Safety of combined targeted and Helixor® *Viscum album* L. therapy in breast and gynecological patients, a real-world data study

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Abbreviations: AE, adverse event; CTx, chemotherapy; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ICI, immune checkpoint inhibitor; IO, integrative oncology; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; mAb, monoclonal antibody; NO, network oncology; i.v., intravenous; s.c., subcutaneous; SmPC, Summary of Product Characteristics; TKI, tyrosine kinase inhibitor; UICC, Union for International Cancer Care; VA, *Viscum album* L.; PARPi, PARP inhibitor; CDKi, CDK 4/6 inhibitor

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Abstract

Background: Newer personalized medicine including targeted therapies such as PARP inhibitors and CDK 4/6 inhibitors have shown to improve survival of breast and gynaecological cancer patients. However, efficacy outcomes may be hampered by treatment discontinuation due to targeted therapy-related adverse drug reactions or resistance. Studies suggest that add-on mistletoe (*Viscum album* L., VA) improves quality of life and ameliorates cytotoxic side effects of standard oncological therapy in cancer patients. The primary objective of this real-world data study was to determine the safety profile of targeted therapy in combination with add-on Helixor® VA therapy in breast and gynecological cancer patients.

Methods: The present study is a real-world data study utilizing demographic and treatment data from the accredited national Network Oncology (NO) registry. The study has received ethics approval. The safety profile of targeted with or without Helixor® VA therapy as well as safety - associated variables were evaluated by univariate and adjusted multivariable regression analyses.

Results: All stage breast or gynecological cancer patients (n = 242) were on average 54.5±14.2 years old. One hundred and sixty patients (66.1%) were in the control (CTRL, targeted therapy) and 82 patients (33.9%) in the combinational (COMB, targeted plus Helixor® VA therapy) group. The addition of Helixor® VA did not hamper the safety profile ($\chi 2$ = 0.107, p-value = 0.99) of targeted therapy. Furthermore, no adverse events and a trend towards an improved targeted therapy adherence were observed in the COMB group.

Conclusions: The present study is the first of its kind showing the applicability of Helixor® VA in combination with targeted therapies. The results indicate that add-on Helixor® VA does not negatively alter the safety profile of targeted therapies in breast and gynaecological cancer patients.

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Introduction

Targeted therapy as the foundation for precision medicine consists of small molecules or monoclonal antibodies that aim to inhibit or induce proteins controling the proliferation, growth and mobility of cancer cells (1). Testing cancer cells for specific biomarkers can help to choose the right targeted therapy, either a monoclonal antibody (mAB), a tyrosine kinase inhibitor (TKI), a PAPR-inhibitor (PARPi) or cyclin-dependent kinase (CDK) 4/6 inhibitors (CDKi). PARPi, e.g. olaparib, rucaparib, niraparib, talazoparib or velaparib, target breast or ovarian cancer cells overexpressing PARP and help to mediate the inhibition of homologous recombination deficiencies in cells (2). CDKis, e.g. palbociclib, ribociclib, and abemaciclib, inhibit the cell cycle progression of cancer cells in patients with advanced or metastatic hormone receptor positive and human epidermal growth factor receptor 2 negative (3). Some drawbacks might be the side effects of targeted therapy, which can hamper patient's quality of life (1), the resistance against targeted therapy, and unexpected treatment responses due to off-target effects (2). Most of the side effects disappear with treatment's end and this may be the reason why some of the targeted therapies will not continuously be taken by the patients or not continuously applied leading to treatment discontinuation and hampering of the efficacy of the treatment. Systematic reviews showed that less than 60% of EMA or FDA (accelerated) oncology drug approvals comprising mABs and TKIs between 2009 and 2013 (EMA) or between 2008 and 2012 (FDA) were effective in improving the overall survival and health related quality of life (4-6). *Viscum album* L. (VA, European white-berry mistletoe) being applied to anti-cancer standard oncological therapy in order to improve the health-related quality of life of cancer patients [7-9] reveals a sound safety profile when combined with targeted therapies such as monoclonal antibodies or immune checkpoint inhibitors [10,11]. Furthermore, it was shown that the addition of VA to targeted therapy was associated with the significant reduction of AE rates in mAB treated cancer patients (10), halved AE rates in Nivolumab-treated advanced or metastasized lung cancer patients (12), and helped to maintain standard oncological therapy in mAB, TKI or ICI treated cancer patients (13). We therefore hypothesized that the application of Helixor® VA would not hamper the safety profile of applied targeted therapy in breast and gynecological cancer patients.

Material and Methods

Study design

Safety of targeted therapy with or without concomitant Helixor® VA extracts was examined in an real-world data study utilizing data from the national oncological registry, Network Oncology,. The primary outcome of the study was to investigate the occurrence of AEs during targeted therapy treatment with

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and without Helixor® VA to assess the AE rate in breast and gynecological cancer. The secondary outcome was the explorative analysis of factors that were associated with the risk of experiencing an AE or treatment adjustment of targeted therapy.

