**Neuroendocrinology Letters** Volume 45 No. 8 2024
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
*Web of Knowledge / Web of Science:* Neuroendocrinol Lett
*Pub Med / Medline:* Neuro Endocrinol Lett



ORIGINAL ARTICLE

# A retrospective observational clinical study of triple negative breast cancer cases treated with Di Bella Method: A preliminary data

**Giuseppe Di Bella[1], Ilaria Moscato[1], Elena Costanzo[1], Giovanni Di Giorgi[1]**

1 Di Bella Foundation, Via Guglielmo Marconi 51 Bologna, 40122 Italy

*Correspondence to:* Dr. Giuseppe Di Bella
Di Bella Foundation, Via Marconi 51, 40122, Bologna, Italy
tel: +39 051 239662; +39 051230369, e-mail: posta@giuseppedibella.it

*Submitted: 2024-06-17 Accepted: 2024-09-09 Published online: 2024-12-22*

*Key words:* **TNBC; somatostatin; prolactin; melatonin; vitamins; DBM**

Neuroendocrinol Lett 2024; **45**(7-8):510–522 **PMID:** 39737501 45072414 

## Abstract

**OBJECTIVES:** Triple-negative breast cancer (TNBC) is a distinct subtype of breast cancer that has a poor prognosis due to the lack of effective therapeutic agents. Since a significant proportion of human surgical samples of TNBC expressed mRNA for the growth hormone (GH), growth hormone-releasing hormone (GHRH), and gonadotropin-releasing hormone (GnRH) receptors, and the mitogenic proliferative activity of GH, GHRH, and GnRH, have been identified as effective therapeutic targets for somatostatin and its analogs and GnRH analogs, Di Bella Method (DBM), a combination of hormonal analogs and vitamins, was introduced to target and inhibit solid tumors. The present study aimed to improve the prognosis of women with TNBC using DBM.

**METHODS:** This retrospective observational study was done on women with TNBC who were diagnosed based on histology, nuclear grade, and immunohistochemical testing for estrogen receptor, HER2/neu, and progesterone receptor. Patients were either treated with standard oncology protocol, including chemotherapy and radiotherapy plus DBM, or with DBM alone. The DBM included a daily combination of somatostatin, octreotide, melatonin, retinoids solubilized in alpha tocopheryl acetate, dopaminergic agonists, bromocriptine, cabergoline, aromatase inhibitors for anti-estrogen function, and low metronomic doses of cyclophosphamide.

**RESULTS:** In this study, 35 patients were enrolled, and their survival was monitored for 5 years during which they received DBM and standard chemotherapy/radiotherapy protocol. These patients had a survival rate of 64% at 5 years, 76% at 3 years, 87% at 2 years, and 100% after 1 year of therapy. On the other hand, 13 patients who received only DBM had a survival rate of 60% at 5 years, 67% at 3 years, 75% at 2 years and 100% after 1 year of therapy. None of the patients had significant adverse events.

**CONCLUSIONS:** Compared to published clinical trials, the DBM improved the prognosis of women with TNBC. However, more standardized clinical trials, including DBM with and without standard therapeutic protocols for TNBC, are warranted.

**Abbreviations:**

| | |
|---|---|
| ATRA | - All Trans Retinoic Acid |
| BC | - Breast Cancer |
| DBM | - Di Bella's Method |
| EGF | - Epidermal Growth Factor |
| EGFR | - Epidermal Growth Factor Receptor 2 |
| ER | - Estrogen Receptor |
| FGF | - Fibroblastic Growth Factor |
| GnRH | - Hormone-releasing hormone gonadotropin |
| GHRH | - GH releasing hormone |
| GH | - Growth Hormone |
| GHR | - Growth Hormone Receptor |
| HIF | - Hipoxia-Inducible factor |
| IGF1-2 | - Insulin-like Growth Factor 1-2 |
| IGFR | - Insulin-like Growth Factor Receptor |
| MRI | - Magnetic Resonance Imaging |
| MLT | - Melatonin |
| PET | - Positron Emission Tomography |
| SST | - Somatostatin |
| SSTR | - Somatostatin Receptor |
| TNBC | - Triple Negative Breast Cancer |
| VEGF | - Vascular Endothelial Growth Factor |

## INTRODUCTION

Triple negative breast cancer (TNBC) is a distinct subtype of breast cancer that has a poor prognosis due to the lack of effective therapeutic agents. A number of histological subtypes that are morphologically and immunophenotypically heterogeneous have been identified in human TNBC surgical samples. Based on histomorphology and immunophenotype, primary TNBC tumors were subdivided into bone marrow, metaplastic, apocrine, and invasive ductal of no special type (IDC-NSTs) carcinomas.

A significant proportion of human surgical samples of TNBC expressed mRNA for growth hormone (GH), growth hormone-releasing hormone (GHRH), and gonadotropin-releasing hormone (GnRH) receptors which were also detected by immunohistochemical and real time RT-PCR techniques in breast tissue (Subramani *et al.* 2017; Wennbo, Törnell, 2000; Boguszewski, Boguszewski, 2019; Zhu *et al.* 2020; Khanlari *et al.* 2018). Furthermore, the mitogenic proliferative activity of GH, GHRH, and GnRH, whose receptors have been identified as effective therapeutic targets for somatostatin and its analogs and GnRH analogs, is well known and documented (Subramani *et al.* 2017; Wennbo, Törnell, 2000; Boguszewski, Boguszewski, 2019; Zhu *et al.* 2020; Khanlari *et al.* 2018).

GH, GHRH and GnRH can also be produced in an autocrine/paracrine way from breast cancer cells (RE Verification of their receptor expression in TNBC confirms the therapeutic antiproliferative indication of their receptor ligands: somatostatin and GnRh analogs. GnRH analogs exert an anti-proliferative effect by inhibiting gonadotropins. It has been documented in the literature that all the transformations of angiogenesis and the growth factors that synergistically contribute to it are negatively regulated by somatostatin and its analogues (Dicitore *et al.* 2022; Aslam *et al.* 2022; Rai *et al.* 2015). The autocrine effect of GH inhibits anchoring and adhesion-growth inhibition mechanisms in breast cancer cells, thereby promoting in vitro tumor growth (Kaulsay *et al.* 2001; Zhang *et al.* 2023; Brunet-Dunand *et al.* 2009; Mukhina *et al.* 2004; Xu *et al.* 2005). In addition, a broad distribution with variable GHR concentrations was observed in many types of both normal and neoplastic cells, with a clear and significant tumor cell prevalence proportional to the proliferative index and the invasive and metastatic capacity (Yan *et al.* 2021; Di Bella *et al.* 2018; Subramani *et al.* 2014).

