

Supplementary Tables

Supplementary Table 1: Summary of analysis populations

	Total
	N
Secondary Endpoint Analysis Population	497
ART analysis population	
Used ART	215
Did not use ART	282
Ovarian analysis population	438
POI analysis population	142
POI and low ovarian reserve population	142
POI negative population	127
Low ovarian reserve/no ART analysis population	238
Low ovarian reserve/no ART/FSH month 3 analysis population	187
POI/FSH month 3 analysis population	111
AFC analysis population	57
Ovulatory/no ART analysis population	93
PRL analysis population	444
TSH analysis population	450

ART= Assisted Reproductive Technology; POI= premature ovarian insufficiency; AFC= antral follicular count, PRL=prolactin; TSH= thyroid stimulating hormone

Supplementary Table 2: Odds ratios for low ovarian reserve from multivariable logistic regression model

Odds Ratio Estimates			
Factor	Point Estimate	95% Wald Confidence Limits*	
ART: Ovarian stimulation by IVF/ICSI on trial vs No ART	0.955	0.508	1.797
ART: Embryo transfer vs No ART	1.021	0.548	1.901
ART: Other ART vs No ART	1.122	0.609	2.068
Age: <35 vs 40-42	0.162	0.086	0.306
Age: 35-39 vs 40-42	0.505	0.286	0.890
Prior chemotherapy: No vs Yes	0.114	0.069	0.189
Prior ET: SERM only vs OFS +/- AI	1.329	0.706	2.499
Prior ET: Other vs OFS +/- AI	1.750	0.942	3.253
Duration prior ET (months)	0.982	0.930	1.037

*Factors are considered associated with low ovarian reserve if the 95% Wald Confidence Limits do not include 1.000. Low Ovarian Reserve is defined as AMH<0.5 ng/ml (yes vs no).

ART= Assisted Reproductive Technology; IVF/ICSI= In Vitro Fertilization/Intracytoplasmic Sperm Injection; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy

Supplementary Table 3: Distribution of 12-month estradiol E2 and FSH, among patients in the low ovarian Reserve/ premature ovarian insufficiency analysis population

	N	Mean	Median	Min	P25	P75	Max
12-month E2 (pg/ml)	142	67	44	5	23	77	619
12-month FSH (IU/L)	142	14	9	0	7	14	167

Supplementary Table 4: Summary of premature ovarian insufficiency (POI) status by low ovarian reserve status

	POI		Total
	Yes	No	
	N (%)	N (%)	N
Low ovarian reserve/POI analysis population	15 (10.6%)	127 (89.4%)	142
Low ovarian reserve			
Yes	15 (100%)	59 (46.5%)	74
No	.	68 (53.5%)	68

Supplementary Table 5: Duration of prior endocrine therapy (months) by premature ovarian insufficiency (POI)

		N	Mean	Median	Min	P25	P75	Max
Low ovarian reserve/POI analysis population	Duration prior ET	142	23	23	18	20	26	30
POI (FSH > 25) at month 12								
Yes	Duration prior ET	15	24	23	18	22	26	30
No	Duration prior ET	127	23	23	18	20	26	30

ET= Endocrine Therapy.

Low Ovarian Reserve and POI are defined as AMH<0.5 ng/ml and FSH>25IU/L at month 12, respectively

Supplementary Table 6: Distribution of 3-month FSH by premature ovarian insufficiency status

	N	Mean	Median	Min	P25	P75	Max
Low ovarian reserve/POI analysis population Patients with useable 3-month FSH samples	111	13	7	3	6	13	65
POI status							
Yes	10	30	31	3	6	45	65
No	101	11	7	3	6	12	53

Low Ovarian Reserve and POI are defined as AMH<0.5 ng/ml and FSH>25IU/L at month 12, respectively

Supplementary Table 7: Distribution of 3-month antral follicular count (AFC) by low ovarian reserve status and premature ovarian insufficiency (POI)

	AFC						
	N*	Mean	Median	Min	P25	P75	Max
AFC analysis patients	57	5	3	0	1	6	35
Low ovarian reserve							
Yes	34	3	2	0	0	4	16
No	23	9	5	0	3	12	35
POI							
Yes	7	1	0	0	0	1	2
No	50	6	4	0	2	7	35

*Analysis performed in 57 of 142 patients in low ovarian reserve and POI analysis populations with AFC assessed. Low Ovarian Reserve and POI are defined as AMH<0.5 ng/ml and FSH>25IU/L at month 12, respectively

Linear regression model for AFC with variables for prior chemotherapy and age at enrolment (n=57)

	Odds ratio Estimate	95% LCL	95% UCL
Intercept	7.81	4.08	11.55
Prior chemotherapy: Yes vs. No	-6.38	-10.1	-2.67
Age: < 35 vs 40-42	5.85	1.31	10.39
Age: 35-39 vs. 40-42	0.81	-3.13	4.75

