Letrozole vs. Tamoxifen as Adjuvant Endocrine Therapy for Postmenopausal Women with Receptor-Positive Breast Cancer

Update of the BIG 1-98 Primary Core Analysis (PCA)

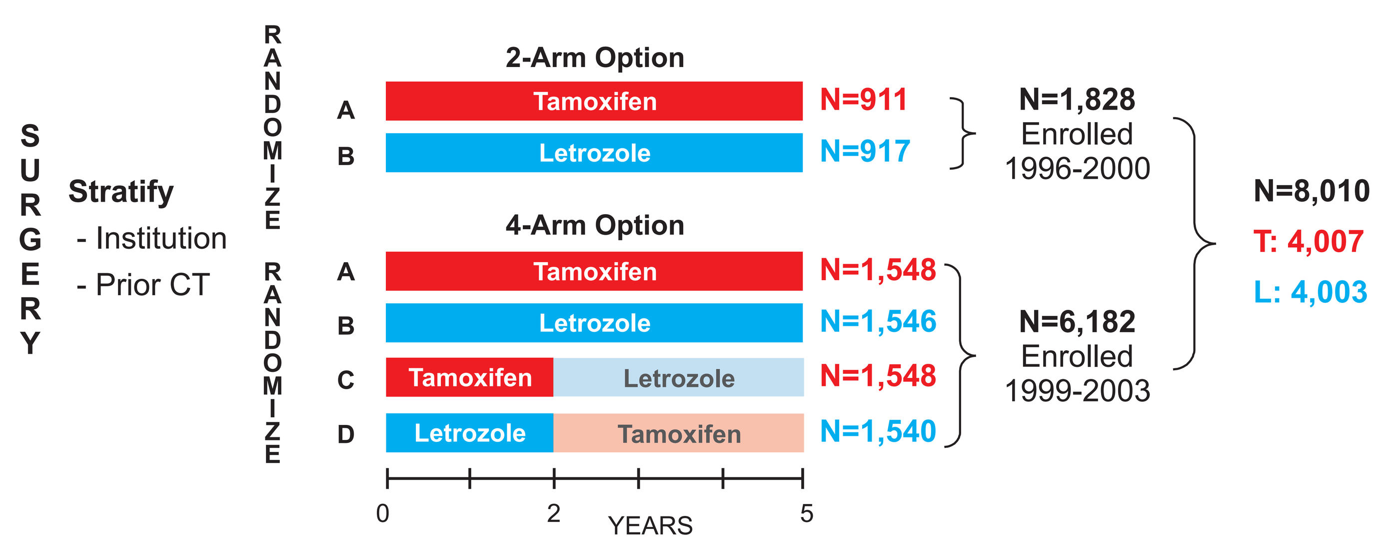
IBCSG

BIG BREASTINTERNATIONALGROUP

Beat Thürlimann for the BIG 1-98 Collaborative & International Breast Cancer Study Groups

