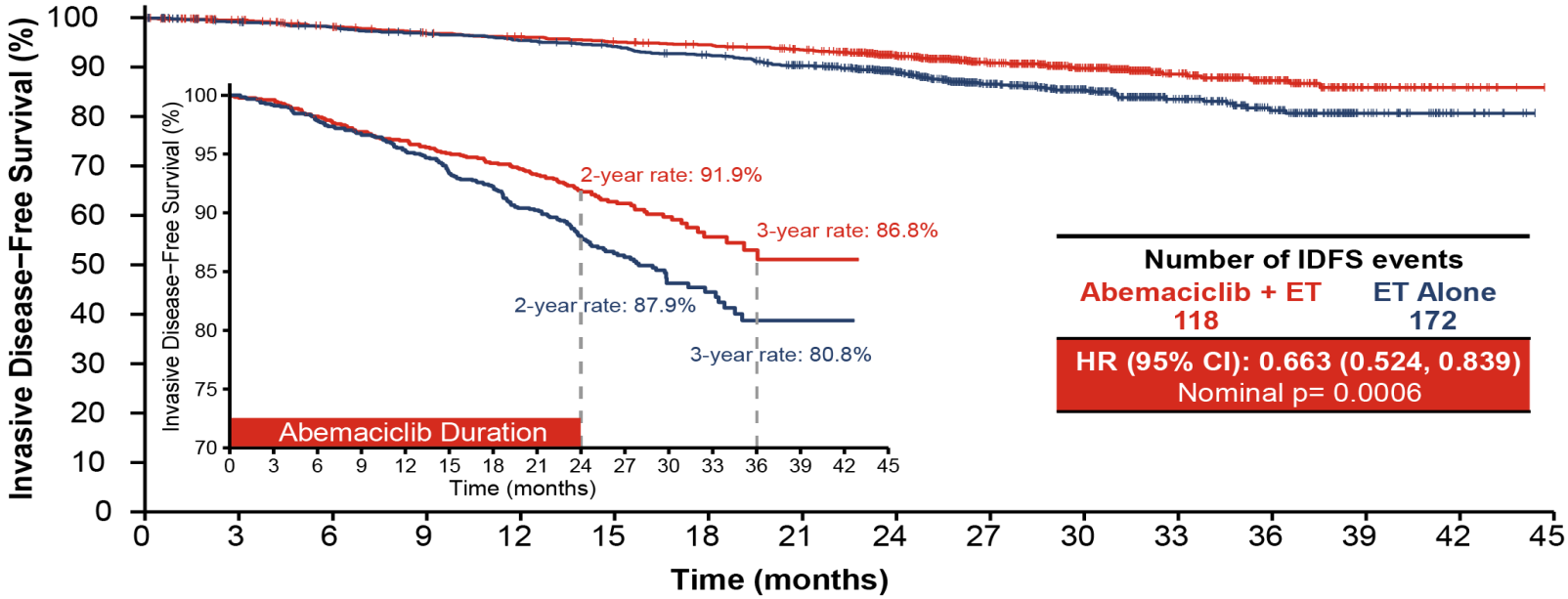
	Abemaciclib + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

As expected, high Ki-67 index was prognostic of worse outcome. However, abemaciclib benefit was consistent regardless of Ki-67 index.

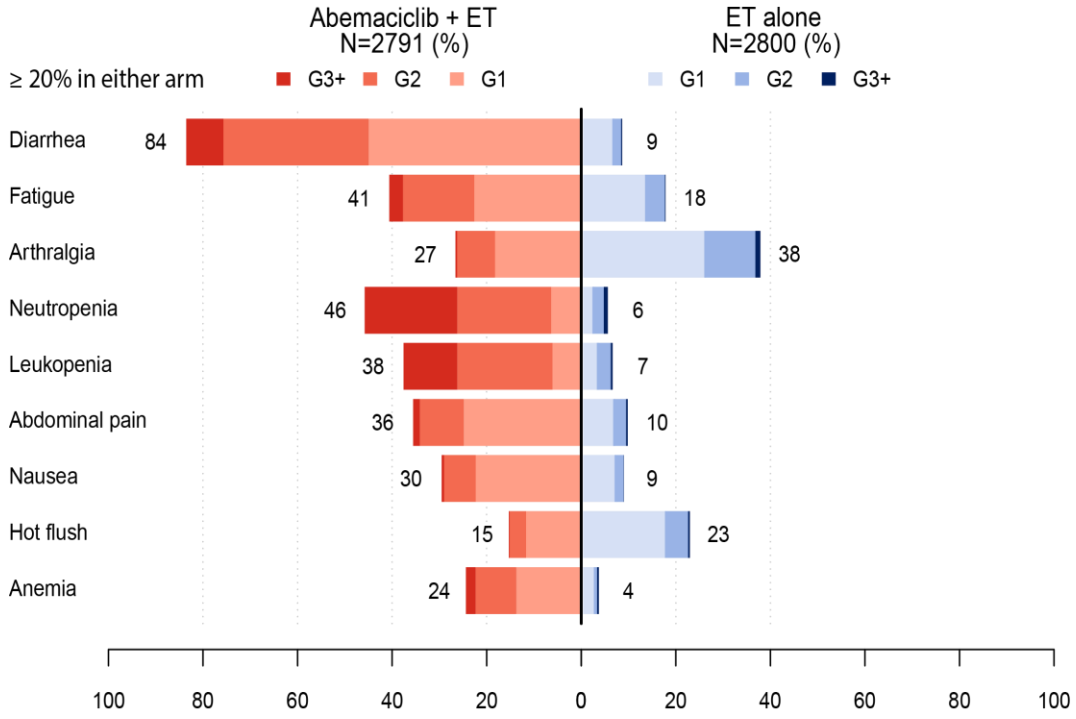
IDFS in ITT Ki-67 High (≥ 20%) Population



Number at risk																
Abemaciclib + ET	1262	1221	1189	1167	1155	1139	1123	1094	870	546	377	203	109	25	2	0
ET Alone	1236	1197	1177	1158	1142	1114	1096	1041	827	520	367	198	107	25	3	0

33.7% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 6.0% at 3 years.

Mature Safety Findings Consistent with Previous Analyses



Median duration of abemaciclib: 23.7 months

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.6
PE	1.0	0.1
ILD	3.2	1.3

Abbreviations: VTE = venous thromboembolic event; PE = pulmonary embolism; ILD = Interstitial lung disease

All patients who received at least one dose of study treatment were included in the safety population

MonarchE Conclusions (1)

- With additional follow-up, adjuvant abemaciclib combined with ET continued to demonstrate clinically meaningful benefit for patients with HR+, HER2-, node-positive, high risk EBC
  - Robust IDFS and DRFS benefit was maintained beyond the 2-year treatment period of abemaciclib

- Safety data set is mature with 90% of patients off study treatment period
  - Data are consistent with known safety profile of abemaciclib and considered acceptable in high risk EBC

MonarchE Conclusions (2)

- **Ki-67 index was prognostic, but abemaciclib benefit was consistent regardless of Ki-67 index**

- **Continued follow-up for efficacy and safety is ongoing until the final assessment of OS**

Is abemaciclib a standard of care in EBC?

- More mature data of iDFS are reassuring
- OS data are of importance (awaited)
- Qol and PROs are very important in this setting
- Financial aspect is important

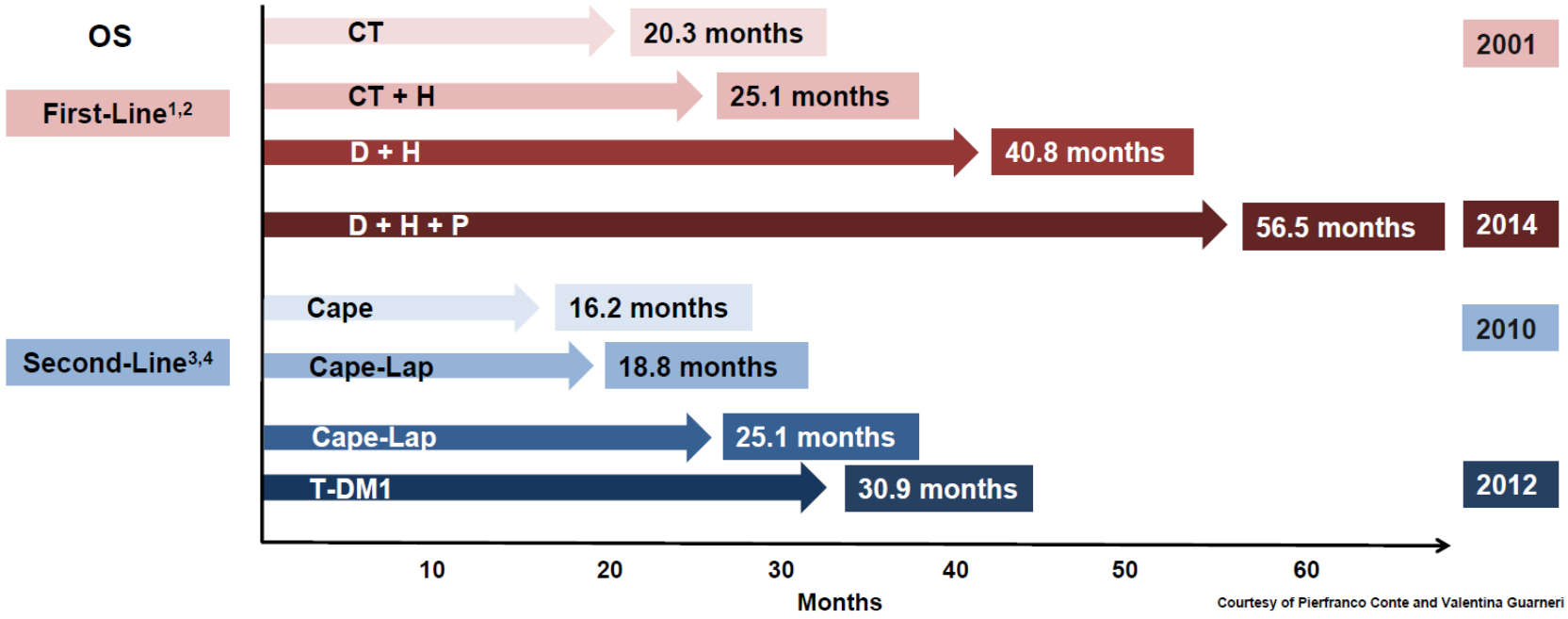
The so far observed results of Abemaciclib in high risk population (= niche) are very encouraging. More mature efficacy and toxicity data are coming.

