A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial

Professor Michael Gnant, MD, FACS
Medical University of Vienna, Vienna, Austria

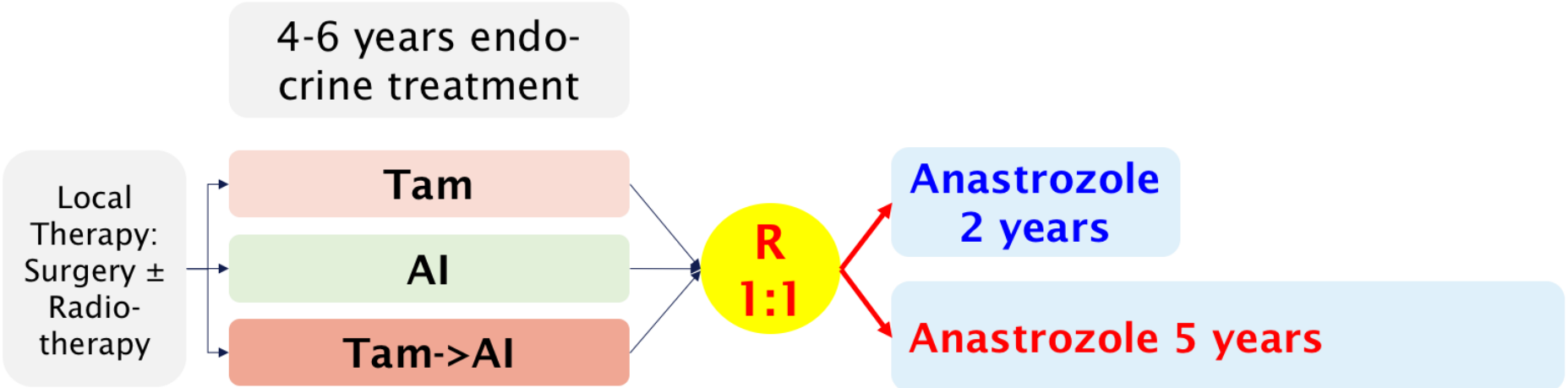
Michael Gnant, Guenther Steger, Richard Greil, Florian Fitzal, Brigitte Mlineritsch, Diether Manfreda, Christoph Tausch, Marija Balic, Peter Dubsky, Martin Moik, Josef Thaler, Daniel Egle, Vesna Bjelic-Radisic, Ursula Selim, Ruth Exner, Christian Singer, Elisabeth Melbinger-Zeinitzer, Ferdinand Haslbauer, Herbert Stoeger, Ruth Helfgott, Paul Sevelda, Harald Trapl, Viktor Wette, Lidija Soelkner, Raimund Jakesz, on behalf of the Austrian Breast and Colorectal Cancer Study Group

ABCSG-16 Background:

- HR+ Breast Cancer shows significant long-term risk of relapse:
  - >50 % of disease relapses occur after the first 5 years of follow-up
  - Since the risk of recurrence persists, extending adjuvant therapy is appealing
- On average...:
  - Aromatase inhibitors for 5 years are better than Tamoxifen for 5 years, but sequencing Tam and AI is an alternative to 5 years of AI
  - Prolonging Tamoxifen (after Tam) is beneficial in premenopause
  - In postmenopausal women, adding additional AI after early Tamoxifen is beneficial
    - Significant benefits after 5 years of Tamoxifen (MA17, NSABP-B33, ABCSG-6a)
    - Borderline/no benefit after previous 2-5 years of AI (MA17R, NSABP-B42, DATA, IDEAL)
  - Extended intermittent Letrozole is not worse than continuous Letrozole (SOLE)
- What is the optimal duration of extended adjuvant AI?

Pan H et al. N Engl J Med 2017; 377:1836-1846. EBCTCG. Lancet 2015; 386:1341-52 Davies C, et al. Lancet 2013: 381:805-16. Goss PE et al. JNCI 2005; 97:1262-71 Jakesz R et al. Lancet 2005; 366:455-62. Goss PE et al. N Engl J Med. 2016; 375: 209-19. Blok EJ, et al. J Natl Cancer Inst 2018 January 1 (Epub ahead of print). Tjan-Heijnen VCG, et al. Lancet Oncol 2017 October 11 Mamounas EP et al, Cancer Res 2017. Regan M, et al. Lancet Oncology 2017; online Nov 17

ABCSG-16 Trial Design



N=3,484

Postmenopausal, HR+, T1-3, N0/N+, M0

Recruitment in 75 centers in Austria, 2004-2010

Median Follow-Up: 106.2 months (102.7-107.7)

Michael Gnant, MD, FACS

ABCSG-16 Study Objectives and End Points

- **Study Objective**
  - Assessing the outcome effects of **additional 2 years *versus* additional 5 years of Anastrozole** after 5 years of adjuvant endocrine therapy
- **Primary endpoint**
  - **Disease free survival (DFS)** - defined as time to any evidence of local or distant metastases, contralateral breast cancer, secondary carcinoma, or death from any cause

    Two types of analyses: starting at randomization and starting two years after randomization (when treatment arms differ)
- **Secondary endpoints**
  - Overall survival (OS) - defined as time to death from any cause (from randomization and 2 years after)
  - Time to contralateral breast cancer – starting at randomization
  - Time to second primary cancer – starting at randomization
  - Time to first clinical fracture – starting two years after randomization

Michael Gnant, MD, FACS

ABCSG-16 Statistics and Sample Size

- 433 events required to detect a significant difference of HR=0.74 with power=85% at a 2-sided alpha=0.05
  - (incl. 5% expected to occur within the first two years, where no difference between treatment arms was expected)
- 3,500 patients to be included
- Each patient to be followed for 10 years
- As the required number of events has been reached
  - SC decision for analysis after 12 years trial duration
  - Data cutoff date: June 30th, 2016
- Analysis Set: **3,469 patients** and **762 DFS** events

ABCSG-16 Patients (I)