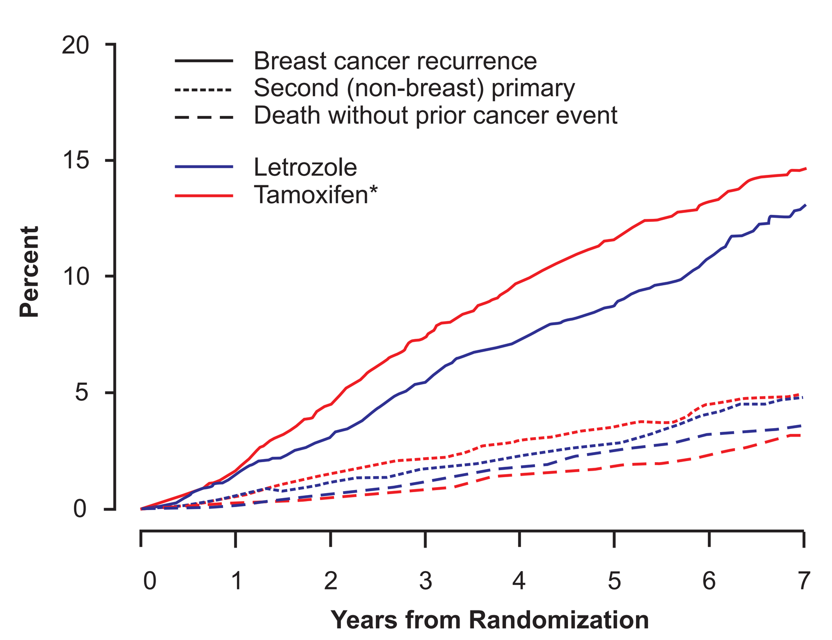
BIG 1-98 PCA Design and Status

- Protocol-defined 10-year update of the PCA
- In the PCA, follow-up for the two sequential treatment arms is censored at the time of the switch.
  - Maximizes the number of patients and events in comparison of Let vs. Tam at early follow-up.
  - Gives more weight to early events, thus potentially biasing this analysis at longer follow-up, especially among cohorts at lower risk for early recurrence.



- Median follow-up 60.5 months (2-arm: 99.1 mos., 4-arm monotherapy 70.3 mos., 4-arm switching 25.1 mos.).
- All patients are off protocol treatment.

Cumulative Incidence of DFS Events (ITT)

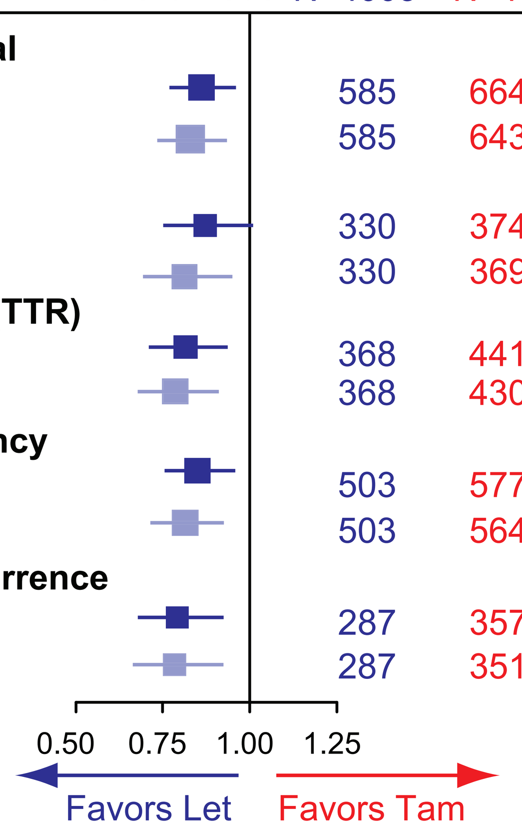


*619 patients received letrozole after the tamoxifen-alone arm was unblinded

Endpoints: ITT and Censored* Results

*Follow-up of the 619 pts who selectively crossed over to receive Let are censored at the time of selective crossover

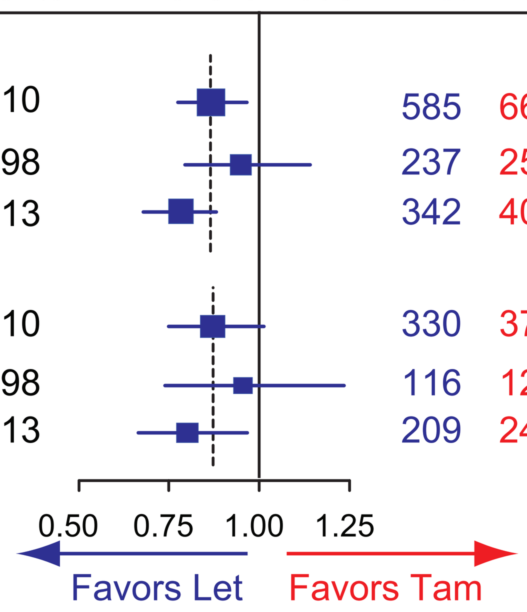
Endpoint	Hazard Ratio	No. of Events Let N=4003	No. of Events Tam* N=4007	HR (95% CI)	P
Disease-Free Survival					
ITT		585	664	0.86 (0.77–0.96)	0.008
Censored		585	643	0.83 (0.74–0.93)	
Overall Survival					
ITT		330	374	0.87 (0.75–1.01)	0.07
Censored		330	369	0.81 (0.70–0.94)	
Time to Recurrence (TTR)					
ITT		368	441	0.82 (0.71–0.94)	0.004
Censored		368	430	0.79 (0.68–0.90)	
DFS no 2nd Malignancy					
ITT		503	577	0.85 (0.75–0.96)	0.008
Censored		503	564	0.81 (0.72–0.92)	
Time to Distant Recurrence					
ITT		287	357	0.79 (0.68–0.92)	0.003
Censored		287	351	0.78 (0.67–0.92)	