It is documented that GH, in synergy with prolactin (PRL), activates a cascade of multiple proliferative phenomena, of which somatostatin and prolactin inhibitors are the physiological, non-toxic antidote. There are scientific proof that the expansion of tumor clones is positively regulated by the mitogenic GH-PRL axis enhanced by the proliferative synergism of the insulin growth factor (IGF)-1, epidermal growth factor (EGF), and all GH-related growth factors (Li *et al.* 2023; Mangili *et al.* 2022). The neoplastic proliferative index is also shown to be strictly dose-dependent on the expression of GH-R and GHRH-R in tumor cells. Inhibition of the GH-PRL-GF mitogenic axis is achieved through the interaction of somatostatin, its analogues and dopamine-2 receptor (D2R) agonist prolactin inhibitors (Li *et al.* 2023; Mangili *et al.* 2022).

The development of cancer cells is a multistep process that involves numerous abnormal signaling and genetic pathways. Therefore, treatment should be approached in a similar multifaceted manner. It is also essential to target cancer stem cells (CSCs) to prevent cancer from recurring. To address this, the Di Bella Method (DBM) was established (Di Bella *et al.* 1979a; Di Bella *et al.* 1979b). The DBM involves administering various specific molecules, each selected based on its mechanism of action against tumor cells, CSCs, proliferation and apoptosis, oncogenes, angiogenesis, molecular analysis, and genetic mutations. Additionally, some molecules are chosen for their protective effects on healthy cells, including the preservation of cell membrane integrity, DNA stability, and mitochondrial function (Di Bella 2010).

The objectives of the DBM biological multitherapy are not aimed at the utopian and misleading stable cytotoxic, cytolytic eradication or ionizing radiation of all tumor cells, but at their physiological reprogramming. This new concept can only be based on a rational multitherapy that intervenes on the multiplicity and variety of the vital functions disrupted by the cancer, gradually bringing them back to normal. It considers cellular destinies that are not necessarily marked as irreversible, but which can be modulated with a non-toxic biological multitherapy, that intervenes sequentially and/or simultaneously and centrally on the strategic targets of neoplastic proliferation and mutability, bringing the many vital reactions deviated by the cancer back to a physiological level. DBM should enhance the

considerable antiproliferative potential of somatostatin (Melhorn *et al.* 2024; O'Toole, Sharma, 2023; Kumar, 2023; Carmona *et al.* 2019; Tartarone *et al.* 2016; Pollak, Schally, 1998) gonadotropin inhibitors, prolactin inhibitor (Li *et al.* 2023; Mangili *et al.* 2022) and the differentiating, immunomodulating, cytostatic antioxidant properties of melatonin (Bhattacharya *et al.* 2019; Zhou *et al.* 2019; Wang *et al.* 2022; Talib *et al.* 2021; Zonta *et al.* 2017; Iravani *et al.* 2020; Samantan, 2022), retinoids when solubilized in Vitamin E (Tratnjek *et al.* 2021; Di Bella L, Di Bella G, 2015; Zuo *et al.* 2016; Jin *et al.* 2022; Castro-Guijarro *et al.* 2022; Hałubiec *et al.* 2021; Ramchatesingh *et al.* 2022),vitamin D3 (Chandler *et al.* 2020; Carlberg, Muñoz, 2022; Wakle *et al.* 2024; Seraphin *et al.* 2023), and vitamin C (Böttger *et al.* 2021; Mussa *et al.* 2022; Zasowska-Nowak *et al.* 2021; Blaszczak *et al.* 2019; Ngo *et al.* 2019; Mikkelsen *et al.* 2021; van Gorkom *et al.* 2019). According to the new concepts, the vitamins in the DBM, from its original biochemical-vital role, has become the essential rational therapeutic role, aimed at achieving organic balance while keeping the relationship between living matter and energy constant.

In the present study, we used DBM in women with TNBC. DBM was used with the standard oncology protocol for TNBC and in some cases DBM was used alone. The study aimed to improve the prognosis of women with TNBC.

## MATERIALS AND METHODS

*Enrolment criteria*

Only patients with a histological diagnosis of breast cancer and measurable disease characteristics according to the Response Evaluation Criteria in Solid Tumors (RECIST) were enrolled.

Thirty-five patients with TNBC with histology, nuclear grade, and immunohistochemical testing for estrogen receptor, HER2/neu, progesterone receptor, Ki67 proliferative index were performed. In addition, instrumental tests were monitored such as PET, CT scan, MRI, and ultrasound.

*Laboratory testing*

Blood tests includes complete blood count, ESR, blood urea nitrogen, glucose, creatinine,, GOT, GPT, GGT, bilirubin, alkaline phosphatase, alpha-fetoprotein, blood ammonia, uric acid, LDH, total and fractionated protein, iron, calcium, , ferritin, electrolytes, FT3, FT4, TSH, GH, IGF1, LH, FSH, Estradiol, Progesterone, Prolactin, Chromogranin, NSE, CEA, Ca 15-3, HE4, Ca 19-9.

*Treatment Protocol*

Patients received a daily combination of somatostatin 4 mg + octreotide 1 mg, melatonin, retinoids solubilized in alpha tocopheryl acetate, dopaminergic agonists, bromocriptine, cabergoline, aromatase inhibitors for anti-estrogen function, low metronomic doses of cyclophosphamide.

In detail, the administered doses include:

- Retinoic acid (ATRA) 0.25 g
- Axerophthol palmitate 0.25 g
- Beta-carotene 1 g. solubilized in alpha tocopheryl acetate 500 g, one tablespoon, approximately 8 ml morning and evening at least 15 minutes before meals Dihydrotachyhisterol 15 drops for every administration of retinoids concurrently with the Retinoids, 30 drops per day
- Somatostatin 4mg with octreotide 1 mg
- Tetracosactide acetate 0.25 mg subcutaneously in the morning, depending on blood pressure and glucose level
- Triptorelin and slow-release LH-FSH analogs 3.75 mg intramuscular every 4 weeks
- Water-solubilized melatonin hydrogen bonded with adenosine, stabilized with 5 mg blister packed tablets of glycine 80 mg per day
- Cabergoline taken orally with the main meal 1 mg (equal to 1/2 tablet) 2 times a week
- Bromocriptine 2.5 mg half tablet taken orally in the morning and evening
- Anastrozole 1 mg tab per day
- Cyclophosphamide 50 mg tab orally, gradual dosage: start with 1 tablet in the morning at breakfast, after one week alternate one day 1 tablet in the morning and one day in the morning only, depending on the complete blood count;
- Ascorbic acid (Vit. C) orally, 1/2 teaspoon (4 g) in a glass of water at noon and in the evening during a meal
- Calcium carbonate 1000 mg/day
- Chondroitin sulfate 250 mg + glucosamine 250 mg one capsule in the morning, noon, and in the evening with meals
- Sucrosomial iron 30 mg tab dose based on serum iron and complete blood count
- Calcium levofolinate 22 mg tablets one per day
- Ursodeoxycholic acid (UDCA) 300 mg to counteract choleric and cholagogic inhibition of SSTs and/or octreotide;
- Na butyrate 500 mg, 3 times a day to inhibit deacetylases and decompaction ofDNA.