II. HER-2 Positive Breast Cancer: An extraordinary progress paving the way to cure this BC molecular subtype ?!

INSTITUT JULES BORDET INSTITUUT

ULB iris

Progress Over Time of Earliest developed agents for HER2-Positive MBC



Cape, capecitabine; CT, chemotherapy; D, docetaxel; H, trastuzumab; Lap, lapatinib; OS, overall survival; P, pertuzumab; T-DM1, trastuzumab emtansine

1. Slamon D, et al. *N Engl J Med.* 2001;15(1);344:783-792. 2. Swain S, et al. *N Engl J Med.* 2015;372(8):724-734. 3. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 4. Verma S, et al. *N Engl J* Med. 2012;367(19):1783-1791.

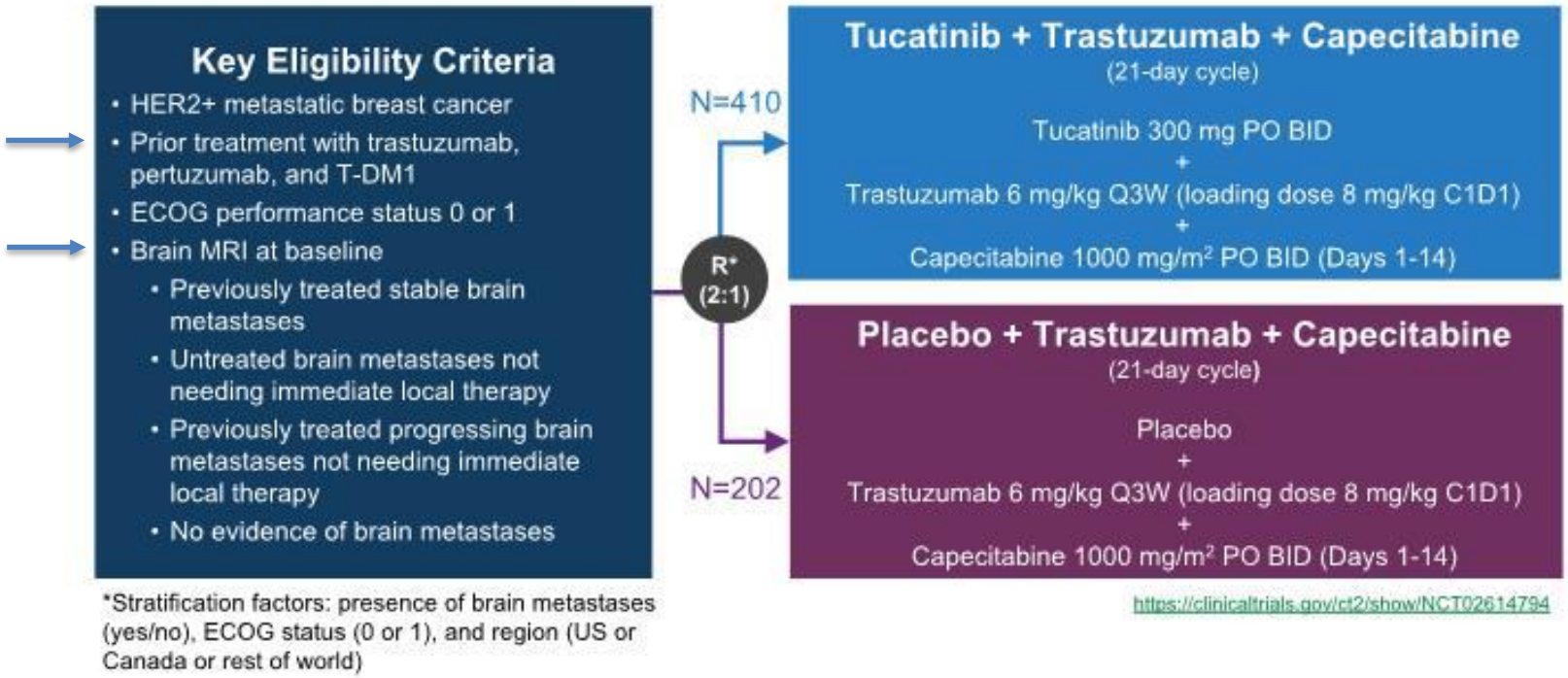
Investigational agents

Progress on the clinical Management of HER2 Positive advanced Breast cancer

- New HER2 agents in ABC
  - Neratinib (NALA)
  - Tucatinib (HER2CLIMB)
  - Pyrotinib
  - Trastuzumab Deruxtecan (DESTINY B03;TULIP)
- Perspectives
  - Antibody drugs conjugates (high versus low HER2 expressors!)

Tucatinib in HER2+ MBC ± Brain metastases

HER2CLIMB Trial Design



*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

This presentation is the intellectual property of the author/presenter. Contact them at rmurthy1@mdanderson.org for permission to reprint and/or distribute.

INSTITUT JULES BORDET INSTITUUT

ULB iris

HER2 CLIMB

Key Baseline Demographics and Disease Characteristics

Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	 Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2,17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Presence/history of brain metastases		198 (48)	93 (46)
Treated, stable		118 (59.6)	55 (59.1)
Untreated		44 (22.2)	22 (23.7)
Treated, progressing		36 (18.2)	16 (17.2)

Baseline characteristics were balanced between endpoint populations and treatment arms

This presentation is the intellectual property of the author/presenter. Contact them at rmurthy1@mdanderson.org for permission to reprint and/or distribute.

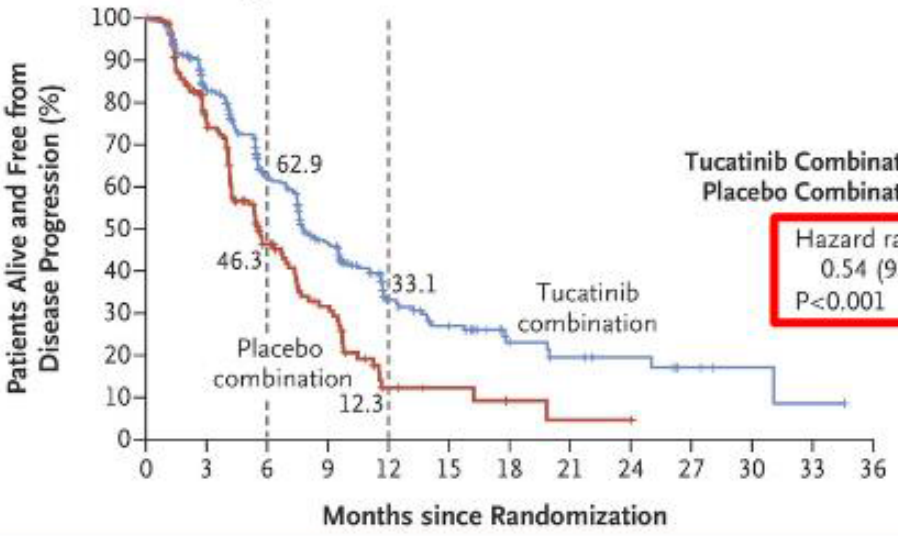
INSTITUT JULES BORDET INSTITUUT

ULB iris

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Progression–free Survival

A Kaplan–Meier Estimates of Progression-free Survival



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

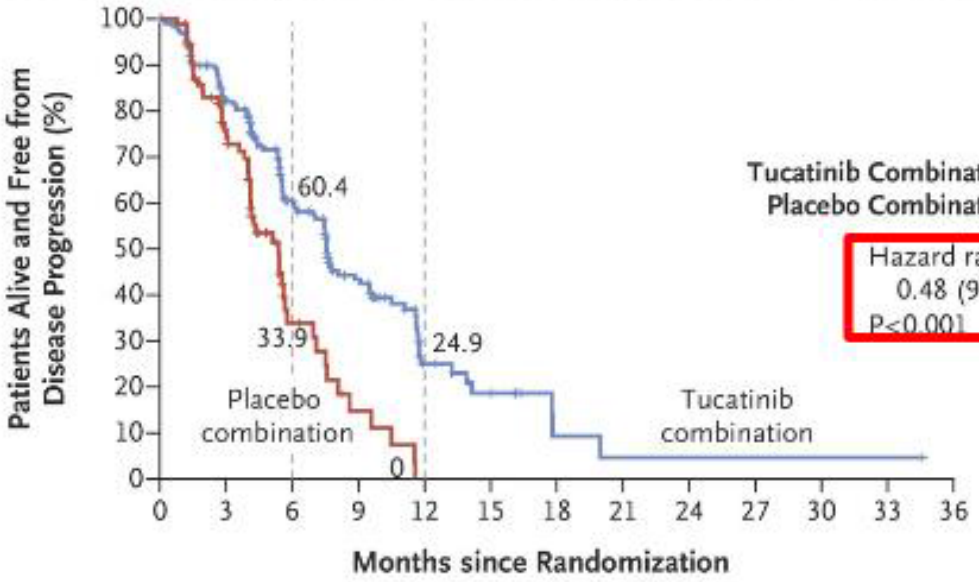
- ORR: 41% (tucatinib) vs. 23% (placebo)

The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

This presentation is the intellectual property of the author/presenter. Contact them at shurvitz@mednet.ucla.edu for permission to reprint and/or distribute.

Progression–free Survival among the Patients with Brain Metastases

A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

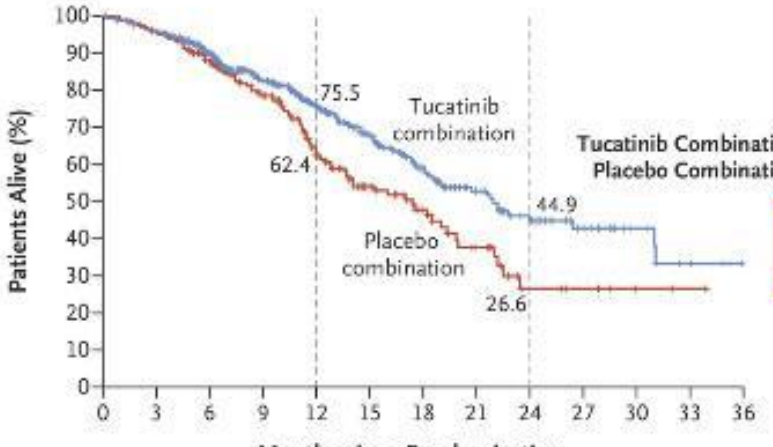
This presentation is the intellectual property of the author/presenter. Contact them at shurvitz@mednet.ucla.edu for permission to reprint and/or distribute.