Description of study participants

Breast and gynecological cancer patients registered in the Network Oncology (NO), an accredited German clinical registry [39], were enrolled in the study until January 2022. Following patients were included: patients who were 18 years or older and of both gender, who gave written consent and who received targeted therapy with or without concomitant Helixor® VA therapy. VA therapy was applied subcutaneously according to the summary of product characteristics (SmPC). Off-label intravenous application was performed in individual cases. The rationale for VA application in patients of the current study was the improvement of HRQL and self-regulation in cancer patients by meliorating cancer and therapy related symptoms. VA was administered at the discretion of the physician. Patients having received a combination of targeted therapy and add-on Helixor® VA therapy were allocated to the "COMB group". The other patients having received targeted therapy without add-on Helixor® VA were allocated to the "CTRL group". The study has been approved by the ethics committee of the Medical Association Berlin (Eth-27/10).

Data source and assessment

Demographic data as well as information on diagnosis and treatment information were retrieved from the NO registry. Aside from targeted therapy and Helixor® VA therapy, information on applied chemotherapy, radiation and surgery were analyzed. AEs were designated according to ICH guidelines topic E2A [41] and were defined as "*any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*". In terms of severity, AEs were evaluated according to the Common Terminology Criteria for AEs (CTCAE) version 5 and designated as serious or non-serious according to ICH guidelines. AEs were classified as preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.1 and grouped by System Organ Classes (SOC).

Statistical methods

Continuous variables were described as median with interquartile range (IQR), categorical variables as frequencies and percentages. Data distributions were inspected graphically using box plots and histograms and were arithmetically examined for skewness. Stepwise backward variable selection with

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Akaike information criterion was performed for consideration of parameters within regression models. P-values <0.05 were considered to be significant. All statistical analyses were performed using the software R (Version 4.2.2), a language and environment for statistical computing. For both groups, baseline characteristics and treatment regimens were compared using the unpaired two-sided Student's t-test for independent samples when data was normally distributed. For non-normally distributed ordinal data the Mann-Whitney U test was applied. For comparison of categorial variables chisquare analysis was performed. All tests were performed two-sided. Univariate two-sided Fisher's exact test or chisquare statistical analysis were performed to detect differences in AE, dose reduction or treatment discontinuation rates between both groups. Adjusted multivariable regression analysis with binary outcome of experienced AE/treatment adjustment (yes/no) was performed to identify associated factors in the study group adjusting for age (in years), tumor origin (breast cancer, ovarian cancer, other cancer including endometrium cancer, tubal cancer, vulva carcinoma, and cervical carcinoma), targeted therapy (mAB, CDK 4/6 inhibitor, TKI, PARPi, ICI), add-on Helixor® VA therapy (yes/no), UICC stage (early I-II/advanced III-IV), surgery (yes/no), chemotherapy (yes/no) and radiation (yes/no). If applicable, Brier scores as comparisons of predicted risks with observed outcomes at individual level where outcome values are either 0 or 1 were indicated [43]. Furthermore, Nagelkerke's R2 values as percentages of variation of the outcome explained by the predictors in the model were indicated, if applicable.

Results

Baseline characteristics

In total two hundred fourty two (n = 242) patients were treated, of these 160 patients (66.1%) with targeted therapy without add-on VA therapy (control group, CTRL) and 82 patients (33,9%) with targeted and add-on VA therapy (combinational group, COMB) until January 2022 (see flowchart, Figure 1).

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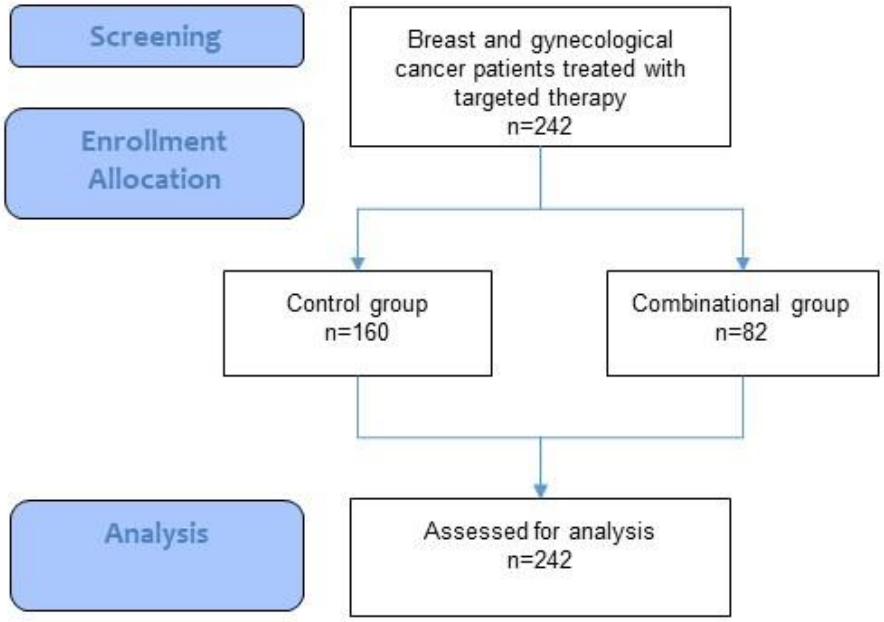

