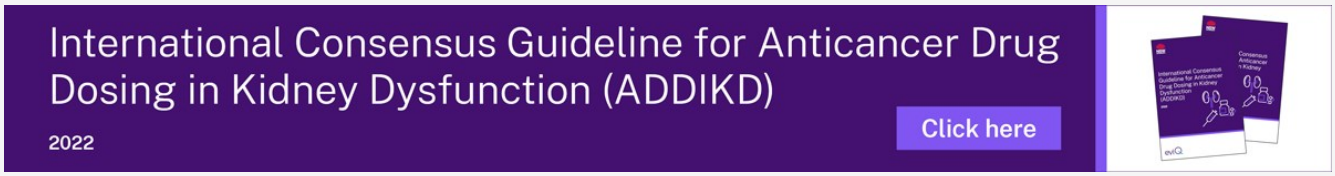
Breast adjuvant letrozole

ID: 30 v.5 **Endorsed** Essential Medicine List

Check for clinical trials in this patient group. Link to Australian Clinical Trials website

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Treatment schedule - Overview

Drug	Dose	Route
Letrozole	2.5 mg ONCE a day	PO

Continuous daily to complete a total of 5 to 10 years of adjuvant endocrine therapy

Drug status: Letrozole is a PBS restricted benefit

Cost: ~ $30 per month

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Continuous treatment		
Letrozole	2.5 mg (PO)	ONCE a day

Continuous daily to complete a total of 5 to 10 years of adjuvant endocrine therapy

Indications and patient population

- Hormone receptor-positive invasive breast cancer in post-menopausal women, for a total of 5 to 10 years of adjuvant endocrine therapy.[1, 2, 3, 4]

Clinical information

Emetogenicity MINIMAL	No antiemetics should be routinely administered before treatment in patients without a history of nausea and vomiting. If patients experience nausea and/or vomiting, consider using the low antiemetic prophylaxis regimen.
Bone mineral density (BMD)	Baseline BMD and repeat as clinically indicated. Lifestyle modification including regular exercise, particularly weight bearing exercises should be encouraged.
Supplements	Consider daily oral supplements of at least calcium 500 mg and vitamin D 400 International Units for the duration of the therapy.
Oestrogen preparations	Oestrogen preparations should be avoided due to insufficient data on safety as systemic absorption of oestrogen may negate the effect of aromatase inhibitors. Minimal use of topical oestrogen therapies for vulvo-vaginal complaints may be considered.
Blood tests	LFTs, lipid studies, calcium and vitamin D at baseline and repeat as clinically indicated.

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

Note: all dose reductions are calculated as a percentage of the starting dose.

Renal impairment
No dose modifications necessary

Hepatic impairment	
Hepatic dysfunction	
Severe	In patients with cirrhosis or severe hepatic impairment reduce the dose by 50% (2.5 mg every other day)

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. References & Disclaimer

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Letrozole		
	Interaction	**Clinical management**
Tamoxifen	Reduced letrozole plasma levels occur when coadministered with tamoxifen	Avoid combination
Oestrogen containing therapies	Negate the pharmacological action of letrozole	Combination contraindicated (minimal use of topical oestrogen therapy for vulvo-vaginal complaints may be considered)
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of letrozole possible due to reduced clearance	Caution advised if combination used - monitor for letrozole toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of letrozole possible due to increased clearance	Caution advised if combination used - monitor for decreased clinical response to letrozole

Administration

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.

Administration

This is a continuous oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

Letrozole

- administer orally ONCE a day
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food
- if nausea develops advise patient to take at night.

Note: missed doses should not be replaced, if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Discharge Information

Letrozole tablets

- Letrozole tablets with written instructions on how to take them.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Nausea and vomiting	
Headache	

Early (onset days to weeks)	
Hot flushes	
Hyperlipidaemia and hypercholesterolaemia	Abnormally elevated levels of lipids and cholesterol in the blood.
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.

Late (onset weeks to months)	
Arthralgia and myalgia	Generalised joint pain or and/or stiffness and muscle aches, often worse upon waking or after long periods of inactivity. Can improve with movement. May be mild or severe, intermittent or constant and accompanied by inflammation. Read more about arthralgia and myalgia
Vaginal atrophy	Read more about vaginal dryness

Delayed (onset months to years)	
Osteoporosis	

Evidence - Initial treatment

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (BIG 1-98) involving 8010 patients comparing five years of treatment with letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole in post-menopausal women with hormone-receptor-positive breast cancer.[5]