INSTITUT JULES BORDET INSTITUUT
ULB iris

San Antonio Breast Cancer Symposium®, December 10-14, 2019

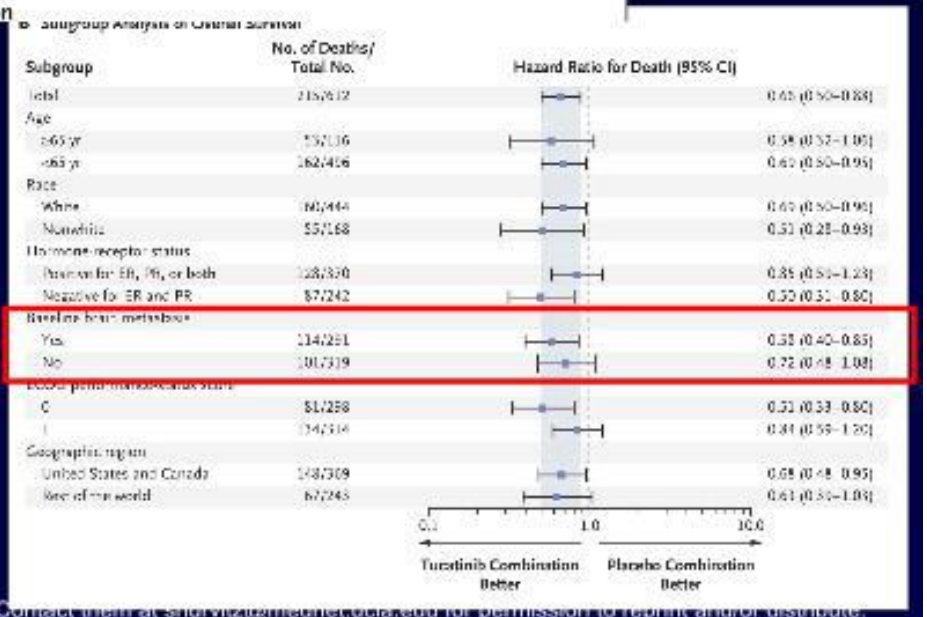
Overall Survival in the Total Population and Prespecified Subgroups.

A Kaplan–Meier Estimates of Overall Survival



	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005



The NEW ENGLAND JOURNAL of MEDICINE

RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

This presentation is the intellectual property of the author/presenter. Contact them at [redacted] for permission to reprint and/or distribute.

Early Studies of Antibody drug conjugates (ADCs) targeting HER2

ADC	Target	Initial Phase I Results	Main Side Effects
T-DXd	Humanized HER2 antibody + topoisomerase-I inhibitor exatecan	RR: 64.2% PFS:10.4 mo. (heavily pre-treated patients)	Gastrointestinal, pulmonary and haematological
SYD985[2]	Trastuzumab + duocarmazine	RR: 33%[2] PFS: 9.4 mo.	Ophthalmologic effects (conjunctivitis and keratitis)

[1] Iwata H et al. J Clin Oncol. 2018, [2] Saura C et al. J Clin Oncol. 2018, [3] Xu B et al. J Clin Oncol. 2018

HER2+ MBC :
Results from 2 ADCs targeting HER2 amplified tumors

STUDY	DESTINY B03		TULIP	
Drugs	**T-DXd vs**	**T-DM1**	**SYD 985 vs**	**TPC**
N° patients	261	263	291	146
mPFS (BICR) (mo)	NR	6.8	7	4.9
ORR % (CR) (confirmed)	79 (16)	34 (9)		
Lung tox (%)	10.5 (93% gr1/2)	1.9	7.6 (2 gr5!)	
Conjunctivitis	-	-	38	-
Kertitis	-	-	38	-

Proposed Therapeutic Algorithm of HER2 amplified MBC in 2021 : An Evolving Field

- 1st L — Taxane + H + P
- 2nd L — T-deruxtecan
  - Active Brain mestastases : Tucatinib + H + Capecitabine
- 3rd L — Tucatinib or Neratinib → T-deruxtecan
  - Capecitabine-based
- 4th L — Chemo + Margetuximab ⇌ T-DM1
- > 4th L — Chemo + H ⇌ H + Lapatinib

HER2 mutated/HR+ MBC : Neratinib + Fulverstrant + Trastuzumab (SUMMIT trial) → ORR 46% ; mDOR 10.9 mo ; mPFS: 8.3 mo

III. Triple Negative Breast Cancer Disease

Progresses on the management of Triple Negative Breast Cancer in 2021

- More on the role of capecitabine in TNBC(adjuvant)
- Role of platinum in the neoadjuvant setting
- Role of Olaparib (PARP inh) in BRCA mutated high risk tumors (Adjuvant setting)
- Update on the role of CPIs in the early and metastatic settings
- Role of Antibody drugs conjugates (Sacituzumab Govitecan)

SYSUCC01 Adjuvant capecitabine trial in early TNBC

Chinese group trial – N = 443 st IIb→IIIc
after completion of « standard » adj CTX/RT
Median follow-up = 57 m

R

« Metronomic » Capecitabine*
650 mg/m 2 continuously
X 1y

83%

5y DFS
HR 0.63 (0.42 – 0.96)
DDFS
HR 0.63 (0.37 – 0.90)

Observation

73%

**** Completed therapy 91%, med dose intensity 85%, H&F syndrome 45% (17% gr3)***

ASCO 2020 – abst 507

INSTITUT JULES BORDET INSTITUUT

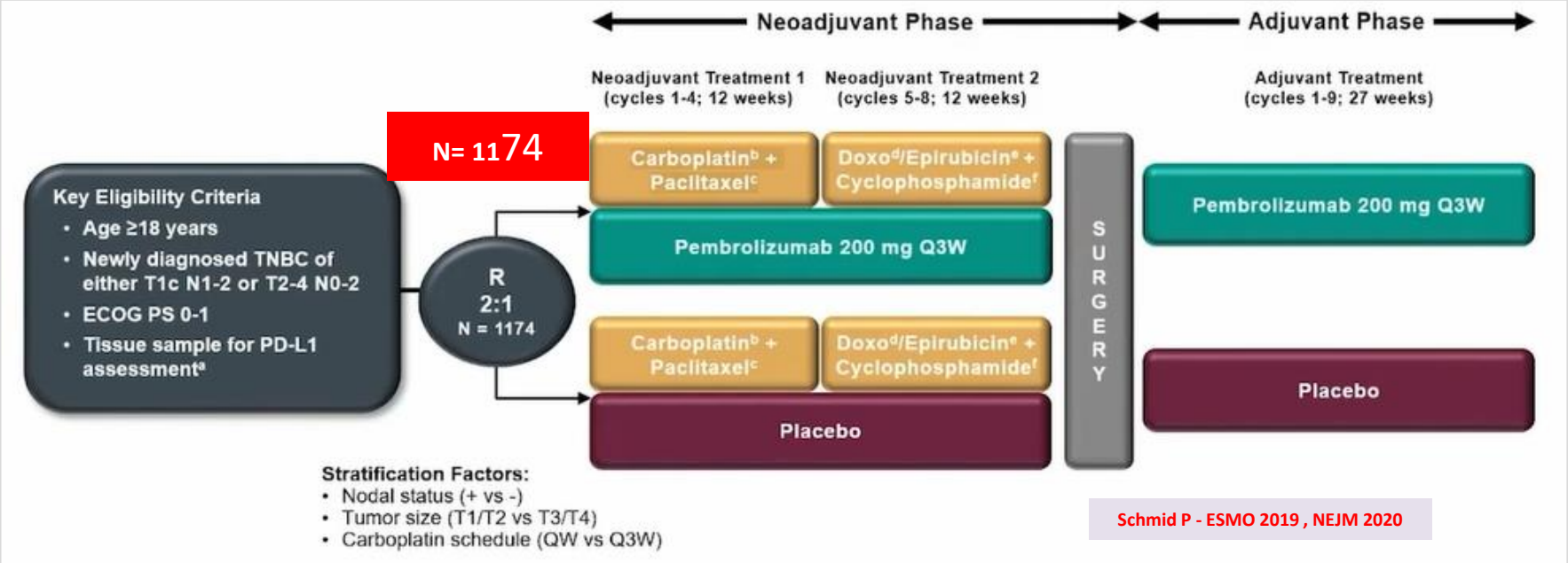
ULB iris

Studies influencing the current therapeutic guidelines in TNBC

Study	Setting	Experimental drug	Outcome
KN522	TNBC (neo/adj)	Pembrolizumab	↑ EFS ↑ PCR Trend OS
Brightness	TNBC (neoadj)	Carboplatin	↑ EFS ↑ PCR
Olympia	BRCA + (adj)	Olaparib	↑ IDFS
KN355	TNBC(1line)	Pembro + Chemo	↑ PFS ↑OS
ASCENT	≥ 2 prior CT	Sacituzumab Govitecan	↑ORR ↑PFS ↑OS