*Safety and Toxicity Assessment*

Only treatment-potentially related adverse events (correlation grades: possible, probable or certain, expressed as absolute frequency (n), relative (%), and 95% confidence interval (CI), as described by the National Cancer Institute (NCICTC) criteria (http://www.eortc.be/services/doc/ctc/) were considered for the toxicity assessment. Note: This is a study of the combined use of drugs that have already passed all the reliability and anticancer activity tests. Therefore, all drugs have already been extensively tested and the

**Tab. 1.** Women characteristics, and time of diagnosis with TNBC and treatment with DBM

| PROTOCOL | DATE OF BIRTH | AGE | DIAGNOSIS | Ki-67 % | DIAGNOSIS DATE | NCI CLASSIFICATION | STAGE | DBM | DBM START AGE | DBM START STAGE | LAST CONTACT | SURVIVAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 445 | 2/17/1961 | 42 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | / | June 2003 | Regional | II B | 2006 | 44 | IV | 2/1/2007 | 3 years |
| 768 | 12/15/1971 | 34 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 38% | October 2005 | Regional | II A | 2007 | 37 | II B | 11/1/2023 | 5 years |
| 2258 | 8/5/1958 | 48 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 68% | January 2006 | Regional | III A | 2009 | 51 | IV | 11/1/2012 | 5 years |
| 2287 | 8/6/1954 | 55 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 40% | June 2009 | Metastatic | IV | 2009 | 55 | IV | 11/1/2023 | 5 years |
| 2946 | 4/9/1975 | 35 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 30% | September 2010 | Regional | II B | 2010 | 35 | II B | 1/2/2024 | 5 years |
| 3649 | 8/13/1969 | 40 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | November 2009 | Regional | II A | 2011 | 42 | IV | 4/17/2012 | 2 years |
| 3866 | 10/27/1951 | 60 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 60% | January 2011 | Localized | I | 2011 | 60 | I | 1/31/2024 | 5 years |
| 3885 | 1/30/1966 | 44 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 60% | January 2010 | Regional | III B | 2011 | 45 | III B | 10/1/2012 | 1 year |
| 3897 | 3/26/1955 | 53 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | / | November 2008 | Regional | II A | 2011 | 56 | IV | 1/27/2013 | 3 years |
| 4583 | 7/9/1947 | 65 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 65% | September 2012 | Localized | II A | 2012 | 65 | II A | 4/1/2015 | 1 year |
| 5029 | 8/5/1950 | 54 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 20% | February 2004 | Localized | II A | 2013 | 61 | IV | 3/1/2015 | 5 years |
| 5223 | 9/14/1976 | 46 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 50% | March 2013 | Regional | I | 2013 | 46 | I | 5/1/2014 | 1 year |
| 5607 | 3/17/1949 | 60 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | / | October 2009 | Localized | I | 2013 | 64 | IV | 8/1/2015 | 5 years |

| PROTOCOL | DATE OF BIRTH | AGE | DIAGNOSIS | Ki-67 % | DIAGNOSIS DATE | NCI CLASSIFICATION | STAGE | DBM | DBM START AGE | DBM START STAGE | LAST CONTACT | SURVIVAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5712 | 3/14/1973 | 40 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 35% | June 2013 | Localized | II A | 2014 | 41 | II A | 1/13/2024 | 5 years |
| 6335 | 1/21/1977 | 37 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 80% | March 2014 | Regional | III B | 2015 | 38 | IV | 6/15/2015 | 1 year |
| 6703 | 1/3/1962 | 50 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 25% | January 2012 | Regional | N.D. | 2015 | 53 | N.D. | 11/22/2015 | 3 years |
| 6705 | 10/2/1976 | 39 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 90% | May 2015 | Localized | I | 2015 | 39 | I | 2/3/2022 | 5 years |
| 7090 | 12/23/1949 | 66 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | July 2015 | Regional | III B | 2015 | 66 | IV | 5/13/2017 | 1 year |
| 7248 | 11/5/1978 | 37 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | October 2015 | Regional | II B | 2015 | 37 | II B | 12/1/2023 | 5 years |
| 8065 | 11/8/1980 | 36 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 25% | June 2016 | Regional | I | 2016 | 36 | I | 4/9/2024 | 5 years |
| 8208 | 4/22/1979 | 37 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | June 2016 | Localized | II A | 2016 | 37 | II B | 5/1/2017 | 1 year |
| 8255 | 4/17/1959 | 57 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 30% | August 2016 | Regional | II A | 2016 | 57 | I B | 3/21/2017 | 1 year |
| 8751 | 4/11/1970 | 47 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 80% | May 2017 | Regional | I B | 2017 | 47 | N.D | 4/1/2022 | 3 years |
| 8918 | 12/1/1963 | 60 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 60% | July 2017 | Regional | III C | 2017 | 60 | III C | 5/1/2019 | 1 year |
| 9167 | 11/20/1975 | 42 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 90% | November 2017 | Regional | III A | 2017 | 42 | III A | 6/20/2024 | 5 years |
| 9285 | 6/22/1961 | 62 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | January 2018 | Regional | III B | 2018 | 62 | III B | Feb-19 | 1 year |

| PROTOCOL | DATE OF BIRTH | AGE | DIAGNOSIS | Ki-67 % | DIAGNOSIS DATE | NCI CLASSIFICATION | STAGE | DBM | DBM START AGE | DBM START STAGE | LAST CONTACT | SURVIVAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9769 | 6/14/1975 | 48 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 80% | November 2018 | Localized | II A | 2018 | 48 | II A | Feb-24 | 5 years |
| 9905 | 10/10/1948 | 71 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 70% | January 2019 | Metastatic | IV | 2019 | 71 | IV | Nov-21 | 2 years |
| 9908 | 9/30/1970 | 49 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 90% | January 2019 | Localized | I | 2019 | 49 | I | 6/5/2024 | 5 years |
| 9961 | 10/23/1941 | 87 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 15% | October 2018 | Regional | III A | 2019 | 88 | III A | 10/26/2023 | 5 years |
| 10136 | 4/1/1960 | 63 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 54% | April 2019 | Regional | 0 | 2019 | 63 | II B | 5/30/2024 | 5 years |
| 10268 | 5/19/1949 | 69 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 22% | September 2018 | Metastatic | IV | 2019 | 70 | IV | 8/1/2020 | 2 years |
| 10588 | 10/27/1961 | 63 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 38% | February 2020 | Regional | III C | 2020 | 63 | III C | 6/20/2022 | 2 years |
| 11208 | 8/13/1962 | 62 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 30% | December 2020 | Localized | II A | 2020 | 62 | II A | 2/23/2024 | 3 years |
| 11469 | 8/31/1952 | 72 | Infiltrating ductal carcinoma TRIPLE NEGATIVE | 40% | November 2020 | Localized | I | 2021 | 72 | I | 1/30/2024 | 3 years |

use of which is approved by international healthcare organizations, but in this context are only used in a new combination. This study was conducted in accordance with the directives set out by The Good Clinical Practices directives and the Helsinki Declaration. Therefore, all patients have given their informed consent to participate in the study.