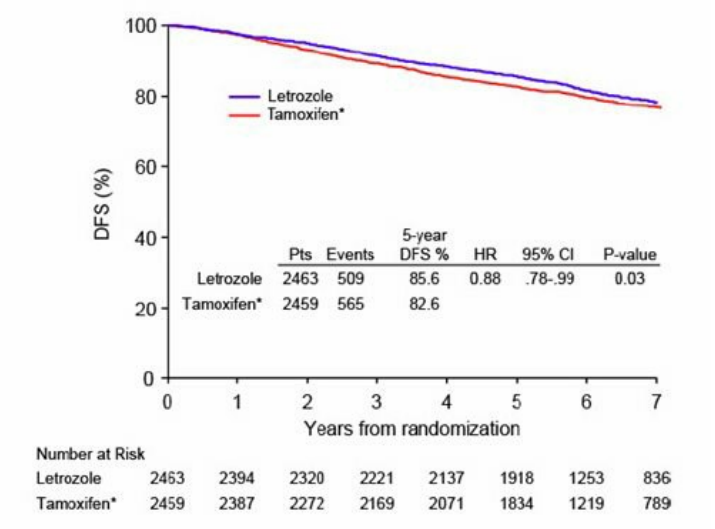
Between March 1998 and March 2000, 1835 women were randomised to monotherapy with either letrozole 2.5 mg daily or tamoxifen 20 mg daily. From April 1999 to May 2003, an additional 6193 women were randomly assigned to one of the four groups.[5]

The primary end point was disease-free survival (DFS) and secondary end points were overall survival (OS), the occurrence of a second non-breast cancer, or death from any cause, safety, time to recurrence and time to distant recurrence.[5]

Efficacy

After a median follow-up of 71 months after randomization, DFS was not significantly improved with either sequential treatment as compared with letrozole alone (HR for tamoxifen followed by letrozole=1.05; 99% CI 0.84-1.32; HR for letrozole followed by tamoxifen=0.96; 99% CI 0.76-1.21). There were more early relapses among women who were assigned to tamoxifen followed by letrozole than among those who were assigned to letrozole alone. The updated analysis of monotherapy (76 month follow-up) also showed that there was a non-significant difference in OS between women assigned to treatment with letrozole and those assigned to treatment with tamoxifen (HR for letrozole=0.87; 95% CI 0.75-1.02; p=0.08).[6]

Kaplan-Meier analysis of DFS from the time of randomisation for the two monotherapy treatment groups (includes 619 patients who crossed over to letrozole)[6]



Cumulative incidence of the recurrence of breast cancer[6]

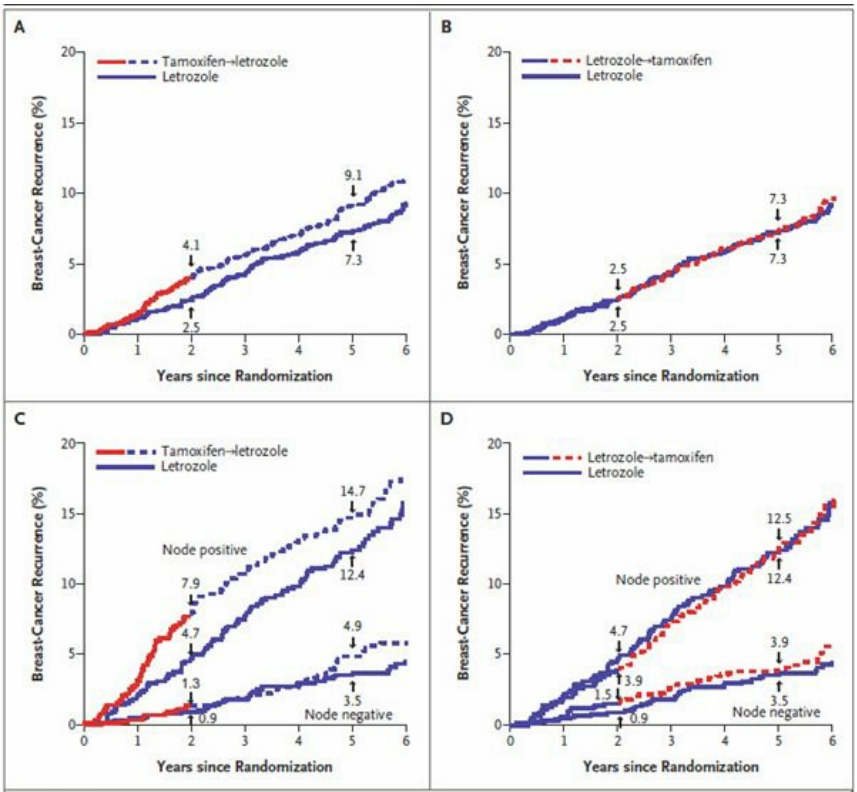


Figure 3. Cumulative Incidence of the Recurrence of Breast Cancer.

Results are shown for letrozole monotherapy as compared with tamoxifen followed by letrozole (Panels A and C) and for letrozole monotherapy as compared with letrozole followed by tamoxifen (Panels B and D). Both overall results (Panels A and B) and results according to nodal status (Panels C and D) are shown. The results are from a competing-risk analysis in which second, nonbreast cancers and deaths without a previous cancer event were considered as competing risks. The numbers of women with a first recurrence of breast cancer were as follows for the group assigned to letrozole monotherapy, the group assigned to tamoxifen followed by letrozole, and the group assigned to letrozole followed by tamoxifen, respectively: local recurrence, 12, 14, and 17 women; cancer in the contralateral breast, 18, 19, and 16; regional recurrence, 7, 3, and 6; distant recurrence, 112, 130, and 105; and recurrence at an unknown site, 0, 3, and 0. Second, nonbreast cancers (64, 65, and 59 in the three groups, respectively) and deaths without a previous cancer event (35, 25, and 33, respectively) were also recorded as first primary-endpoint events.

