Getting Real with Ribociclib:

Bridging the RCT and RWE universe with evidence across ~8000 patients

By:

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. N Engl J Med. 2016;375(18):1738-1748 | 2. Slamon DJ, et al. N Engl J Med. 2020;382(6):514-524 | 3. Im SA, et al. N Engl J Med. 2019;381(4):307-316 | 4. De Laurentiis M, et al. Breast cancer research and treatment. 2021;189(3):689-99.

When considering options for aBC....

- The majority of oncologists and women surveyed report that **overall survival** is their #1 treatment goal[1-3]

- Overall Survival is the gold standard endpoint for efficacy measures in oncology trials[4]

USFDA: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Defined as: **"time from randomization until death from any cause and is measured in the intent-to-treat population."**

"Overall survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint."

1. Zanotti G, et al. *BMC Cancer*. 2017:17(1):393. | 2. Meaningful goals in the management of mBC. White paper. Pfizer, Inc. June 2017. https://www.breastcancervision.com/sites/default/files/section-pdf/mbc_goals-whitepaper_final_with_date.pdf. Accessed on Feb 5, 2020 | 3. Global status of advanced / metastatic breast cancer: 2005-2015 Decade Report; Final report. Pfizer, Inc: March 2016. https://www.abcglobalalliance.org/pdf/Decade-Report_Full-Report_Final.pdf. Accessed on Feb 5, 2020 | 4. National Cancer Institute: Surveillance, Epidemiology, and End Results Program (SEER). Cancer stat facts: female breast cancer. https://seer.cancer.gov/statfacts/html/breast.html. Accessed on Feb 5, 2020 \ 4. 1. US Food and Drug Administration. Clinical trial endpoints for the approval of cancer drugs and biologics. Available at: https://www.fda.gov/media/71195/download. Accessed June 16, 2022

Ribociclib is the only CDK4/6 inhibitor to show statistically significant OS across all three phase III trials

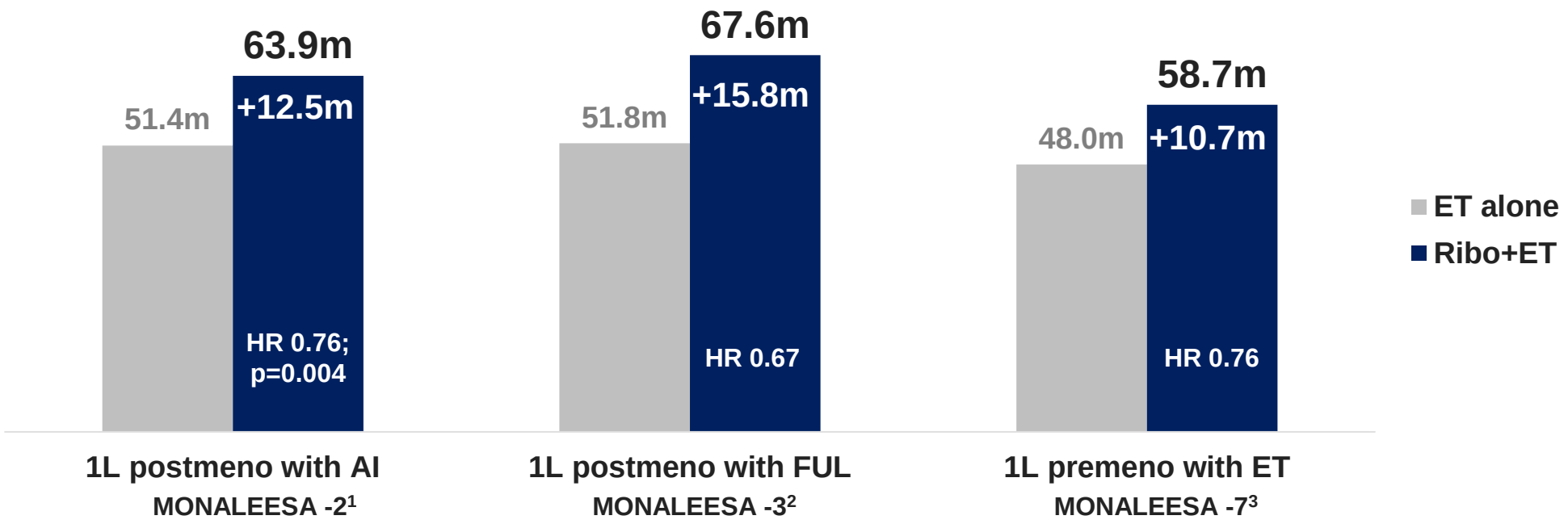
	Ribociclib			Abemaciclib		Palbociclib	
Trial	MONALEESA-2[1,2]	MONALEESA-3[3,4]	MONALEESA-7[5,6]	MONARCH-2[7,8]	MONARCH-3[9]	PALOMA-2[10,11]	PALOMA-3[12,13]
Line of therapy	1st	1st & 2nd	1st	1st & 2nd	1st	1st	1st & 2nd
Menopausal status	Post (N-668)	Post (N=726)	Pre (N=672)(IIT) (N=495)(AI)	Post (N=551) Pre/Peri (N=114)	Post (N=493)	Post (N=666)	Post (N=413) Pre (N=108)
ET	AI	Fulvestrant	AI	Fulvestrant	AI	AI	Fulvestrant
Significant OS	✓	✓	✓	✓	Pending	✗	✗

ET, Endocrine therapy

1L, first line; 2L, second line; aBC, advanced breast cancer; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival. **1**. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021. **2.** Hortobagyi GN, Stemmer SM, Burris HA, et al. *N Engl J Med*. 2016;375(18):1738-1748. **3.** Slamon DJ, Neven P, Chia S, et al. *J Clin Oncol.* 2018;36(24):2465-2472. **4.** Slamon DJ, et al. *N Engl J Med.* 2020;382(6):514-524. **5.** Im SA, et al. *N Engl J Med*. 2019;381(4):307-316. **6.** Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-915. **7.** Sledge GW Jr, et al. *JAMA Oncol*. 2020;6(1):116-124. **8.** Sledge GW Jr, Toi M, Neven P, et al. *J Clin Oncol*. 2017;35(25):2875-2884. **9.** Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646. **10.** Finn RS, et al. *N Engl J Med.* 2016;375(20):1925-1936. **11**. Rugo HS, Finn RS, Diéras V, et al. *Breast Cancer Res Treat.* 2019;174(3):719-729. **12.** Finn RS, et al. Overall survival (OS) With First-Line Palbociclib Plus Letrozole (PAL+LET) Versus Placebo Plus Letrozole (PBO+LET) in Women With Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer (ER+/HER2- ABC): Analyses From PALOMA-2. Presented at ASCO Meeting; June 3-7, 2022. **13.** Turner NC, et al. *N Engl J Med.* 2018;379(20):1926-1936. **14.** Turner NC, Ro J, André F, et al. *N Engl J Med.* 2015;373(3):209-219.

mOS of ~5 years when given as 1L across endocrine partners or menopausal status

Addition of Ribociclib to 1L ET increased mOS by ~1year



ET: Endocrine Therapy | mOS: median Overall Survival | Ribociclib is not approved for usage in combination with Tamoxifen. Please refer to complete prescribing information before use. `

1. Hortobagyi GN, et al. N Engl J Med 2022;386:942-50 | 2. Neven P, et al. Updated Overall Survival Results From the First-Line Population in the Phase III MONALEESA-3 Trial of Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Fulvestrant Presented at ESMO 2021 LBA 4 | 3. Lu YS, et al. Clin Cancer Res (2022) 28 (5): 851–859.

