Table 1. Chemical structure of hGnRH-I agonists (GnRHa) and hGnRH-II agonists (GnRHa-II) evaluated against breast cancer.

	SEQUENCE	**MAIN CLINICAL INDICATION (DRUGBANK AND FDA)**	**CLINICAL USE IN BREAST CANCER**
hGnRH-I (Gonadorelin)	Pyro-Glu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}- Gly^{6}-Leu^{7}-Arg^{8}-Pro^{9}-Gly^{10}-NH_2 (Matsuo et al., 1971).	For evaluating the functional capacity and response of the gonadotropes of the anterior pituitary.	Information not available, only for GnRHa.
		For evaluating residual gonadotropic function of the pituitary following removal of a pituitary tumor by surgery and/or irradiation.	
		Ovulation induction therapy.	
GnRHa	**SEQUENCE**	**MAIN CLINICAL INDICATION (DRUGBANK AND FDA)**	**CLINICAL USE IN BREAST CANCER**
Triptorelin	Pyro-Glu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-**D-Trp^{6}**-Leu^{7}-Arg^{8}-Pro^{9}-Gly^{10}-NH_2 (Günthert et al., 2005; von Alten et al., 2006; Pagani et al., 2014; Kwok et al., 2015; Bellet et al., 2016; Frampton, 2017).	Palliative treatment of advanced prostate cancer	In premenopausal women with early BC letrozole in combination with triptorelin induces a more intense estrogen suppression than tamoxifen with triptorelin (Rossi et al., 2008).
			In healthy premenopausal women coadministration of triptorelin and exemestane resulted in greater estrogen suppression than when triptorelin was given alone (Jannuzzo et al., 2009).
			In premenopausal women with HR+ early BC, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence (Pagani et al., 2014).
		Controlled ovarian hyperstimulation therapy.	In premenopausal women with BC, concurrent administration of triptorelin and chemotherapy, compared with chemotherapy alone, was associated with higher long-term probability of ovarian function recovery, however there was no significant difference in DFS (Lambertini et al., 2015).
			In premenopausal women with BC, treatment with exemestane plus triptorelin had estradiol levels consistent with levels reported in postmenopausal women on aromatase inhibitors (Bellet et al., 2016).
			In premenopausal women who received adjuvant chemotherapy for HR+, HER2 negative (HER2-) BC, neither detrimental nor beneficial

			effect of concurrent administration OFS was detected (Regan et al., 2017).
			In premenopausal women with stage cT2 to 4b, any N, M0, HR+ and HER2- BC receiving letrozole neoadjuvant, OFS was achieved more quickly and maintained more effectively with degarelix than with triptorelin (Dellapasqua et al., 2019).
			In premenopausal women with early BC undergoing OFS with triptorelin, the treatment with letrozole and zolendronic acid, improves DFS (Perrone et al., 2019).
Goserelin	Pyro-Glu[1]-His[2]-Trp[3]-Ser[4]-Tyr[5]-**D-Ser(But)[6]**-Leu[7]-Arg[8]-Pro[9]-**Aza-Gly[10]**-NH_2 (Dowsett et al., 1992; Boccardo et al., 1994; Jonat et al., 1995; Jakesz et al., 2002; Jonat et al., 2002; de Haes et al., 2003; International Breast Cancer Study Group et al., 2003; Karlsson et al., 2011; Kim et al., 2015; Moore et al., 2015).	In combination with flutamide for management of locally confined carcinoma prostate.	In pre y perimenopausal women with metastatic BC, goserelin produced objective response rates and duration of remission at least comparable to those seen following oophorectomy (Kaufmann et al, 1989).
		Palliative treatment of advanced carcinoma prostate.	In premenopausal women with early BC, the addition of goserelin to ajuvant chemotherapy was associated with more benefit in DFS and overall survival rates (Recchia et al., 2015).
		The management of endometriosis.	In premenopausal women with HR+ BC, OFS with goserelin plus tamoxifen compared with tamoxifen only provided more benefit in DFS (Kim et al., 2016).
			In premenopausal women with prior endocrine-resistant HR+, HER2- advanced BC, palbociclib combined with fulvestrant and goserelin was an effective treatment to extend DFS (Loibl et al., 2017).
		Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.	In premenopausal women at ≥ 30% lifetime risk breast cancer, OFS with goserelin is a potential regimen for BC risk reduction (Howell et al., 2018).
			In premenopausal women with HR+, HER2-, tamoxifen-pretreated metastatic BC, fulvestrant plus goserelin provides a new option for the treatment (Kim et al., 2018).
		Palliative treatment of advanced BC in pre- and perimenopausal women.	In premenopausal o perimenopausal women with advanced HR+, HER2- BC, overall survival was longer with a CDK4/6 inhibitor plus endocrine therapy, (including goserelin) than endocrine therapy alone (Im et al., 2019; Tripathy et al., 2018).
Buserelin	Pyro-Glu[1]-His[2]-Trp[3]-Ser[4]-Tyr[5]-**D-Ser(But)[6]**-Leu[7]-Arg[8]-**Pro-NHET[9]** (Baumann et al., 1993; Klijn et al., 2000; Aguilar-Rojas et al., 2012; Di Lauro et al., 2014; Di Lauro et al., 2015).	May be used in the treatment of HR+ cancers such as prostate cancer o BC.	In premenopausal women with metastatic BC, buserelin was associated with objective remission and stable disease (Klijn et al., 1984; Klijn et al., 1985).
		May be used in estrogen-dependent conditions (such as endometriosis or uterine fibroids).	In premenopausal women with BC, buserelin plus cytostatics more effectively caused ovarian ablation than cytostatic treatment alone (Falkson et al., 1991).