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer



Schmid P - ESMO 2019 , NEJM 2020

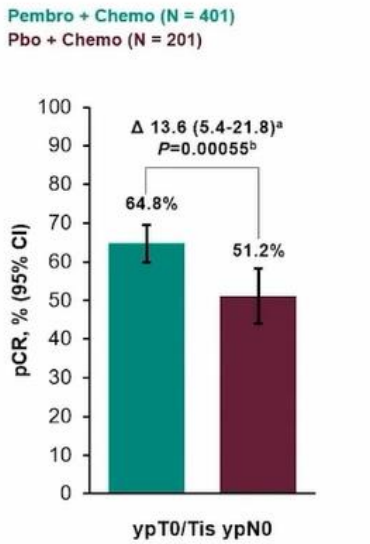
INSTITUT JULES BORDET INSTITUUT

ULB iris

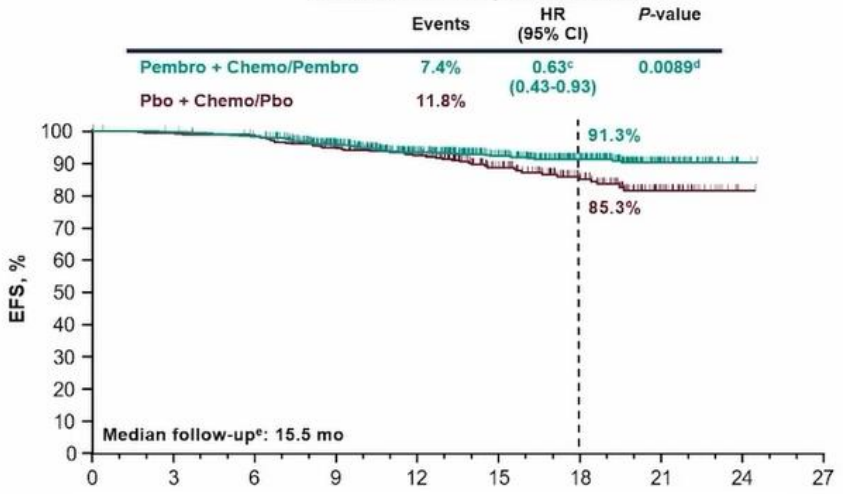
ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Primary pCR Endpoint at IA1[1]



First EFS Analysis at IA2[1]



Schmid P - ESMO 2019 , NEJM 2020

H1 (15mo) pCR Data

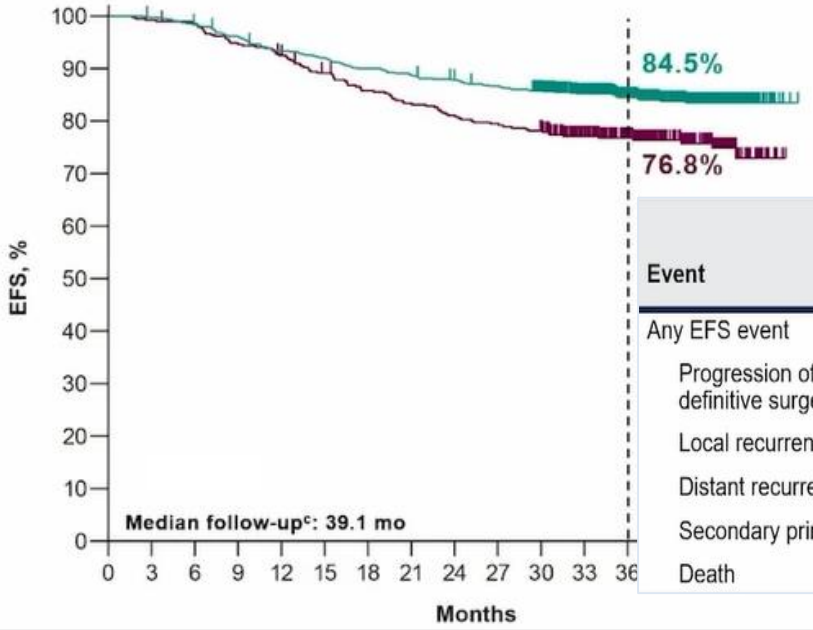
INSTITUT JULES BORDET INSTITUUT

ULB iris

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Statistically Significant and Clinically Meaningful EFS at IA4



Event	All Subjects, N = 1174	
	Pembro + Chemo/Pembro N = 784	Pbo + Chemo/Pbo N = 390
Any EFS event	123 (15.7%)	93 (23.8%)
Progression of disease that precludes definitive surgery	14 (1.8%)	15 (3.8%)
Local recurrence[a]	28 (3.6%)	17 (4.4%)
Distant recurrence	60 (7.7%)	51 (13.1%)
Secondary primary malignancy[b]	6 (0.8%)	4 (1.0%)
Death	15 (1.9%)	6 (1.5%)

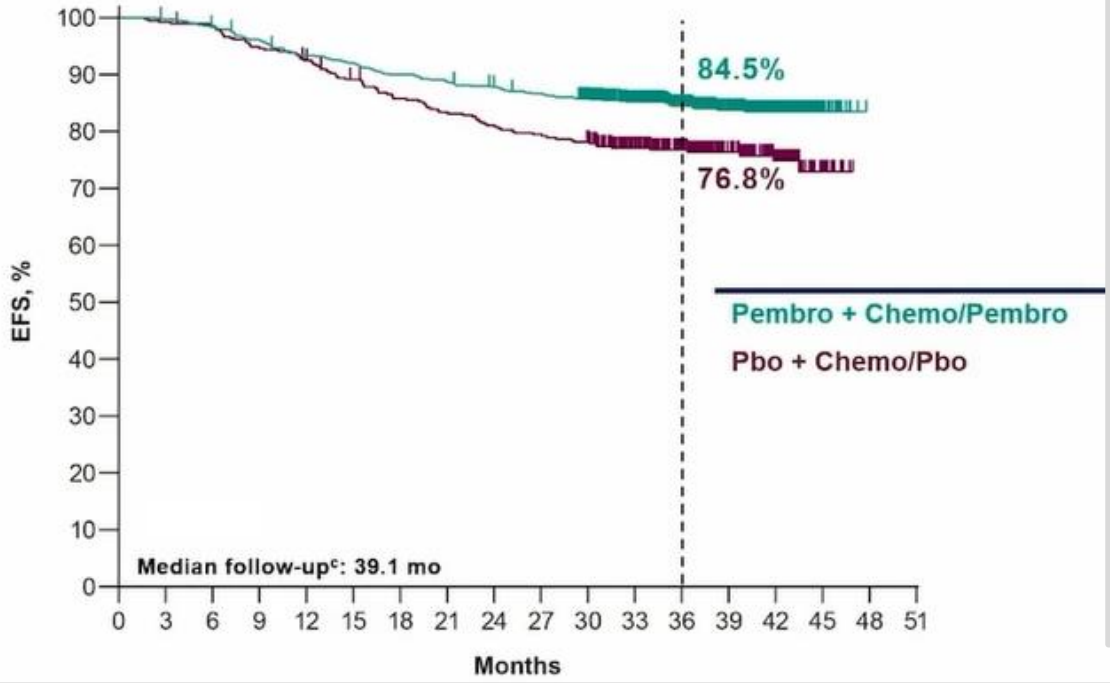
INSTITUT JULES BORDET INSTITUUT

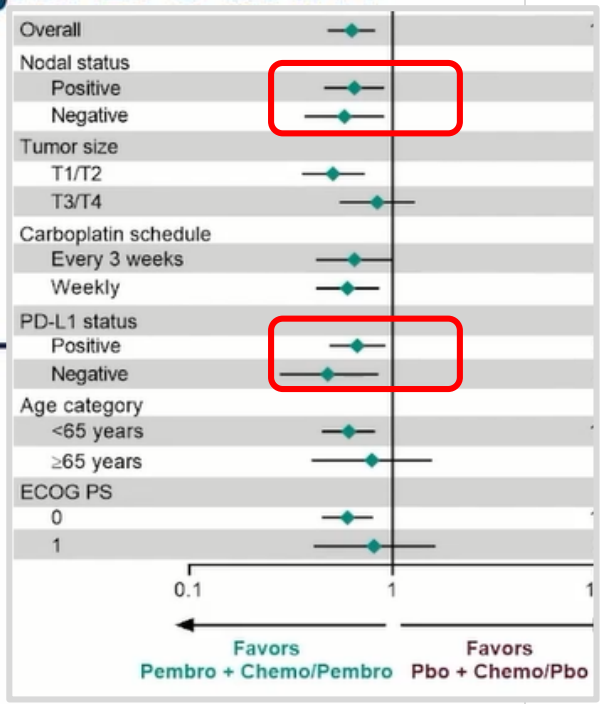
ULB iris

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Statistically Significant and Clinically Meaningful EFS at IA4





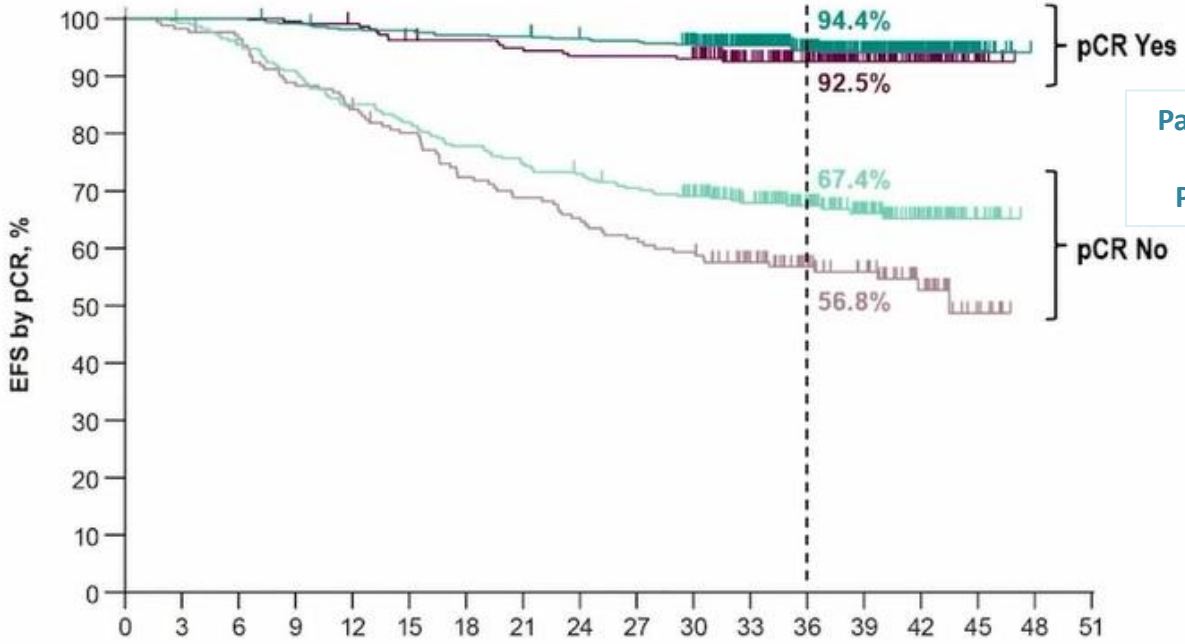
INSTITUT JULES BORDET INSTITUUT

ULB iris

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

EFS by pCR (ypT0/Tis ypN0)