Real World Evidence with Ribociclib demonstrates results consistent with Phase III studies

COMPLEEMENT-1: De Laurentiis M, et al. Breast Cancer Research and Treatment 2021;189: 689–699 | RIBANNA: Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065

Real World Evidence with Ribociclib demonstrates results consistent with Phase III studies

Phase 3b international study of ribociclib plus letrozole as first-line therapy in men and women who have not received prior ET for HR+, HER2- ABC[1]

TOTAL POPULATION: 3,246 patients

Ongoing prospective German study of real-world efficacy of ribociclib (RIB) + aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with HR+, HER2- ABC[2]

TOTAL POPULATION: 2,598 patients

1. De Laurentiis M, et al. Breast Cancer Research and Treatment 2021;189: 689–699 | 2. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065

Study designs covered ~5800 patients from real-world practice

CompLEEment

Expanding the study of ribociclib (LEE011) in advanced breast cancer

N=3000 (planned, final enrollment 3,246 patients)[1]

- Men and women (any menopausal status) with HR+, HER2– ABC
- No prior endocrine therapy for ABC
  - – DFI >12 months from completion of (neo)adjuvant therapy required if NSAI
- ≤ line of chemotherapy for ABC
- ECOG performance status of ≤2
- CNS metastases permitted if stable for > 4weeks

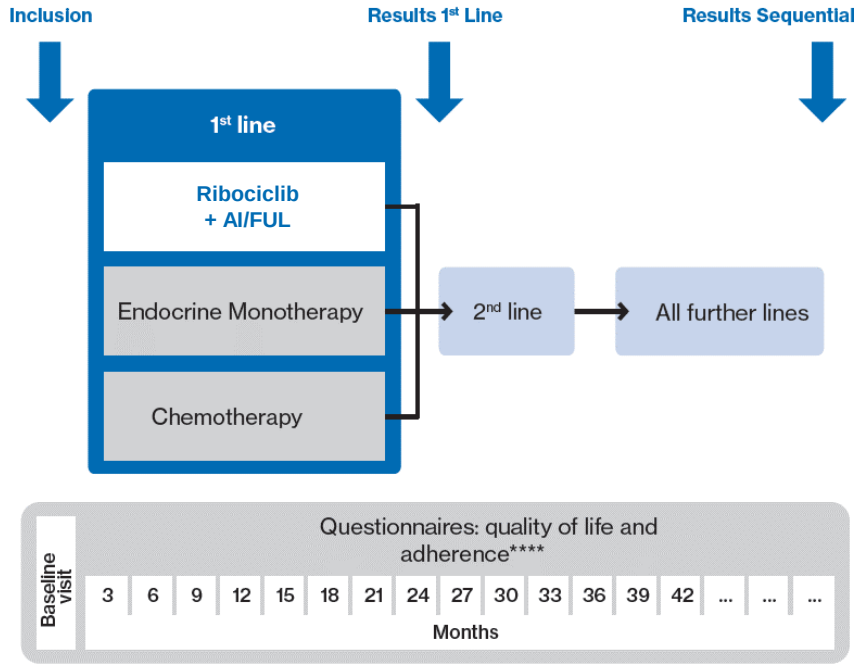
Ribociclib + letrozole
Treatment until disease progression

Primary Endpoint
- Safety and tolerability

Secondary Endpoints
- Time to progression
- Overall response rate
- Clinical benefit rate
- Patient-reported outcomes

RIBANNA

N= 3,020 planned, current enrollment 2,598



Eligibility Criteria:[3]
- Adult postmeno. women with histologically confirmed HR+/HER2- aBC
- No prior systemic treatment for aBC
- No contraindications
- No involvement in a randomised clinical trial (participation in other NIS is permitted).

EORTC QLQ = European Organization for Research and Cancer Treatment Quality of Life Questionnaire; HADS-D = Hospital Anxiety and Depression Scale (German version); MMAS-8 = Morisky Medication Adherence Scale

1. De Laurentiis, et al. Presented at: 2018 American Society of Clinical Oncology; June 1-5, 2018; Chicago, IL, USA. Abstract 1056. | 2. Wockel A, et al. Poster presented at San Antonio Breast Cancer Symposium - December 4–8, 2018. Poster OT3-02-01 | 3. Fasching P, et al. Real-world effectiveness of ribociclib + aromatase inhibitor, or endocrine monotherapy, or chemotherapy as first-line treatment in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer: the RIBANNA study. Poster presented at ESMO, Munich, Germany, 19 Oct – 23 Oct 2018. Poster ID P3881

CompLEEment

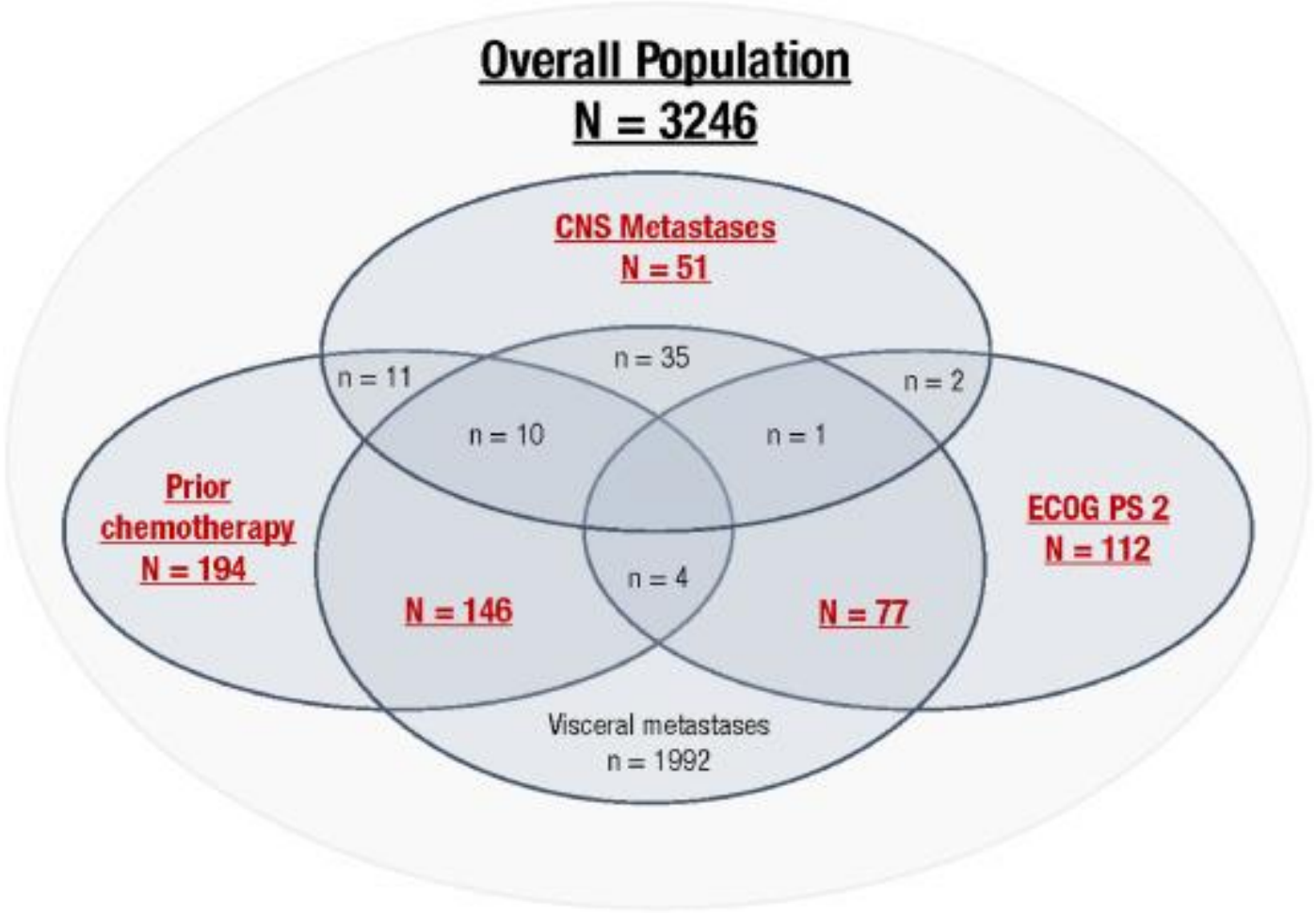
Expanding the study of ribociclib (LEE011) in advanced breast cancer

Clinical evidence from CompLEEment-1 study.