Toxicity

Toxicities were primarily grade 1 or 2 with hot flushes, arthritis, arthralgia and myalgia more common in the letrozole group.

Adverse events[6] (all grades)	Tamoxifen % (n=1540)	Letrozole % (n=1534)	Tamoxifen -> Letrozole % (n=1540)	Letrozole -> Tamoxifen % (n=1526)	p-value
CVA or TIA	2	1	2	2	0.74

Adverse events[6] (all grades)	Tamoxifen % (n=1540)	Letrozole % (n=1534)	Tamoxifen -> Letrozole % (n=1540)	Letrozole -> Tamoxifen % (n=1526)	p-value
Thromboembolic events	5	2	5	4	<0.001
Cardiac events*	6	7	7	6	0.45
Hypercholesterolaemia	30	53	41	44.5	<0.001
Vaginal bleeding	10	5	7.5	6	<0.001
Hot flushes	43	38	44	42	0.003
Fractures	7	10	9	7.5	0.02
Arthralgias and myalgias	30	35	32	33	0.05

CVA: cerebrovascular accident; TIA: transient ischaemic attack
** cardiac events included ischaemic heart disease, arrhythmia, cardiac failure, cardiopathy, valvular disease, changes in the electrocardiogram, sudden cardiac death, and cardiac event not otherwise specified*

Cardiovascular, cerebrovascular and thromboembolic events for aromatase inhibitors compared to tamoxifen[7]

Trial	Trmt arms	Cardiovascular	Cerebrovascular	Thromboembolic
ATAC[4,33,76]	A vs. T	Ischemic cardiovascular disease: 4.1% vs. 3.4%, $p = 0.1$ Cardiovascular deaths: 2% vs. 1%, p = NR	Ischemic cerebrovascular events: 2.0% vs. 2.8%, $p = 0.03$ Cerebrovascular deaths: <1% vs. 1%, p = NR	Venous thromboembolic events: 2.8% vs. 4.5%, $p = 0.0004$, OR 0.61, 95% CI 0.46 to 0.80 Deep venous thromboembolic events: 1.6% vs. 2.4%, $p = 0.02$
BIG 1–98[6]	L vs. T	All cardiac events: 5.5% vs. 5.0%, $p = 0.48$ Ischemic heart disease: 2.2% vs. 1.7%, $p = 0.21$ Cardiac failure: 1.0% vs. 0.6%, $p = 0.14$ Other cardiovascular events: 0.8% vs. 0.2%, $p = 0.014$	Cerebrovascular accident or TIA: 1.4% vs. 1.4%, $p = 0.90$	Thromboembolic events: 2.0% vs. 3.8%, $p < 0.001$
IES[8]	T → E vs. T	Cardiovascular events: 20.8% vs. 18.9%, $p = 0.09$ Ischemic cardiovascular disease: 9.9% vs. 8.6%, $p = 0.12$	NR	Thromboembolic events: 1.9% vs. 3.1%, $p = 0.01$
ITA[9]	T → A vs. T	Cardiovascular diseases: 7.9% vs. 9.3%, $p = 0.04$	NR	NR
ABCSG-8/ARNO-95[10]	T → A vs. T	Myocardial infarction: <1% vs. <1%, $p = 1.0$	NR	Embolism: <1% vs. <1%, $p = 0.064$ Thromboses: <1% vs. <1%, $p = 0.034$[a]
MA.17[11]	T → L vs. T → placebo	Cardiovascular disease: 5.8% vs. 5.6%, $p = 0.76$ Myocardial infarction: 0.3% vs. 0.4% New or worsening angina: 1.2% vs. 0.9% Angina requiring PTCA: 0.1% vs. 0.3% Angina requiring CABG: 0.2% vs. 0.5%	Stroke/TIA: 0.7% vs. 0.6%	Thromboembolic event: 0.4% vs. 0.2%

Note: Significant differences are shown in bold face.
Abbreviations: →, followed by; A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimadex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; CABG, coronary artery bypass graft; CI, confidence interval; E, exemestane; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; NR, not reported; OR, odds ratio; PTCA, Percutaneous Transluminal Coronary Angioplasty; T, tamoxifen; TIA, Transient Ischemic Attack; Trmt, treatment; vs, versus.
[a] Favours anastrozole.

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Evidence - Late switch

The evidence supporting prolonged endocrine therapy is provided by a phase III multicentre, international, randomised trial (MA.17) involving 5187 patients comparing letrozole with placebo in post menopausal women with early stage breast cancer within 3 months of completion of 5 years of tamoxifen therapy.[8]

Between August 1998 and September 2002, 2593 patients were randomised to receive letrozole 2.5 mg daily and 2594 patients were randomised to receive placebo daily for 5 years.