		2 Years Anastrozole N=1,731 n (%)	5 Years Anastrozole N=1,738 n (%)	Total N=3,469 n (%)
Median age	years (range)	65 (38-84)	64 (29-84)	64 (29-84)
pT-stage	pT1	1,253 (72.4)	1,254 (72.2)	2,507 (72.3)
	pT2/pT3/pTx	474 (27.4)	480 (27.6)	954 (27.5)
	Unknown	4 (0.2)	4 (0.2)	8 (0.2)
pN-stage	Negative	1,139 (65.8)	1,162 (66.9)	2,301 (66.3)
	Positive	551 (31.8)	523 (30.1)	1,074 (31.0)
	Unknown	4 (0.2)	4 (0.2)	8 (0.2)
Grading	G1	247 (14.3)	261 (15.0)	508 (14.6)
	G2/Gx	1,133 (65.5)	1,102 (63.4)	2,235 (64.4)
	G3	326 (18.8)	348 (20.0)	674 (19.4)
	Unknown	25 (1.4)	27 (1.6)	51 (1.5)
Hormone Receptor	ER+/PR+	1,354 (78.2)	1,330 (76.5)	2,684 (77.4)
	Any negative	375 (21.7)	401 (23.1)	776 (22.4)
	Unknown	2 (0.1)	7 (0.4)	9 (0.3)

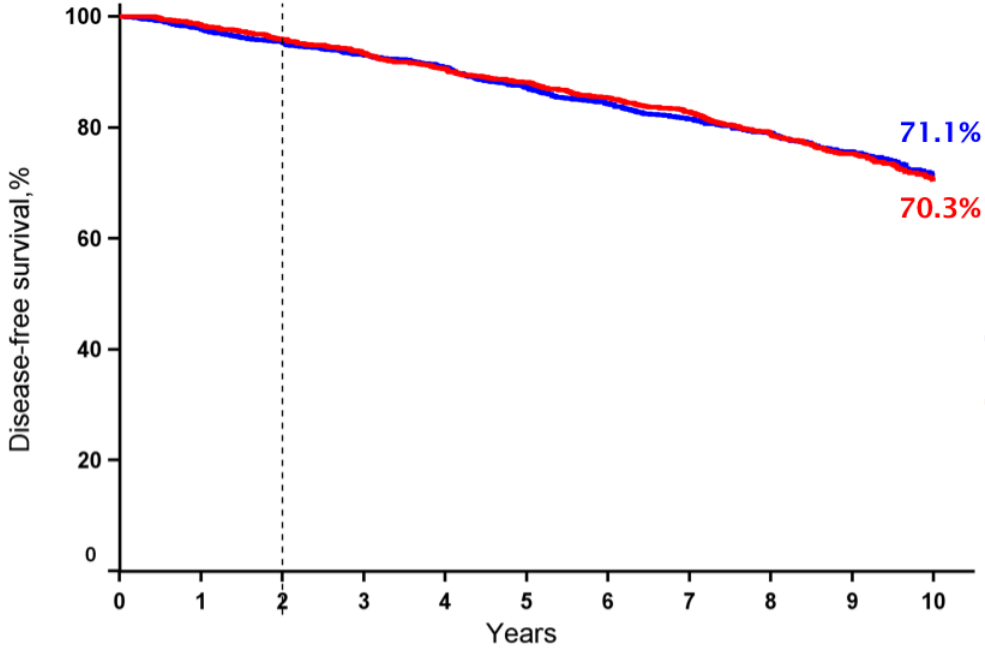
Michael Gnant, MD, FACS

ABCSG-16 Patients (II)

		2 Years Anastrozole N=1,731 n (%)	5 Years Anastrozole N=1,738 n (%)	Total N=3,469 n (%)
Type of surgery	Breast-conserving	1,360 (78.6)	1,406 (80.9)	2,766 (79.7)
	Mastectomy	370 (21.4)	329 (18.9)	699 (20.1)
	Unknown	1 (0.1)	3 (0.1)	4 (0.2)
Radiotherapy	yes	1,373 (79.3)	1,407 (81.0)	2,780 (80.1)
	no	355 (20.5)	327 (18.8)	682 (19.7)
	Unknown	3 (0.24)	4 (0.2)	7 (0.2)
Chemotherapy	Containing anthracycline	246 (14.2)	236 (13.6)	482 (13.9)
	Containing taxane	93 (5.4)	95 (5.5)	188 (5.4)
	Other chemotherapy	167 (9.6)	163 (9.4)	330 (9.5)
	No chemotherapy	1,223 (70.7)	1,241 (71.4)	2,464 (71.0)
	Unknown	2 (0.1)	3 (0.2)	5 (0.1)
Endocrine therapy in first 5 years	Tamoxifen	884 (51.1)	880 (50.6)	1,764 (50.9)
	Tamoxifen + AI	722 (41.7)	723 (41.6)	1,445 (41.6)
	AI	125 (7.2)	135 (7.8)	260 (7.5)