Pas de Capecitabine
Pas d'Olaparib
Pas de Cross over

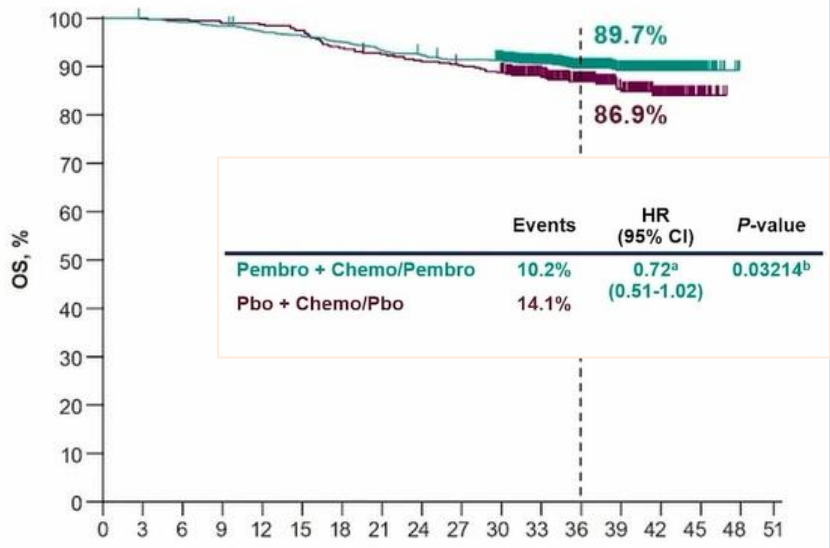
INSTITUT JULES BORDET INSTITUUT

ULB iris

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

OS



INSTITUT JULES BORDET INSTITUUT

ULB iris

ESMO VIRTUAL PLENARY 2021

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

1ère grande Ph III randomisée + Pembro en NAC/Adjuvant

2 Endpoints Primaires : + (pCR et EFS)

Trend en OS

« Pt Based CT + Pembro NAC → Adjuvant

= New standard of Care in High Risk Early TNBC «

? Toutes les patientes ?

? Adjuvant (1 an) si pCR ?

? + ou vs Capec; ou Olaparib si non pCR ?

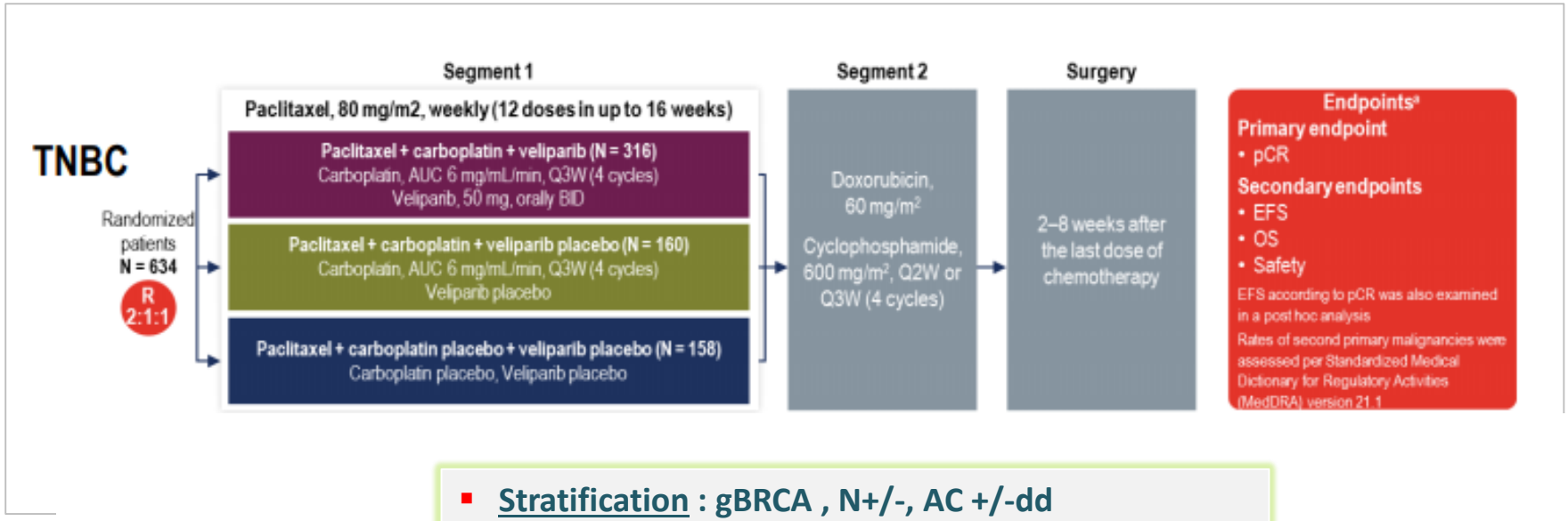
? Quelle chimio ? Carbo ?

Courtesy C. Duhem

EVENT-FREE SURVIVAL, OVERALL SURVIVAL, AND SAFETY OF ADDING VELIPARIB PLUS CARBOPLATIN OR CARBOPLATIN ALONE TO NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER AFTER ≥4 YEARS OF FOLLOW-UP: BRIGHTNESS, A RANDOMIZED PHASE 3 TRIAL

ESMO 2021

Sibylle Loibl[1,2], William M. Sikov[3], Jens Huober[4], Hope S. Rugo[5],



- **<u>Stratification</u> : gBRCA , N+/-, AC +/-dd**
- **<u>Etudie</u> : VELIPARIB +/- , CARBOPLATINE +/-**

INSTITUT JULES BORDET INSTITUUT

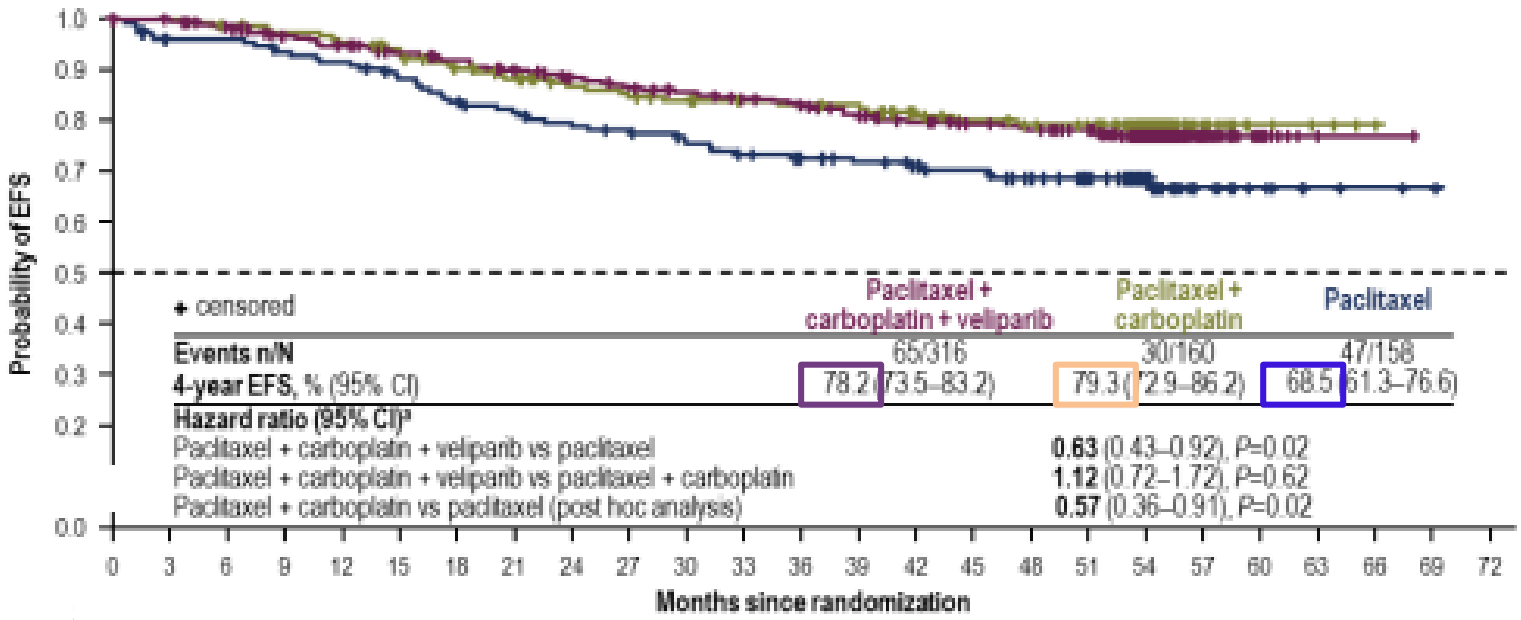
ULB iris

EVENT-FREE SURVIVAL, OVERALL SURVIVAL, AND SAFETY OF ADDING VELIPARIB PLUS CARBOPLATIN OR CARBOPLATIN ALONE TO NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER AFTER ≥4 YEARS OF FOLLOW-UP: BRIGHTNESS, A RANDOMIZED PHASE 3 TRIAL

ESMO 2021

Sibylle Loibl[1,2], William M. Sikov[3], Jens Huober[4], Hope S. Rugo[5],

EFS



INSTITUT JULES BORDET INSTITUUT

ULB iris

EVENT-FREE SURVIVAL, OVERALL SURVIVAL, AND SAFETY OF ADDING VELIPARIB PLUS CARBOPLATIN OR CARBOPLATIN ALONE TO NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER AFTER ≥4 YEARS OF FOLLOW-UP: BRIGHTNESS, A RANDOMIZED PHASE 3 TRIAL