## RESULTS

In this study, 35 patients were enrolled and their detailed information including age, type of TNBC, when DBM was initiated were included in Table 1. The mean age of women was 52.3 ±12.9 years. When DBM was initiated, 11 out of 35 were TNBC stage IV, 6 were stage III, 9 were stage II, and 7 were stage I, and one was not determined. Furthermore, the percentage of Ki-67 in the breast tissue of each patient was determined and ranged from 20 to 90% (Table 1).

During DBM treatment, women survival was monitored at 1, 2, 3 and 5 years. The number of patients considered gradually decreased over time due to the lack of updated data, until 25 patients with documentation present, 16 of whom are still being monitored (Table 2). At the same time, we extrapolated data from 13 patients, 12 of whom underwent surgery and 1 who underwent Di Bella therapy without undergoing any previous treatment. Again, during the follow-up, we did not receive any updates and the number of patients progressively decreased from 13 to 10, of which 6 are still alive.

The results obtained in the 35 patients who had been treated with the DBM, and the

**Tab. 2.** Survival of TNBC patients treated with DBM during a five-year-follow-up

| **Patients who had received DBM therapy with standard protocol for TNBC** | **Total patients 35** | **%** |
|---|---|---|
| 1-year survival | 35\35 | 100% |
| 2-years survival | 26\30 | 87% |
| 3-years survival | 22\29 | 76% |
| 5-years survival | 16\25 | 64% |
| **Patients who had only DBM therapy and after surgery** | **Total patients 13** | **%** |
| 1-year survival | 13\13 | 100% |
| 2-years survival | 9\12 | 75% |
| 3-years survival | 8\12 | 67% |
| 5-years survival | 6\10 | 60% |

standard therapeutic protocol for TNBC, had a survival rate of 64% at 5 years, 76% at 3 years, 87% at 2 years and 100% after 1 year of therapy (Table 2). On the other hand, the 13 patients who did not undergo chemotherapy or radiotherapy had a survival rate 60% at 5 years, 67% at 3 years, 75% at 2 years and 100% after 1 year of therapy.

## DISCUSSION

Considering that TNBC usually has an inauspicious prognosis, and that survival is often very low, patients treated with DBM had higher survival rates compared with those who undertook only standard oncology protocols, as demonstrated in the IMpassion130 study (Schmid *et al.* 20118). In the latter phase 3 study, women with TNBC treated with atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel had median overall survival of 21.3 and 17.6 months, respectively. In the present study, patients treated with DBM and chemotherapy, or DBM alone had median survival more than 60 months.

According to the American Cancer Society https://www.cancer.org/cancer/types/breast-cancer /about/types-of-breast-cancer/triple-negative.html cases

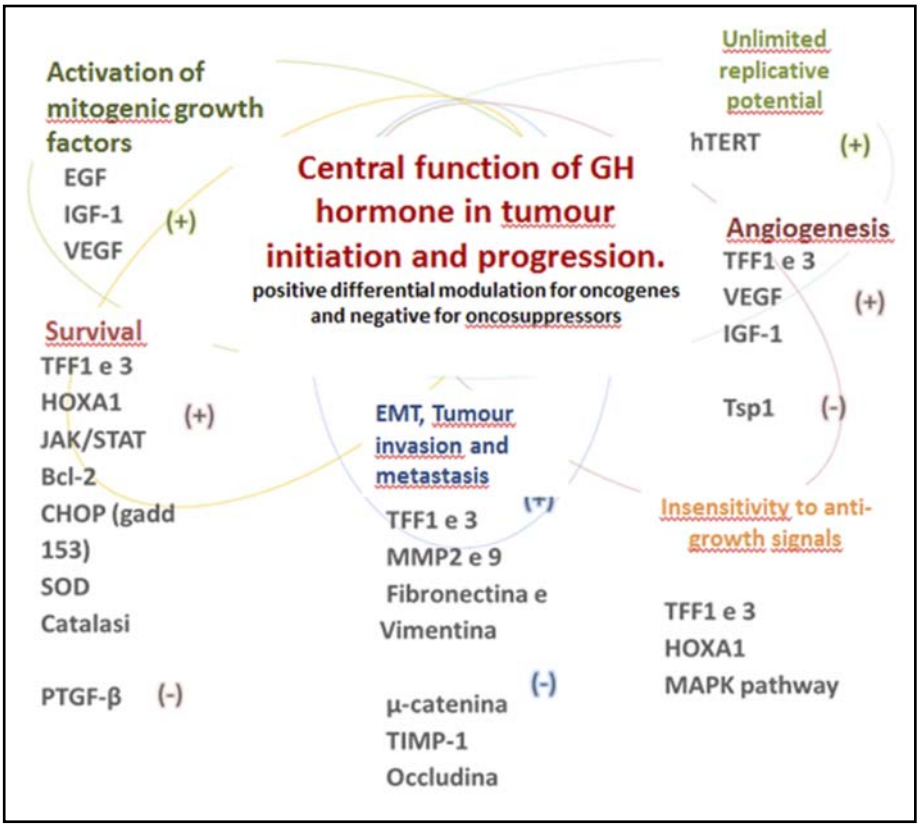


**Fig. 1.** TFF 1 and 3: trefoil factor; HOXA 1: homeobox 1; MAPK: mitogen-activated protein kinase; MMP2 and MMP9: matrix metalloproteinases 2 and 9; JAK/STAT: janus kinase proteins; BCL-2: B-cell lymphoma; CHOP: C/EBP homologous protein; SOD: superoxide dismutase; VEGF: vascular endothelial growth factor; IGF-1: insulin-like growth factor 1; EGF: epidermis growth factor; hTERT: human telomerase reverse transcriptase. Oncogenic proliferative functions of growth hormone (GH).