ABCSG-16 Disease-Free Survival

Time from randomization to first DFS event

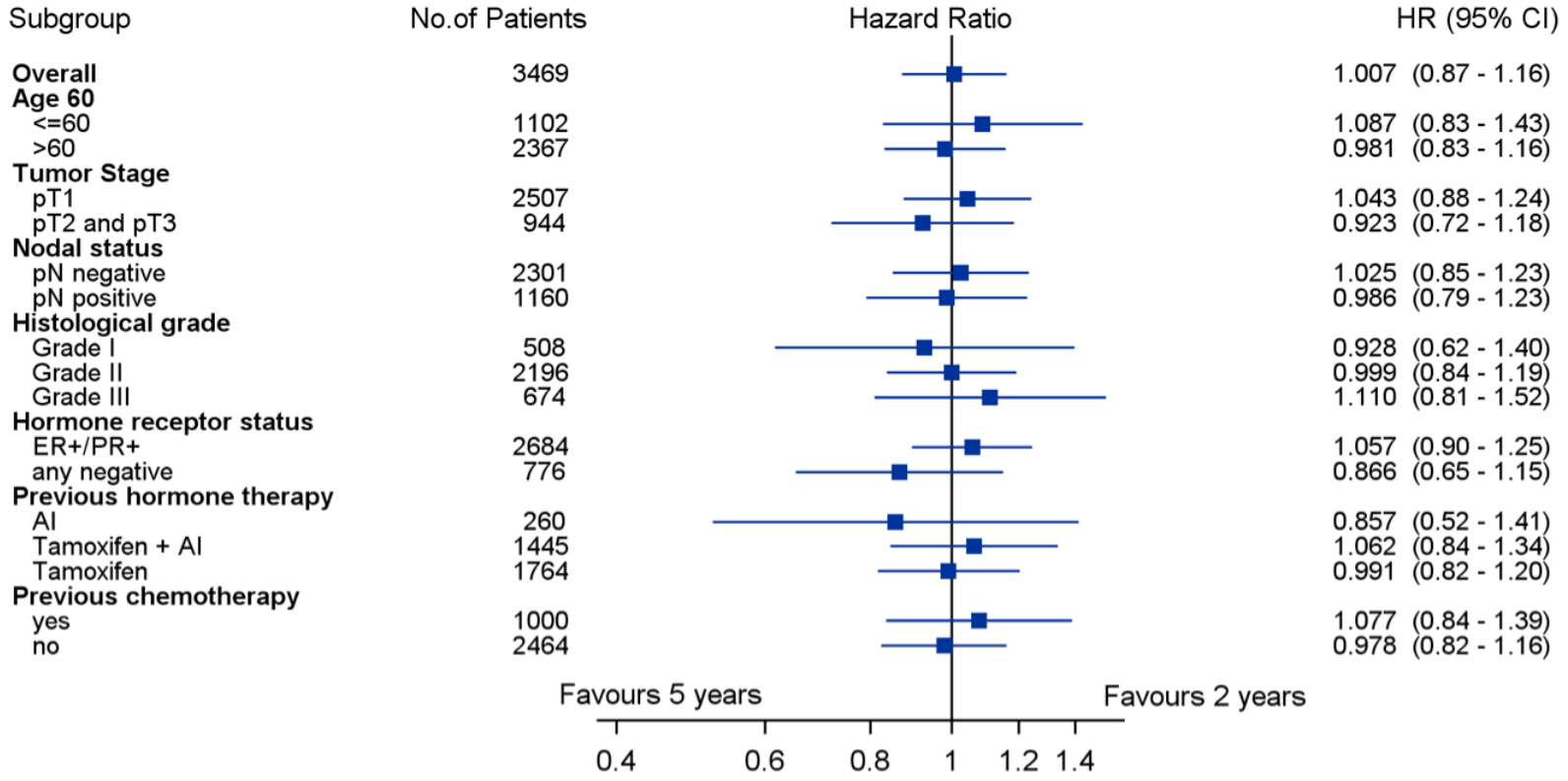


Patients at risk:

2 years	1731	1651	1601	1538	1477	1368	1206	990	741	540	214
5 years	1738	1667	1605	1551	1485	1399	1233	1026	779	554	209

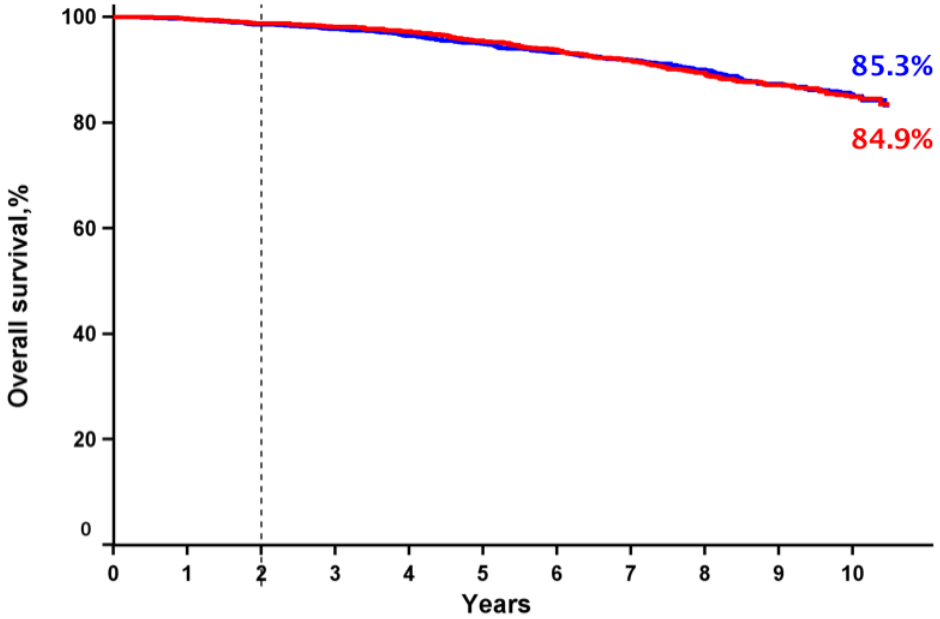
	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	378/1,731	1.007 (0.87, 1.16)	0.925
5 years	384/1,738		

ABCSG-16 DFS Subgroups



ABCSG-16 Secondary End Point: Overall Survival

Time from randomization to death from any cause



Patients at risk:

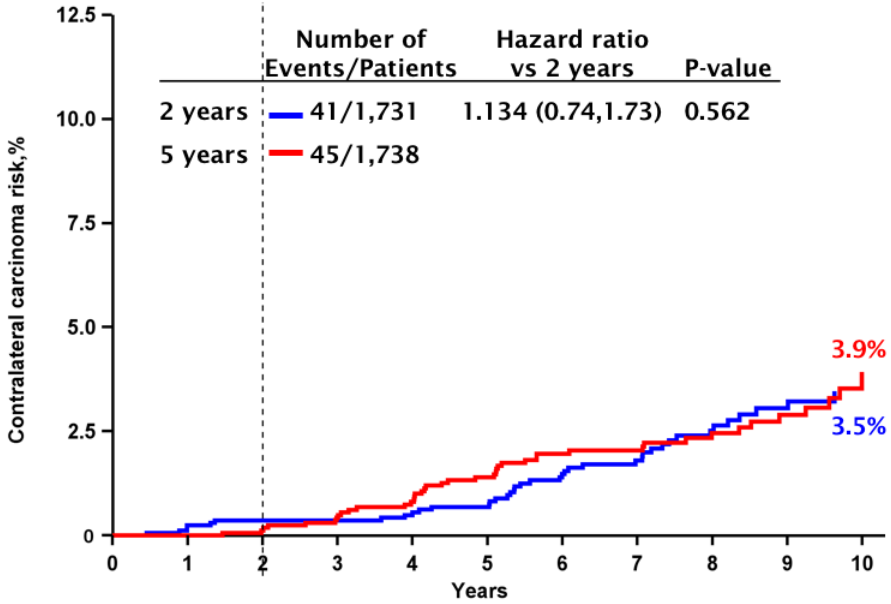
2 years	1731	1689	1661	1626	1594	1518	1352	1125	901	701	381
5 years	1738	1694	1659	1637	1606	1533	1362	1156	920	710	361