The control of distant recurrence events seen at 26 months median follow-up (HR .73) (*N Engl J Med* 353:2747-2757, 2005) appears to have predicted the overall survival advantage suggested now (at 60.5 months median follow-up), regardless of selective crossover.

DFS and OS by Nodal Status (ITT)

	No. of Patients	Hazard Ratio	No. of Events Let	No. of Events Tam*	HR (95% CI)	P
Disease-Free Survival						
All patients	8010		585	664	0.86 (0.77–0.96)	0.008
Node negative	4598		237	252	0.95 (0.79–1.13)	
Node positive	3313		342	404	0.79 (0.68–0.91)	
Overall Survival						
All patients	8010		330	374	0.87 (0.75–1.01)	0.07
Node negative	4598		116	123	0.95 (0.74–1.23)	
Node positive	3313		209	247	0.81 (0.67–0.97)	



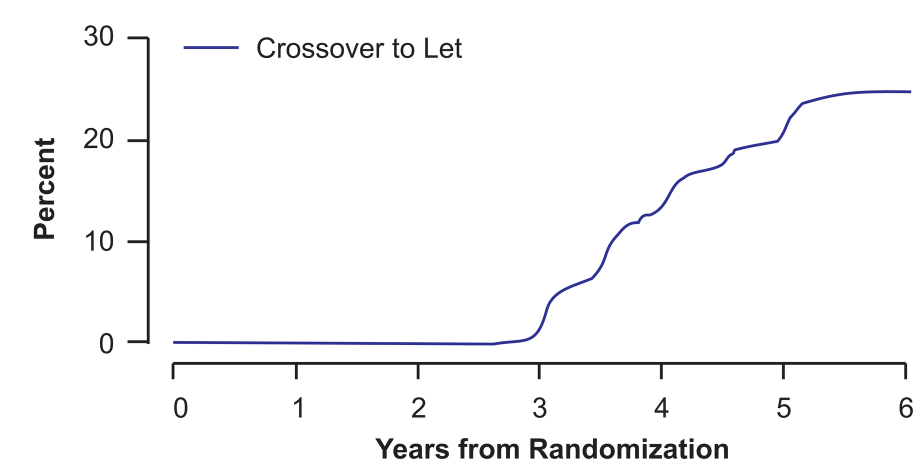
Interaction of nodal status and treatment not significant (P = 0.11, DFS), (P = 0.28, OS)

*619 patients on the Tam-alone arm crossed over to Let.

Selective Crossover in Tamoxifen-alone Arm

- In 2005, the Data and Safety Monitoring Committee recommended informing patients randomly assigned to receive Tam-alone (Arm A) of the inferiority of Tam in this and other AI trials.
- The BIG 1-98 Steering Committee amended the protocol to offer Let to patients assigned Tam-alone; the other 3 treatment arms (B, C, and D) remain blinded.
- 619 of the 2,459 (25.2%) patients on Tam-alone arm selectively crossed over to Let
  - Most (612 pts) from the 4-arm option
  - Most patients who crossed over did so during years 3-5 (see figure below)
  - Median duration of Let after selective crossover was 18 months
- Patients who crossed over to Let were more likely to have node-positive disease (47% vs. 29%) and tumors > 2 cm (35% vs. 26%) compared with those who remained on Tam.