Supplementary Table 8: Odds ratios for pregnancy (yes vs no) from multivariable logistic model including continuous AMH

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
AMH (continuous)*	1.208	1.019	1.431
ART: Ovarian stimulation by IVF/ICSI on trial vs No ART	1.135	0.595	2.162
ART: Embryo transfer vs No ART	2.392	1.159	4.939
ART: Other ART vs No ART	1.325	0.701	2.504
Age: <35 vs 40-42	4.814	2.545	9.106
Age: 35-39 vs 40-42	2.670	1.583	4.504
Prior chemotherapy: No vs Yes	0.739	0.441	1.238
Prior ET: SERM only vs OFS +/- AI	1.091	0.565	2.105
Prior ET: other vs OFS +/- AI	1.090	0.568	2.090
Duration prior ET (months)	0.957	0.906	1.012

ART= Assisted Reproductive Technology; IVF/ICSI= In Vitro Fertilization/Intracytoplasmic Sperm Injection; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy * n=438 of whom 316 had pregnancy

Supplementary Table 9: Distribution of ovarian reserve by ART use

	AMH < 0.5 ng/ml*		0.5 <= AMH < 1.5 ng/ml		1.5 <= AMH		Total	
	N	%	N	%	N	%	N	%
Ovarian reserve analysis population	209	100.0	101	100.0	128	100.0	438	100.0
ART use								
Yes	102	48.8	43	42.6	55	43.0	200	45.7
No	107	51.2	58	57.4	73	57.0	238	54.3

*defined as low ovarian reserve

ART= Assisted Reproductive Technology

Supplementary Table 10: FSH values at month 3 by pregnancy status

		N*	Mean	Median	Min	P25	P75	Max
3-month FSH (IU/L)	Pregnancy status							
	Yes	134	9.6	7.1	1.7	5.3	9.8	45.7
	No	53	13.0	8.6	2.6	6.2	12.7	65.2

*Analysis performed on the population with low ovarian reserve assessment, and did not use ART and had available FSH at month 3 (n=187)

Supplementary Table 11: Odds ratios for spontaneous pregnancy (yes vs no) from multivariable logistic model including 3-month FSH

Odds Ratio Estimates			
Effect*	Point Estimate	95% Wald Confidence Limits	
Age: <35 vs 40-42	11.558	4.156	32.143
Age: 35-39 vs 40-42	5.066	2.104	12.197
Prior chemotherapy: No vs Yes	0.550	0.251	1.205
Prior ET: SERM only vs OFS +/- AI	2.108	0.756	5.876
Prior ET: other vs OFS +/- AI	1.572	0.603	4.100
Duration prior ET (months)	0.944	0.863	1.032
3-month FSH	0.960	0.925	0.996

ART= Assisted Reproductive Technology; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy *Analysis performed on the population with ovarian reserve assessment, and did not use ART and had available FSH at month 3 (n=187)

Supplementary Table 12: Proportion of patients in low ovarian reserve/POI analysis population that had oligomenorrhea, according to POI status

	Oligomenorrhea (before 12-month sample)				Total	
	Yes		No			
	N	%	N	%	N	%
Low ovarian reserve/POI analysis population	51	35.9	91	64.1	142	100.0
POI (FSH > 25) at month 12						
Yes	11	73.3	4	26.7	15	10.6
No	40	31.5	87	68.5	127	89.4

Supplementary Table 13: Distribution of 3- and 12-month AMH and FSH by oligomenorrhea status before month 12

		N miss	N*	Mean	Median	Min	P25	P75	Max
3-month AMH (ng/ml)	Oligomenorrhea								
	Yes	2	38	2.0	0.6	0.0	0.0	3.7	9.7
	No	7	80	1.1	0.6	0.0	0.1	1.5	8.4
12-month AMH (ng/ml)	Oligomenorrhea								
	Yes	0	40	2.6	0.9	0.0	0.2	3.0	18.8
	No	0	87	1.4	0.8	0.0	0.3	1.9	14.9
3-month FSH (IU/L)	Oligomenorrhea								
	Yes	2	38	11.9	6.8	2.5	5.1	14.3	43.6
	No	8	79	10.4	7.4	0.3	6.2	11.3	53.1
12-month FSH (IU/L)	Oligomenorrhea								
	Yes	0	40	8.8	8.1	0.3	5.1	11.6	21.0
	No	0	87	9.8	8.5	1.1	6.6	11.6	24.0

*Analysis performed on the low ovarian reserve/POI population who did not have POI (n=127 / 142)

Supplementary Table 14: Patient and treatment characteristics in the population with known ovulatory status