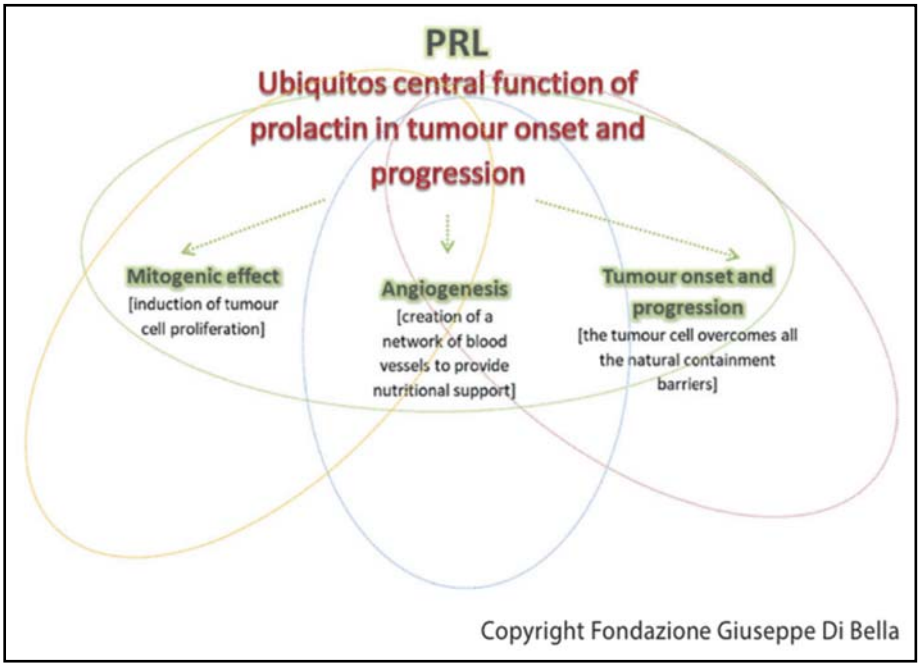


**Fig. 2.** Prolactin has a central role in tumor onset and progression through mitogenic effect and angiogenesis.

of relapse after surgery and oncological treatments are not considered in the official survival statistics, therefore since cases of progression as such have been eliminated, the data reported by the official statistics are overestimated. However, according to data from the American Cancer Society, in cases of TNBC progression or metastasis, survival does not exceed 12 months. The official 5-year survival statistics are partial and therefore only refer to the minority of cases that have not relapsed after surgery and cancer treatment. Therfore, the present study showed the significant imporvement of the DBM multitherapy to patients with TNBC.

The key features in DBM therapy are the biological multitherapeutic targeting effect including CSC, proliferation index, angiogenesis, and the physiological reprogramming of the cancer cells by bringing many vital reactions deviated by the cancer back to a physiological level. Numerous studies on the biological functions of GH document the oncogenic induction of its over-expression and the dose-dependent relationship between the extent of GH/IGF1/GHR expression and proliferative and aggressive characteristics of neoplastic clones (Vacas *et al.* 2016; Murphy *et al.* 2020; Basu, Kopchick, 2023) (Fig. 1). GH, GHR, GHRH and GHRHR concentrations are markedly higher in breast tumor tissues than in physiological and peritumoral receptor expression, with a dose-dependent proliferative index (Vacas *et al.* 2016; Murphy *et al.* 2020; Basu, Kopchick, 2023). It has been shown that a broad distribution with variable GHR concentrations was observed in many types of both normal and neoplastic cells, with a clear and significant tumor cell prevalence proportional to the proliferative index and the invasive and metastatic capacity (Yan *et al.* 2021; Di Bella *et al.* 2018; Subramani *et al.* 2014). Cytoplasmic synthesis of GHR at the endoplasmic reticulum and Golgi apparatus was also documented, and showed that GH in serum circulates complexed with Growth Hormone-Binding Protein (GHBP) (Schilbach, Bidlingmaier, 2015; Matsoukas, Spyroulias, 2017; Fisker, 2006). Human serum GHBP contains the extra-cellular portion of GHR and can be produced by a specific proteolytic shredding of the GHR extracellular domain. The extracellular protein portion that binds the hormone is therefore common to both GHR and GHBP. The nuclear receptor also has the same protein portion that binds the GH present in both the GHR and the GHBP. The presence of GHR in the nucleus confirms the hypothesis that the internalized GH inside the cell can modulate the transcription of specific genes.

Furthermore, the proteins that regulate GH secretion by the pituitary have been implicated in breast neoplasm (Subramani *et al.* 2017; Wennbo, Törnell, 2000; Boguszewski, Boguszewski, 2019; Zhu *et al.* 2020), and it has been shown that expression of Pit-1 increases the expression of GH mRNA and proliferation in human breast cancer cells (Martinez-Ordoñez *et al.* 2018; Ben-Batalla *et al.* 2010; Seoane *et al.* 2019). GH promotes the immortalization of breast epithelial cell lines by increasing the mRNA and protein levels of the human telomerase catalytic subunit, hTERT (Emerald *et al.* 2007; Yang *et al.* 2023; Nguyen *et al.* 2022; Romaniuk-Drapała *et al.* 2021). Also, autocrine GH inhibits anchoring and adhesion mechanisms in breast cancer cells, promoting in vitro tumor growth (Kaulsay *et al.* 2001; Zhang *et al.* 2023; Brunet-Dunand *et al.* 2009; Mukhina *et al.* 2004; Xu *et al.* 2005). In addition, GH increases metastatic breast carcinomas by interrupting cell – cell contact and by increasing cell migration and invasion (Baskari *et al.* 2017; Brittain

*et al.* 2017; Zhang *et al.* 2015), and the expression of GH can increase the activity of telomerase and extend a primary breast epithelial cell line's ability to replicate (Banks *et al.* 2010; Emerald *et al.* 2007; Bayne, Liu, 2005; Jaiswal, Yadava, 2020);. Therefore, the expression of autocrine GH thus meets the criteria to be considered an oncogene for human breast cells (Perry *et al.* 2006; Wang *et al.* 2023).

PRL has a dual function: as a circulating hormone and as a cytokine. This understanding is based on the production of PRL and the distinct regulation sites, on its binding to the membrane receptors of the cytokine receptor superfamily and on the activation of signalling pathways that promote cell growth and survival (Fig.2).

There is growing evidence that PRL plays a role in different types of cancer in reproductive and non-reproductive tissues through local production or accumulation. The expression of both PRL and its receptor in human tumor cell lines of different origins provides further support of its action as an autocrine/paracrine growth factor (Li *et al.* 2023; Mangili *et al.* 2022). The scientific evidence of the decisive active role PRL plays in tumorigenesis should include its inhibitors in all oncology protocols. Its receptors are co-expressed on plasma membranes with those of the GH to which they dimerize (Fig.3).

Tumor expansion only occurs when there is tumor angiogenesis. It has been documented in the literature that all the transformations of angiogenesis and the growth factors that synergistically contribute to it are negatively regulated by somatostatin and its analogues (Dicitore *et al.* 2022; Aslam *et al.* 2022; Rai *et al.* 2015). All the other DBM components, although to a lesser extent than somatostatin, adversely regulate angiogenesis (Fig.3). If neoplastic expansion has a forced transformation into angiogenesis, and if angiogenesis is inhibited by somatostatin, its indication in all cancers, whether or not SSTR is present, is further clarified and documented.