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145 ***Figure 1*** *Flowchart of the study*

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147 The mean age of the total cohort was 54.6 ±14.2 years. The most prevalent cancers were breast cancer
148 (87.6%) and ovarian cancer (10.3%). 9 patients (2.1%) had other cancer, see table 1. The cancer entities
149 and the targeted therapies were balanced between both groups. The highest proportion of patients in
150 the COMB group were patients with breast cancer (91.5%) followed by patients with ovarian cancer
151 (7.3%). The same order with respect to proportions was observed in the CTRL group. 17.5% of all-stage
152 breast cancer patients and 62% of UICC stage IV breast cancer patients in the presented study were
153 hormone receptor positive and HER2 negative, data not shown. 58.5% of the breast cancer patients
154 were HER2 positive, data not shown.

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157 ***Table 1. Characteristics of patients***

Patient Characteristics	Total cohort n = 242	CTRL n = 160	COMB n = 82	Significance p-value
Age at first diagnosis, years, mean (SD)	54.5 (14.2)	54.7(14.4)	54.3 (13.7)	0. 84[2)]
Cancer entity, n (%)				1.13[3)]
Breast, n (%)	212 (87.6)	136 (85)	75 (91.5)	
Ovarian, n (%)	25 (10.3)	19 (11.9)	6 (7.3)	
Other[1)], n (%)	5 (2.1)	5 (3.1)	0 (0)	
UICC stage				0.08[2)]
0	1 (0.4)	1 (0.6)	0	
I	49 (20.2)	26 (16.3)	23 (28.0)	
II	86 (35.5)	55 (34.4)	31 (37.8)	

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III	49 (20.2)	39 (24.4)	10 (12.2)
IV	44 (18.2)	29 (18.1)	15 (18.3)
NA	13 (5.4)	10 (6.3)	82 (3.7)

Characteristics of the patients included in the study, total cohort and respective treatment groups; IQR, interquartile range, [1)]other includes endometrium cancer, tubal cancer, vulva cancer, cervix cancer; [2)]Student's t-test; [3)]Pearson's chi-square test; n, number; %, percent; UICC, Union for International Cancer Control

Oncological treatment

Cancer-related surgery was performed in 208 patients (86%) and radiation in 140 patients (57.9%) with almost balanced proportions of patients in both treatment groups, respectively ($CTRL_{surgery}$ 87.5% vs. $COMB_{surgery}$ 82.9%; $CTRL_{radiation}$ 55% vs. $COMB_{radiation}$ 63.4%), see table 2. Chemotherapy (CTx) was applied to 229 patients (94.6%), with balanced proportions in both groups, see table 2. Chemotherapy lasted in median 147 days (Interquartile Range – IQR: 92 – 360 days). As to targeted therapy, monoclonal antibodies were the most applied targeted therapies (79.8%), followed by CDKis (10.7%), ICIs (5.4%), TKIs (2.5%) and PARPis (1.7%), see table 3.

Table 2. Characteristics of oncological therapy

Patient Characteristics	Total cohort n = 242	CTRL n = 160	COMB n = 82	Significance p-value
Surgery				0.91
yes	208 (86.0)	140 (87.5)	68 (82.9)	
no	27 (11.2)	19 (11.9)	8 (9.8)	
NA	7 (2.9)	1 (0.6)	6 (7.3)	
Radiation				0.08
yes	140 (57.9)	88 (55.0)	52 (63.4)	
no	95 (39.3)	71 (44.4)	24 (29.3)	
NA	7 (2.9)	1 (0.6)	6 (7.3)	
CTx				0.51
yes	229 (94.6)	153 (95.6)	76 (92.7)	
no	13 (5.4)	7 (4.4)	6 (7.3)	

CTx, chemotherapy; n, number; %, percent

Characterization of targeted therapy

Table 3 characterizes the various targeted therapies applied to the two different groups. The proportions of applied targeted therapy types were balanced between both groups. Targeted therapy lasted in median 295.5 days (IQR 108.5 – 476.5 days). Twenty six patients (10.7%) received CDK 4/6-

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inhibitors with the highest proportion of patients receiving palbociclib, see table 3. Two hundred six (84.1%) of the patients received monoclonal antibodies with trastuzumab or the combination pertuzumab/trastuzumab being the most applied mAB followed by bevacizumab. Atezolizumab was the most applied immune checkpoint inhibitor (4.5%) in these patients followed by pembrolizumab. Four (1.7%) patients received PARP-inhibitors with olaparib being more often applied (1.2%) than niraparib (0.4%). Latter was not applied in the COMB group. Finally yet importantly, six patients received TKI-inhibitors with lapatinib (1.7%) being more often applied than erlotinib, nintedanib and pazopanib (all 0.4%). The latter three were not applied in the COMB group. Even though some of the mABs, TKIs or PARP-inhibitors were not applied in the COMB group, probably due to the smaller sample size than the CTRL group, the spectrum of targeted therapy was balanced between both groups as shown by the non-significant difference as shown in table 3.

