Abemaciclib for high risk ER+ HER2- early breast cancer and implications for OPTIMA

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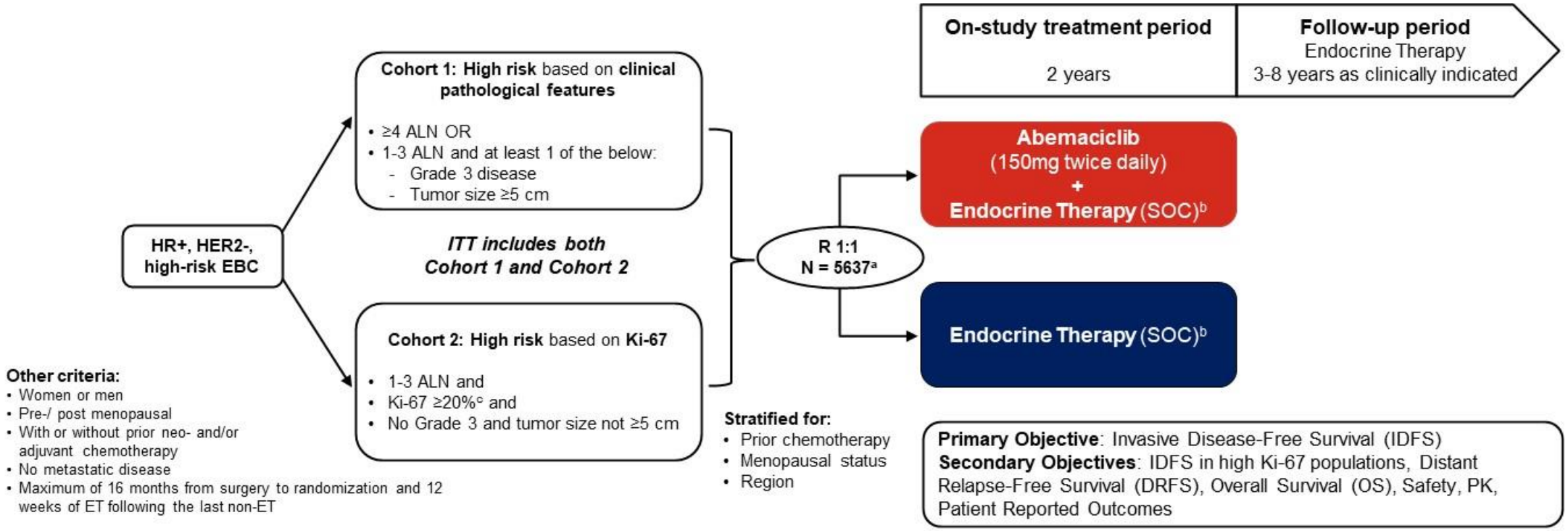
monarchE: Adjuvant Abemaciclib In Early Stage Breast Cancer

- Adjuvant abemaciclib combined with ET previously demonstrated clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in HR+, HER2–, node-positive, high risk early breast cancer (EBC)

- Initial follow-up was limited with median 15.5 months. A subsequent analysis from an additional follow-up efficacy and safety analysis at a median follow-up of 27 months, performed at the request of health authorities

- The role of Ki-67 index, a marker of cellular proliferation as a prognostic and predictive biomarker, is further explored

monarchE Study Design (NCT03155997)



[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

Baseline Characteristics of ITT

		Abemaciclib + ET N=2808, %	ET Alone N=2829, %
Age	Median (range)	51 (23-89)	51 (22-86)
Age categories	<65 years	84.4	85.4
Gender	Female	99.3	99.5
Menopausal Status[1]	Premenopausal	43.5	43.5
	Postmenopausal	56.5	56.5
Prior Chemotherapy[1]	Neoadjuvant	37.0	37.0
	Adjuvant	58.5	58.2
	None	4.5	4.7
Baseline ECOG PS	0	85.7	83.8
Pathologic Tumor Size	<2 cm	27.8	27.1
	2 - 5 cm	48.9	50.2
	≥5 cm	21.6	21.6
Number of Positive Lymph Nodes	1-3	39.8	40.4
	≥4	59.9	59.6
Histological Grade	Grade 1	7.4	7.6
	Grade 2	49.0	49.3
	Grade 3	38.7	37.6
Central Ki-67	<20%	33.9	34.4
	≥20%	44.9	43.6
	Unavailable	21.1	21.8