ESMO 2021

Sibylle Loibl[1,2], William M. Sikov[3], Jens Huober[4], Hope S. Rugo[5],

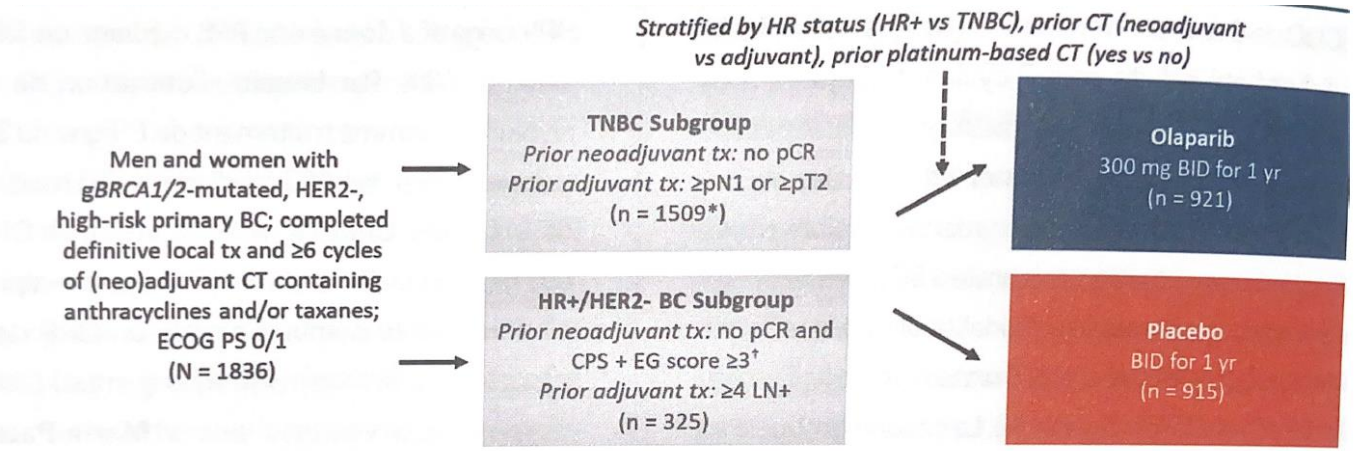
- + Carbo en NAC → ↑ Significative du taux - de pCR
  - de l'EFS
  - données OS : Immatures
- Indépendamment du status gBRCA
- Pas de toxicité à moyen terme

These findings support the inclusion of carboplatin in neoadjuvant chemotherapy for stage II-III TNBC, irrespective of g*BRCA* status

Courtesy C. Duhem

Breast Cancer with mutations in DNA damage response pathway genes (BRCA – mutated tumors)

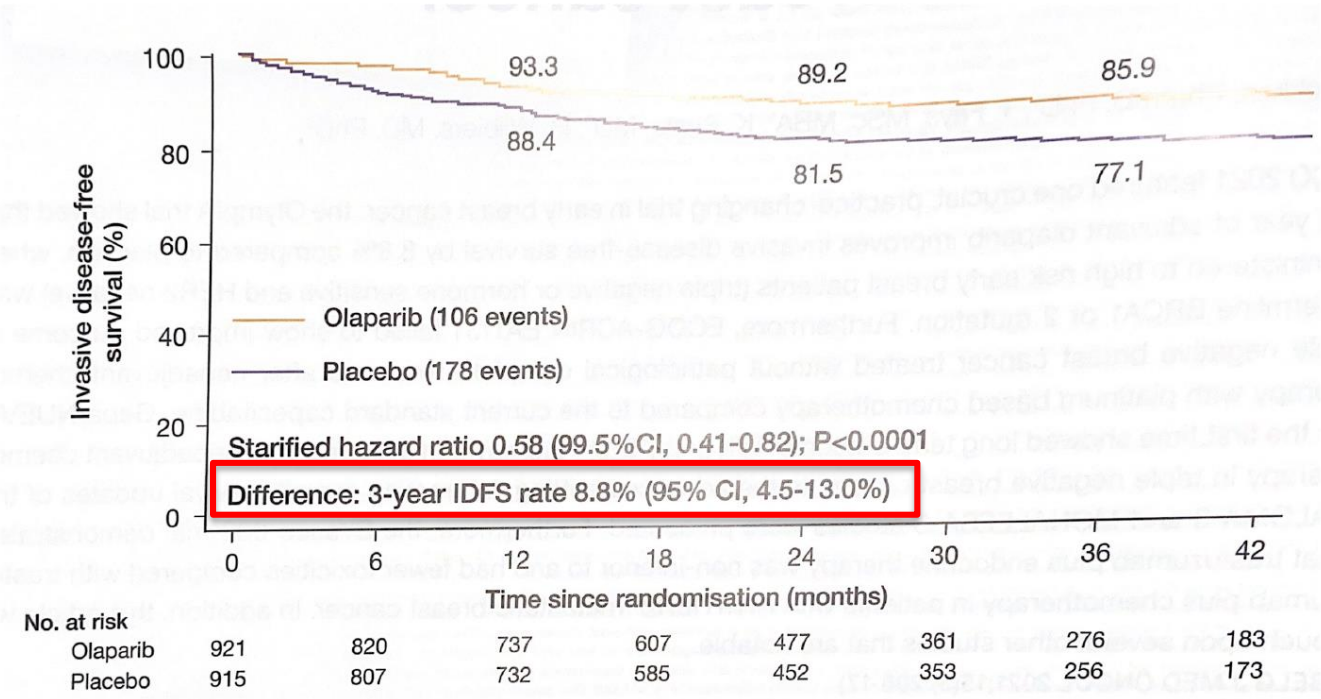
OlympiA TRIAL – Study design



Adapted from Tutt. NEJM. 2021;[Epub]. NCT02032823.

BC, breast cancer; CPS, clinical and pathologic stage; CT, chemotherapy; EG, estrogen-receptor status and histologic grade; ER, estrogen receptor; HR, hormone receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; pCR, pathologic complete response; TNBC, triple-negative breast cancer; tx, treatment.

Invasive disease-free survival in the phase III Olympia trial



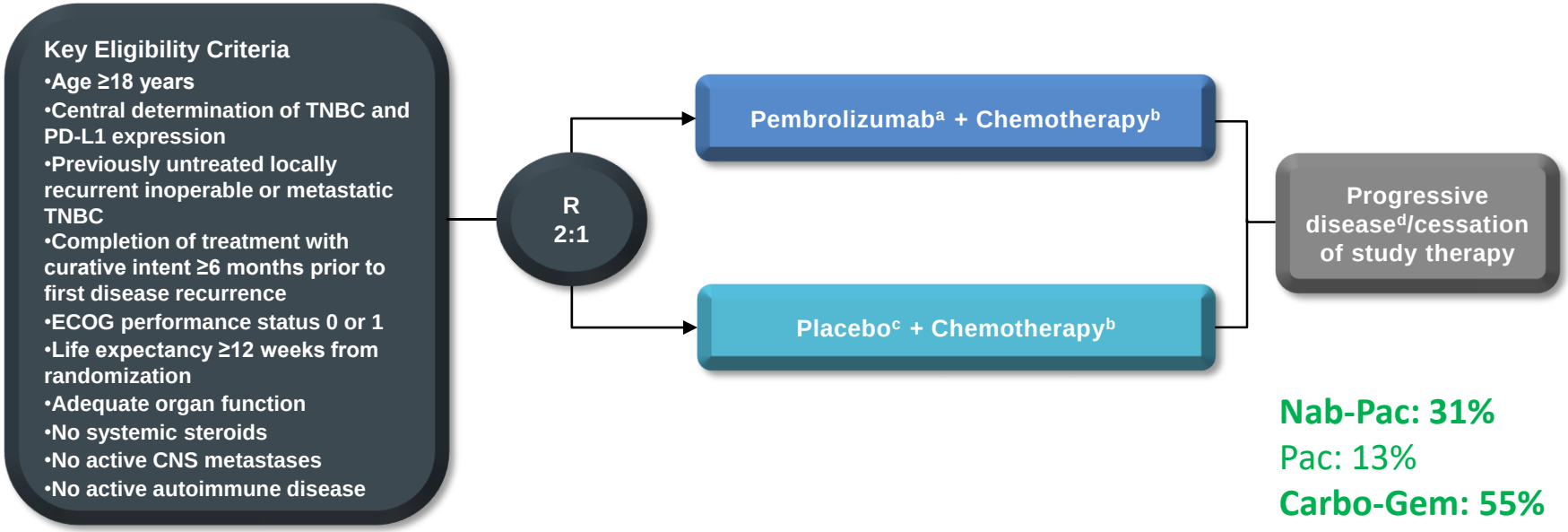
Blokken et al, BJMO V15 – september 2021

Chemo ± CPIs in metastatic TNBC: A summary

PDL1+ subsets	IMpassion 131 (VIRTUAL ESMO congress 2020)	IMpassion 130 (MUNICH ESMO congress 2018)	KEYNOTE 355 (ASCO20 Virtual)
N	292	369	323 (2:1)
Minimum DFI	12m	12m	6m (20% < 12m)
> 3 involved sites	15%	20%	43% (≥ 3)
Chemo backbone	paclitaxel	nab paclitaxel	nab paclitaxel, paclitaxel, gem/carbo
Prior chemo for EBC	52% taxane	51% taxane	22% prior same class
No prior chemo	29% de novo	35% chemo-naive	32% de novo
PDL1+ rate	45% (SP142, IC≥1%)	41% (SP142, IC≥1%)	38% (22C3, CPS≥10)
	PFS ≈ OS ≤	PFS ↑ « OS ↑ »	PFS ↑

Question de corticoïdes?
Type de chimiothérapie ? Taxol vs Nab PacliT ?