Table 3. Characterization of targeted therapy

Patient Characteristics	Total cohort n = 242	CTRL n = 160	COMB n = 82	Significance p-value
CDKi, n (%)	**26 (10.7)**	**17 (10.6)**	**9 (11.0)**	**1.0**
abemaciclib, n (%)	4 (1.7)	1 (0.6)	3 (3.7)	
palbociclib, n (%)	18 (7.4)	14 (8.8)	4 (4.9)	
ribociclib, n (%)	5 (2.1)	3 (1.9)	2 (2.4)	
mAB, n (%)	**206 (84.1)**	**136 (85.0)**	**70 (85.4)**	**1.0**
bevacizumab, n (%)	47 (19.4)	35 (2.19)	12 (14.6)	
denusomab, n (%)	8 (3.3)	4 (2.5)	4 (4.9)	
glembatumumab, n (%)	1 (0.4)	1 (0.6)	0	
pertuzumab, n (%)	2 (0.8)	1 (0.6)	1 (1.2)	
pertuzumab/trastuzumab, n (%)	62 (25.6)	30 (18.8)	32 (39.0)	
rituximab, n (%)	2 (0.8)	1 (0.6)	1 (1.2)	
trastuzumab, n (%)	74 (30.6)	55 (34.4)	19 (23.2)	
trastuzumab-emtasin, n (%)	3 (1.2)	3 (1.9)	0	
ICI, n (%)	**13 (5.4)**	**8 (5)**	**5 (6.1)**	**1.0**
atezolizumab, n (%)	11 (4.5)	7 (4.4)	4 (4.9)	
pembrolizumab, n (%)	2 (0.8)	1 (0.6)	1 (1.2)	
PARPi, n (%)	**4 (1.7)**	**3 (1.9)**	**1 (1.2)**	**1.0**
niraparib, n (%)	1 (0.4)	1 (0.6)	0	
olaparib, n (%)	3 (1.2)	2 (1.3)	1 (1.2)	
TKI, n (%)	**6 (2.5)**	**4 (2.5)**	**2 (2.4)**	**1.0**
erlotinib, n (%)	1 (0.4)	1 (0.6)	0	
lapatinib, n (%)	4 (1.7)	2 (1.3)	2 (2.4)	
nintedanib, n (%)	1 (0.4)	1 (0.6)	0	
pazopanib, n (%)	1 (0.4)	1 (0.6)	0	

Targeted therapy including CDK 4/6 inhibitors (CDKi), immune checkpoint inhibitors (ICI), monoclonal antibodies (mAB), PARP-inhibitors (PARPi), TKI-inhibitors (TKI) and combinations of them. n, number; %, percent. Numbers of patients in the various therapy groups may not sum up to 100 percent as some patients have received a combination of targeted therapies. CDKi, CDK 4/6-inhibitors; ICI, immune checkpoint inhibitors; mAB, monoclonal antibody; PARPi, PARP-inhibitor; TKI, TKI-inhibitors

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As to add-on VA treatment in the COMB group Helixor® A (68.3%) and Helixor® M (25.6%) were the most frequently applied Helixor® VA extracts in the study group, data not shown. Hereby, the most applied combination of Helixor® A, M and P were with monoclonal antibodies (81.7%). Furthermore, Helixor® A and Helixor® M were also combined with CDKis (11%), see table 4, mainly abemaciclib, palbociclib and ribociclib. Also, both Helixor® remedies were (only in breast cancer patients) combined with the immune checkpoint inhibitors (6.1%) such as atezolizumab and pembrolizumab. Lapatinib was the only TKI (2.4%) which was combined with Helixor® VA in breast cancer patients. Figure 2 represents the specific treatment pattern of targeted therapy in the COMB group, where patients received Helixor® VA therapy in addition to the targeted therapy. Here, the mAB combination pertuzumab and trastuzumab (39%) represents the most applied targeted therapy followed by the monocolonal antibodies bevacizumab (14.6%), denusomab (4.9%), the immune checkpoint inhibitor atezolizumab (4.9%), and the CDKis palbociclib (4.9%) and abemaciclib (3.7%). Univariate analysis revealed that there were no significant correlations between additional Helixor® VA treatment and age ($\chi^2 = 55.5$, $p = 0.53$), additional Helixor® VA treatment and surgery ($\chi^2 = 0.01$, $p = 0.919$) and add-on Helixor® VA treatment and tumor type ($\chi^2 = 2.28$, $p = 0.13$), data not shown. A clinical meaningful significant association was found between add-on Helixor® VA treatment and increasing UICC stage ($\chi^2 = 12.37$, $p = 0.00044$).