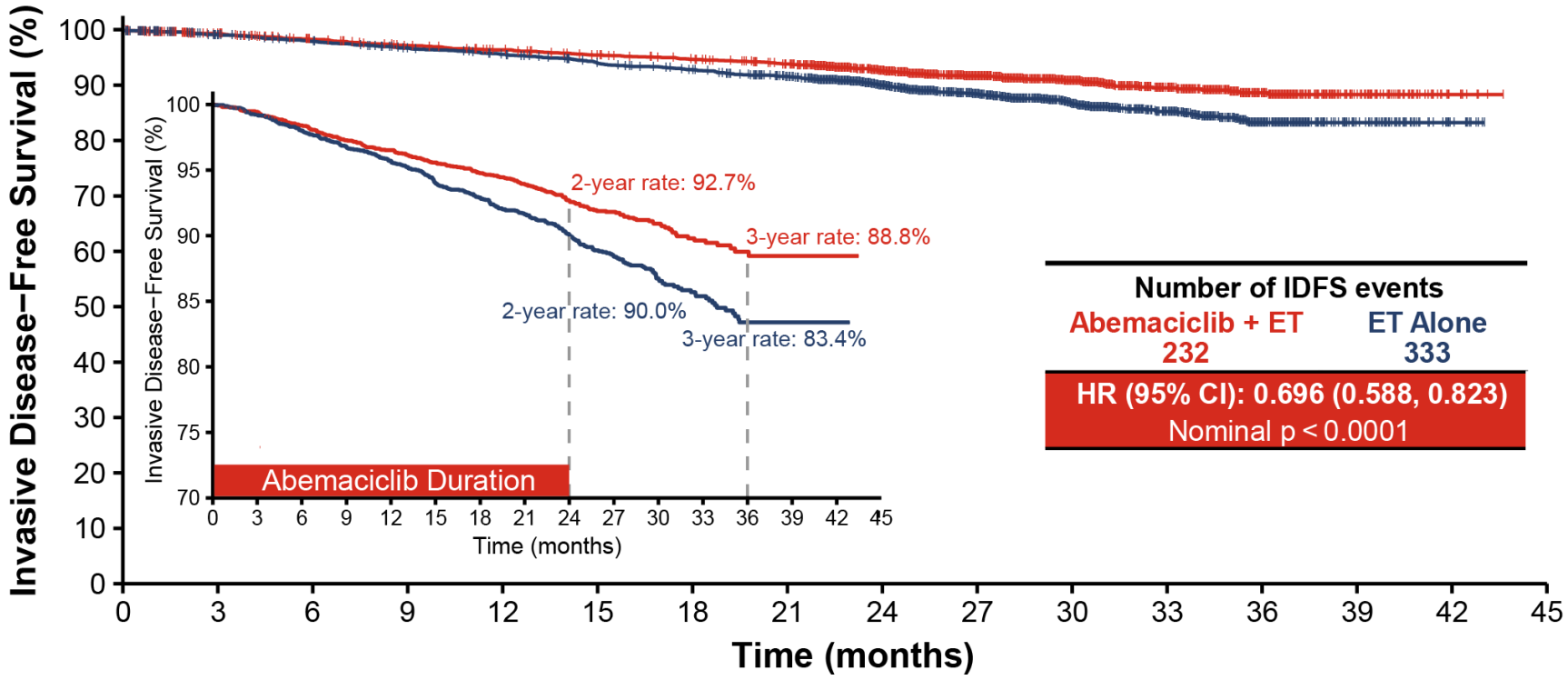
Note: data generated at Primary Outcome analysis (July 2020); where values do not add up to 100%, remaining data are missing, unavailable, or could not be assessed