Largest real world study across the CDK 4/6 inhibitors

COMPLEEMENT-1: De Laurentiis M, et al. Breast Cancer Research and Treatment 2021;189: 689–699

Diverse subgroup population representative of real-word practice



- ✓ Diverse large population with subgroups more representative of real-world practice and not well studied in CDK4/6 inhibitor RCTs[1]*
- ✓ Included patients treated with prior chemotherapy for advanced disease, patients with ECOG performance status 2, patients with stable CNS metastases, premenopausal status, diverse race and age compared to RCTs[1]

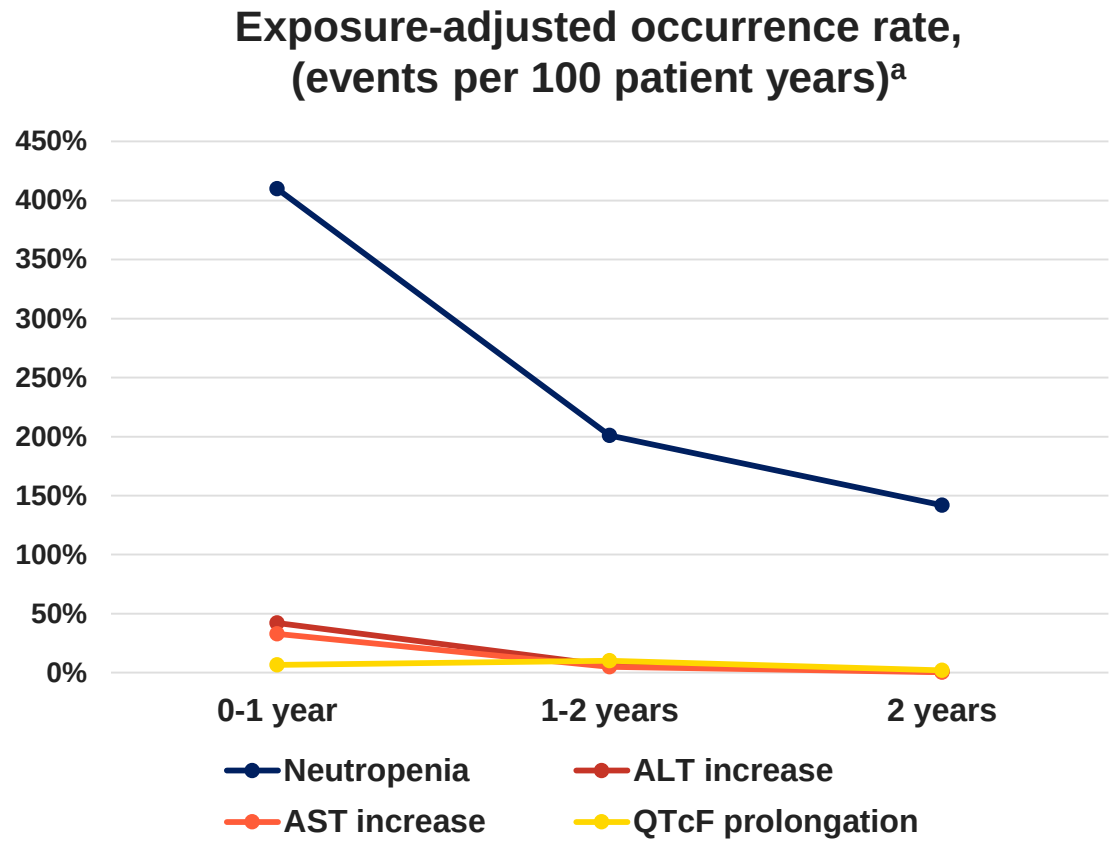
Schematic (not to scale) of the patient subgroups of special interest in this analysis of the CompLEEment-1 study (full analysis set). Red text denotes the 5 subgroups evaluated; additional patient overlaps (patients included in >1 subgroup) are indicated in blue. | *Palbociclib and abemaciclib trials. | CNS, central nervous system; CDK 4/6i, Cyclin-Dependent Kinases 4/6 Inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status, RCT, randomized control trials.

1. De Laurentiis M, et al Breast cancer research and treatment. 2021;189(3):689-99. | 2. Cottu P, et al. Subgroup analysis of the phase IIIb CompLEEment-1 trial. Breast. 2022;62:75-83..

Safety profile was predictable, manageable & similar to Phase III RCTs; and events reduced with prolonged exposure[1]

CompLEEment
Expanding the study of ribociclib (LEE011) in advanced breast cancer

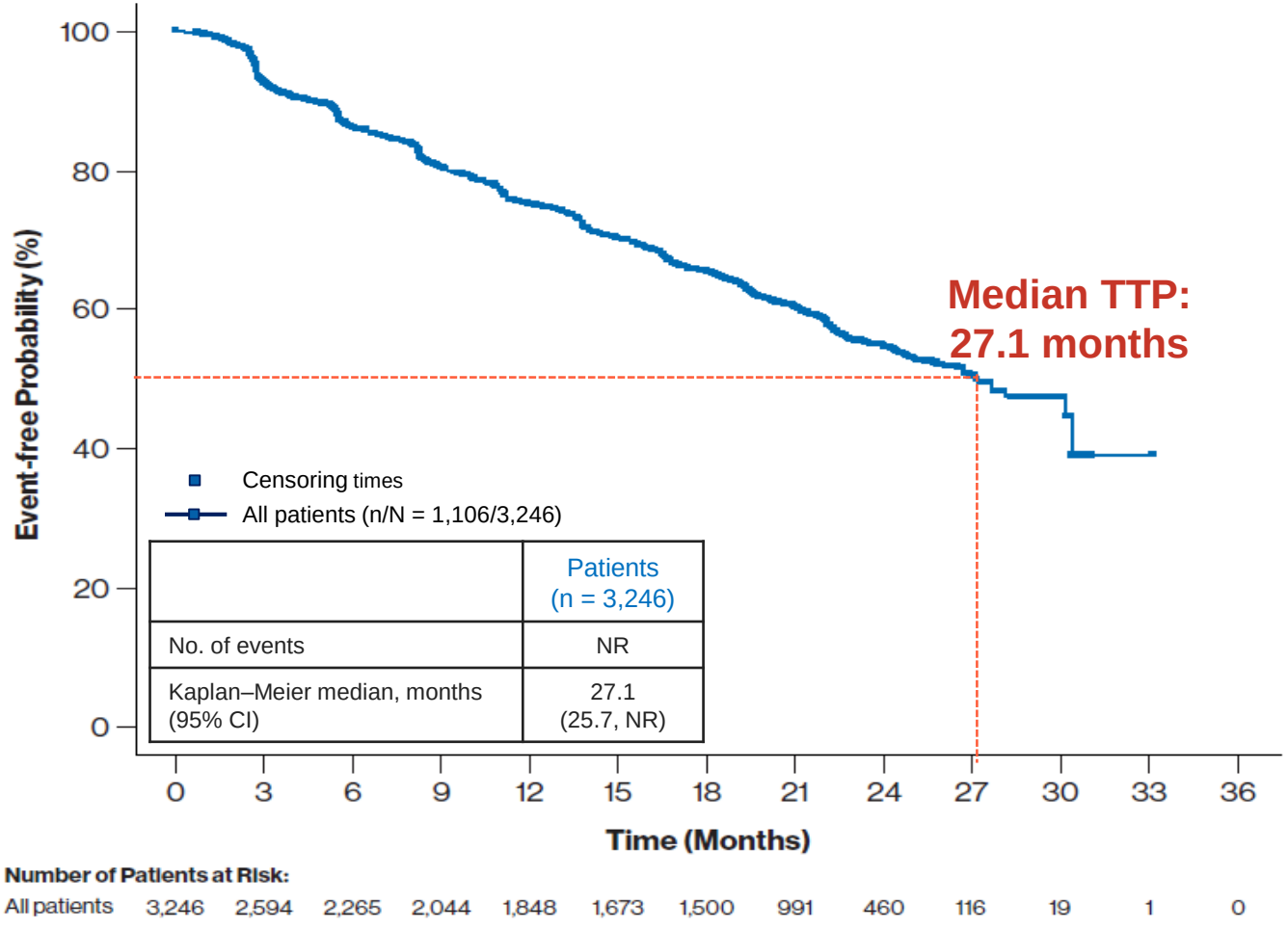
AEs, n (%)	All patients (N=3,246)	
	All grades	Grade≥3
AEs	3,203 (98.7)	2,461 (75.8)
Treatment related	3,091 (95.2)	2,192 (67.5)
SAEs	702 (21.6)	590 (18.2)
Treatment related	203 (6.3)	178 (5.5)
Fatal SAEs	62 (1.9)	61 (1.9)
Treatment related	14 (0.4)	14 (0.4)
AEs leading to discontinuation	528 (16.3)	310 (9.6)
Treatment related	418 (12.9)	237 (7.3)
AEs leading to dose adjustment/interruption	2,434 (75.0)	2,095 (64.5)
Treatment related	2,235 (68.9)	1,964 (60.5)