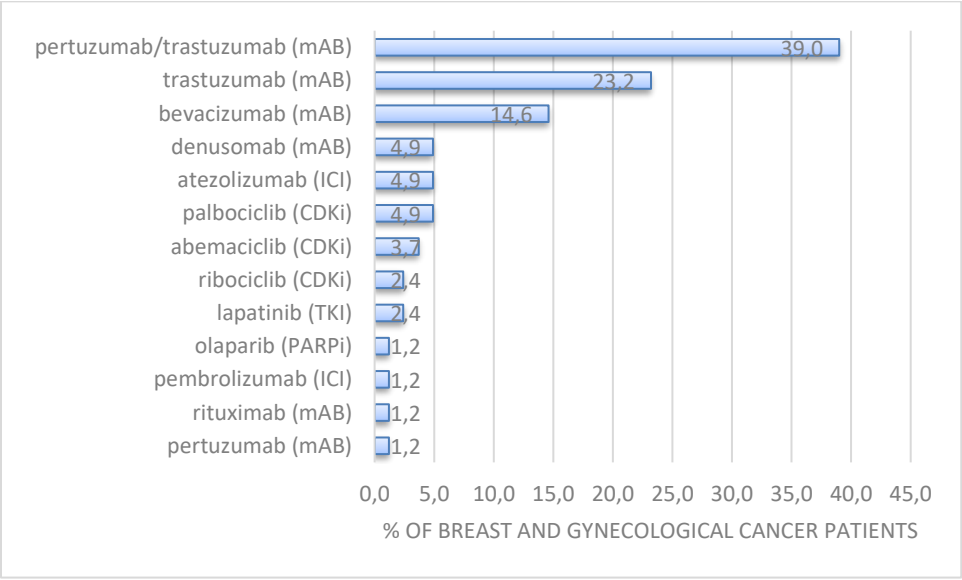

Figure 2. *Proportion of cancer patients receiving various targeted therapy in combination with Helixor® VA therapy (COMB group, n = 82). CDK 4/6 inhibitors (CDKi), immune checkpoint inhibitors (ICI), monoclonal antibodies (mAB), PARP-inhibitors (PARPi), TKI-inhibitors (TKI)*

AEs related to targeted and combinational treatment

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The total AE frequency was 4.1% (as to the number of AEs per total patient number) with 10 AEs in a total of 242 patients see table 4. With respect to treatment groups, 10 AEs (6.3%) were observed in the CTRL and no adverse event was observed in patients of the COMB group. The AE frequencies ($\chi 2 = 0.107$, p-value = 0.99) did not significantly differ between both groups. No serious AEs and serious adverse reactions (ICH) [41] were documented for the total study cohort. No deaths from study-drug toxic effects were reported.

Table 4. Targeted adverse events per treatment group

System Organ Class	Adverse event (AE)	Total n = 242	CTRL n = 160	COMB n = 82
gastrointestinal disorders	nausea	2	a[1)], d[4)]	-
	appetite loss	1	d[4)]	-
	vomiting	1	d[4)]	-
general disorders and administration site conditions	pain	1	c[3)*]	-
	temperature elevated	1	b[2)*]	-
	fatigue	1	e[5)]	-
	neck stiffness	1	e[5)]	-
	impaired vision	1	e[5)]	-
skin and subcutaneous tissue disorder	erythema	1	e[5)]	-
Total number of AEs		10	10	-
Total number of patients experiencing AE		5	5	0
AE per patient frequency (AE events divided by number of all patients, n (%)[§)]		4.13%[§]	6.25%	0
Patient with AE frequency (patient experiencing an AE divided by number of all patients) [§§)]		2.07%[§§)]	3.13%	0

*Adverse events per treatment group classified as MedDRA (MedDRA Version 24.0.[1]) preferred terms and grouped by System Organ Class; [1)]pertuzumab; [2)]trastuzumab; ; [3)]trastuzumab/pertuzumab, [4)]niraparib; [5)]pazopanib, *treatment was discontinued; AE, adverse event; [§)] comparison AE frequency COMB group vs. CTRL group:* $\chi^2 = 0.107$, p-value = 0.99; *[§§)] comparison AE frequency COMB group vs. CTRL group:* $\chi^2 = 1.3$, p-value = 0.25

The most often reported AE in the total study cohort was nausea, see table 4. In terms of System Organ Class (SOC) most AEs were 'general disorders and administration site conditions' (n = 5, 2.5% total, 3.1% for the CTRL group), followed by 'gastrointestinal disorders' (n = 4, 1.7% for the total group, 2.5% for the CTRL group,) and ,skin and subcutaneous tissue disorder' (n = 1, 0.4% for the total group, 0.6% for the CTRL group), see table 4 and figure 3.