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	192/1,731	1.007 (0.82,1.23)	0.947
5 years	194/1,738		

Michael Gnant, MD, FACS

ABCSG-16 Secondary End Points

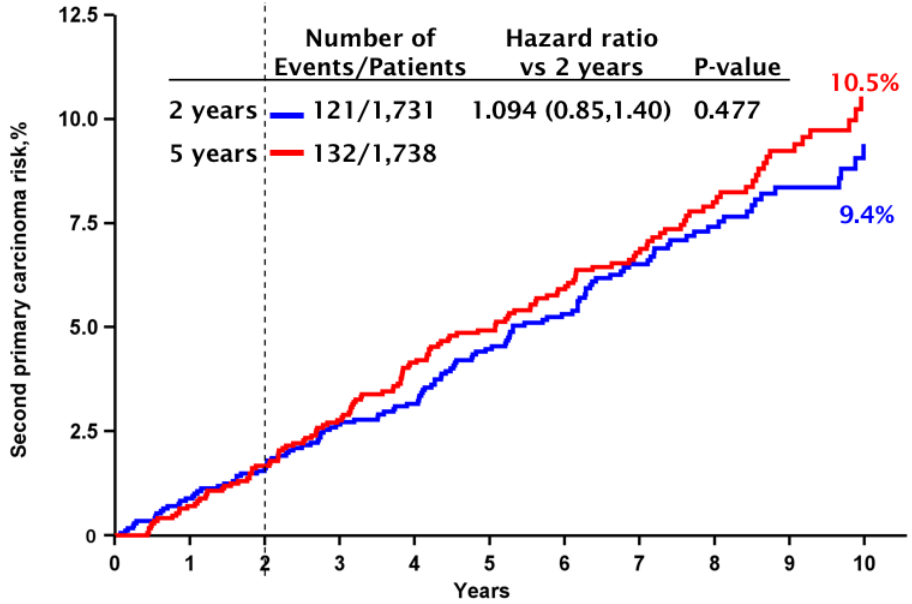
Contralateral Breast Cancer



Patients at risk:

2 years	1731	1662	1629	1585	1528	1448	1282	1058	794	588	252
5 years	1738	1676	1639	1602	1539	1454	1279	1065	821	599	235

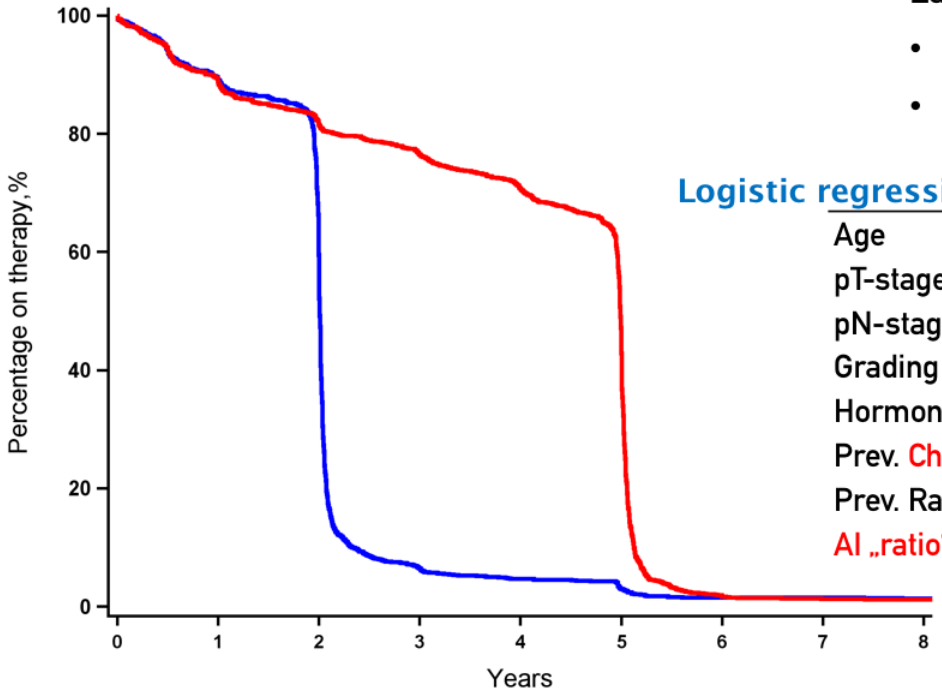
Secondary Primary Cancer



Patients at risk:

2 years	1731	1656	1616	1559	1502	1417	1261	1040	785	583	245
5 years	1738	1668	1618	1571	1502	1424	1253	1043	800	583	229

