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Efficacy and safety of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in younger patients (pts) with HR+/HER2− early breast cancer (EBC) in NATALEE

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DECLARATION OF INTERESTS

Dr Sherene Loi receives research funding to her institution from Novartis, Bristol Myers Squibb, Puma Biotechnology, AstraZeneca/Daiichi Sankyo, Roche-Genentech and Seagen. Dr Sherene Loi has acted as consultant to Roche-Genentech, MSD, Gilead Sciences, Astra Zeneca/Daiichi Sankyo, Bristol Myers Squibb, Novartis, Eli Lilly, Amaroq Therapeutics, Mersana Therapeutics, Domain Therapeutics, and BioNTech.

Background

- The NATALEE trial demonstrated a statistically significant iDFS benefit with ribociclib (RIB) + NSAI over NSAI alone in a broad population of pts with HR+/HER2− EBC at risk of recurrence[1,2]
  - At data cutoff of July 21, 2023:
    - Hazard ratio for iDFS: 0.749 (95% CI 0.628-0.892; *P*=.0006)[2]
    - Absolute iDFS benefit at 3 years: 3.1%[2]
  - iDFS benefit was consistent regardless of stage or nodal status[1,2]
- Three years of ribociclib at 400 mg was well tolerated in NATALEE[3]
  - Neutropenia was the most common AE in the RIB + NSAI arm[3]
- This analysis evaluated ribociclib efficacy and safety in younger pts (here defined as aged <40 y), who historically present with more aggressive disease[4] and generally have worse outcomes than pts aged ≥40 y[5-8]

AE, adverse event; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; pt, patient; RIB, ribociclib

References: 1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Hortobagyi G, et al. Oral presented at: SABCS 2023. Oral GS03-03. **3.** Barrios C, et al. Oral presented at: ESMO Breast 2024. **4.** Nasim Z, et al. *World J Oncol.* 2020;11(3):88-97. **5.** Luen SJ, et al. *Ann Oncol*. 2023;34(4):397-409. **6.** Bharat A, et al. *J Surg Oncol.* 2009;100(3):248-251. **7.** de la Rochefordiere A, et al. *Lancet*. 1993;341(8852):1039-1043. **8.** Gnerlich JL, et al. *J Am Coll Surg*. 2009;208(3):341-347.

NATALEE study design[1-4] and age group analysis

- Adult pts with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Distant recurrence-free survival
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Endpoints compared in pts <40 y vs ≥40 y in this analysis

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan−Meier method

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Data cutoff: July 21, 2023

CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, pt-reported outcome; pt, patient; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points.

[a] Enrollment of pts with stage II disease was capped at 40%. [b] 5101 pts were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.

References: 1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol.* 2023;15:1-16. **4.** Hortobagyi, et al. Oral presented at: SABCS 2023. Oral GS03-03.

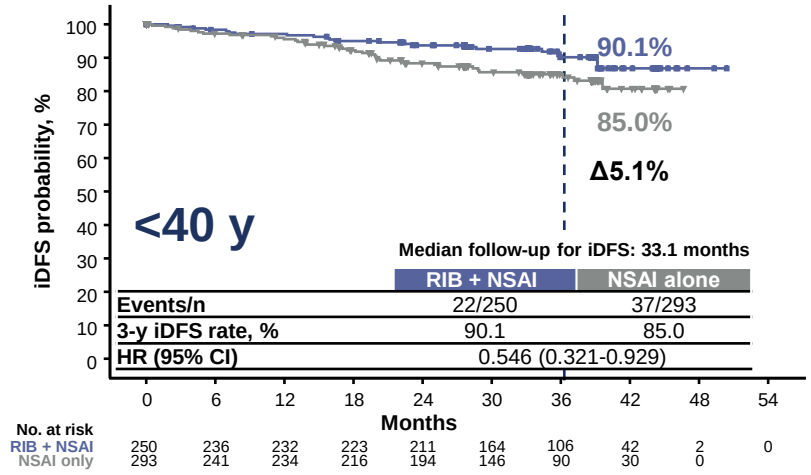
Demographics and baseline characteristics