The primary end point was disease-free survival (DFS) and secondary end points were overall survival (OS), quality of life, and long-term safety.[8]

The trial was unblinded in 2003 and crossover was allowed after the first interim analysis demonstrated a statistically significant effect on DFS and a trend toward a survival advantage in the letrozole group. 1579 women chose to switch to letrozole (PLAC-LET group) and 804 remained in the placebo group (PLAC-PLAC group). Patients in the PLAC-LET group were younger, had a better performance status, and were more likely to have had node-positive disease, axillary dissection, and adjuvant chemotherapy than those in the PLAC-PLAC group.[9] In the PLAC-LET group the median time from the end of tamoxifen to the start of letrozole was 2.8 years.

Efficacy

Original randomisation: letrozole or placebo within 3 months of completing tamoxifen

After a median follow-up of 30 months, women in the letrozole arm had significantly better DFS (HR=0.58, 95% CI 0.45-0.76, p<0.001) and distant DFS (HR=0.60, 95% CI 0.43-0.84, p=0.002) than women in the placebo arm.[10]

The 4-year DFS for patients receiving letrozole was 94.4% and for patients receiving placebo was 89.8%. OS was the same in both arms (HR=0.82, 95% CI 0.57-1.19, p=0.3), however in the node positive cohort, OS was significantly improved with letrozole (HR=0.61, 95% CI 0.38-0.98, p=0.04).[10]

Kaplan-Meier curves for (A) DFS and (B) OS[10]

(A)

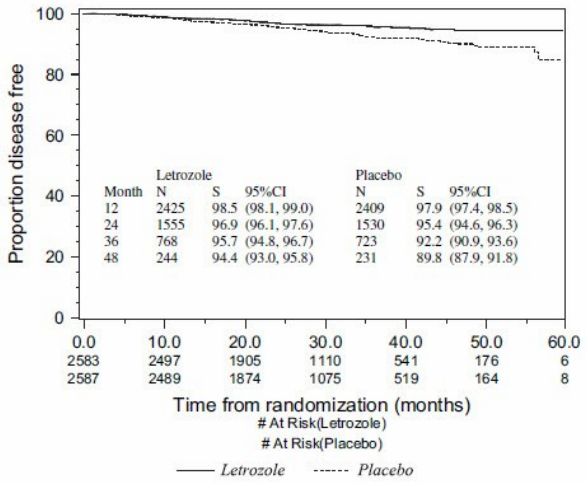


Fig. 2. Kaplan–Meier curves for disease-free survival. An event is defined as recurrence of breast cancer (breast, chest wall, regional nodes, or distant metastasis) or a contralateral breast cancer (whichever occurs first). N = number at risk; S = survival percent, with 95% confidence intervals in parentheses.

(B)

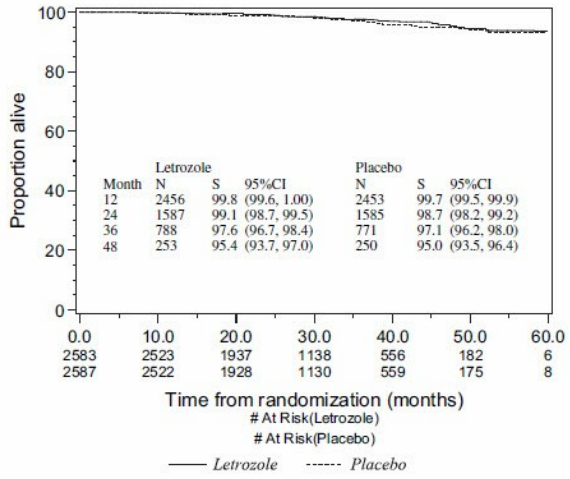


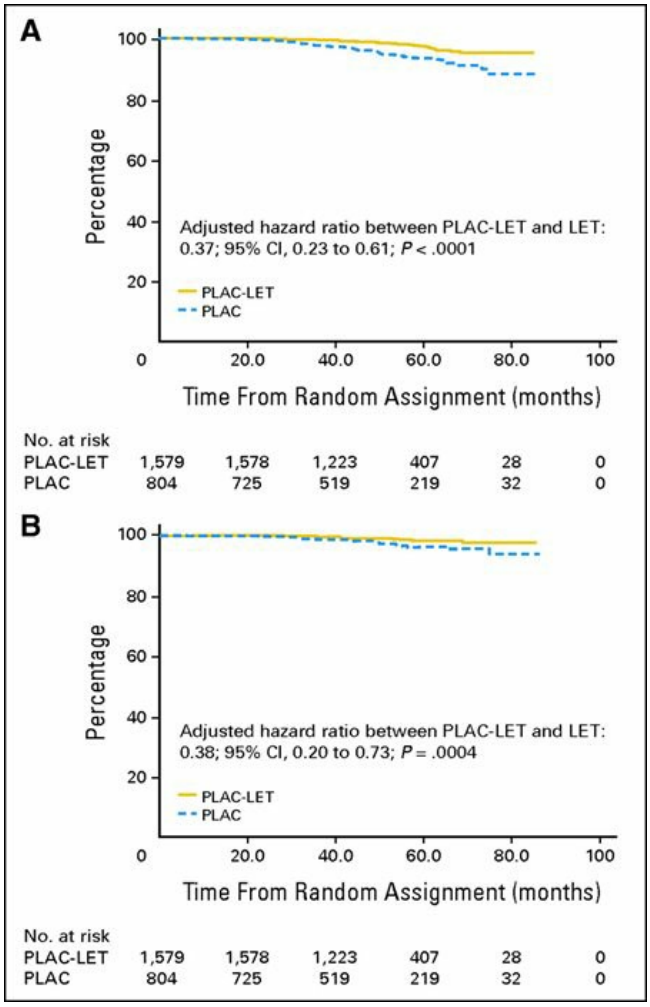
Fig. 6. Kaplan–Meier curves for overall survival. An event is defined as death from any cause. N = number at risk; S = survival percent, with 95% confidence intervals in parentheses.