[1]Per Interactive Web Response System (IWRS)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = Endocrine Therapy

Efficacy Results in the ITT Population

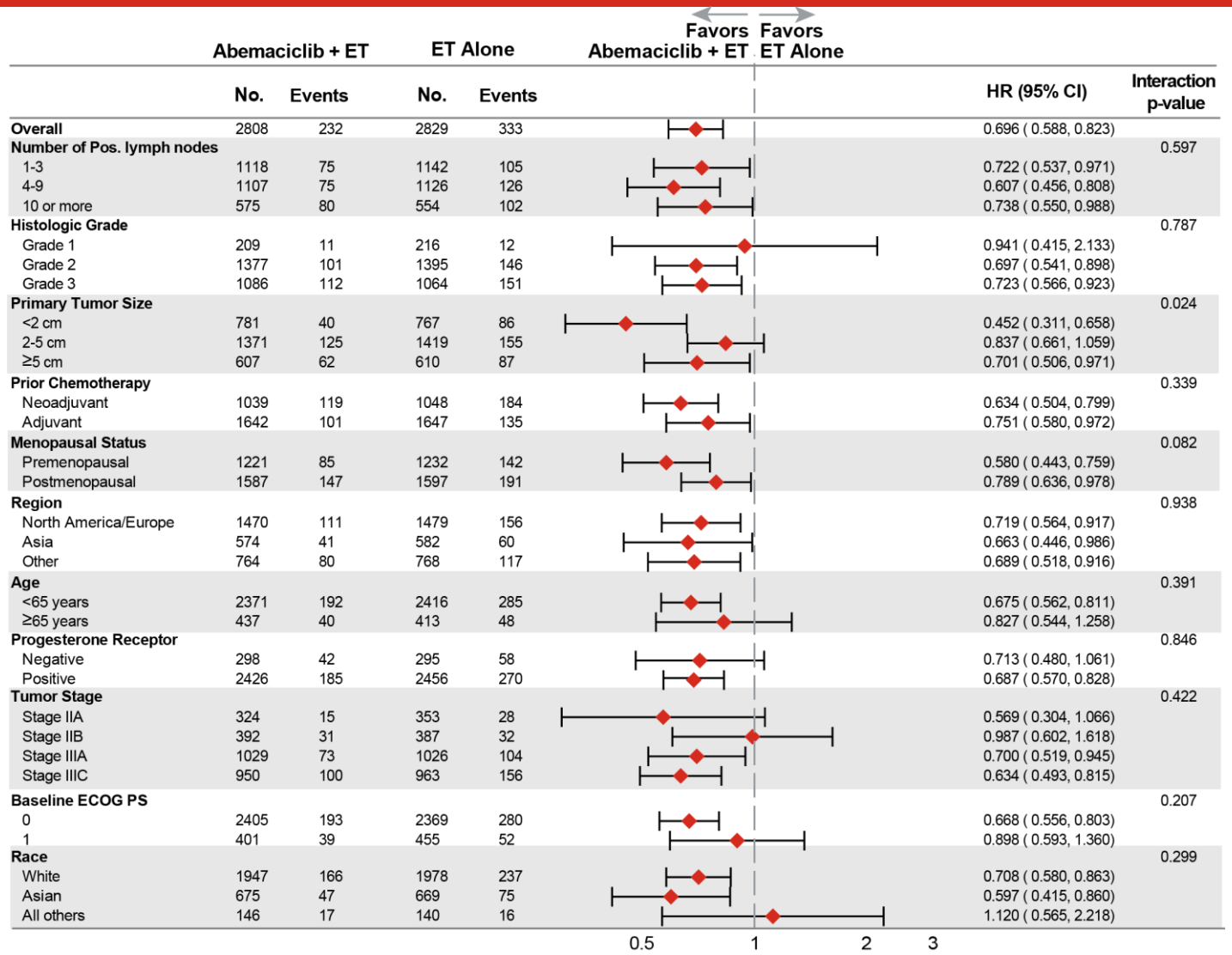
IDFS Benefit Maintained with Additional Follow-up in ITT population