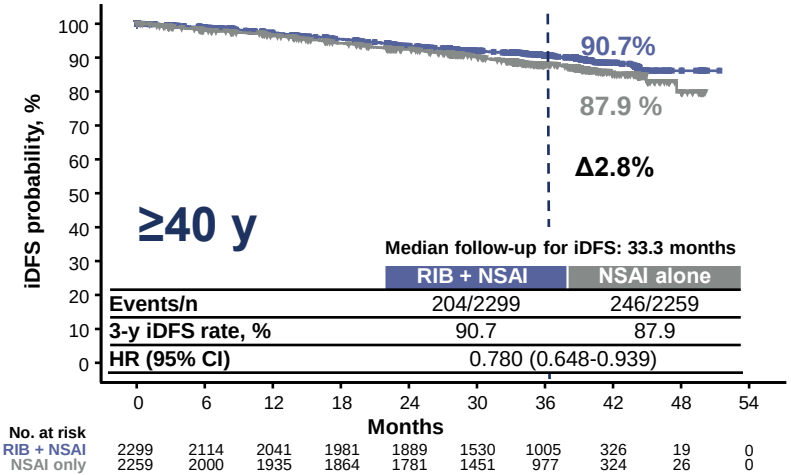
Parameter	Age <40 y			Age ≥40 y		
	RIB + NSAI n=250	NSAI alone n=293	Total n=543	RIB + NSAI n=2299	NSAI alone n=2259	Total n=4558
Median age, y	36.0	37.0	36.0	54.0	54.0	54.0
Premenopausal, n (%)	237 (94.8)	276 (94.2)	513 (94.5)	888 (38.6)	856 (37.9)	1744 (38.3)
Race, n (%)[a]						
White	155 (62.0)	192 (65.5)	347 (63.9)	1721 (74.9)	1676 (74.2)	3397 (74.5)
Asian	63 (25.2)	57 (19.5)	120 (22.1)	278 (12.1)	277 (12.3)	555 (12.2)
Other	23 (9.2)	27 (9.2)	50 (9.2)	171 (7.4)	196 (8.7)	367 (8.1)
AJCC 8th ed. anatomic stage, n (%)[b]						
Stage II	82 (32.8)	98 (33.4)	180 (33.1)	929 (40.4)	936 (41.4)	1865 (40.9)
Stage III	166 (66.4)	195 (66.6)	361 (66.5)	1362 (59.2)	1317 (58.3)	2679 (58.8)
N stage at Dx, n (%)[c]						
NX	18 (7.2)	24 (8.2)	42 (7.7)	256 (11.1)	240 (10.6)	496 (10.9)
N0	50 (20.0)	62 (21.2)	112 (20.6)	645 (28.1)	675 (29.9)	1320 (29.0)
N1	120 (48.0)	137 (46.8)	257 (47.3)	929 (40.4)	912 (40.4)	1841 (40.4)
N2/N3	57 (22.8)	66 (22.5)	123 (22.7)	425 (18.5)	401 (17.8)	826 (18.1)
Histopathological grade at Dx, n (%)[d,e]						
G1	13 (5.2)	17 (5.8)	30 (5.5)	205 (8.9)	223 (9.9)	428 (9.4)
G2	132 (52.8)	167 (57.0)	299 (55.1)	1327 (57.7)	1284 (56.8)	2611 (57.3)
G3	67 (26.8)	77 (26.3)	144 (26.5)	452 (19.7)	472 (20.9)	924 (20.3)
Ki67 status at Dx, n (%)[f,g]						
≤20%	61 (24.4)	86 (29.4)	147 (27.1)	877 (38.1)	868 (38.4)	1745 (38.3)
>20%	120 (48.0)	142 (48.5)	262 (48.3)	803 (34.9)	811 (35.9)	1614 (35.4)
Unknown	69 (27.6)	65 (22.2)	134 (24.7)	619 (26.9)	580 (25.7)	1199 (26.3)
ER+ prior to surgery, mean ± SD, %	83.8 ± 25.5[h]	83.0 ± 23.1[i]	83.4 ± 24.2[j]	87.8 ± 19.1[k]	87.5 ± 18.7[l]	87.7 ± 18.9[m]
PR+ prior to surgery, mean ± SD, %	59.8 ± 34.6[n]	58.0 ± 33.0[o]	58.8 ± 33.7[p]	64.3 ± 33.1[q]	63.5 ± 32.6[r]	63.9 ± 32.8[s]
Prior neoadjuvant chemotherapy, n (%)	150 (60.0)	182 (62.1)	332 (61.1)	935 (40.7)	913 (40.4)	1848 (40.5)
Prior endocrine therapy, n (%)	203 (81.2)	230 (78.5)	433 (79.7)	1623 (70.6)	1575 (69.7)	3198 (70.2)