	Subsequent Pregnancy status				Total	
	Yes		No			
	N	%	N	%	N	%
Ovulatory status analysis patients*	54	58.1	39	41.9	93	100.0
Ovulatory status						
Ovulating	32	57.1	24	42.9	56	60.2
Not ovulating	22	59.5	15	40.5	37	39.8
Age at enrollment (years)						
<35	22	78.6	6	21.4	28	30.1
35-39	25	62.5	15	37.5	40	43.0
40-42	7	28.0	18	72.0	25	26.9
Prior chemotherapy						
No	22	52.4	20	47.6	42	45.2
Yes	32	62.7	19	37.3	51	54.8
Prior ET						
OFS +/- AI	13	65.0	7	35.0	20	21.5
SERM only	18	58.1	13	41.9	31	33.3
other	23	54.8	19	45.2	42	45.2

*Ovulatory status based on progesterone at month 6 in patients who did not yet achieve pregnancy and who did not use ART

		N	Mean	Median	Min	P25	P75	Max
Duration of prior ET	Pregnancy status							
	Yes	54	23.8	23.4	18.0	20.0	28.1	31.7
	No	39	23.6	23.7	18.0	20.1	26.8	29.9

OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy

Supplementary Table 15: Odds ratios for spontaneous pregnancy (yes vs no) from multivariable logistic model including 6-month ovulatory status

Odds Ratio Estimates			
Effect*	Point Estimate	95% Wald Confidence Limits	
		Ovulatory status: Ovulating vs Not ovulating	1.407
Age: <35 vs 40-42 years	10.465	2.842	38.535
Age: 35-39 vs 40-42 years	4.429	1.385	14.170
Prior chemotherapy: No vs Yes	0.608	0.231	1.605
Prior ET: SERM only vs OFS +/- AI	0.915	0.243	3.448
Prior ET: other vs OFS +/- AI	0.852	0.243	2.984
Duration prior ET (months)	1.005	0.890	1.135

ART= Assisted Reproductive Technology; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy * Ovulatory status based on progesterone at month 6 in patients who did not yet achieve pregnancy and who did not use ART (n=93)

Supplementary Table 16: Patient and treatment characteristics including 3-month prolactin (PRL) and thyroid stimulating hormone (TSH) categorization by pregnancy status

	Pregnancy status				Total	
	Yes		No			
	N	%	N	%	N	%
All secondary endpoint population patients	368	74.0	129	26.0	497	100.0
Serum PRL						
High	12	66.7	6	33.3	18	3.6
Normal	314	73.7	112	26.3	426	85.7
Not available	42	79.2	11	20.8	53	10.7
Serum TSH						
High	14	77.8	4	22.2	18	3.6
Normal	313	73.6	112	26.4	425	85.5
Low	4	57.1	3	42.9	7	1.4
Not available	37	78.7	10	21.3	47	9.5

Supplementary Table 17: Odds ratios for pregnancy (yes vs no) from multivariable logistic model including 3-month TSH

Odds Ratio Estimates			
Effect*	Point Estimate	95% Wald Confidence Limits	
ART: Ovarian stimulation by IVF/ICSI on trial vs No ART	0.971	0.512	1.842
ART: Embryo transfer vs No ART	2.183	1.039	4.586
ART: Other ART vs No ART	1.197	0.638	2.243
Age: <35 vs 40-42 years	5.165	2.788	9.568
Age: 35-39 vs 40-42 years	2.969	1.770	4.981
Prior chemotherapy: No vs Yes	0.935	0.588	1.485
Prior ET: SERM only vs OFS +/- AI	1.301	0.673	2.516
Prior ET: other vs OFS +/- AI	1.050	0.552	1.998
Duration prior ET (months)	0.965	0.913	1.019
Serum TSH: Abnormal vs Normal	0.971	0.375	2.509

ART= Assisted Reproductive Technology; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy

*Analysis performed in the population of 450 patients with 3-month TSH (excludes pregnant within 3m)

Supplementary Table 18: Odds ratios for pregnancy (yes vs no) from multivariable logistic model including 3-month prolactin

Odds Ratio Estimates			
Effect*	Point Estimate	95% Wald Confidence Limits	
ART: Ovarian stimulation by FIVET/ICSI on trial vs No ART	0.957	0.503	1.824
ART: Embryo transfer vs No ART	2.468	1.143	5.331
ART: Other ART vs No ART	1.241	0.658	2.339
Age: <35 vs 40-42 years	5.829	3.096	10.973
Age: 35-39 vs 40-42 years	3.108	1.839	5.253
Prior chemotherapy: No vs Yes	0.930	0.581	1.489
Prior ET: SERM only vs OFS +/- AI	1.314	0.673	2.564
Prior ET: other vs OFS +/- AI	1.032	0.540	1.974
Duration prior ET (months)	0.967	0.915	1.022
Prolactin: High vs Normal	0.593	0.201	1.749

ART= Assisted Reproductive Technology; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET= Endocrine Therapy

*Analysis performed in the population of 444 patients with 3-month Prolactin(excludes pregnant within 3m)