Late switch to letrozole (median 2.8 years after completing tamoxifen)

At median follow-up of 5.3 years from initial randomisation on MA.17, DFS (adjusted HR=0.37; 95% CI 0.23-0.61; p<0.0001) and distant DFS (HR=0.39; 95% CI 0.20-0.74; p=0.004) were superior in the PLAC-LET group compared to the PLAC-PLAC group.[9]

(These results should be viewed in the context of an adjusted, retrospective multivariate analysis where the intervention was self-selected; and not as a prospective, randomised trial. As a consequence, the effect on OS cannot be addressed in these patients.)

Kaplan-Meier curves for (A) DFS and (B) distant DFS[9]



Toxicity

Hot flushes, anorexia, arthralgia, myalgia, and alopecia were all statistically significantly more common in those receiving letrozole, and vaginal bleeding was statistically significantly more common in those receiving placebo. More patients receiving letrozole had a fracture, a new diagnosis of osteoporosis, or cardiovascular disease on study, but only the incidence of self-reported new osteoporosis was statistically significantly different between the two arms. Diagnoses of new osteoporosis were reported by 364 patients, 209 (8.1%) of those receiving letrozole and 155 (6.0%) of those receiving placebo (p=0.003), with median times to occurrence of 0.70 years for those receiving letrozole and 0.52 years for those receiving placebo.[10]

When toxicity was assessed by age there was no difference between letrozole- and placebo- treated patients aged ≥ 70 years.[11]

Toxicity[11]

Table 4. Percent of Patients With Acute Toxicities (grade 1 to 4) by Age and Treatment

	Patient Age (years)								
	< 60			60-69			≥ 70		
Toxicity	Letrozole	Placebo	*P*	Letrozole	Placebo	*P*	Letrozole	Placebo	*P*
No. of patients	1,063	1,089		834	860		681	642	
Edema	20	18	.25	22	19	.14	25	27	.31
Hypertension	3	4	.28	7	6	.38	6	6	.86
Hot flushes	68	66	.18	59	52	.003	40	35	.09
Fatigue	35	36	.50	39	37	.49	45	44	.84
Sweating	37	35	.29	30	28	.61	20	20	.95
Anorexia	4	2	.14	6	5	.63	9	6	.11
Constipation	13	14	.64	13	15	.35	16	16	.84
Diarrhea	6	5	.32	7	7	.75	8	10	.19
Nausea	11	12	.51	14	11	.06	10	13	.10
Vaginal bleeding	8	12	.007	4	6	.08	4	3	.47
Infection w/o neutropenia	5	4	.45	5	4	.47	5	5	.91
Arthritis	4	4	.44	7	6	.40	9	7	.15
High cholesterol*	16	16	.63	17	18	.73	15	14	.55
Dizziness	16	16	.85	18	14	.07	21	23	.40
Insomnia	7	7	.51	7	4	.014	4	4	.86
Depression	6	5	.61	5	5	.80	5	5	.62
Headache	30	30	.93	28	28	.86	22	19	.11
Arthralgia	27	19	< .001	26	20	.005	21	24	.24
Myalgia	15	12	.03	15	12	.09	14	12	.26
Bone pain	5	4	.41	6	7	.27	5	6	.70
Dyspnea	4	5	.37	6	5	.33	9	10	.73
Alopecia	5	4	.24	5	3	.03	4	3	.21
Vaginal dryness	8	8	.93	5	4	.16	2	1	.15

*Change from normal to high from χ^2 test for the comparison in the incidence of toxicity between letrozole and placebo.

Cardiovascular, cerebrovascular and thromboembolic events for aromatase inhibitors compared to tamoxifen[7]