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

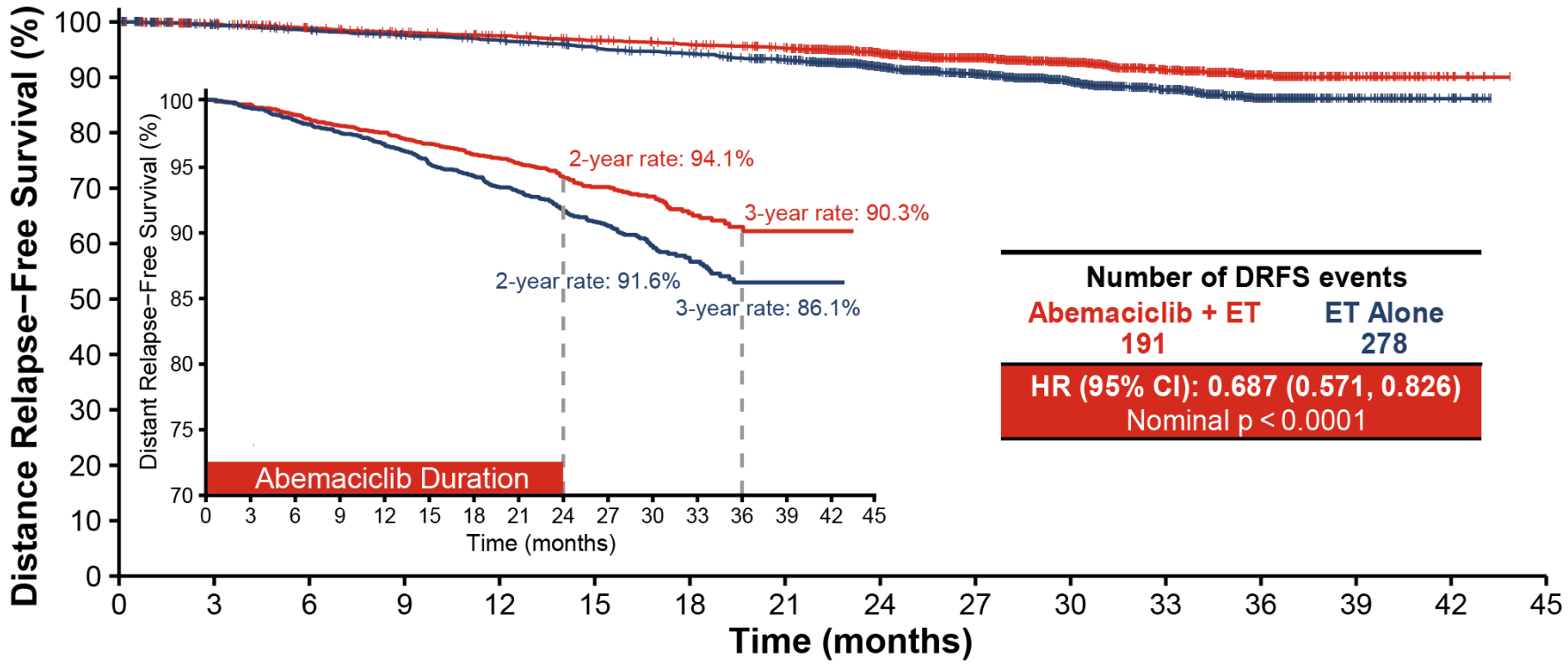
30.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 5.4% at 3 years.