AJCC, American Joint Committee on Cancer; Dx, diagnosis; ER, estrogen receptor; G, grade; NSAI, nonsteroidal aromatase inhibitor; PR, progesterone receptor; pt, patient; RIB, ribociclib; SD, standard deviation

[a] Race was unknown for 9 pts (3.6%) on RIB and 17 (5.8%) on NSAI alone among pts <40 y and for 129 (5.6%) on RIB and 110 (4.9%) on NSAI alone among pts ≥40 y. [b] 14 pts had Stage I disease. [c] N stage at Dx was unknown for 5 pts (2.0%) on RIB and 4 (1.4%) on NSAI alone among pts <40 y and for 44 (1.9%) on RIB and 31 (1.4%) on NSAI alone among pts ≥40 y. [d] Among pts <40 y, 3 (1.2%) on RIB and 3 (1.0%) on NSAI alone had GX. Among pts ≥40 y, 28 (1.2%) on RIB and 29 (1.3%) on NSAI alone had GX. [e] Histopathological grade at Dx was not assessed or unknown for 35 pts (14%) on RIB and 29 (9.9%) on NSAI alone among pts <40 y and for 287 (12.5%) on RIB and 251 (11.1%) on NSAI alone among pts ≥40 y. [f] Not required for all pts; used to identify high-risk Stage IIA G2 N0. [g] Determined locally at initial Dx. [h] n=189. [i] n=226. [j] n=415. [k] n=1919. [l] n=1863. [m] n=3782. [n] n=169. [o] n=214. [p] n=383. [q] n=1691. [r] n=1626. [s] n=3317.

RIB + NSAI showed iDFS benefit in pts aged <40 and ≥40 y





- iDFS benefit of RIB + NSAI was observed regardless of menopausal status[a]
  - <40 y: premenopausal (n=513)—HR, 0.592 (95% CI, 0.345-1.015); postmenopausal (n=30)—not estimable due to small sample size
  - ≥40 y: premenopausal (n=1744)—HR, 0.730 (95% CI, 0.522-1.019); postmenopausal (n=2814)—HR, 0.812 (95% CI, 0.649-1.016)
- The absolute differences in 3-y iDFS rates between the RIB + NSAI and NSAI-only arms, when adjusted for menopausal status and prior neoadjuvant CT, were similar to those without adjustment (Δ4.0% for pts <40 y and Δ2.9% for pts ≥40 y)

CT, chemotherapy; HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; pt, patient; RIB, ribociclib

[a] Premenopausal women were required to receive goserelin in addition to RIB + NSAI or NSAI alone.