Trial	Trmt arms	Cardiovascular	Cerebrovascular	Thromboembolic
ATAC[4,33,76]	A vs. T	**Ischemic cardiovascular disease: 4.1% vs. 3.4%, $p = 0.1$**	**Ischemic cerebrovascular events: 2.0% vs. 2.8%, $p = 0.03$**	**Venous thromboembolic events: 2.8% vs. 4.5%, $p = 0.0004$, OR 0.61, 95% CI 0.46 to 0.80**
		Cardiovascular deaths: 2% vs. 1%, p = NR	**Cerebrovascular deaths: <1% vs. 1%, p = NR**	**Deep venous thromboembolic events: 1.6% vs. 2.4%, $p = 0.02$**
BIG 1–98[6]	L vs. T	**All cardiac events: 5.5% vs. 5.0%, $p = 0.48$** **Ischemic heart disease: 2.2% vs. 1.7%, $p = 0.21$** **Cardiac failure: 1.0% vs. 0.6%, $p = 0.14$** **Other cardiovascular events: 0.8% vs. 0.2%, $p = 0.014$**	**Cerebrovascular accident or TIA: 1.4% vs. 1.4%, $p = 0.90$**	**Thromboembolic events: 2.0% vs. 3.8%, $p < 0.001$**
IES[8]	T → E vs. T	**Cardiovascular events: 20.8% vs. 18.9%, $p = 0.09$** **Ischemic cardiovascular disease: 9.9% vs. 8.6%, $p = 0.12$**	**NR**	**Thromboembolic events: 1.9% vs. 3.1%, $p = 0.01$**
ITA[9]	T → A vs. T	**Cardiovascular diseases: 7.9% vs. 9.3%, $p = 0.04$**	**NR**	**NR**
ABCSG-8/ARNO-95[10]	T → A vs. T	**Myocardial infarction: <1% vs. <1%, $p = 1.0$**	**NR**	**Embolism: <1% vs. <1%, $p = 0.064$** **Thromboses: <1% vs. <1%, $p = 0.034$[a]**
MA.17[11]	T → L vs. T → placebo	**Cardiovascular disease: 5.8% vs. 5.6%, $p = 0.76$** **Myocardial infarction: 0.3% vs. 0.4%** **New or worsening angina: 1.2% vs. 0.9%** **Angina requiring PTCA: 0.1% vs. 0.3%** **Angina requiring CABG: 0.2% vs. 0.5%**	**Stroke/TIA: 0.7% vs. 0.6%**	**Thromboembolic event: 0.4% vs. 0.2%**

Note: Significant differences are shown in bold face.
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[a] Favours anastrozole.

Evidence - Extended adjuvant therapy

The evidence regarding extended adjuvant therapy with letrozole 2.5 mg daily is provided by three trials- GIM 4, NSABP B-42, and SOLE.[2, 3, 4]

GIM 4[2]

This trial compared the addition of 2-3 vs 5 years of letrozole in 2056 postmenopausal women with hormone receptor positive breast cancer who had already received 5 years of initial adjuvant endocrine therapy with tamoxifen. The primary end point was invasive disease free survival (IDFS) and secondary end points were overall survival (OS) and safety.

NSABP B-42[3]

This trial compared the addition of 5 years of letrozole vs placebo in 3966 postmenopausal women with hormone receptor positive breast cancer who had already received 5 years of initial adjuvant endocrine therapy with an aromatase inhibitor, or tamoxifen followed by an aromatase inhibitor. The primary end point was disease free survival (DFS) and secondary end points included OS, breast cancer-free interval, distant recurrence, incidence of osteoporotic fractures, and incidence of arterial thrombotic events.

SOLE[4]

This trial compared the addition of 5 years of continuous letrozole vs intermittent letrozole (daily for 9 months followed by a 3 month break in years 1 to 4 then daily in year 5) in 4851 postmenopausal women with hormone receptor positive breast cancer who had already received 4 to 6 years of initial adjuvant endocrine therapy. The primary end point was DFS and secondary end points included breast cancer-free interval, distant recurrence-free interval, OS, and adverse events.

A review by van Hellemond et al suggests considering extended adjuvant endocrine therapy with aromatase inhibitors for a total of 5 to 10 years treatment only in women with high-risk early breast cancer who tolerate treatment well.[1]

Efficacy

GIM 4[2]

After a median follow up of 11.7 years, the 12 year DFS was 62% (95% CI, 57 to 66) in the 2 to 3 year extended treatment group vs 67% (95% CI, 62 to 71) in the 5 year extended group (HR = 0.78, 95% CI, 0.65 to 0.93; p=0.0064). The 12 year OS was 84% (95% CI, 82 to 87) vs 88% (95% CI, 86 to 90) respectively.

NSABP B-42[3]

After a median follow up of 6.9 years, the 7 year DFS was 81.3% (95% CI, 79.3 to 83.1) in the placebo group vs 84.7% (95% CI, 82.9 to 86.4) in the letrozole group (HR = 0.85, 95% CI, 0.73 to 0.999; p=0.048). The 7 year OS was 92.3% (95% CI, 90.9 to 93.5) vs 91.8% (95% CI, 90.4 to 93.0) respectively.

SOLE[4]

After a median follow up of 84 months, the 7 year DFS was 81.4% (95% CI, 79 to 83) in the intermittent treatment group vs 81.5% (95% CI, 79.8 to 83.1) in the continuous treatment group (HR = 1.03, 95% CI, 0.91 to 1.17). There was no statistically significant difference between either group for any of the secondary end points.