ABCSG-16 Treatment Adherence

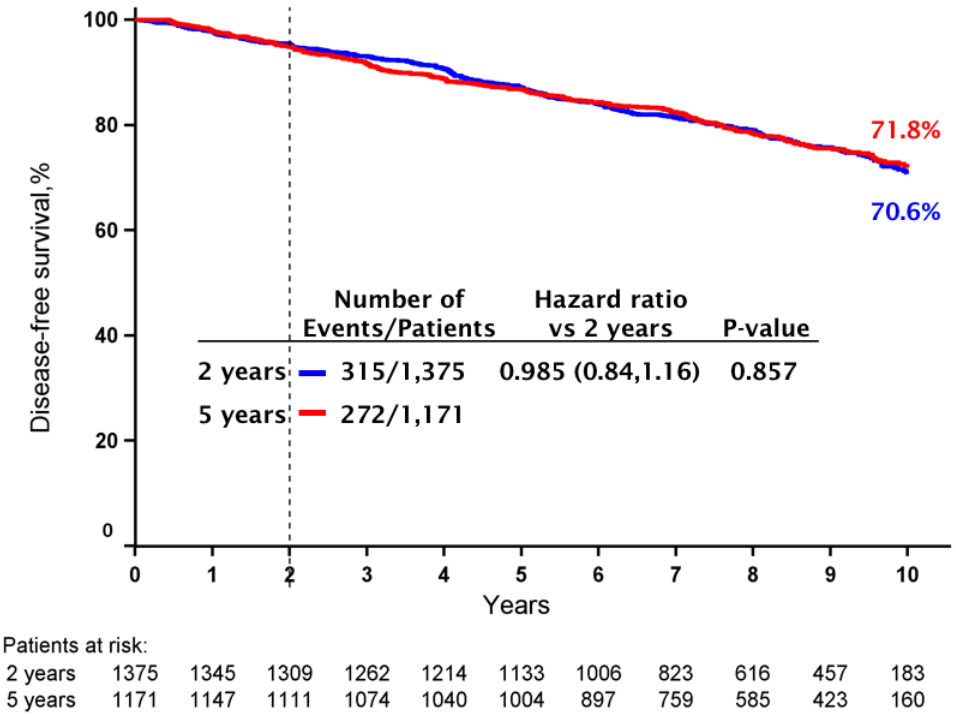


	2 years	5 years
Early/late EOT	421 (24.3%)	706 (40.6%)
• without event	356 (20.6%)	567 (32.6%)
• for DFS event	65 (3.8%)	139 (8.0%)

Logistic regression: Non-Adherent *vs* Adherent		Odds Ratio (95% CI)	P-value
Age	>60 vs ≤60	1.07 (0.89, 1.29)	0.4454
pT-stage	pT2/pT3 *vs* pT1/pTX	1.01 (0.83, 1.22)	0.9560
pN-stage	positive *vs* negative	0.93 (0.77, 1.12)	0.4187
Grading	G3 *vs* G1/G2/GX	1.21 (0.98, 1.51)	0.0806
Hormone Receptor	ER+/PR+ vs any neg.	0.91 (0.75, 1.10)	0.3190
Prev. Chemotherapy	yes *vs* no	0.79 (0.63, 0.98)	0.0303
Prev. Radiotherapy	yes *vs* no	1.10 (0.90, 1.35)	0.3660
AI „ratio“	continuous	0.65 (0.49, 0.86)	0.0030

Adherent patients:
all patients on treatment for 5 (±0.5) years in 5-years arm
all patients on treatment for 2 (±0.5) years in 2-years arm
all patients with DFS event during their treatment phase

Exploratory: DFS in „Adherent“ Patients only



Time to contralateral breast cancer

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	35/1,375	1.071 (0.66,1.73)	0.781
5 years	32/1,171		

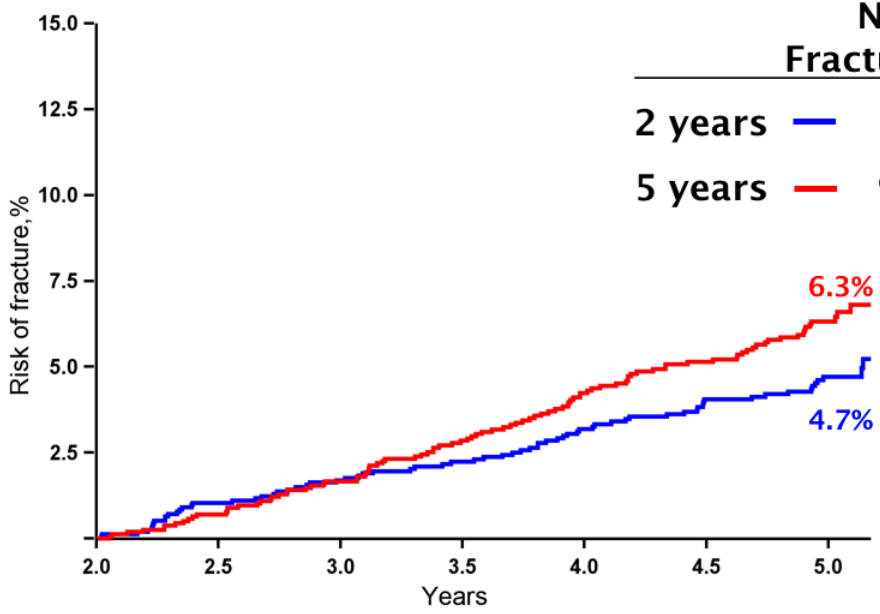
Time to second primary cancer

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	101/1,375	1.250 (0.95,1.64)	0.106
5 years	109/1,171		

DFS in Adherence Subgroup including patients with AEs

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	336/1,474	0.976 (0.84,1.14)	0.755
5 years	311/1,354		

ABCSG-16 Fractures



	Number of Fractures/Patients	Hazard ratio vs 2 years	P-value
2 years	71/1,556	1.353 (1.00,1.84)	0.053
5 years	98/1,571		

Patients at risk:

2 years	1556	1515	1480	1439	1386	1313	843
5 years	1571	1549	1514	1477	1416	1347	857

ABCSG-16 Summary

- In postmenopausal hormone-receptor positive breast cancer patients receiving 5 years of standard adjuvant endocrine therapy (Tamoxifen, Aromatase Inhibitor, sequence), additional 5 years of Anastrozole **did not improve disease-free survival** as compared to additional 2 years of Anastrozole.
- ABCSG-16 did not show a difference between additional 2 years versus additional 5 years of Anastrozole in terms of secondary end points
  - Overall survival (OS)
  - Time to contralateral breast cancer
  - Time to second primary cancer
- There were **more fractures** in the study arm of 5 additional years of Anastrozole.

Conclusion and Perspectives

- After 5 years of standard endocrine therapy, 2 additional years of Anastrozole are sufficient – there is no benefit of continuing/escalating endocrine treatment beyond 7 years.
- This is also true for those patients who are adherent to extended therapy (presumably a tolerability-“priviledged“ subgroup).
- Extension of Anastrozole treatment to 5 additional years leads to increased side effects including fractures, and should be avoided.
- In the future, translational research may identify molecular characteristics that indicate benefit of prolonged extended therapy.


Thank You!