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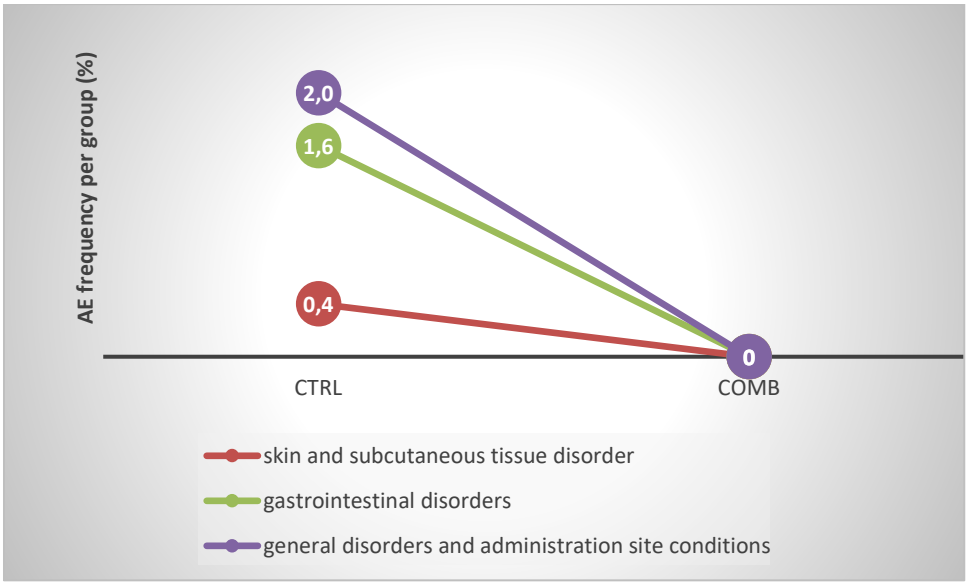

Figure 3. *AE frequency during targeted therapy treatment per group in % illustrated as system organ class categories. Left, % AE control group, right, % AE combinational group*

We investigated in a next step whether the targeted therapy was continuously applied or whether any differences in disruption or dose reduction were observed between both groups. Table 5 shows the difference of proportion of patients between both groups who experienced a targeted therapy -related AE, a dose reduction or discontinuation of targeted therapy.

Table 5. Discontinuation/dose reduction or AE due to targeted therapy

	Total cohort n = 242	CTRL n = 160	COMB n = 82	Significance p-value
AE due to targeted treatment, n (%)	5 (2.1)	5 (3.1)	0	0.254
Disruption of targeted treatment, n (%)	6 (2.9)	5 (3.1)	1 (1.2)	0.642
Dose reduction of targeted treatment, n (%)	8 (3.3)	5 (3.1)	3 (3.7)	1.0
Any event (AE or therapy adjustment [§)], n (%)	14 (5.8)	10 (6.3)	3 (4.9)	0.586

Information on the continuation of targeted therapy; [§]comparison COMB group vs. CTRL group: (χ^2 = 0.020, p = 0.88)

We found that the proportion of patients experiencing any of these three events was smaller in the group receiving additional Helixor® VA (COMB) and the Pearson's chi-square analysis indicated a negative association between both parameters (χ^2 = 0.02, p = 0.88), but not being statistically significant. As to therapy adjustment, we observed five (3.1%) disruptions of targeted treatment in the CRTL group with four discontinuations of trastuzumab (mAB) therapy and one of denusomab (mAB). Furthermore, we observed in the CTRL group five dose reductions (3.1%) with one dose reduction of

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pertuzumab (mAB), one of trastuzumab (mAB), one of niraparib (PARP-inhibitor), one of pazopanib (TKI), and one dose reduction and disruption of ribociclib (CDKi), see table 5. In the COMB group, the following was documented: one dose discontinuations (1.2%) of pertuzumab and three (3.7%) dose reductions (two of pertuzumab and one of pertuzumab/trastuzumab), see table 5.

Factors associated with occurrence of AE, treatment discontinuation or dose disruption in targeted therapy

Multivariable logistic regression analysis adjusting for demographic (age), treatment-related (surgery, chemotherapy, radiation, targeted therapy, Helixor® VA therapy) and tumour stage-related (UICC) variables revealed a negative correlation between AE/treatment adaption and Helixor® VA application, see figure 4.