KEYNOTE-355 Study Design



Nab-Pac: 31%
Pac: 13%
Carbo-Gem: 55%

Current analysis: PFS outcomes for each chemotherapy partner and key secondary efficacy endpoints

* **Primary Endpoints: PFS and OS in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population**
* **Secondary Endpoints: ORR, DCR, DOR**
* **Exploratory Endpoint: Consistency of treatment effect in all patients and in those with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) according to on-study chemotherapy partner**

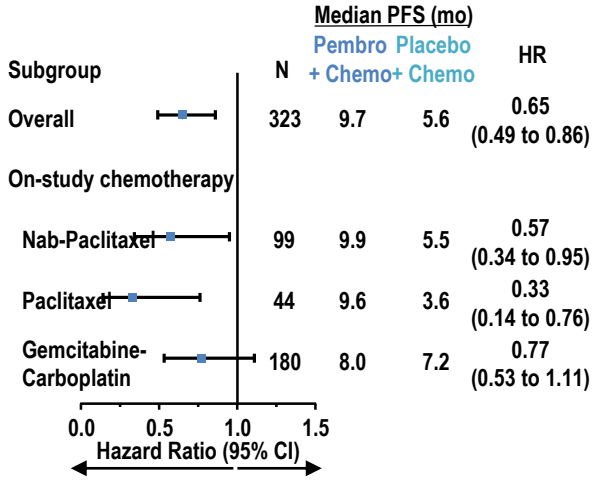
Hugo Rugo

INSTITUT JULES BORDET INSTITUUT

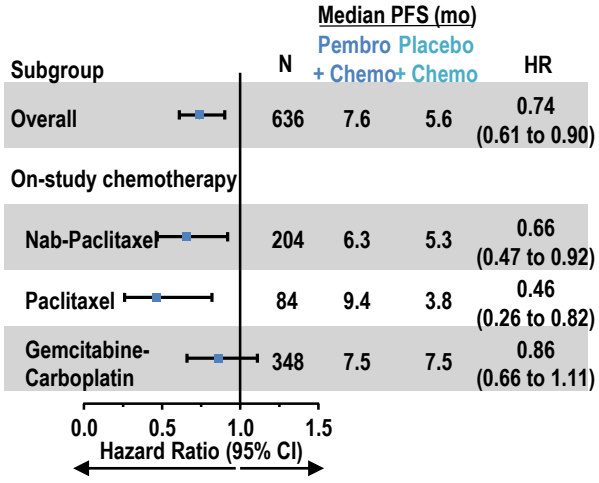
ULB iris

KEYNOTE-355 : PFS in Subgroups by Chemotherapy regimen

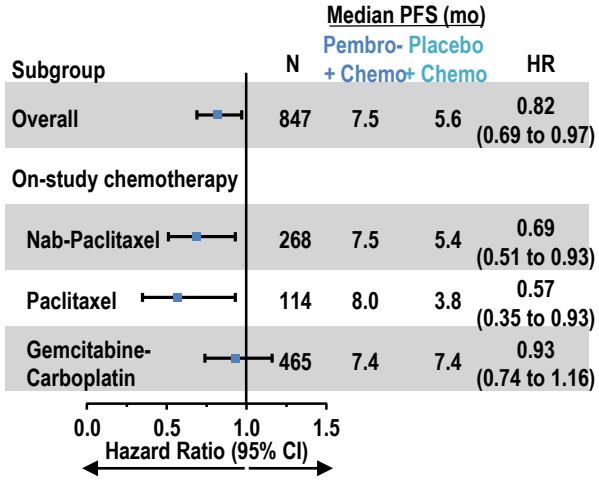
PD-L1 CPS ≥10



PD-L1 CPS ≥1



ITT



In subgroup analysis, PFS with pembrolizumab + CT was improved regardless of CT partner

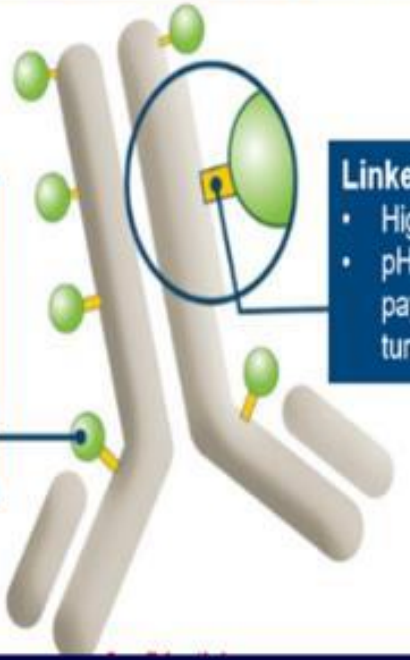
INSTITUT JULES BORDET INSTITUUT

ULB iris

Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

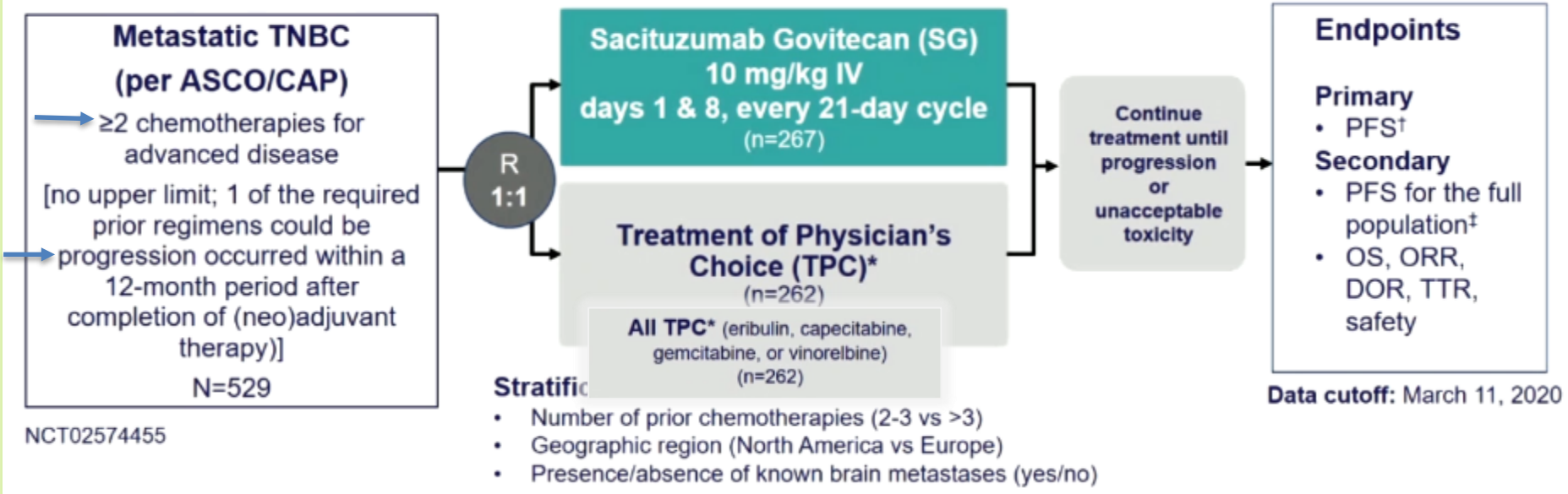
Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

5

This presentation is the intellectual property of the author/presenter. Contact them at shurvitz@mednet.ucla.edu for permission to reprint and/or distribute.

ASCENT
Clinical Trial

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Data cutoff: March 11, 2020

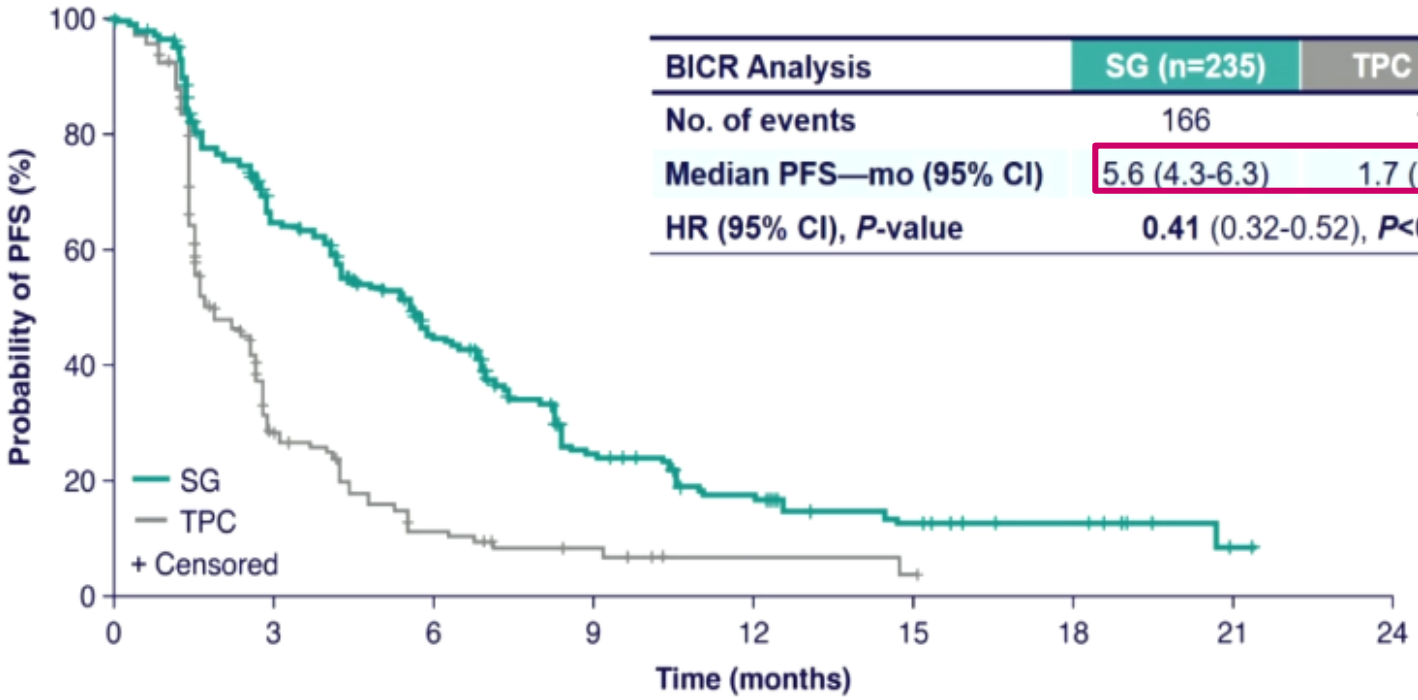
INSTITUT JULES BORDET INSTITUUT

ULB iris

ASCENT Clinical Trial

(Sacituzumab Govitecan)