Timing of Selective Crossover from Tam to Let



Adverse Events

The AEs listed below were collected every 6 months via check boxes on the CRF (exception arthralgia and myalgia were write-ins) and graded according to CTC version 2.

	Grade 1-5				Grade 3-5			
	Let N=3975		Tam* N=3988		Let N=3975		Tam* N=3988	
	n	(%)	n	(%)	n	(%)	n	(%)
CVA/TIA	57	1.4	59	1.5	57	1.4	59	1.5
Thromboembolic event	81	2.0	164	4.1	40	1.0	96	2.4
Cardiac event	221	5.6	215	5.4	110	2.8	69	1.7
Ischemic heart disease	84	2.1	66	1.7	55	1.4	34	0.9
Cardiac failure	40	1.0	30	0.8	26	0.7	16	0.4
Other cardiovascular event (excluding hyper/hypotension)	34	0.9	18	0.5	3	<0.1	0	0.0
Hypercholesterolemia (mostly non-fasting)	1937	48.7	962	24.1	18	0.5	8	0.2
Vaginal bleeding	157	3.9	320	8.0	3	<0.1	6	0.2
Nausea	389	9.8	414	10.4	6	0.2	9	0.2
Vomiting	123	3.1	117	2.9	6	0.2	8	0.2
Hot flushes	1399	35.2	1575	39.5	grades 3-5 undefined			
Night sweating	586	14.7	673	16.9	grades 3-5 undefined			
Bone fractures	299	7.5	226	5.7	98	2.5	56	1.4
Arthralgia	870	21.9	657	16.5	87	2.2	56	1.4
Myalgia	312	7.8	294	7.4	29	0.7	22	0.6

Grade	0	1	2	3	4
Hypercholesterolemia	WNL	>ULN-300 mg/dL >ULN-7.75 mmol/L	>300-400 mg/dL >7.75-10.34 mmol/L	>400-500 mg/dL >10.34-12.92 mmol/L	>500 mg/dL >12.92 mmol/L

Sites of First Failure (DFS events)

	Let n	Let (%)	Tam* n	Tam* (%)
Failures (events)	585	14.6	664	16.6
Local	35	0.9	49	1.2
Contra breast	35	0.9	45	1.1
Regional	22	0.5	18	0.4
Distant soft tissue	16	0.4	25	0.6
Bone	122	3.0	132	3.3
Viscera	130	3.2	159	4.0
2nd (non-breast) malignancy	123	3.1	142	3.5
Death w/o prior cancer event	99	2.5	90	2.2
Unknown	3	<0.1	4	<0.1
Total patients	4003		4007	

Second Malignancies

	Let (n)	Tam* (n)
2nd (non-breast) malignancy	123	142
Colon	17	22
Endometrial	8	23
Lung	11	16
Melanoma	13	3
Renal	4	14
Ovarian	9	10
Other	58	55
Total patients	4003	4007

*619 patients on the Tam-alone arm crossed over to Let.

Deaths

	Let (n)	Tam* (n)
Deaths	330	374
Death after cancer event	231	284
Death w/o prior cancer event	99	90
Cerebrovascular	8	8
Thromboembolic	5	4
MI	7	3
CHF	7	6
Other cardiovascular	4	6
Sepsis	8	6
Other/unknown	60	57
Total patients	4003	4007

Conclusions

- This update of the BIG 1-98 PCA supports findings of the monotherapy analysis at 76 months median follow-up (*Cancer Res* 2009;69[Suppl.2]:13).
- This update suggests an overall survival benefit for Let compared to Tam and confirms that Let significantly prolongs DFS and time to distant recurrence compared with Tam despite the selective crossover to Let of 619 patients assigned Tam-alone.
- In prospective subgroup analyses according to nodal status, Let was better than Tam for all endpoints—significantly in the node-positive cohort.
- At this point in follow-up, all patients have completed study treatment, and adverse events are consistent with known safety profiles of aromatase inhibitors and Tam.

Steering Committee

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