Toxicity

Adverse events[2]

	2–3-year letrozole group (n=983)			5-year letrozole group (n=977)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Arthralgia	263 (26·8%)	21 (2·1%)	1 (0·1%)	311 (31·8%)	27 (2·8%)	2 (0·2%)
Myalgia	65 (6·6%)	7 (0·7%)	0	95 (9·7%)	9 (0·9%)	0
Hot flashes	119 (12·5%)	NA	NA	127 (13·4%)	NA	NA
Alopecia	31 (3·1%)	NA	NA	35 (3·6%)	NA	NA
Hypercholesterolaemia	31 (3·2%)	1 (0·1%)	0	22 (2·3%)	0	0
Hypertension	7 (0·7%)	0	0	18 (1·8%)	1 (0·1%)	0
Cardiovascular event*	0	1 (0·1%)	0	5 (0·5%)	1 (0·1%)	0
Thrombosis or embolism	0	1 (0·1%)	0	1 (0·1%)	4 (0·4%)	0
Nausea	18 (1·9%)	1 (0·1%)	0	28 (2·9%)	2 (0·2%)	0
Vomiting	4 (0·4%)	1 (0·1%)	0	8 (0·8%)	0	0
Constipation	5 (0·5%)	1 (0·1%)	0	9 (0·9%)	0	0
Muscle cramps	16 (1·6%)	1 (0·1%)	0	15 (1·5%)	0	0
Diarrhoea	8 (0·8%)	1 (0·1%)	0	9 (0·9%)	1 (0·1%)	0
Mucositis	3 (0·3%)	0	0	1 (0·1%)	1 (0·1%)	0
Abdominal pain	31 (3·1%)	0	0	32 (3·3%)	1 (0·1%)	0
Allergic reaction	5 (0·5%)	0	0	4 (0·4%)	1 (0·1%)	0
Asthenia	53 (5·4%)	0	0	67 (6·8%)	3 (0·3%)	0
Weight gain	14 (1·4%)	0	0	18 (1·8%)	1 (0·1%)	0
Depression	14 (1·4%)	0	1 (0·1%)	26 (2·6%)	3 (0·3%)	0
Osteoporosis†‡	47 (4·3%)	NA	NA	81 (8·3%)	NA	NA
Bone fractures†	5 (0·5%)	NA	0	9 (0·9%)	NA	NA

NA=not applicable. *Cardiovascular events include the following Common Terminology Criteria for Adverse Events (version 2.0) categories: cardiac arrhythmia and cardiac general. †Osteoporosis and bone fractures were classified as present or absent without grading. ‡103 patients (10·4%) in the 2–3-year letrozole group and 79 (8·0%) in the 5-year letrozole group had osteoporosis at baseline and were not included.

Table 2: Adverse events by treatment group

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History

Version 5

Date	Summary of changes
30/08/2022	Protocol reviewed at Medical Oncology reference committee meeting. Late switch information from ID 31 Breast adjuvant letrozole (late switch) added to evidence section. Evidence updated with extended adjuvant therapy information. Clinical information oestrogen preparations updated to include topical oestrogen therapies. Clinical information vaccinations block removed. Version number changed to V.5. Next review in 4 years.

Version 4

Date	Summary of changes
12/10/2020	Protocol reviewed electronically by Medical Oncology Reference Committee. Treatment duration changed to a total of 5 to 10 years in treatment schedule, indications and patient information. Version number changed to V.4. Next review 5 years.

Version 3

Date	Summary of changes
17/01/2008	Addition of long term toxicities from review article
11/01/2010	Reviewed, new dose modifications and transferred to eviQ
05/05/2010	Link to Patient Information - "Managing Oral Cancer Treatments at Home" removed as chemotherapy safe handling is inappropriate for this treatment.
17/01/2011	New format to allow for export of protocol information. Protocol version number changed to *V.2.* Antiemetics and premedications added to the treatment schedule. Additional Clinical Information, Key Prescribing table and Key Administration table combined into new section titled Clinical Considerations. Drug specific information placed behind the drug name link.
27/04/2012	Protocol reviewed at Medical Oncology Reference Committee meeting. Removed link to safe handling (as for antineoplastics). Next review in 1 year.
21/04/2013	PBS restrictions updated.
24/06/2013	Evidence updated.
30/06/2013	Protocol reviewed by committee via email survey. No changes and next review in 2 years.
22/06/2015	Protocol reviewed electronically by Medical Oncology Reference committee. No changes and next review in 2 years
18/02/2016	Discussion with Medical Oncology Reference Committee Chairs and protocol to be reviewed every 5 years. Next review due in 4 years.
31/05/2017	Transferred to new eviQ website. Version number change to V3.

As ID 30 Breast adjuvant letrozole replaces an existing approved protocol, the individual History section is included below

for consistency in documentation.

ID 31 Breast adjuvant letrozole (late switch) version 4	
Date	**Summary of changes**
17/01/2008	Addition of long term toxicities from review article
11/01/2010	Reviewed, new dose modifications and transferred to eviQ
05/05/2010	Link to Patient Information - "Managing Oral Cancer Treatments at Home" removed as chemotherapy safe handling is inappropriate for this treatment.
17/01/2011	New format to allow for export of protocol information. Protocol version number changed to *V.2.* Antiemetics and premedications added to the treatment schedule. Additional Clinical Information, Key Prescribing table and Key Administration table combined into new section titled Clinical Considerations. Drug specific information placed behind the drug name link.
27/04/2012	Protocol reviewed at Medical Oncology Reference Committee meeting. Removed link to safe handling (as for antineoplastics. Next review in 1 year.
24/06/2013	Evidence updated.
30/06/2013	Protocol reviewed by committee via email survey. No changes and next review in 2 years.
22/06/2015	Protocol reviewed electronically by Medical Oncology Reference committee. No changes and next review in 2 years.
18/02/2016	Discussion with Medical Oncology Reference Committee Chairs and protocol to be reviewed every 5 years. Next review due in 4 years.
31/05/2017	Transferred to new eviQ website. Version number change to V.3.
09/10/2019	Duration changed in treatment schedule, indications and patient information. Version number changed to V.4.
12/10/2020	Protocol reviewed electronically by Medical Oncology Reference Committee. Reference added in indications section. Next review in 5 years.