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

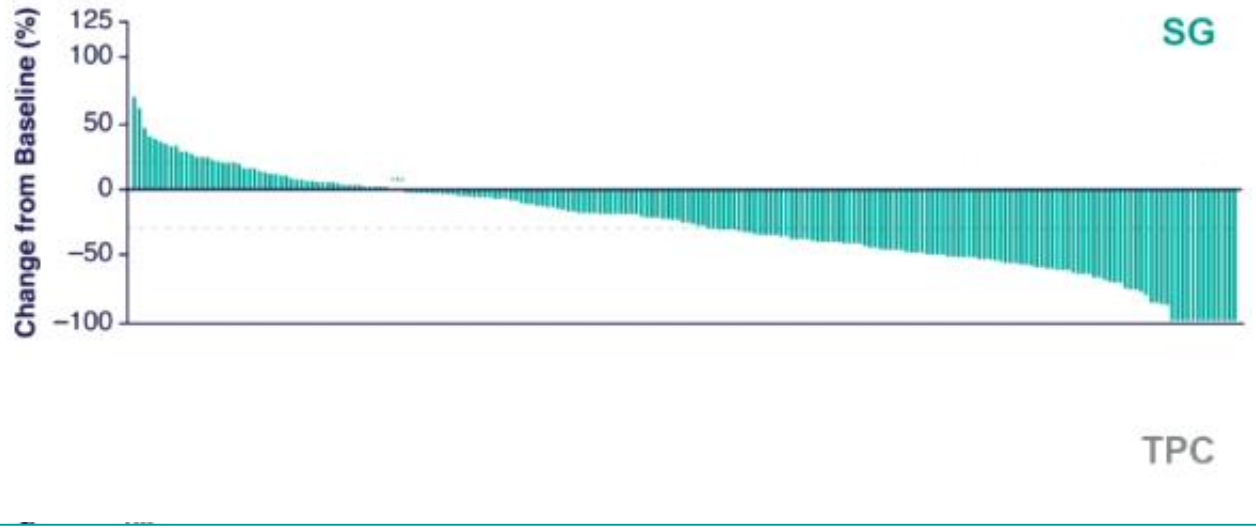
INSTITUT JULES BORDET INSTITUUT

ULB iris

ASCENT Clinical Trial

(Sacituzumab Govitecan)

Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	

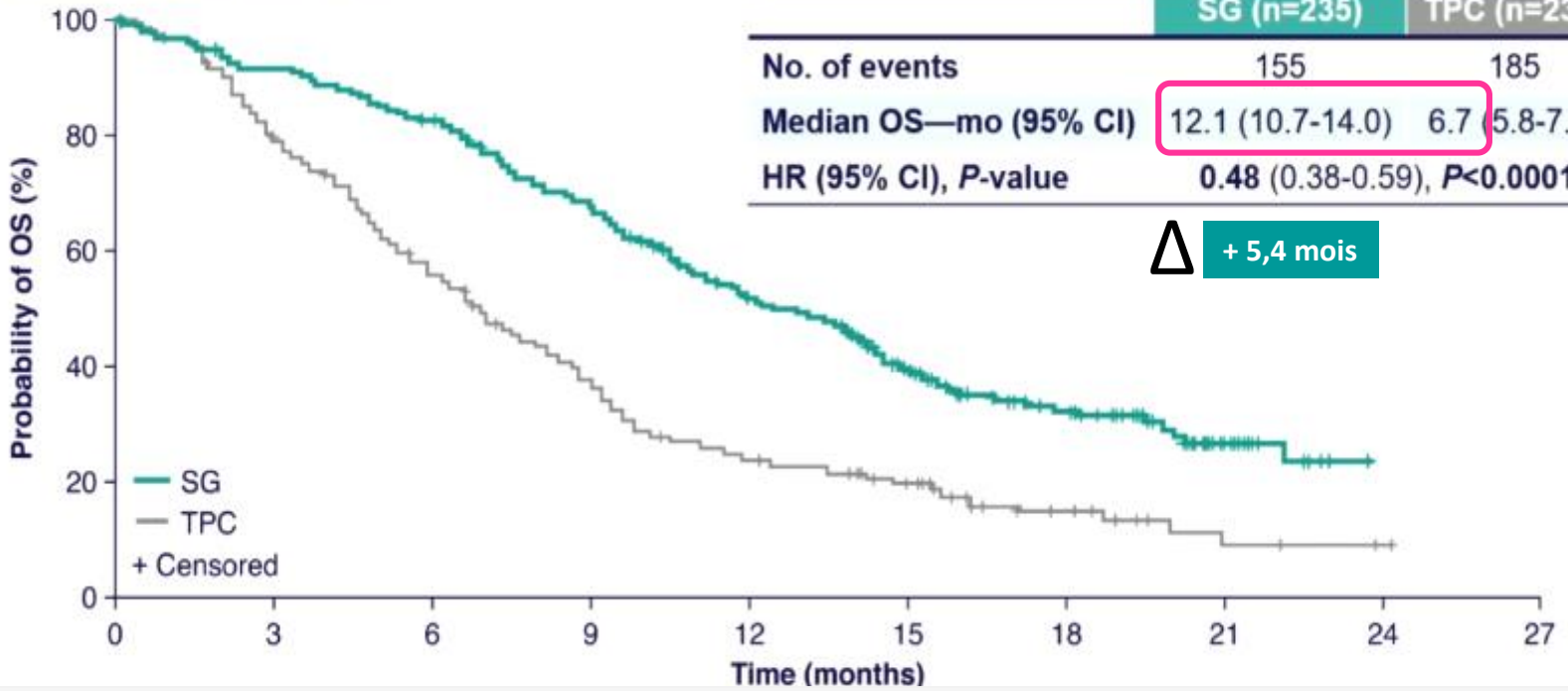
INSTITUT JULES BORDET INSTITUUT

ULB iris

ASCENT
Clinical Trial

(Sacituzumab Govitecan)

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Δ + 5,4 mois

INSTITUT JULES BORDET INSTITUUT

ULB iris

ASCENT Clinical Trial

(Sacituzumab Govitecan)

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

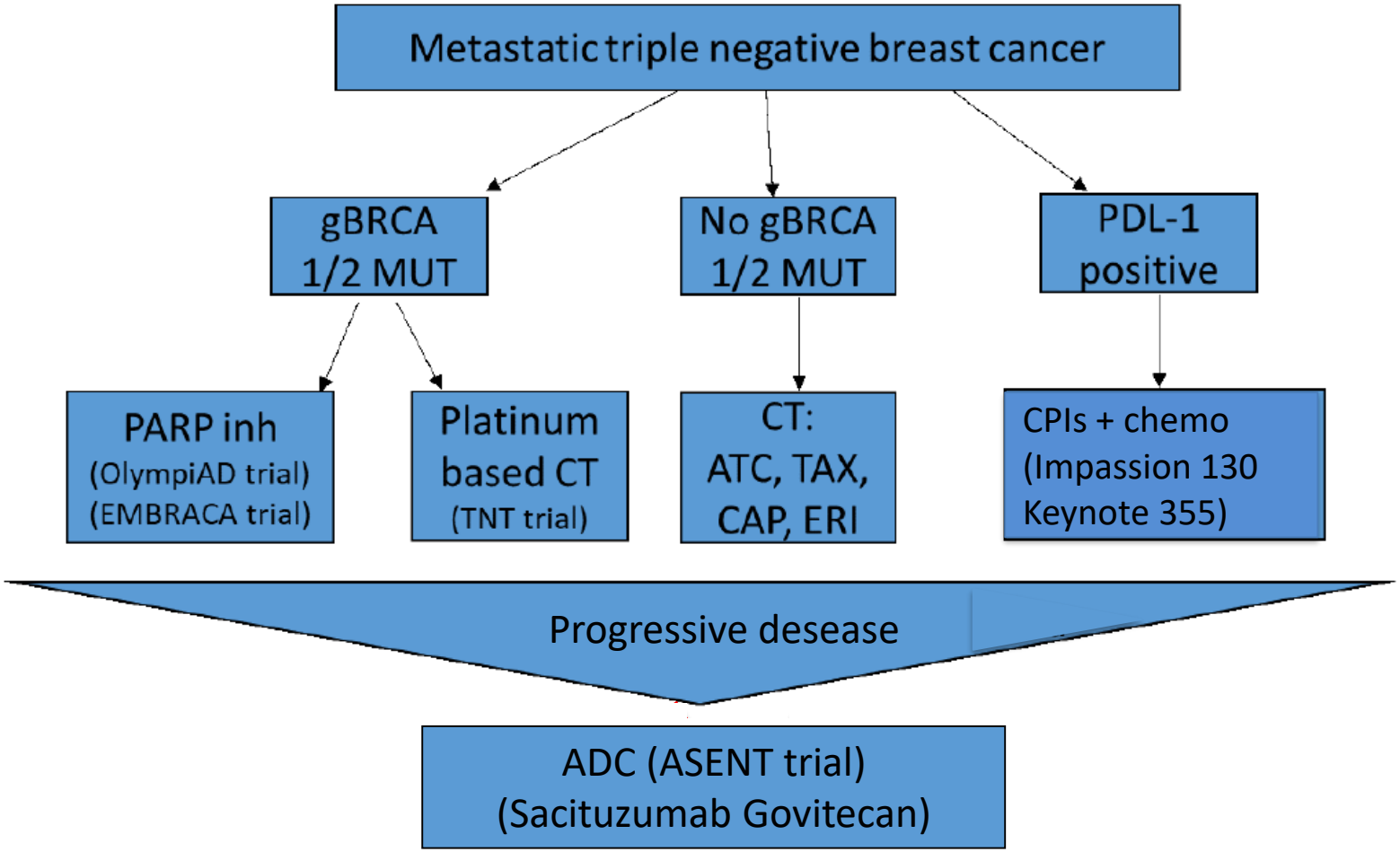
		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

→ **Arrêt = 4,7 %**

INSTITUT JULES BORDET INSTITUUT

ULB iris

Current standard-of-care treatments in metastatic triple-negative breast cancer and future perspective



Genomic Aberrations in Breast Cancer That Guide Precision Medicine: An Evolving Field

Gene	Aberration	Aberration, %	Targeted Drug(s)
Evidence based (from phase II or III trials)			
HER2	Amplification	20	Trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib
HER2	Activating mutations (nonamplified *HER2*)	2	
PIK3CA	Activating mutations	30-40	Alpelisib
BRCA1/2	Inactivating germline mutations	5	Olaparib, talazoparib
NTRK	Gene fusion	< 1	Larotrectinib
PD-L1	Expression by IHC	40	Atezolizumab + nab-paclitaxel
Emerging			
ESR1	Mutations	30-40	Fulvestrant, other SERDs
PTEN	Inactivating mutations or methylation	20	PI3K, AKT, and mTOR inhibitors
MYC	Amplification	16	BET inhibitors
C-MET	Amplification or mutation	15	MET inhibitors (cabozantinib)
FGFR1-4	Amplification	10	FGFR inhibitors
CDH1	Inactivating mutations	7	Wnt inhibitors
AKT	Activating mutations	2	AKT and mTOR inhibitors (MK-2206, everolimus

Thank you

INSTITUT
JULES BORDET
INSTITUUT

ULB iris