Retinoic acid and MLT interact with CSCs, identified in a variety of tumors, which act as a clonogenic nucleus to give origin to new tumor growth. CSCs show clonogenic properties of self-renewal and flexibility, and help define specific tumor microenvironments (TMEs). The interaction between CSCs and TMEs is thought to work as a dynamic support system that promotes the generation and maintenance of CSCs. The interaction between CSCs and TMEs creates the foundation for a new multi-therapy approach including MLT, ATRA and D3. Among the synergistic mechanisms of ATRA and D3 is the heterodimerization of the RXR nuclear receptors of ATRA and VDR of D3. The biomolecular mechanisms of ATRA and MLT on the CSCs and the homeostatic mechanisms on the hypoxia of MLT were also studied. It strongly activates blood tissue exchanges and the perfusion of organs and tissues physiologically regulates the partial oxygen tension and pH, thus counteracting the causes of hypoxia and the subsequent high expression of HIF (HIF1α, HIF-2α), which are powerful oncogenic transcription factors. Na butyrate can create an epigenetic context for chromatin relaxation, which is essential for interaction with the transcription factors

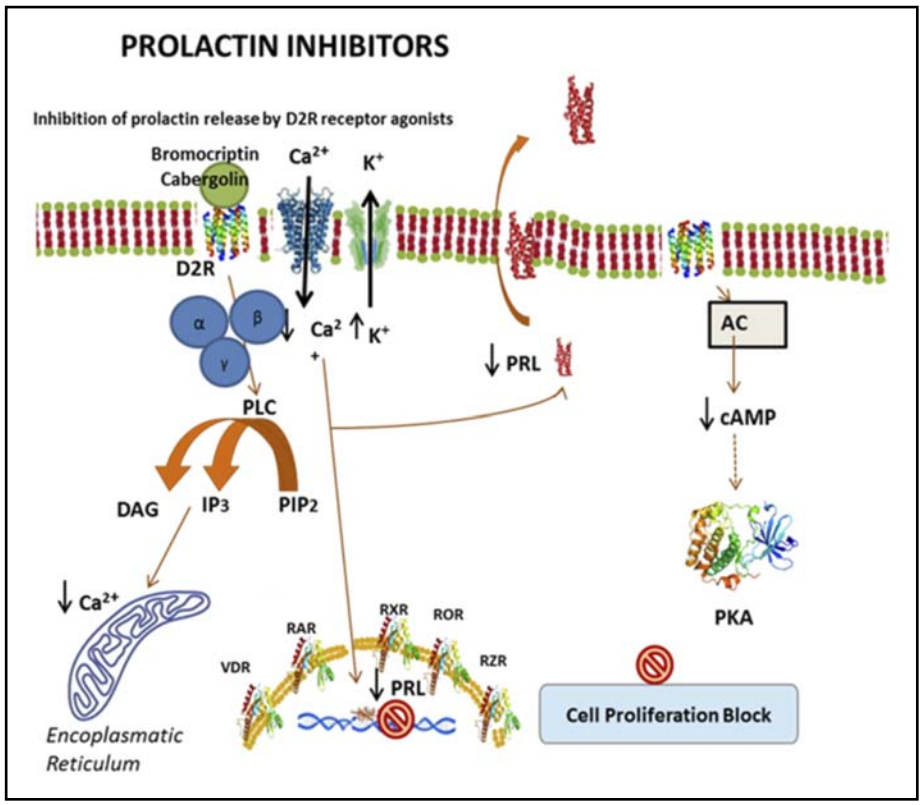


**Fig. 3.** AC: adenylate cyclase; C-AMP: cyclic Adenosine Monophosphate; PKA: protein kinase A; PRL: prolactin; D2R: dopamine receptor 2; PLC: phospholipase; PIP2: phosphoinositol biphosphate; DAG: diacylglycerol; IP3: inositol triphosphate; RAR: retinoic acid receptors; ROR: orphan retinoid-MLT receptors; RZR: Z retinoid-MLT receptors; VDR: vitamin D receptors; RXR: retinoic acid receptors. Bromocriptin and cabergolin are inhibitors of prolactin release, binding D2R receptor. The activation of D2R receptor induces different mechanism in cell until proliferation block

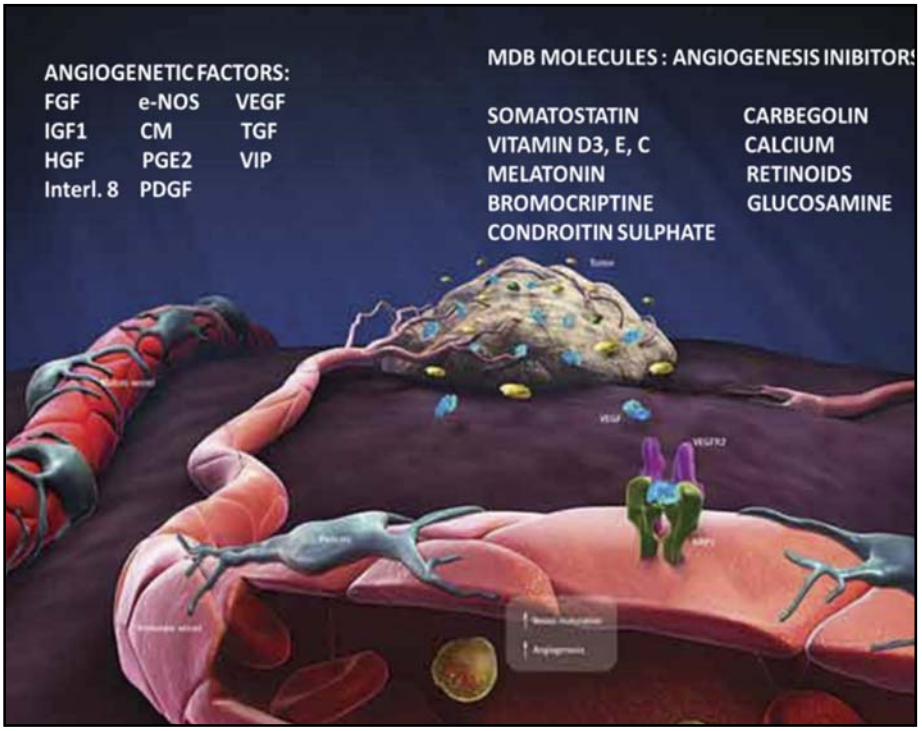


**Fig. 4.** Angiogenesis-promoting factors and angiogenesis inhibitors

of the family of "Zinc Fingers" and "Homeodomains", including transcription factors activated by nuclear receptors of DBM components such as retinoids, vitamin D and melatonin involved in differentiation processes. Retinoic acid works by creating specific and complex differentiating orientations. The role of melatonin is also important; in fact, besides regulating the physiological perfusion of organs and tissues, it regulates the blood-tissue exchanges, and multiple events that can have an impact on the molecular dynamics of cancer stem cells.

## CONCLUSIONS

In TNBC, the DBM biological multitherapy increased survival of patients with TNBC compared patients treated with standard protocols, and with no significant adverse events or toxicity. The data conforms to the published results of the DBM in other types of cancers to verify the rationality of this biological multitherapy and the anti-tumor synergy of somatostatin, prolactin inhibitors, GnRH analogs, MLT, retinoids, solubilized in tocopherols, vitamins D3 and C, proteoglycans, calcium and sodium butyrate. These results warrants the need of more standardized clinical trials of DBM in women with TNBC.