Backup Slides

ABCSG-16 Inclusion criteria

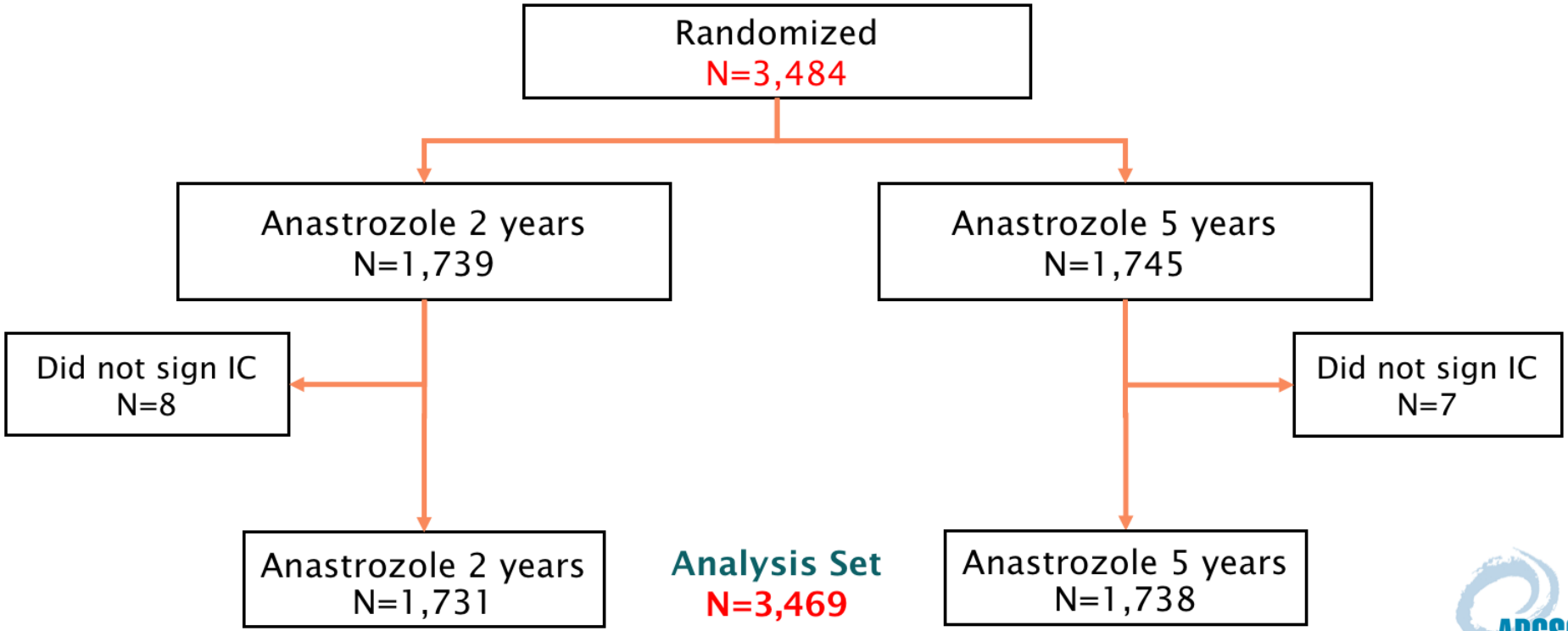
1. Postmenopausal patients with histologically verified invasive or minimal invasive breast cancer after radical local treatment, with or without prior chemotherapy and/or radiotherapy
2. Absence of distant metastases
3. No recurrence at the time of randomization
4. TNM-classification at the time of diagnosis: T1-3, N0 und N+, M0
5. Positive estrogen- and/or progesterone-receptor status before commencement of primary endocrine therapy
6. Endocrine therapy for 5 years, maximal deviation ± 12 months
7. Interruption of therapy (after initial therapy) 12 months at most
8. Informed Consent before randomization

Michael Gnant, MD, FACS

ABCSG-16 Exclusion criteria

1. Premenopausal patients or patients with indeterminable menopausal status at the time of randomization
2. Manifest secondary malignant tumor or status post secondary malignant tumor (exceptions)
3. General contra-indication or hypersensitivity towards anastrozole
4. in situ-carcinoma of any size with or without Mb. Paget mammary disease. T4-tumors
5. Unknown or negative hormone receptor status at the time of diagnosis or time of commencement of primary endocrine therapy
6. Known liver and/or renal insufficiency
7. Performance Index > 3 acc. to WHO
8. Regular intake of hormone preparations or Hormone Replacement Therapy > 6 months since primary operation of the mammary carcinoma
9. Serious concomitant diseases preventing the administration of adjuvant therapy and/or follow-up care according to the protocol
10. Insufficient willingness of the patient to cooperate
11. Legal incapacitation and/or other circumstances preventing the patient from fully grasping the nature, importance and implications of the clinical trial
12. Psychiatric disorder (ICD) at the time of entering the study (especially alcohol dependence)

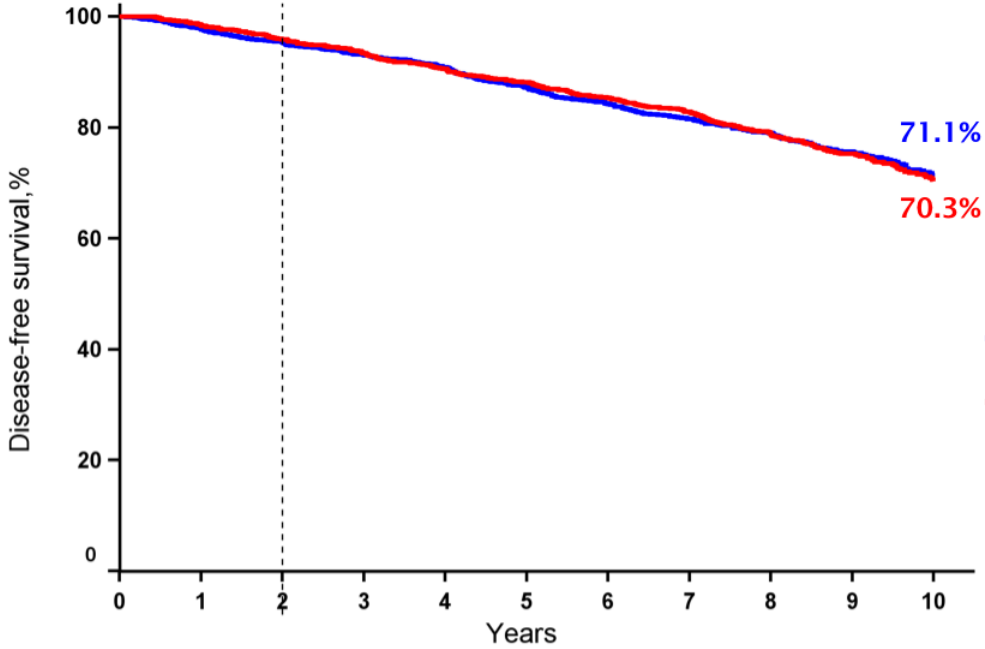
ABCSG-16 CONSORT



Michael Gnant, MD, FACS

ABCSG-16 Disease-Free Survival

Time from randomization to first DFS event



Patients at risk:

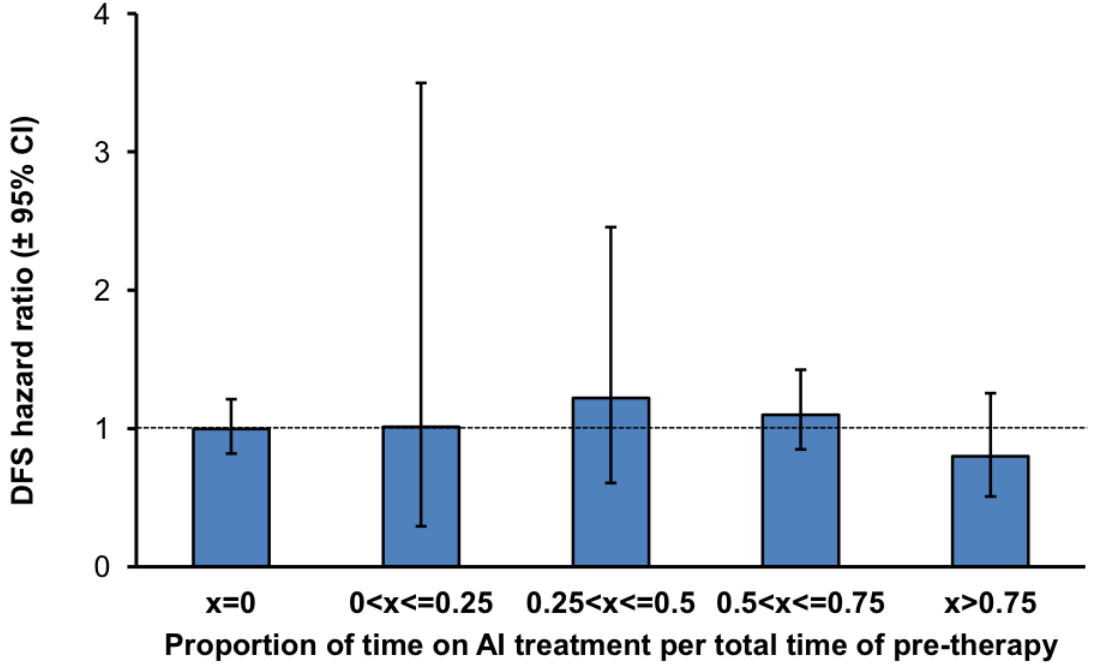
2 years	1731	1651	1601	1538	1477	1368	1206	990	741	540	214
5 years	1738	1667	1605	1551	1485	1399	1233	1026	779	554	209

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	378/1,731	1.007 (0.87, 1.16)	0.925
5 years	384/1,738		

ABCSG-16 DFS and Prior Endocrine Therapies

Proportion (x) of time on Tamoxifen and AI during first 5 years:

0 Tamoxifen only
1 AI only

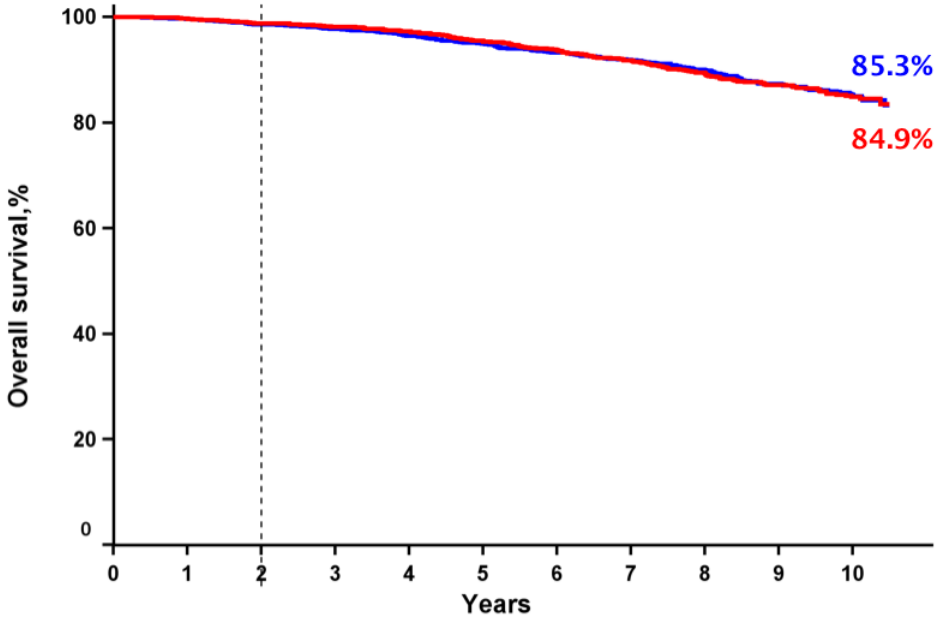


N	1714	71	231	1022	347
Events	399	10	32	231	77
p-value	0.966	0.986	0.576	0.469	0.331

Michael Gnant, MD, FACS

ABCSG-16 Secondary End Point: Overall Survival

Time from randomization to death from any cause



Patients at risk:

2 years	1731	1689	1661	1626	1594	1518	1352	1125	901	701	381
5 years	1738	1694	1659	1637	1606	1533	1362	1156	920	710	361