AE, Adverse Event; N, number of patients; SAE, Serious Adverse Event. ALT alanine aminotransferase, AST aspartate aminotransferase, QTcF QT interval corrected for heart rate using Fridericia's formula | a. Number of events divided by the corresponding sum of the exposure duration, where duration of exposure in patient-treatment years is duration of exposure in time interval. Neutropenia: Includes "neutropenia" and "neutrophil count decreased"

1. De Laurentiis M, et al Breast cancer research and treatment. 2021;189(3):689-99.

Efficacy: prolonged TTP with high event free probability[1]



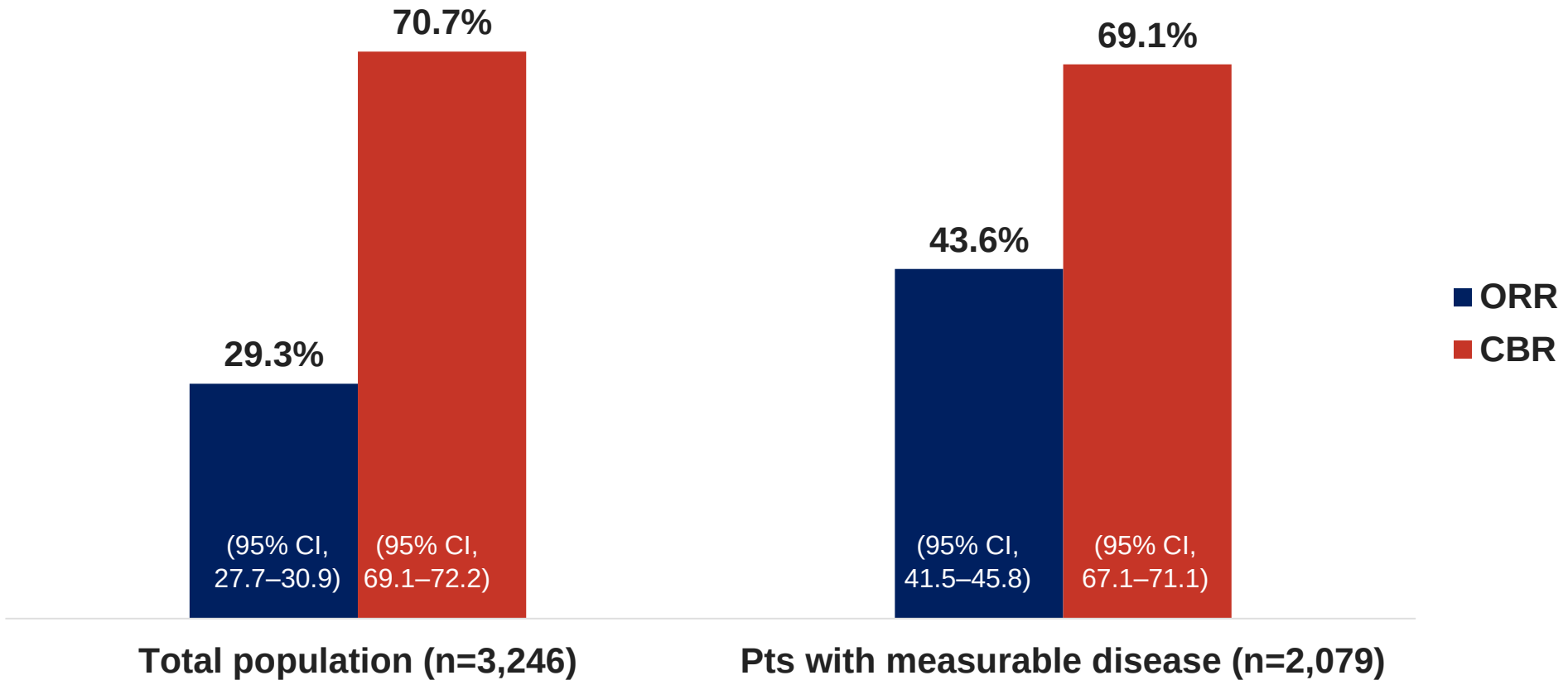
Percentage Event-free Probability Estimates (95% CI)		
12 Months	24 Months	33 Months
75.1% (73.4, 76.7)	**54.7%** (52.5, 56.8)	**39.0%** (27.5, 50.4)

Under an exploratory analysis, mPFS was 26.7m
(95% CI 24.8-30.1)

CI, confidence interval; NR, not reached; TTP, Time To Progression

1. De Laurentiis M, et al Breast cancer research and treatment. 2021;189(3):689-99.

Efficacy: Improved response in patients with measurable disease



Patients who had measurable disease at baseline | CI, confidence interval; CBR, clinical benefit rate; ORR, Overall Response Rate.|

1. De Laurentiis M, et al Breast cancer research and treatment. 2021;189(3):689-99.

CDK 4/6 inhibitors & CNS metastases in Phase III RCTs

	Patients with CNS metastases
MONALEESA-2[1] Ribociclib + Letrozole	*excluded*
MONALEESA-3[2] Ribociclib + Fulvestrant	8 patients (stable CNS metastases)
MONALEESA-7[3] Ribociclib + NSAI/TAM*	*excluded*
PALOMA-2[4,5] Palbociclib + Letrozole	2 patients with CNS metastases included (9 developed during trial)
PALOMA-3[6,7] Palbociclib + Fulvestrant	5 patients with CNS metastases included (2 developed during trial)
MONARCH-2[8] Abemaciclib + Fulvestrant	*excluded*
MONARCH-3[9] Abemaciclib + AI	*excluded*

- **CompLEEment Is a phase IIIb real world study including 51 patients with CNS metastases.**[10] *(results on next slide)*

- Abemaciclib had a Phase II non-randomized study in HR+, HER2- patients with CNS metasases (n=58)[11]
  - 3 (5%) patients were confirmed responders
  - Primary Endpoint: Intracranial ORR 6%
  - Secondary Endpoint: Intracranial CBR 25%