Consistent benefits of RIB + NSAI were observed for other survival endpoints

Parameter	Age <40 y N=543		Age ≥40 y N=4558	
	RIB + NSAI N=250	NSAI alone N=293	RIB + NSAI N=2299	NSAI alone N=2259
RFS				
Events, n	20	33	172	215
3-y rate, %	91.4	86.7	92.2	89.4
3-y ΔRFS, %	**4.7**		**2.8**	
HR (95% CI)	**0.561 (0.320-0.982)**		**0.753 (0.616-0.920)**	
DRFS				
Events, n	18	31	160	196
3-y rate, %	92.2	87.5	92.7	90.4
3-y ΔDRFS, %	**4.7**		**2.3**	
HR (95% CI)	**0.539 (0.300-0.968)**		**0.771 (0.626-0.950)**	
DDFS				
Events, n	19	33	185	223
3-y rate, %	91.8	86.7	91.5	89.1
3-y ΔDDFS, %	**5.1**		**2.4**	
HR (95% CI)	**0.534 (0.302-0.943)**		**0.783 (0.644-0.952)**	
OS				
Events, n	8	10	76	78
3-y rate, %	96.7	94.8	97.0	96.2
3-y ΔOS, %	**1.9**		**0.8**	
HR (95% CI)	**0.729 (0.287-1.854)**		**0.915 (0.667-1.255)**	

- The findings for RFS, DRFS, and DDFS were consistent regardless of menopausal status

DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RFS, recurrence-free survival; RIB, ribociclib

Pts aged <40 and ≥40 y had similar safety profiles

Safety set[a], n (%)	Age <40 y (N=516)		Age ≥40 y (N=4451)	
	RIB + NSAI N=249	NSAI alone N=267	RIB + NSAI N=2276	NSAI alone N=2175
Total AEs[b]	245 (98.4)	225 (84.3)	2229 (97.9)	1920 (88.3)
AEs[b] in >20% in RIB + NSAI arm				
Neutropenia[c]	178 (71.5)	21 (7.9)	1401 (61.6)	92 (4.2)
Arthralgia	97 (39.0)	112 (41.9)	845 (37.1)	946 (43.5)
Headache	74 (29.7)	52 (19.5)	501 (22.0)	363 (16.7)
COVID-19	72 (28.9)	41 (15.4)	465 (20.4)	304 (14.0)
SARS-CoV-2 test positive[d,e]	72 (28.9)	40 (15.0)	460 (20.2)	292 (13.4)
Nausea	61 (24.5)	25 (9.4)	527 (23.2)	165 (7.6)
Fatigue	60 (24.1)	33 (12.4)	504 (22.1)	289 (13.3)
Hot flush	60 (24.1)	68 (25.5)	426 (18.7)	421 (19.4)
ALT increased	29 (11.6)	19 (7.1)	463 (20.3)	117 (5.4)
Serious AEs[b,f]	21 (8.4)	24 (9.0)	336 (14.8)	232 (10.7)
AEs[b] leading to discontinuation of any study treatment	27 (10.8)	10 (3.7)	497 (21.8)	124 (5.7)
AEs[b] leading to discontinuation[g] in >1% in RIB + NSAI arm				
ALT increased	8 (3.2)	0	172 (7.6)	2 (0.1)
AST increased	3 (1.2)	0	68 (3.0)	0
Arthralgia	2 (0.8)	4 (1.5)	35 (1.5)	45 (2.1)