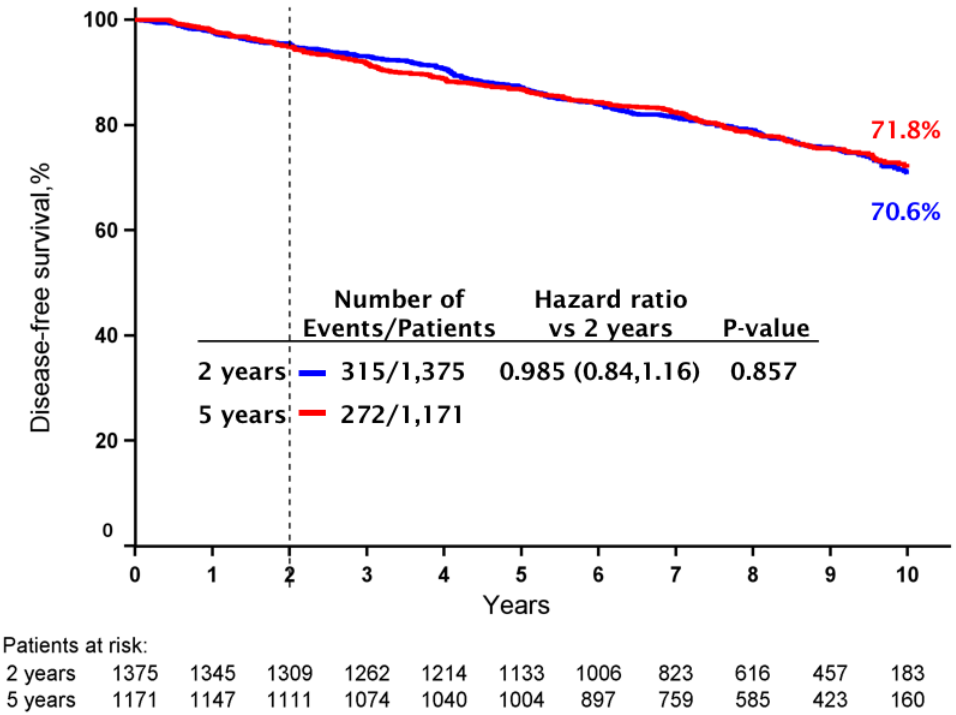
	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	192/1,731	1.007 (0.82,1.23)	0.947
5 years	194/1,738		

Michael Gnant, MD, FACS

ABCSG-16 Events

	All Events				First Events			
	from randomization		from 2 years after randomization		from randomization		from 2 years after randomization	
	2y	5y	2y	5y	2y	5y	2y	5y
Disease free survival event	522 (30.2)	534 (30.7)	433 (27.0)	459 (28.6)	378 (21.8)	384 (22.1)	301 (18.8)	315 (19.6)
Local recurrence	52 (3.0)	45 (2.6)	46 (2.9)	45 (2.8)	50 (2.9)	36 (2.1)	44 (2.7)	36 (2.2)
Distant recurrence	116 (6.7)	118 (6.8)	89 (5.6)	93 (5.8)	102 (5.9)	101 (5.8)	76 (4.7)	76 (4.7)
Contralateral breast cancer	41 (2.4)	45 (2.6)	35 (2.2)	43 (2.7)	37 (2.1)	34 (2.0)	31 (1.9)	32 (2.0)
Second primary cancer	121 (7.0)	132 (7.6)	94 (5.9)	104 (6.5)	117 (6.8)	130 (7.5)	90 (5.6)	102 (6.4)
Death	192 (11.1)	194 (11.2)	169 (10.6)	174 (10.8)	74 (4.3)	88 (5.1)	60 (3.7)	74 (4.6)
with prior recurrence	118 (6.8)	106 (6.1)	109 (6.8)	100 (6.2)				
without prior recurrence	74 (4.3)	88 (5.1)	60 (3.7)	74 (4.6)				

Exploratory: DFS in „Adherent“ Patients only



Time to contralateral breast cancer

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	35/1,375	1.071 (0.66,1.73)	0.781
5 years	32/1,171		

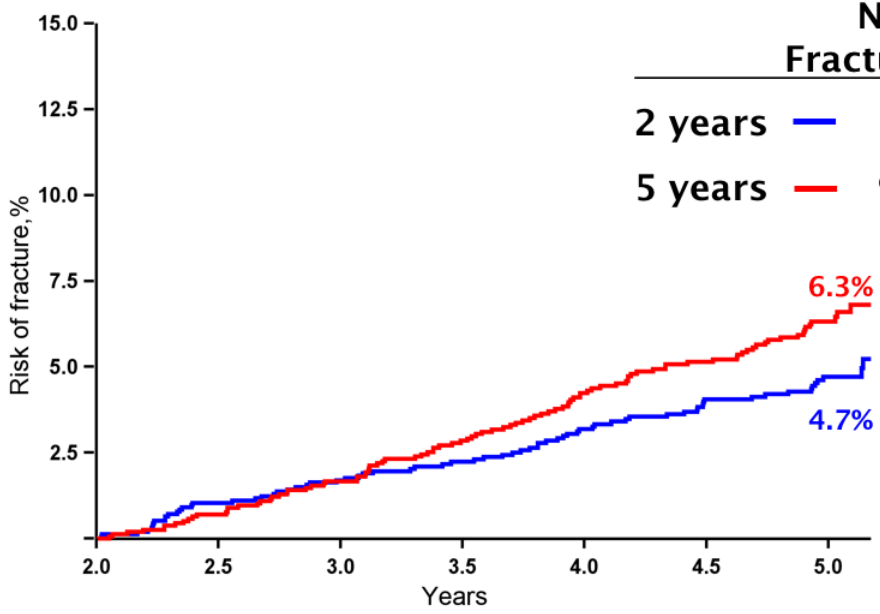
Time to second primary cancer

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	101/1,375	1.250 (0.95,1.64)	0.106
5 years	109/1,171		

DFS in Adherence Subgroup including patients with AEs

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	336/1,474	0.976 (0.84,1.14)	0.755
5 years	311/1,354		

ABCSG-16 Fractures



	Number of Fractures/Patients	Hazard ratio vs 2 years	P-value
2 years	71/1,556	1.353 (1.00,1.84)	0.053
5 years	98/1,571		

Patients at risk:

2 years	1556	1515	1480	1439	1386	1313	843
5 years	1571	1549	1514	1477	1416	1347	857