## DATA ACCESS STATEMENT

Data not available - participant consent. The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

## AUTHOR CONTRIBUTION STATEMENT

Giuseppe Di Bella: conceptualization, methodology, writing original draft. Ilaria Moscato: data curation, writing, formal analysis, investigation. Elena Costanzo: writing, data curation, investigation. Giovanni Di Giorgi: formal analysis, data curation. All authors reviewed the results and approved the final version of the manuscript.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## FUNDING STATEMENT

The authors did not receive support from any organization for the submitted work.

REFERENCES

1 Aslam M, Idrees H, Ferdinandy P, Helyes Z, Hamm C, Schulz R (2022). Somatostatin Primes Endothelial Cells for Agonist-Induced Hyperpermeability and Angiogenesis In Vitro. Int J Mol Sci. **23**(6): 3098. doi: 10.3390/ijms23063098. PMID: 35328517; PMCID: PMC8949535.

2 Banks WA, Morley JE, Farr SA, Price TO, Ercal N, Vidaurre I, et al. (2010). Effects of a growth hormone-releasing hormone antagonist on telomerase activity, oxidative stress, longevity, and aging in mice. Proc Natl Acad Sci USA. **107**(51): 22272–7. doi: 10.1073/pnas.1016369107. Epub 2010 Dec 6. PMID: 21135231; PMCID: PMC3009756.

3 Baskari S, Govatati S, Madhuri V, Nallabelli N, K PM, Naik S, et al. (2017). Influence of autocrine growth hormone on NF-κB activation leading to epithelial-mesenchymal transition of mammary carcinoma. Tumour Biol. **39**(10): 1010428317719121. doi: 10.1177/1010428317719121. PMID: 29022487.

4 Basu R, Kopchick JJ. (2023). GH and IGF1 in cancer therapy resistance. Endocr Relat Cancer. **30**(9): e220414. doi: 10.1530/ERC-22-0414. PMID: 37283510.

5 Bayne S, Liu JP. (2005). Hormones and growth factors regulate telomerase activity in ageing and cancer. Mol Cell Endocrinol. **240**(1–2): 11–22. doi: 10.1016/j.mce.2005.05.009. PMID: 16005142.

6 Ben-Batalla I, Seoane S, Garcia-Caballero T, Gallego R, Macia M, Gonzalez LO, et al. (2010). Deregulation of the Pit-1 transcription factor in human breast cancer cells promotes tumor growth and metastasis. J Clin Invest. **120**(12): 4289–302. doi: 10.1172/JCI42015. Epub 2010 Nov 8. PMID: 21060149; PMCID: PMC2993584.

7 Bhattacharya S, Patel KK, Dehari D, Agrawal AK, Singh S. (2019). Melatonin and its ubiquitous anticancer effects. Mol Cell Biochem. **462**(1–2): 133–155. doi: 10.1007/s11010-019-03617-5. Epub 2019 Aug 26. PMID: 31451998.

8 Blaszczak W, Barczak W, Masternak J, Kopczyński P, Zhitkovich A, Rubiś B.(2019). Vitamin C as a Modulator of the Response to Cancer Therapy. Molecules. **24**(3): 453. doi: 10.3390/molecules24030453. PMID: 30695991; PMCID: PMC6384696.

9 Boguszewski CL, Boguszewski MCDS. (2019). Growth Hormone's Links to Cancer. Endocr Rev. **40**(2): 558–574. doi: 10.1210/er.2018-00166. PMID: 30500870.

10 Böttger F, Vallés-Martí A, Cahn L, Jimenez CR. (2021). High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. J Exp Clin Cancer Res. **40**(1): 343. doi: 10.1186/s13046-021-02134-y. PMID: 34717701; PMCID: PMC8557029.

11 Brittain AL, Basu R, Qian Y, Kopchick JJ. (2017). Growth Hormone and the Epithelial-to-Mesenchymal Transition. J Clin Endocrinol Metab. **102**(10): 3662–3673. doi: 10.1210/jc.2017-01000. PMID: 28938477.

12 Brunet-Dunand SE, Vouyovitch C, Araneda S, Pandey V, Vidal LJ, Print C, et al. (2009). Autocrine human growth hormone promotes tumor angiogenesis in mammary carcinoma. Endocrinology. **150**(3): 1341–52. doi: 10.1210/en.2008-0608. Epub 2008 Oct 30. PMID: 18974274.

13 Carlberg C, Muñoz A. (2022). An update on vitamin D signaling and cancer. Semin Cancer Biol. **79**: 217–230. doi: 10.1016/j.semcancer.2020.05.018. Epub 2020 May 30. PMID: 32485310.

14 Carmona Matos DM, Jang S, Hijaz B, Chang AW, Lloyd RV, Chen H, et al. (2019). Characterization of somatostatin receptors (SSTRs) expression and antiproliferative effect of somatostatin analogues in aggressive thyroid cancers. Surgery. **165**(1): 64–68. doi: 10.1016/j.surg.2018.05.077. Epub 2018 Nov 8. PMID: 30415874.

15 Castro-Guijarro AC, Vanderhoeven F, Mondaca JM, Redondo AL, Zoppino FCM, Fernandez-Muñoz JM, et al. (2022). Combination Treatment of Retinoic Acid Plus Focal Adhesion Kinase Inhibitor Prevents Tumor Growth and Breast Cancer Cell Metastasis. **11**(19): 2988. doi: 10.3390/cells11192988. PMID: 36230951; PMCID: PMC9564078.

16 Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, Bubes V, et al. (2020); VITAL Research Group. Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. JAMA Netw Open. **3**(11): e2025850. doi: 10.1001/jamanetworkopen.2020.25850. Erratum in: JAMA Netw Open. 2020 Dec 1;3(12):e2032460. doi: 10.1001/jamanetworkopen.2020.32460. PMID: 33206192; PMCID: PMC7675103.

17 Chen YJ, Zhang X, Wu ZS, Wang JJ, Lau AY, Zhu T, et al. (2015). Autocrine human growth hormone stimulates the tumor initiating capacity and metastasis of estrogen receptor-negative mammary carcinoma cells. Cancer Lett. **365**(2): 182–9. doi: 10.1016/j.canlet.2015.05.031. Epub 2015 Jun 9. PMID: 26070963.

18 Christopoulos PF, Msaouel P, Koutsilieris M. (2015). The role of the insulin-like growth factor-1 system in breast cancer. Mol Cancer. **14**: 43. doi: 10.1186/s12943-015-0291-7. PMID: 25743390; PMCID: PMC4335664.

19 de Ostrovich KK, Lambertz I, Colby JK, Tian J, Rundhaug JE, Johnston D, et al. (2008). Paracrine overexpression of insulin-like growth factor-1 enhances mammary tumorigenesis in vivo. Am J Pathol. **173**(3): 824–34. doi: 10.2353/ajpath.2008.071005. Epub 2008 Aug 7. PMID: 18688034; PMCID: PMC2527085.