Consistent IDFS Treatment Benefit Observed in Prespecified Subgroups



	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction p-value
	No.	Events	No.	Events		
Overall	2808	232	2829	333	0.696 (0.588, 0.823)	
Number of Pos. lymph nodes						0.597
1-3	1118	75	1142	105	0.722 (0.537, 0.971)	
4-9	1107	75	1126	126	0.607 (0.456, 0.808)	
10 or more	575	80	554	102	0.738 (0.550, 0.988)	
Histologic Grade						0.787
Grade 1	209	11	216	12	0.941 (0.415, 2.133)	
Grade 2	1377	101	1395	146	0.697 (0.541, 0.898)	
Grade 3	1086	112	1064	151	0.723 (0.566, 0.923)	
Primary Tumor Size						0.024
<2 cm	781	40	767	86	0.452 (0.311, 0.658)	
2-5 cm	1371	125	1419	155	0.837 (0.661, 1.059)	
≥5 cm	607	62	610	87	0.701 (0.506, 0.971)	
Prior Chemotherapy						0.339
Neoadjuvant	1039	119	1048	184	0.634 (0.504, 0.799)	
Adjuvant	1642	101	1647	135	0.751 (0.580, 0.972)	
Menopausal Status						0.082
Premenopausal	1221	85	1232	142	0.580 (0.443, 0.759)	
Postmenopausal	1587	147	1597	191	0.789 (0.636, 0.978)	
Region						0.938
North America/Europe	1470	111	1479	156	0.719 (0.564, 0.917)	
Asia	574	41	582	60	0.663 (0.446, 0.986)	
Other	764	80	768	117	0.689 (0.518, 0.916)	
Age						0.391
<65 years	2371	192	2416	285	0.675 (0.562, 0.811)	
≥65 years	437	40	413	48	0.827 (0.544, 1.258)	
Progesterone Receptor						0.846
Negative	298	42	295	58	0.713 (0.480, 1.061)	
Positive	2426	185	2456	270	0.687 (0.570, 0.828)	
Tumor Stage						0.422
Stage IIA	324	15	353	28	0.569 (0.304, 1.066)	
Stage IIB	392	31	387	32	0.987 (0.602, 1.618)	
Stage IIIA	1029	73	1026	104	0.700 (0.519, 0.945)	
Stage IIIC	950	100	963	156	0.634 (0.493, 0.815)	
Baseline ECOG PS						0.207
0	2405	193	2369	280	0.668 (0.556, 0.803)	
1	401	39	455	52	0.898 (0.593, 1.360)	
Race						0.299
White	1947	166	1978	237	0.708 (0.580, 0.863)	
Asian	675	47	669	75	0.597 (0.415, 0.860)	
All others	146	17	140	16	1.120 (0.565, 2.218)	

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.