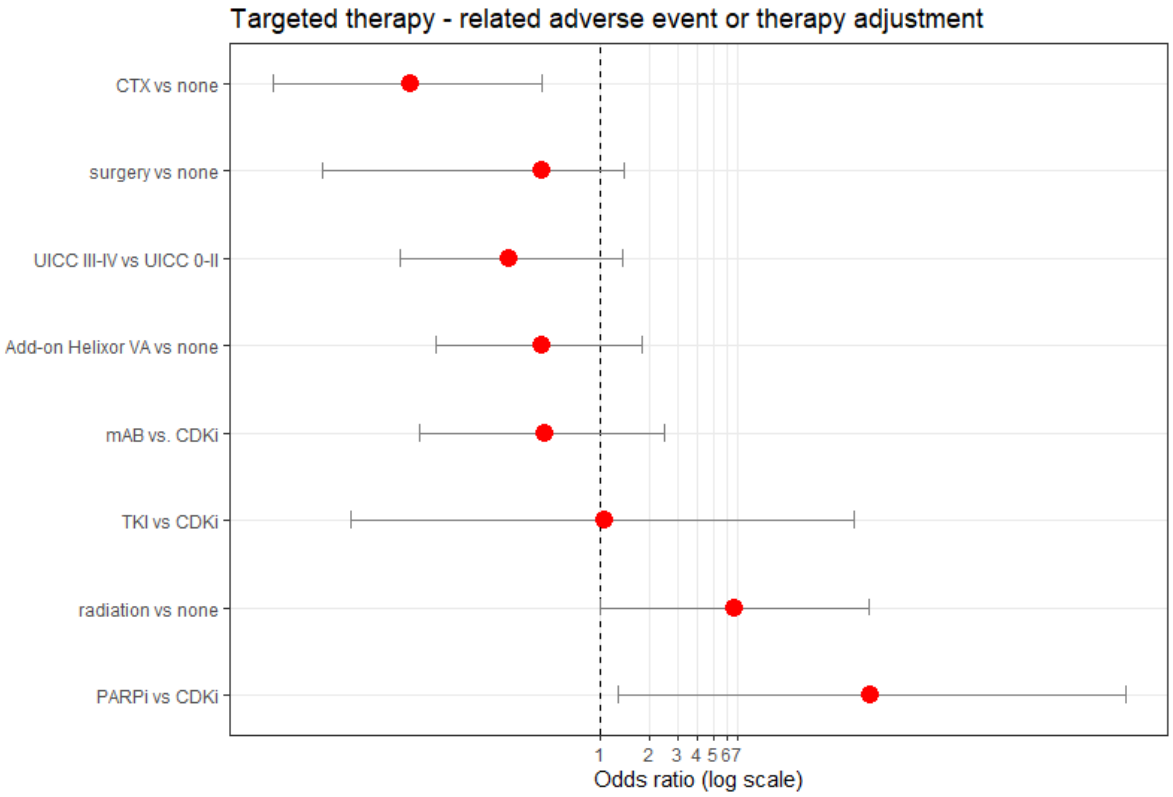

Figure 4. *Association factors for a targeted therapy – related adverse event or therapy adjustment (dose reduction, treatment disruption). Multivariable logistic regression (n = 222) adjusting for age, the UICC stage and add-on Helixor® VA treatment, as well as surgery, chemotherapy (CTX), radiation and the respective type of targeted therapy. CDKi, CDK 4/6-inhibitors; ICI, immune checkpoint inhibitors; mAB, monoclonal antibody; PARPi, PARP-inhibitor; TKI, TKI-inhibitors Brier Score, 0.046, Nagelkerke_R2, 0.2145; AE, adverse event*

Here we found lower odds representing a 56% reduced (but not significant) probability of AE/dose reduction/treatment disruption of the targeted therapy when Helixor® VA therapy was added

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compared to no addition of Helixor® VA therapy, see figure 4. These results were not significant; however, the Nagelkerke's R2 value of 0.20 indicated a medium size effect according to Cohen. Thus, no significant associations between the safety profile of the targeted treatment and the Helixor® VA treatment were seen. Interestingly, radiation or the therapy with PARP-inhibitors significantly increased the probability of an AE/treatment adaption, respectively, see figure 4. Conversely, a former chemotherapy was associated with a significant reduction of an AE or treatment adaption of the targeted therapy. Neither age, tumor stage, surgery, nor the addition of mABs or TKIs had any significant effect on an AE/treatment adaption of the targeted therapy.

Discussion

In the present real-world data study we evaluated the safety profile of targeted therapy in combination with add-on Helixor® VA therapy in breast and gynecological cancer patients. Our findings show that additional Helixor® VA therapy does not impair the safety profile of targeted therapy in breast and gynecological cancer patients.

As to the differences in the baseline characteristics, we found no significant misbalances as to age, tumor stage, tumor type or oncological treatment. The slightly higher (but not significant) proportion of patients receiving radiation therapy in the group receiving additional Helixor® VA therapy might be correlated with a slightly (but not significant) higher percentage of early tumors in this group (14,15). While the proportions of breast and ovarian cancer patients seem to be balanced between the control and in the combinational group, other cancer types such as cervix cancer were under-represented. As to systemic oncological treatment, the high proportion of patients receiving trastuzumab in both arms of the present study correlates with the high proportion of patients with breast cancer overexpressing the HER2 neu protein (17). Another targeted therapy group is the group of CDKi, mainly represented in our study by palbociclib, which has been approved for hormone receptor positive, HER2 neu negative locally advanced or metastasized breast cancer in combination with an aromatase inhibitor (18). Palbociclib has been applied in the present study by 7.4% of breast cancer patients being in the same range of available stage IV HR+ and HER2- breast cancer patients. The third targeted therapy group documented in our study is the ICI group, mostly atezolizumab, which is approved for the therapy of triple negative (HR-/HER2-) metastasized or locally advanced unresectable breast cancer with PD-L1 expression ≥1% (19). Concerning the fourth targeted group in our study, the PARP inhibitors, olaparib has been approved for patients with advanced ovarian cancer with BRCA mutations in the fourth line while niraparib has been approved as a maintenance therapy for high-grade serous non-mucinous epithelial ovarian cancer. Ovarian cancer is rare in accordance with the proportional small application rate of the orphan drugs olaparib and niraparib in our study. The fifth targeted group

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being applied in our study is the group of TKIs mostly represented by lapatinib, which is used in breast cancer overexpressing HER2neu (20). Thus, our real-world data study mirrors the current application situation of the five mentioned targeted groups including mABs, ICIs, TKIs, PARPi and CDKi in breast and gynecological cancer patients. Furthermore, it is the first of its kind showing the applicability of Helixor® VA applications in addition to these targeted therapy groups.