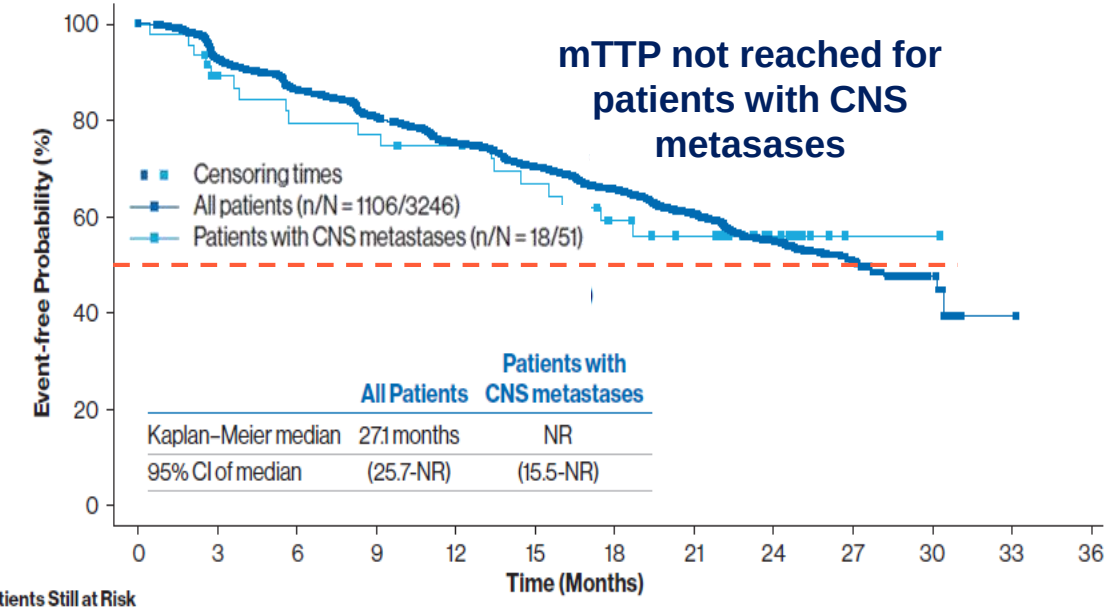
ABC, Advanced Breast cancer; CDK 4/6i, Cyclin-Dependent Kinases 4/6 Inhibitor; CNS, central nervous system; HER2, Human Epidermal Growth Factor Receptor-2; HR, Hormone Receptor;

1. Hortobagyi GN, New England journal of medicine. 2016;375(18):1738-48 | 2. Slamon DJ, et al, Journal of Clinical Oncology. 2018;36(24):2465-72. | 3. Tripathy D, et al. Lancet Oncology. 2018;19(7):904-15. | 4. Finn RS, et al. N Engl J Med. 2016;375(20):1925-1936. | 5. Rugo HS, et al. Breast Cancer Res Treat. 2019;174(3):719-729. | 6. Turner NC, et al. N Engl J Med. 2018;379(20):1926-1936. | 7. Turner NC, Ro J, André F, et al. N Engl J Med. 2015;373(3):209-219 | 8. Sledge GW Jr, et al. JAMA Oncol. 2020;6(1):116-124.| 9. Goetz MP, et al. J Clin Oncol. 2017;35(32):3638-3646. | 10. Cottu P, et al. The Breast 2022; 62: 75–83 | 11. Tolaney S, et al. Clin Cancer Res 2021;26:5310–9

Consistent efficacy across subgroups of clinical interest

CompLEEment
Expanding the study of ribociclib (LEE011) in advanced breast cancer

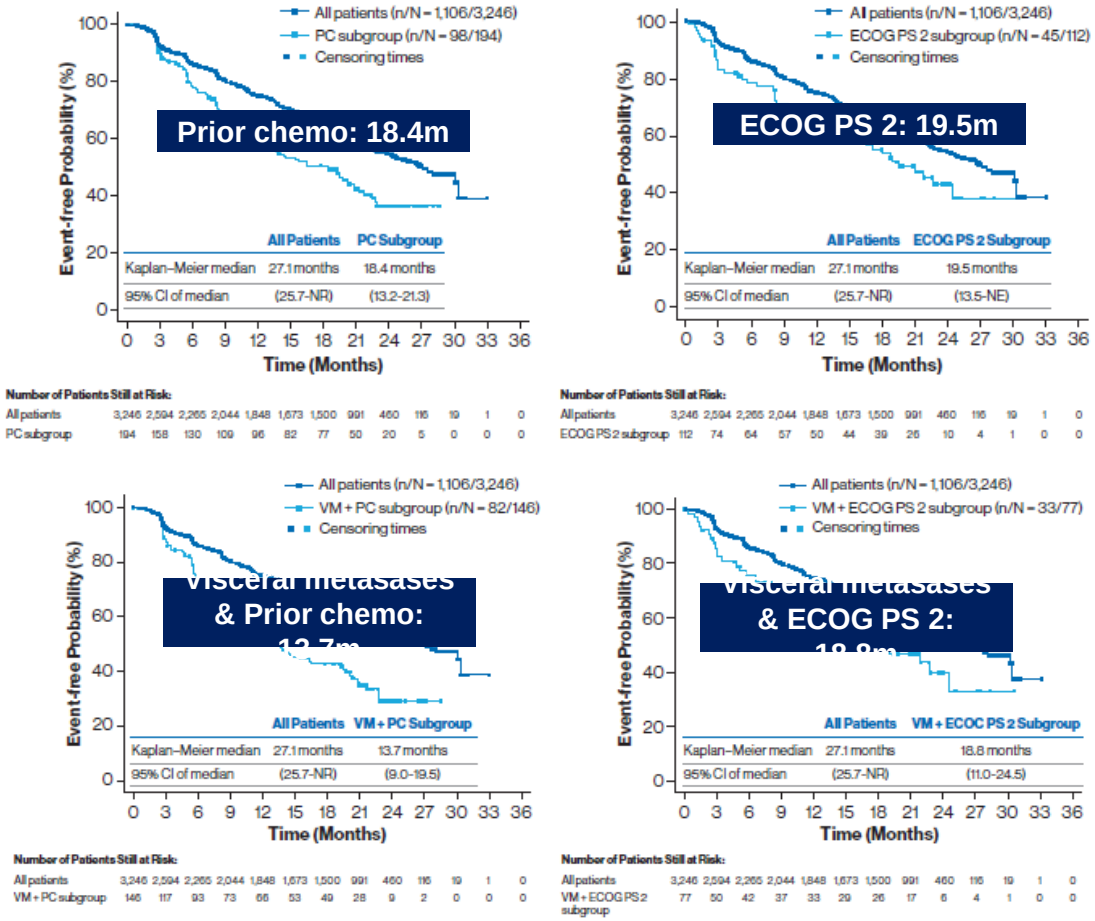
mTTP: Overall population (27.1m) vs. patients with CNS metasases (n=51)



Number of Patients Still at Risk

All patients	3246	2594	2265	2044	1848	1673	1500	991	460	116	19	1	0
Patients with CNS metastases	51	38	33	32	30	26	21	16	8	1	1	0	0