		May be used in assisted reproduction.	In premenopausal women with advanced BC, the effect of cyclophosphamide, doxorubicin and fluoruracil plus buserelin showed a high response rate (Falkson et al., 1992).
			In premenopausal women with BC, combining OFS with buserelian and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate, more DFS and longer overall survival (Klijn et al., 2000).

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hGnRH-II	Pyro-Glu^{1}-His^{2}-Trp^{3}-Ser^{4}-His^{5}- Gly^{6}-Trp^{7}-Tyr^{8}-Pro^{9}-Gly^{10}-NH_2 (Chen et al., 1998).	Information not available.	Information not available.
		EXAMPLES OF USES REPORTED IN CANCER MODELS hGnRH-II may be involved in the inhibition of endometrial cancer cell growth (HEC-1A) (Park et al., 2009). hGnRH-II can promote apoptosis rate and inhibit cell proliferation of estrogen receptor-negative endometrial cancer cells (HEC-1A) in a dose-dependent manner (Zhao et al., 2010).	
GnRHa-II	**SEQUENCE**	**MAIN CLINICAL INDICATION (DRUGBANK AND FDA)**	**CLINICAL USE IN BREAST CANCER**
[D-Lys6]-GnRH-II	Pyro-Glu^{1}-His^{2}-Trp^{3}-Ser^{4}-His^{5}-**D-Lys** ^{6}-Trp^{7}-Tyr^{8}-Pro^{9}-Gly^{10}-NH_2 (von Alten et al., 2006).	Information not available.	Information not available.
		EXAMPLES OF USES REPORTED IN CANCER MODELS [D-Lys6]-GnRH-II has potent antiproliferative effect on SKOV-3 human ovarian cancer cell line (Gründker et al., 2004). Cytotoxic conjugate prepared by the attachment of the chemotherapeutical agent daunorubicin to [D-Lys6]-GnRH-II had significantly higher long-term cytotoxic than cytostatic effects in human breast (MCF-7) and colon (HT-29) cancer cell lines (Szabó et al., 2015).	

Pyro-Glu; pyroglutamic acid. His; L-histidine. Trp; L-tryptophan. Ser; L-serine. Tyr; L-tyrosine. Gly; L-glycine. Leu; L-leucine. Arg; L-arginine. Pro; L-proline. D-Trp; D-tryptophan. D-Ser(But); D-serine ter-butyl. NHET; N-ethylamide. Aza-Gly; azaglycine (stands for glycine in which the α-CH has been replaced by a nitrogen atom); BC: breast cancer; HR+: hormone receptor positive; DFS: disease free survival; HER2-: HER2 negative; OFS: ovarian function suppression; FDA: United States Food and Drug Administration (https://www.accessdata.fda.gov/scripts/cder/daf/); DRUGBANK: https://www.drugbank.ca