Abemaciclib Treatment Effect Over Time

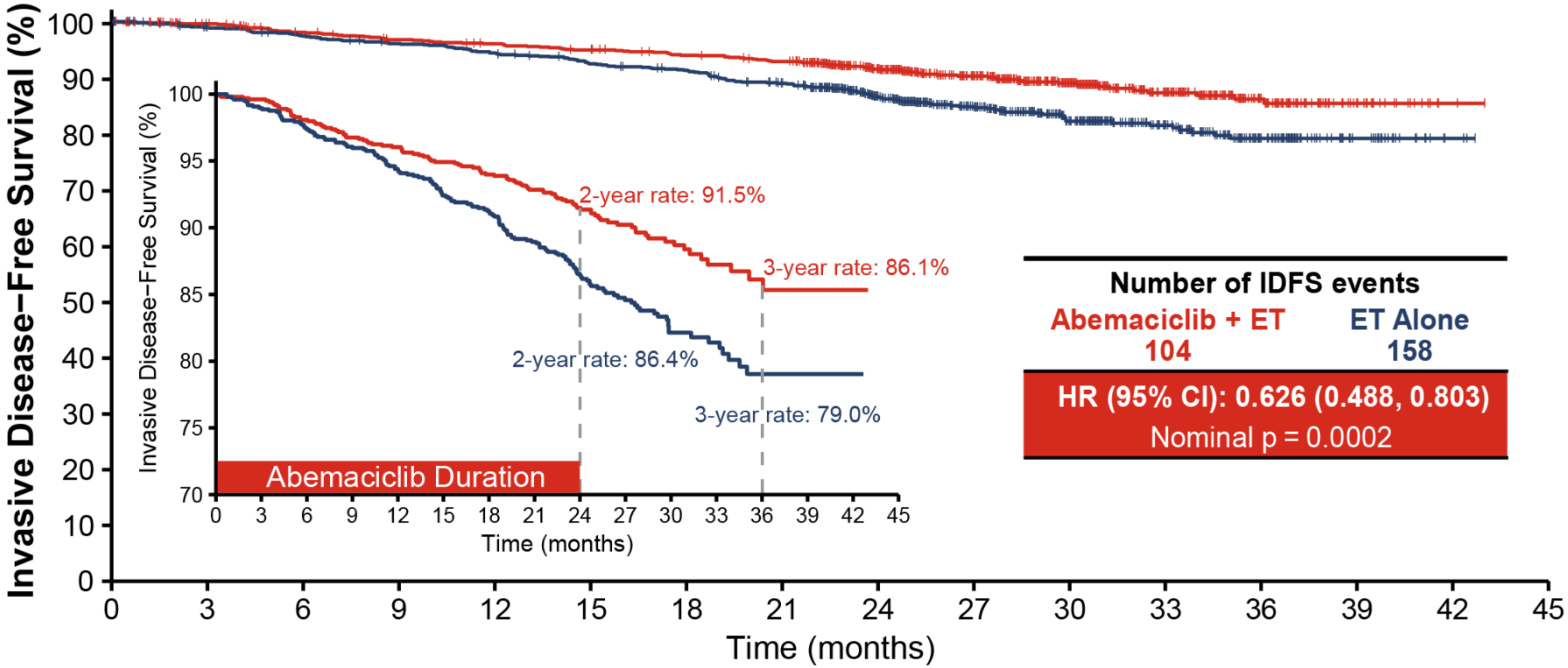
Analysis landmark	IDFS			DRFS		
	Events		Piecewise HR* (95% CI**)	Events		Piecewise HR* (95% CI**)
	Abemaciclib + ET	ET alone		Abemaciclib + ET	ET alone	
Year 0-1	93	116	0.795 (0.589, 1.033)	67	91	0.732 (0.520, 0.987)
Year 1-2	98	146	0.681 (0.523, 0.869)	85	129	0.675 (0.507, 0.875)
Year 2+	41	71	0.596 (0.397, 0.855)	39	58	0.692 (0.448, 1.032)

* Piecewise hazard ratio was estimated using piecewise exponential model to assess the yearly treatment effect size
** 95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

Increasing magnitude of IDFS and DRFS effect size from the first year to the second year, with maintained treatment benefit beyond the 2-year study treatment period.