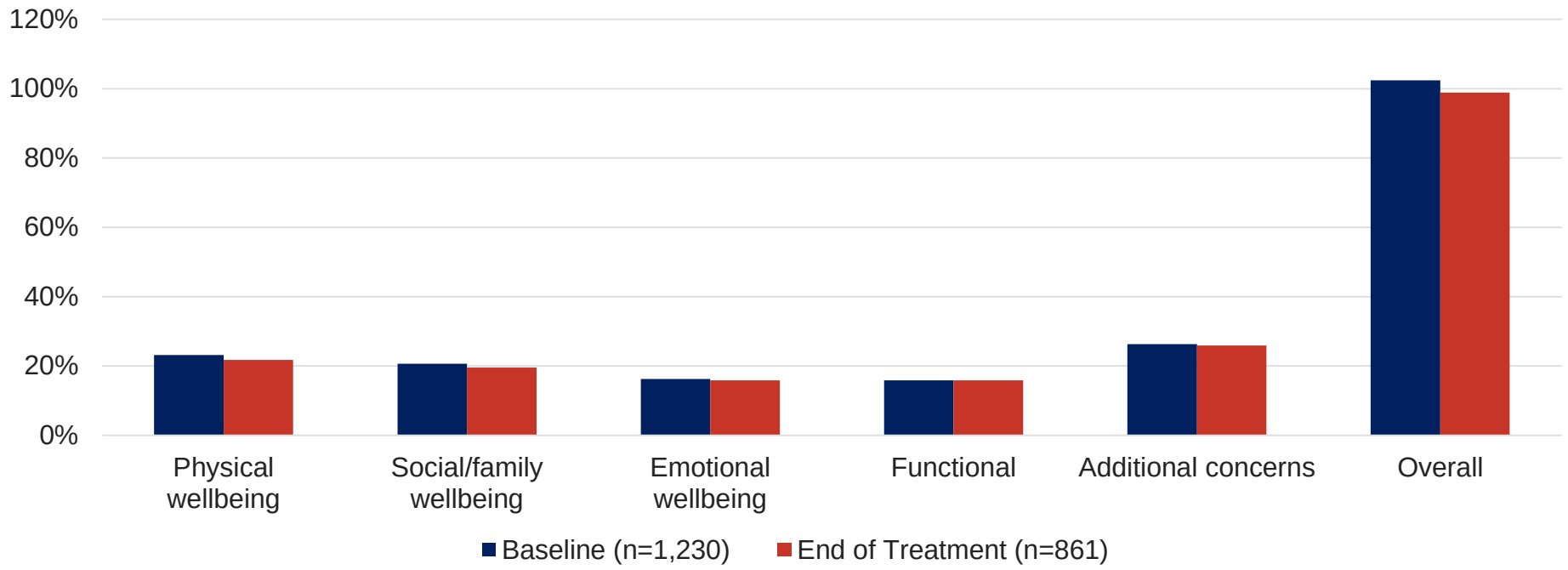
mTTP: Overall population (27.1m) vs. subgroups of special clinical interest



mTTP: median time to progression; CI, confidence interval; NR, not reached;

1. Cottu P, et al. The Breast 2022; 62: 75–83

Patient-reported Outcomes – Change From Baseline in FACT-B Emotional and Functional Well-being Scores[1]



The median delay to first occurrence of a clinically relevant deterioration (≥7-point decrease) in overall FACTB score was not reached, implying that quality of life (QoL) was maintained while on treatment.

Patients who had measurable disease at baseline | CI, confidence interval; CBR, clinical benefit rate; ORR, Overall Response Rate.|

1. De Laurentiis M, et al Updated Results From the Phase IIIb CompLEEment-1 Study of Ribociclib Plus Letrozole in the Treatment of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2–Negative Advanced Breast Cancer Poster presented at the 2020 American Society of Clinical Oncology; May 29 – 31, 2020. Poster 1055

Clinical evidence from RIBANNA

German ongoing, prospective, non-interventional

1. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065

RIBANNA: Study design & Patient characteristics

Total population N=2,598 Data cut off Oct 11, 2021

Full Analysis Set (n=2,187) Excluding screening failures and locked patients.

	Mean Age (yrs)	Menopausal status	ECOG PS	metasases: CNS, Liver, Lung	metasases: Bone only	metasases: Skin, Lymph nodes etc
Ribociclib + AI/ FUL (n=1,849)	65.5	Post: 89% Pre: 10%	0: 44% >1: 56%	42.6%	30.8%	24.3%
Endocrine monotherapy (n=193)	70.7	Post: 92% Pre: 7%	0: 35% >1: 65%	26.8%	47.9%	15%
Chemotherapy (n=145)	61.6	Post: 85% Pre: 14%	0: 42% >1: 58%	67.1%	15.0%	14.3%

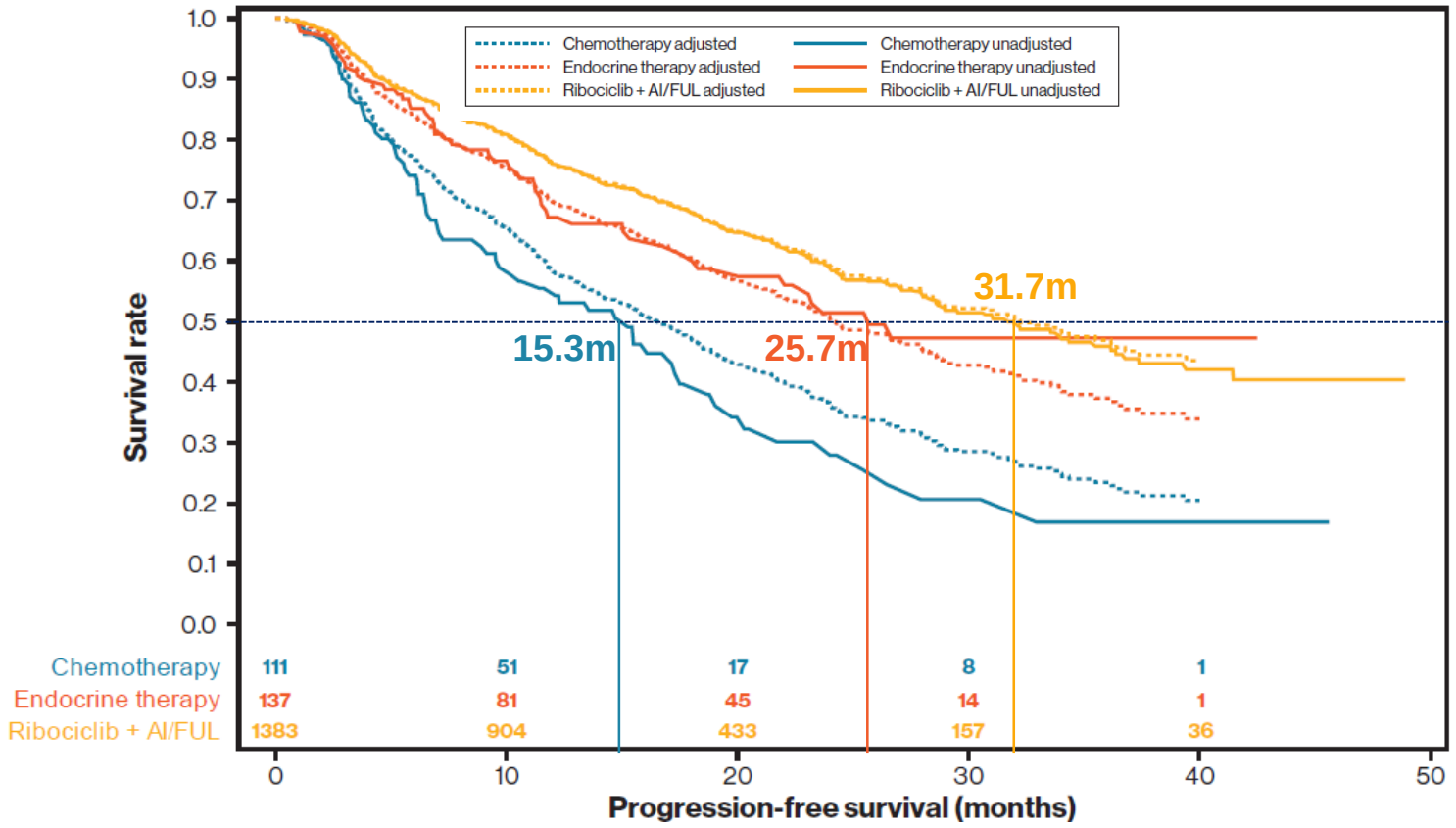
All parameters had patients with missing values

Current fourth Interim Analysis is safety and efficacy from the full analysis set (n=2187) excluding patients with missing data on ECOG performance status (n=291), metastatic status (n=118), and histological grading status (n=227).

1. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065 | 2. Wockel A, et al. Poster presented at San Antonio Breast Cancer Symposium® – December 8-11, 2020 Virtual Symposium. Poster PS10-16

RIBANNA: Study design & Patient characteristics

Progression free survival from the Full Analysis Set



Unadjusted mPFS

Ribociclib +AI/FUL	Endocrine Therapy	Chemotherapy
31.7 months	25.7 months	15.3 months

*Analysis excludes few patients with missing data in some effects 1L, first-line; AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FUL, fulvestrant; PFS, progression-free survival

1. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065

Safety and treatment

- The safety profile was similar to that observed in the MONALEESA studies[1]
- The most frequent treatment-emergent AEs (all grade) in the RIB+AI/FUL cohort were neutropenia (24.2%), nausea (23.7%), fatigue (22.2%), and leukopenia (18.8%)[1]
- AEs of Special interest[1]:

AE of special interest, n (%)	RIB+AI/FUL cohort (n=2090), n (%)		ET cohort (n=229), n (%)		CT cohort (n=175), n (%)	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
QTc prolongation	3.5%	0.6%	-	0%	0.6%	0.6%
ALT increase	3.7%	2%	-	0%	0.6%	0%
AST increase	3.6%	1.6%	-	0%	0.6%	0%
Increased blood bilirubin levels	0.6%	0.2%	-	0%	1.1%	0%

1L, first-line; AE, adverse event; AI, aromatase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, chemotherapy; ET, endocrine therapy; FUL, fulvestrant; RIB, Ribociclib

1. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065

Outcomes reported in phase III trials are achievable in real-world practice

RWE

RCTs

	Ribociclib				
	CompLEEment-1 (N = 3,246)	**RIBANNA[2] (N=2,598)**	**MONALEESA-2[3,4] (N=668)**	**MONALEESA-7[5,6] (N=672)**	**MONALEESA-3[7] N=726**
ET partner	Letrozole	AI/FUL	Letrozole	AI / Tam	Fulvestrant
Median PFS	**26.7 months**	**31.7 months**	**25.3 months**	**27.5 months (AI only)**	**33.6 months (1L pfs)**
Control group HR(CI)	NA	ET alone: 25.7 months (18.0–NR) Chemo: 15.3 months (9.5–17.5)	vs 16 months 0.56 (0.43-0.72)	vs 13.8 months with AI 0.57 (0.44-0.74)	vs 19.2 months (1L pfs) 0.55 (0.42-0.72)
Dose reductions due to AEs, n (%)	68.9%	32.3% (not reported for control arm)	55% vs 4%	33% vs 6%	33% vs 3%
Discontinuations due to AEs, n (%)	12.9%	Not reported	8% vs 2%	7% vs 3%	9% vs 4%
Most common grade 3 or 4 AEs (≥5%) in the ribociclib group	Neutropenia, leukopenia, abnormal LFTs	Neutropenia, Leukopenia, Nausea, abnormal LFTs	Neutropenia, leukopenia, abnormal LFTs, hypertension, lymphopenia	Neutropenia, leukopenia	Neutropenia, leukopenia, abnormal LFTs,

1. De Laurentiis M, et al. Breast cancer research and treatment. 2021;189(3):689-99. | 2. Luftner D, et al. Real-world efficacy of ribociclib (RIB)+aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. Poster presented at the 2022 ASCO annual meeting, Chicago, USA & Online, June 3-7, 2022. Poster abstract 1065 | 3. Hortobagyi GN, et al. N Engl J Med 2022;386:942-50 | 4. Hortobagyi GN, et al. N Engl J Med. 2016;375(18):1738-1748 | 5. Im SA, et al. N Engl J Med. 2019;381(4):307-316. | 6. Bardia A, et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; October 19–23, 2018; Munich, Germany Poster 330P | 7. Slamon DJ, et al. N Engl J Med 2020;382:514-24.

Guidelines recommendations for Ribociclib

NCCN GUIDELINES

Preferred Regimens
First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b]
- Selective ER down-regulator (fulvestrant, category 1)[c] + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[c]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b]

[b] In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown overall survival benefit in the first-line setting

ESMO

First-line treatment. CDK4/6 inhibitors combined with ET are the standard-of-care for ER-positive, HER2-negative MBC, with improved progression-free survival (PFS) and OS and a good toxicity profile seen in several trials [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 scores: 3-5].[25-31] ET plus CDK4/6 inhibition yields similar or better efficacy versus ChT[32,33] and is associated with less toxicity, making it the preferred treatment unless a patient has imminent organ failure. Although there is little data on use of CDK4/6 inhibitors after progression on CDK4/6 inhibitors, rechallenge may be possible after a treatment-free interval of ≥12 months based on evidence regarding rechallenge with other therapies.

CDK4/6 inhibitors are effective in *de novo* or recurrent MBC, in cases of primary or secondary endocrine resistance, in postmenopausal or premenopausal women [the latter with a luteinising hormone-releasing hormone (LH-RH) agonist] and in men (with an LH-RH agonist). For patients who did not relapse on an aromatase inhibitor (AI), or within 12 months of stopping adjuvant AI, a CDK4/6

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer Version 3.2022 -May 7, 2022; pg BINV-P | 2. Gennari A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer Ann Oncol 2021;32(12):1475-1495

Ribociclib RCTs with perfect ESMO-MCBS Score

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Ribociclib is the only CDK4/6i to achieve a score of 4 in 1L & 2L Postmenopausal patients and 5 in Pre/ perimenopausal patients with HR+/HER2- ABC[1]

Study	Treatment	Patient	OS Gain	PFS Gain	QoL	ESMO-MCBS Score
MONALEESA-2[2]	Ribociclib+ Letrozole	1st line postmenopausal	+ 12.5 months HR: 0.76	+ 9.3 months HR: 0.57	maintained	4
MONALEESA-3	Ribociclib+ Fulvestrant	1st line & 2nd line postmenopausal	+ 15.6 months HR: 0.72	+ 7.7 months HR: 0.59	maintained	4
MONALEESA-7	Ribociclib+ Endocrine therapy†	1st line Premenopausal or Perimenopausal	+ 16 months HR: 0.71	+ 10.8 months HR: 0.55	IMPROVED	5

Only therapies achieving a grade of 4 or 5 are considered to indicate a proven clinical benefit[5]

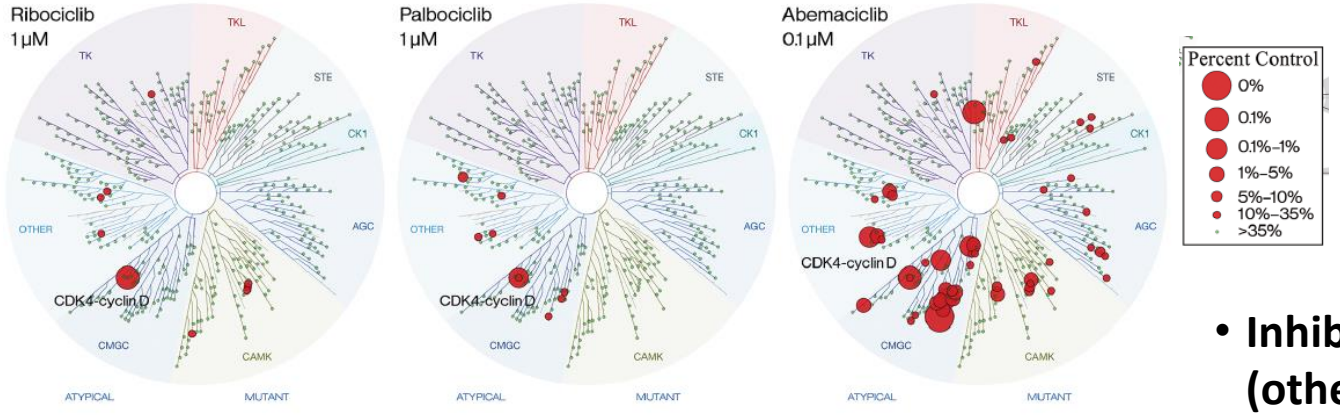
ABC, Advanced Breast cancer; CDK 4/6i, Cyclin-Dependent Kinases 4/6 Inhibitor; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; mOS, Median Overall Survival; PFS: Progression Free Survival; QoL, Quality of Life.