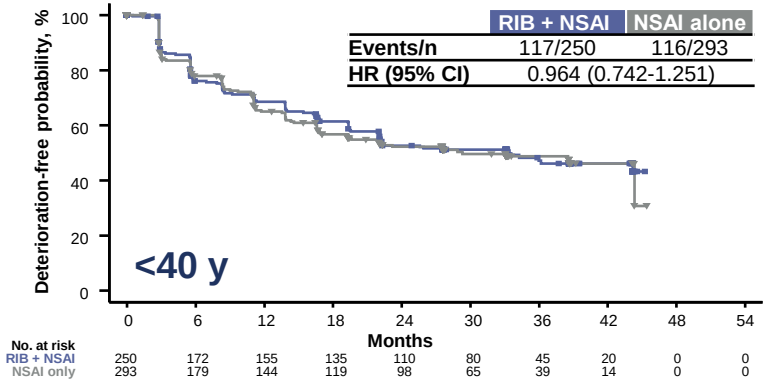
- RIB dose reductions due to AEs were similar between age groups: 26.5% in the <40-y group and 22.4% in the ≥40-y group[h]
- A lower percentage of pts aged <40 vs ≥40 y discontinued RIB early for any reason (28.4% vs 36.3%) or due to AEs (9.6% vs 20.6%)[i]
  - Discontinuation due to AEs without prior RIB dose reduction occurred in 4.4% of pts aged <40 y and 15.0% of pts aged ≥40 y[h]

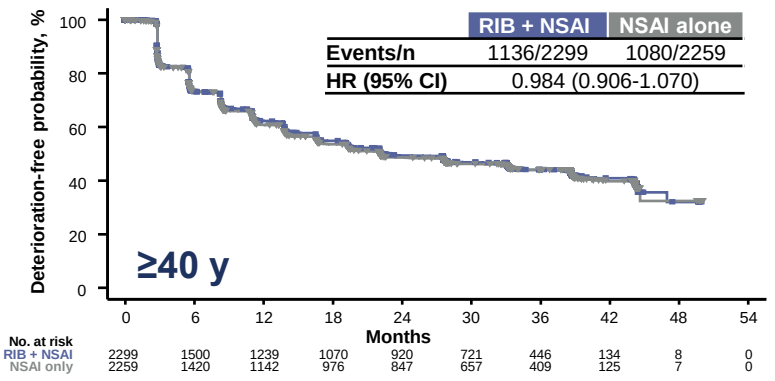
[a] Includes all pts who received ≥1 dose of study drug. [b] All grades. [c] Includes neutropenia, febrile neutropenia, neutrophil count decreased, and granulocytopenia. [d] Only reported as all-grade events. [e] Spontaneously reported (no solicited collection). [f] All were <1% in any arm. [g] Any component. [h] In the safety set. [i] In the ITT population.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ITT, intent-to-treat; NSAI, nonsteroidal aromatase inhibitor; pt, patient; RIB, ribociclib

QOL was similar between arms in pts aged <40 and ≥40 y

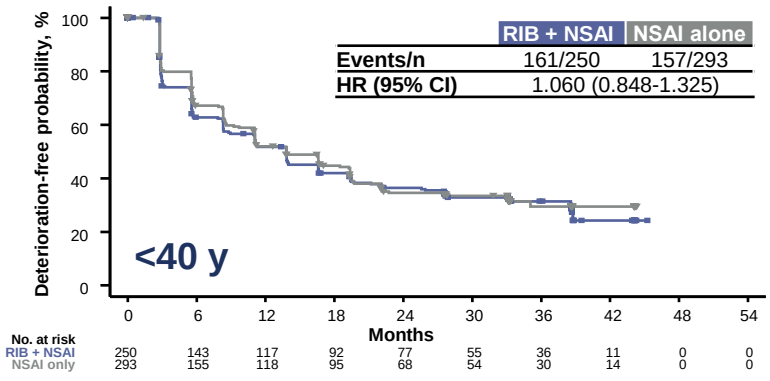
EORTC QLQ-C30 physical functioning and global health status were not altered by addition of RIB regardless of age