Efficacy Results in Ki-67 Subpopulation

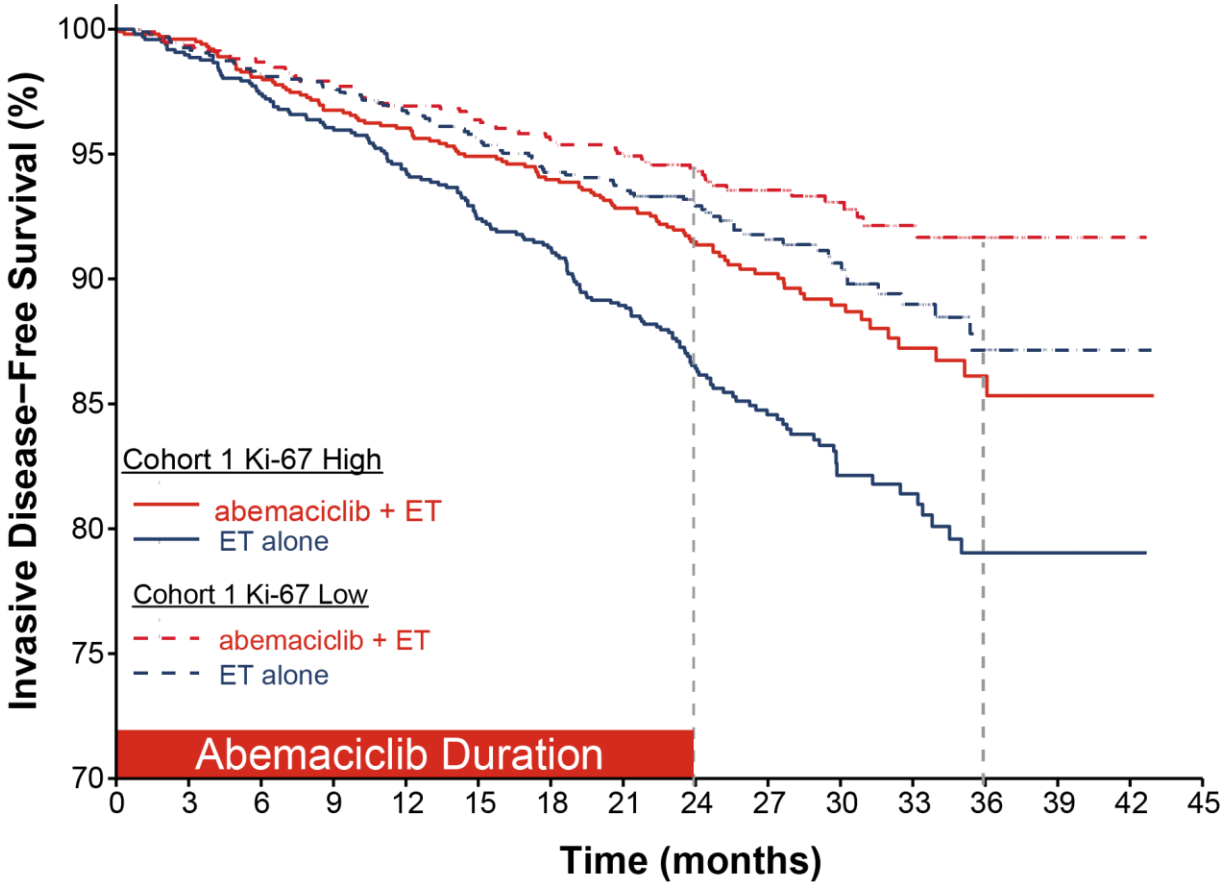
IDFS in Cohort 1 Ki-67 High (≥ 20%) Population



Number at risk																
Abemaciclib + ET	1017	989	963	946	936	922	908	894	733	484	348	203	109	25	2	0
ET Alone	986	955	938	922	906	883	868	835	687	457	333	197	107	25	3	0

37.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 7.1% 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%	