As we could not see any significant differences between both groups as to targeted therapy – related discontinuation, dose reduction or AE, we conclude that the combinational therapy with Helixor® VA does not impair the safety profile of the targeted therapy. Interestingly, compared to a 3% rate in the control group, no AE was observed in the combinational group indicating a possible trend towards lower AE rates here. We could observe this trend also for treatment discontinuations with lower rates in the targeted therapy plus Helixor® VA group. The differences were not significant though, probably due to the small sample size. Our results are in line with three other observational studies indicating the safety of combined treatment of VA extracts with monoclonal antibodies (10), immune checkpoint inhibitors (11) and targeted therapy including mABs, ICIs and TKIs (13).

In the present study no significant changes in the safety profile of targeted therapy due to add-on Helixor® VA were observed. Nevertheless, former clinical studies could show that in combination with chemotherapy, Helixor® VA therapy reduces the AE rate in cancer patients and thus helps to maintain standard oncological therapy.

In a multicenter, randomized open prospective clinical trial it has been shown that Helixor® VA therapy concomitantly taken with polychemotherapy significantly reduced the AEs including fatigue and pain in 233 patients with breast, ovarian or non-small cell lung cancer (26). The same study also revealed that the quality of life in patients receiving the combinational therapy was significantly improved (26). In another open randomized clinical trial, tumor- and therapy-related side effects (pain, nausea/vomiting, diarrhea and appetite loss) were reduced in breast cancer patients receiving chemotherapy (CAF) plus a Helixor® VA containing mistletoe therapy compared to those receiving only chemotherapy (CAF) (27). This in turn led to fewer discontinuations of the standard therapy. A former real-world data study investigated the safety profile of mAB therapies with add-on Helixor® VA therapy (10). Here the probability of an AE was five times higher in those patients that were treated with mAB therapy compared to patients treated with a combination of mAB and Helixor® VA therapy (10). The possible reason why we do not see such changes may be that breast and gynecological cancer patients could represent a cancer class with better-tolerated targeted therapy regimes and could therefore have had a potential lower risk of therapy discontinuations compared to other cancer patients not being evaluated in this study. We could show this discrepancy in a former study where we found that

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breast cancer patients compared to patients with e.g. gastrointestinal or respiratory oncological diseases had a 94% reduced risk of discontinuation of standard oncological therapy (13).

Our results are limited by the non-randomized character of the study. However, the compared groups were balanced reducing the risk of comparing heterogeneous patient groups as to tumor type, disease stage or oncological treatment. In addition, biases were reduced by multivariable logistic regression in the safety analyses where potential confounders were addressed. The frequency of AE seem to be lower than the AE frequency reported in clinical studies (21-24) indicating a possible underreporting of AEs in our study. We assume that this may be due to documentation and spontaneous reporting biases being in line with a systematic review (25). Therefore, our findings may need to be cautiously interpreted. Nevertheless, our study represents the real-world application situation of targeted therapy with or without add-on Helixor® VA therapy.

Conclusion

The present real-world data study reveals a first insight on safety aspects of concomitant targeted and Helixor® VA treatment in breast and gynecological cancer patients. The results indicate that add-on Helixor® VA does not negatively alter the safety profile of all five targeted therapy groups investigated. Furthermore, no adverse events and a trend towards an improved targeted therapy adherence were observed in the COMB group. In addition, adjusted multivariable regression analysis revealed a trend towards a reduction of disadvantageous events including AE, dose reduction or treatment discontinuation. Further clinical studies with a larger sample size including other cancer entities are initiated.

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Declarations

Ethics approval and consent to participate

This study is an observational study. The Network Oncology (NO) registry study has been approved by the ethical committee of the Medical Association Berlin (Berlin - Ethik-Kommission der Ärztekammer Berlin). The reference number is Eth-27/10. Written informed consent has been obtained from all patients prior study enrolment. The study complies with the principles laid down in the Declaration of Helsinki.

Consent for publication

All authors consented to this manuscript's publication.

Availability of data and material

All relevant data are included in this manuscript.

Competing interest

Dr. Schad reports grants from Helixor Heilmittel GmbH, Iscador AG and ABNOBA GmbH outside the submitted work. Dr. Thronicke declares that she has no competing interests.

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Author's contributions

AT: made substantial contributions to the design of the study and planning, collected, interpreted and analysed data, drafted the manuscript, revised the manuscript critically and gave final approval of the version to be published. FS: made substantial contributions to the design of the study and planning, the collection and interpretation of data, revised the manuscript critically, and gave final approval of the version to be published.

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