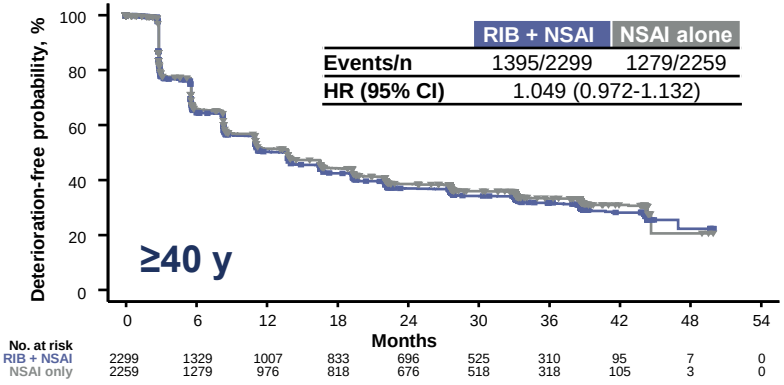
TTFD of physical functioning[a]





TTFD of global health status[b]





[a] Based on a minimum observable difference in physical functioning scale score of <-13.3. [b] Based on a minimum observable difference in GHS scale score of <-16.7.
GHS, global health status; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; PRO, pt-reported outcome; pt, patient; QOL, quality of life; RIB, ribociclib; TTFD, time to first deterioration

Conclusions

- Adjuvant treatment with RIB at 400 mg for 3 y in combination with NSAI showed a consistent treatment benefit over NSAI alone in pts with HR+/HER2− EBC, including in pts <40 y
  - RIB + NSAI demonstrated an iDFS benefit vs NSAI alone in both age groups, reducing the relative risk of invasive disease or death by 45.4% and 22.0%, with a 3-y absolute iDFS benefit of 5.1% and 2.8%, in pts <40 y and ≥40 y, respectively
- Safety profiles were similar in pts aged <40 and ≥40 y, and no new safety signals of RIB at 400 mg were identified in either age group
  - Pts aged <40 y were less likely than pts aged ≥40 y to discontinue RIB due to AEs and to do so without a prior RIB dose reduction, emphasizing the tolerable safety profile of RIB in this population
- Quality of life was similar between patients on RIB + NSAI and patients on NSAI alone regardless of age

These results from NATALEE demonstrate that 3 years of ribociclib at 400 mg consistently provides an iDFS benefit in patients with stage II or stage III HR+/HER2− EBC regardless of age, including in younger patients, who have historically shown worse treatment outcomes

AE, adverse event; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSAI, nonsteroidal aromatase inhibitor; pt, patient; RIB, ribociclib

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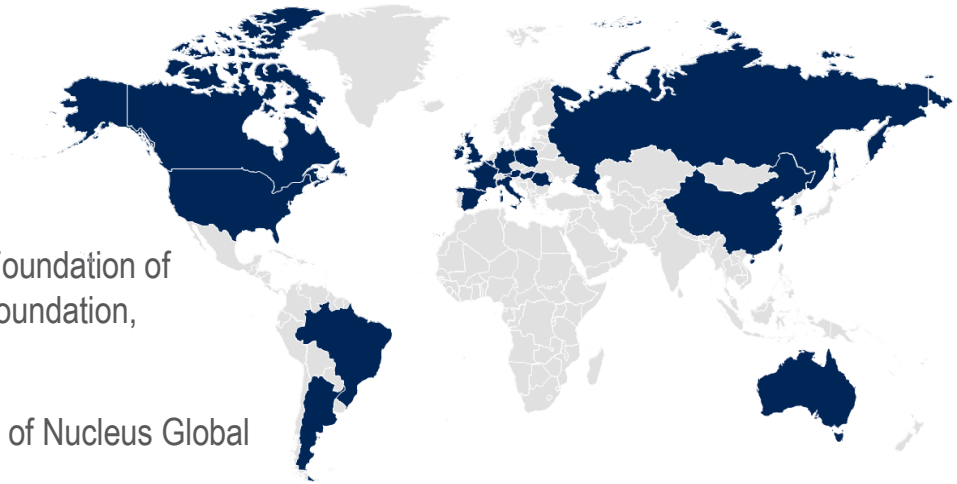

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