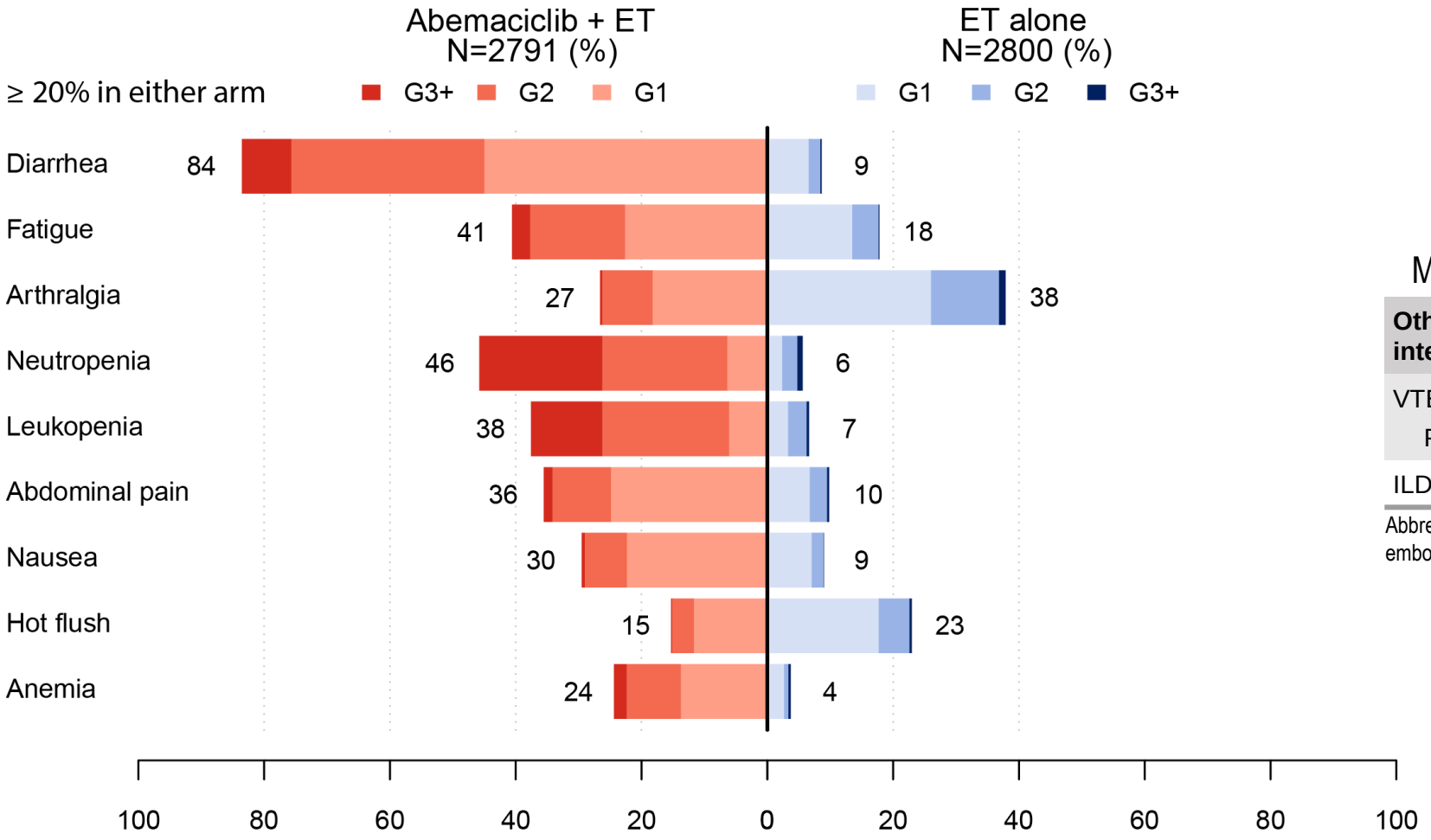
Ki-67 is prognostic

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.

Safety Results

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

Conclusions

- 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

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

Trials with other CDK 4/6 inhibitors

- Palbociclib
  - PALLAS Trial (adjuvant)
  - PENELOPE B Trial (adjuvant after neoadjuvant chemotherapy)
  - Both of these trials were negative
- Ribociclib
  - NATALEE Trial (3 years treatment)
  - Results expected in 2025

Implications for OPTIMA Trial

- **Patients in the OPTIMA Trial can receive adjuvant abemaciclib**

- Adjuvant abemaciclib has received market authorization by the EMA and MHRA within it's licensed indication but not restricted by Ki67 (as per FDA approval)

- There is currently an Expanded Access Programme that allows for the use in NHS patients

- NICE Final Guidance adjuvant abemaciclib for patients within it's licensed indication (not restricted by Ki67) published on the 17th June 2022
  - Abemaciclib with endocrine therapy is recommended, within its marketing authorization, as an option for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence, defined as pathological tumour involvement in
    - at least 4 positive axillary lymph nodes, or
    - 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:

      grade 3 disease (defined as at least 8 points on the modified Bloom-Richardson grading system or equivalent), or

      primary tumour size of at least 5 cm