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07 Jun 2023

Patient information - Breast cancer adjuvant - Letrozole

Patient's name:

Your treatment

It is important to understand that letrozole is not a traditional chemotherapy drug and has a different way of working. It works by reducing hormones which stops the cancer cells growing and spreading. The treatment schedule below explains how the drug for this treatment is given.

Letrozole

This treatment is continuous. Hormonal treatment is given for 5 to 10 years in total. Your doctor will advise you how long to take the treatment for. Do not stop taking letrozole tablets without telling your doctor.

Day	Treatment	How it is given
Continuous	**Letrozole** (*LET-roe-zole*)	Take orally ONCE a day at the same time each day, with or without food. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you suddenly become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you notice any pain or swelling in your legs or arms or if you develop any sudden shortness of breath or chest pain

Emergency contact details

Ask your doctor or nurse from your treating team who to contact if you have a problem

Daytime: .....

Night/weekend: .....

Other instructions: .....

.....

.....

.....

Other information about your treatment

Treatment delays

There may be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope

with the treatment. Your doctor will explain if you need any delays to your treatment and the reason why.

Blood tests and monitoring

You may need to have blood tests while you are receiving this treatment. Your doctor or nurse will tell you when to have these blood tests.

Hormonal cancer treatment

Certain types of breast cancer need oestrogen to grow. This treatment works by reducing the supply of oestrogen to these cancer cells.
Some people may experience hair thinning with this treatment. This is usually mild and rarely results in significant hair loss.
You must not take any medications that contain oestrogen while you are having this treatment. This includes some oral contraceptives, hormone replacement therapy (HRT) and oestrogen creams. Ask your doctor or pharmacist for more information.

Other medications given during this treatment

- **Calcium and vitamin D supplements:** you may be given some calcium and vitamin D tablets. Your doctor or nurse will tell you how and when to take these.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Anti-sickness medication is usually not needed but may help in some people. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Headache	• You can take paracetamol if you have a headache. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.**

Early (onset days to weeks)	
Hot flushes	• You may get flushing of your face, sweating and sensations of heat. • Avoid alcohol, coffee, tea and spicy foods, as they can make hot flushes worse. • Wear lightweight clothes made from natural fibres; dress in layers. • Put a cold, wet towel against your neck during hot flushes. • Talk to your doctor or nurse about other ways to manage these symptoms.
High blood cholesterol levels	• This treatment may increase your blood cholesterol levels. This is not a side effect you will notice. • Your cholesterol levels will be checked during your treatment.
Extra fluid in the body (fluid retention)	• You may gain weight over a short amount of time. • Your hands and feet may become swollen, appear red or feel hot and uncomfortable. • Wear loose clothing and shoes that are not too tight. • Try not to stand up or walk around too much at one time. • If your ankles or legs get swollen, try raising them. • Make sure that any cuts or areas of broken skin are treated as soon as possible. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above or gain 1 to 2 kg in a week.** • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you become short of breath.**

Late (onset weeks to months)	
Joint and muscle pain and stiffness	• You may get muscle, joint or general body pain and stiffness. • Applying a heat pack to affected areas may help. • Talk to your doctor or nurse about other ways to manage these symptoms. You may need medication to help with any pain.
Vaginal changes	• You may get a dry vagina. • This may cause pain or discomfort during sex. • Use a vaginal moisturiser. • Before sex use a water-based lubricating gel. • Talk to your doctor or nurse about other ways to manage these symptoms.

Delayed (onset months to years)	
Weak and brittle bones (osteoporosis)	• Your bones may fracture easily and may become painful. • You may have trouble moving around. • You may find it hard to perform daily chores. • Try to do some weight-bearing exercise for 30 minutes at least three times a week. • Watch out for slippery floors and make sure walkways are well lit. • Take calcium and vitamin D supplements if prescribed by your doctor. • You may have regular tests to check your bones both before and during treatment. • Tell your doctor or nurse if you get any of the signs or symptoms listed above.

General advice for people having cancer treatment

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Vaccinations such as flu and tetanus vaccines are safe to receive while you are having treatment. If you are unsure, check with your doctor before you have any vaccinations.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support.

Breast cancer information

- Australasian Lymphology Association – lymphoedema.org.au
- Australasian Menopause Society – menopause.org.au
- Breast Cancer Network Australia – bcna.org.au
- National Breast Cancer Foundation – nbcf.org.au
- YWCA Encore breast cancer exercise program – ywcaencore.org.au

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- CHILL Cancer related hair loss – scalpcooling.org
- eviQ Cancer Treatments Online – eviQ.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi

- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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