1. ESMO Magnitude of Clinical Benefit Scorecard. ESMO-MCBS https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=ribociclib , Palbociclib, Abemaciclib accessed on June 18, 2022 | 2. MONALEESA 2 ESMO-MCBS Score card: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-9-1 | 3. MONALEESA 3 ESMO-MCBS Score card: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-161-1 | 4. MONALEESA 7 ESMO-MCBS Score card: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-158-1 | 5. Thomssen C, Luftner D, Untch M, et al. International consensus conference for advanced breast cancer. Lisbon 2019: ABC5 Consensus – assessment by a German group of experts. Breast Care. 2020;15:82-95.

The 3 CDK 4/6 inhibitors are different

CDK4/6 inhibitors: Selectivity and off-target inhibition

- **Inhibition of CDK4 targets BC cells, while inhibition of CDK6 may lead to hematological AEs**
- **Kryxana is more selective to CDK4 than 6, while Palbociclib inhibits CDK 4 and 6 equally**



No. off-target kinases inhibited[2]†	Ribociclib	Palbociclib	Abemaciclib
	4	13	52

- **Inhibition of off-targets (other than CDK4/6) may lead to AEs like GI**
- **Abemaciclib shows a different AE profile with more Diarrhea, VTE, ILD (?)**

detailed CDK-family selectivity analyses. The third-generation drugs are primarily CDK4 and CDK6 inhibitors yet they have distinct differences. Palbociclib has equivalent CDK4/cyclin D_3 and CDK6/cyclin D_1 potency while both ribociclib and abemaciclib are significantly more potent toward CDK4/cyclin D_3 (ribociclib is 5-fold, abemaciclib is 9-fold; Table 1). Toward

binding pocket. Integrating clinical drug exposures into the analysis predicts that both palbociclib and ribociclib are CDK4/6 inhibitors, abemaciclib inhibits CDK4/6/9, and dinaciclib is a broad-spectrum CDK inhibitor (CDK2/3/4/6/9). Understanding

1. Sunkyu K et al Oncotarget, 2018, Vol. 9, (No. 81), pp: 35226-35240 |2. Chen P, Lee NV, Hu W, et al. Mol Cancer Ther. 2016;15(10):2273-2281

Ribociclib exhibits higher selectivity for CDK 4 and more drug available to penetrate and act on tumor cells[1-3†]

Breast Cancers Cells Are Dependent on CDK4 Expression and Express Higher Levels of CDK6 compared with CDK6[1,4-7]

	RIBOCICLIB	Abemaciclib	Palbociclib
Preferential inhibition of CDK4 vs CDK6[1]* IC_{50} (µM)	**x8**	x6	x1
Free drug concentration (fold difference)[2†]	**x22**	x1	x1

†Based on preclinical activity. Preclinical activity does not necessarily correlate with clinical outcomes. The data above is not presented to discuss the efficacy and safety information of the mentioned products. `

CDK, cyclin-dependent kinase.

*Free drug concentration is based upon unbound C_{ave} values, determined in human pharmacokinetic studies. Values are normalized to palbociclib.[2,3]

1. Kim S, Tiedt R, Loo A, et al. Oncotarget. 2018;9(81):35226-35240. | 2. Chen P, Lee NV, Hu W, et al. Mol Cancer Ther. 2016;15(10):2273-2281. [Supplemental Information] | 3. Chen P, Lee NV, Hu W, et al. Mol Cancer Ther. 2016;15(10):2273-2281. | 4.The Human Protein Atlas. CDK4. https://www.proteinatlas.org/ENSG00000135446-CDK4/pathology. Accessed March 29, 2019. | 5.The Human Protein Atlas. CDK6. https://www.proteinatlas.org/ENSG00000105810-CDK6/pathology. Accessed March 29, 2019. | 6. Cancer Genome Atlas Network. Nature. 2012 Oct 4; 490(7418): 61–70. | 7. Data on File. Novartis Pharma AG.

Summary & Conclusions

- Outcomes from RCTs can be replicated in real world experience
- Guidelines recommend **early usage of CDK 4/6 inhibitors** for patients with HR+, HER2- aBC[1,2]
- Ribociclib is the only CDK 4/6 inhibitor to
  - Demonstrate **longest yet median OS of 63.9 months** (*HR 0.76, p-0.004*) from the MONALEESA 2 study, vs 51.4 months with letrozole[3,4]
  - Significantly **improve OS across lines of therapy, endocrine partner and menopausal status**[3,5,6]
  - Achieve an **ESMO MCBS score of 4&5** across the phase III studies[7]
  - Demonstrate **similar efficacy & safety in 5800 real world cases**[8,9]
- Ribociclib also has demonstrated consistent efficacy across patient subgroups including **CNS metasases, Visceral metasases, chemo-treated & ECOG ≥2**[8]
- The **3 CDK4/6 inhibitors are different** basis**:**
  - CDK 4 selectivity & off target inhibition[10-11]
  - Free drug concentration[11-16]
  - Potential impact on observed differences in efficacy & safety

1. NCCN Guidelines® Breast Cancer Version 3.2022 -May 7, 2022; pg BINV-P | 2. Gennari A, et al. ESMO Clinical Practice Guideline in MBC Ann Oncol 2021;32(12):1475-1495 | 3. Hortobagyi GN, et al. N Engl J Med 2022;386:942-50 |4. ABC Sixth International Consensus Conference Updates Guidelines for. https://ascopost.com/issues/march-10-2022/abc-sixth-international-consensus-conference-updates-guidelines-for-advanced-breast-cancer/ accessed on June 18, 2022 | 5. Neven P, et al. Updated OS Results From MONALEESA-3 Trial of Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Fulvestrant Presented at ESMO 2021 LBA 4 | 6. Lu YS, et al. Clin Cancer Res (2022) 28 (5): 851–859.| 7. ESMO Magnitude of Clinical Benefit Scorecard. ESMO-MCBS https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=ribociclib , Palbociclib, Abemaciclib accessed on June 18, 2022 | 8. De Laurentiis, et al. Presented at: 2018 American Society of Clinical Oncology; June 1-5, 2018; Chicago, IL, USA. Abstract 1056. | 9. Wockel A, et al. Poster presented at San Antonio Breast Cancer Symposium - December 4–8, 2018. Poster OT3-02-01 | 3. Fasching P, et al. Real-world effectiveness of ribociclib + aromatase inhibitor, or endocrine monotherapy, or chemotherapy as first-line treatment in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer: the RIBANNA study. Poster presented at ESMO, Munich, Germany, 19 Oct – 23 Oct 2018. Poster ID P3881 | 10. Sunkyu K et al Oncotarget, 2018, Vol. 9, (No. 81), pp: 35226-35240 |11. Chen P, Lee NV, Hu W, et al. Mol Cancer Ther. 2016;15(10):2273-2281 | 12. Kim S, Tiedt R, Loo A, et al. Oncotarget. 2018;9(81):35226-35240. | 13.The Human Protein Atlas. CDK4. https://www.proteinatlas.org/ENSG00000135446-CDK4/pathology. Accessed March 29, 2019. | 14.The Human Protein Atlas. CDK6. https://www.proteinatlas.org/ENSG00000105810-CDK6/pathology. Accessed March 29, 2019. | 15. Cancer Genome Atlas Network. Nature. 2012 Oct 4; 490(7418): 61–70. | 16. Data on File. Novartis Pharma AG.

Thank you!