20 Di Bella G, Colori B, Scanferlato R. (2018). The over-expression of GH/GHR in tumour tissues with respect to healthy ones confirms its oncogenic role and the consequent oncosuppressor role of its physiological inhibitor, somatostatin: a review of the literature. Neuro Endocrinol Lett. **39**(3): 179–188. PMID: 30431745

21 Di Bella L, Di Bella G. (2015). Solution of retinoids in vitamin E in the Di Bella Method biological multitherapy. Neuro Endocrinol Lett. **36**(7): 661–76. PMID: 26859589.

22 Dicitore A, Saronni D, Gaudenzi G, Carra S, Cantone MC, Borghi MO, et al. (2022). Long-term effects of somatostatin analogues in rat GH-secreting pituitary tumor cell lines. J Endocrinol Invest. **45**(1): 29–41. doi: 10.1007/s40618-021-01609-1. Epub 2021 Jun 14. PMID: 34128215; PMCID: PMC8741688.

23 Emerald BS, Chen Y, Zhu T, Zhu Z, Lee KO, Gluckman PD, et al. (2007). AlphaCP1 mediates stabilization of hTERT mRNA by autocrine human growth hormone. J Biol Chem. **282**(1): 680–90. doi: 10.1074/jbc.M600224200. Epub 2006 Nov 3. PMID: 17085453.

24 Fisker S. (2006). Physiology and pathophysiology of growth hormone-binding protein: methodological and clinical aspects. Growth Horm IGF Res. **16**(1): 1–28. doi: 10.1016/j.ghir.2005.11.001. Epub 2005 Dec 15. PMID: 16359897.

25 Hałubiec P, Łazarczyk A, Szafrański O, Bohn T, Dulińska-Litewka J. (2021). Synthetic Retinoids as Potential Therapeutics in Prostate Cancer-An Update of the Last Decade of Research: A Review. Int J Mol Sci. **22**(19): 10537. doi: 10.3390/ijms221910537. PMID: 34638876; PMCID: PMC8508817.

26 Herbert BS, Wright WE, Shay JW. (2001). Telomerase and breast cancer. Breast Cancer Res. 2001. **3**(3): 146–9. doi: 10.1186/bcr288. PMID: 11305948; PMCID: PMC138678.

27 Ianza A, Sirico M, Bernocchi O, Generali D. (2021). Role of the IGF-1 Axis in Overcoming Resistance in Breast Cancer. Front Cell Dev Biol. **9**: 641449. doi: 10.3389/fcell.2021.641449. PMID: 33829018; PMCID: PMC8019779.

28 Imbalzano KM, Tatarkova I, Imbalzano AN, Nickerson JA. (2009). Increasingly transformed MCF-10A cells have a progressively tumor-like phenotype in three-dimensional basement membrane culture. Cancer Cell Int. **9**: 7. doi: 10.1186/1475-2867-9-7. PMID: 19291318; PMCID: PMC2666639.

29 Iravani S, Eslami P, Dooghaie Moghadam A, Moazzami B, Mehrvar A, et al. (2020). The Role of Melatonin in Colorectal Cancer. J Gastrointest Cancer. **51**(3): 748–753. doi: 10.1007/s12029-019-00336-4. PMID: 31792737.

30 Jaiswal RK, Yadava PK. (2020). Assessment of telomerase as drug target in breast cancer. J Biosci. **45**: 72. PMID: 32515354.

31 Jin Y, Teh SS, Lau HLN, Xiao J, Mah SH. (2022). Retinoids as anticancer agents and their mechanisms of action. Am J Cancer Res. **12**(3): 938–960. PMID: 35411232; PMCID: PMC8984900.

32 Kaulsay KK, Zhu T, Bennett W, Lee KO, Lobie PE. (2001). The effects of autocrine human growth hormone (hGH) on human mammary carcinoma cell behavior are mediated via the hGH receptor. Endocrinology. **142**(2): 767–77. doi: 10.1210/endo.142.2.7936. PMID: 11159849.

33 Khanlari M, Schally AV, Block NL, Nadji M. (2018). Expression of GHRH-R, a Potentially Targetable Biomarker, in Triple-negative Breast Cancer. Appl Immunohistochem Mol Morphol. **26**(1): 1–5. doi: 10.1097/PAI.0000000000000622. PMID: 29206714.

34 Kumar U. (2023). Somatostatin and Somatostatin Receptors in Tumour Biology. Int J Mol Sci. **25**(1): 436. doi: 10.3390/ijms25010436. PMID: 38203605; PMCID: PMC10779198.

35 Li R, Yang Y, Lan H, Wang Y, Ge Z, Liu X, et al. (2023). A Novel Mechanism of hPRL-G129R, a Prolactin Antagonist, Inhibits Human Breast Cancer Cell Proliferation and Migration. Endocrinology. **164**(12): bqad158. doi: 10.1210/endocr/bqad158. PMID: 37934803.

36 Li S, Zhou J, Wu H, Lu Q, Tai Y, Liu Q, et al. (2018). Oncogenic transformation of normal breast epithelial cells cocultured with cancer cells. Cell Cycle. **17**(16): 2027–2040. doi: 10.1080/15384101.2018.1511510. Epub 2018 Sep 18. PMID: 30160604; PMCID: PMC6224270.

37 Mangili F, Esposito E, Treppiedi D, Catalano R, Marra G, Di Muro G, et al. (2022). DRD2 Agonist Cabergoline Abolished the Escape Mechanism Induced by mTOR Inhibitor Everolimus in Tumoral Pituitary Cells. Front Endocrinol (Lausanne). **13**: 867822. doi: 10.3389/fendo.2022.867822. PMID: 35721701; PMCID: PMC9204243.

38 Martinez-Ordoñez A, Seoane S, Cabezas P, Eiro N, Sendon-Lago J, Macia M, et al. (2018). Breast cancer metastasis to liver and lung is facilitated by Pit-1-CXCL12-CXCR4 axis. Oncogene. **37**(11): 1430–1444. doi: 10.1038/s41388-017-0036-8. Epub 2018 Jan 11. PMID: 29321662.

39 Matsoukas MT, Spyroulias GA. (2017). Dynamic properties of the growth hormone releasing hormone receptor (GHRHR) and molecular determinants of GHRH binding. Mol Biosyst. **13**(7): 1313–1322. doi: 10.1039/c7mb00130d. PMID: 28561845.

40 Melhorn P, Mazal P, Wolff L, Kretschmer-Chott E, Raderer M, Kiesewetter B. (2024). From biology to clinical practice: antiproliferative effects of somatostatin analogs in neuroendocrine neoplasms. Ther Adv Med Oncol. **16**: 17588359241240316. doi: 10.1177/17588359241240316. PMID: 38529270; PMCID: PMC10962050.

41 Mikkelsen SU, Gillberg L, Lykkesfeldt J, Grønbæk K. (2021). The role of vitamin C in epigenetic cancer therapy. Free Radic Biol Med. **170**: 179–193. doi: 10.1016/j.freeradbiomed.2021.03.017. Epub 2021 Mar 28. PMID: 33789122.

42 Mukhina S, Mertani HC, Guo K, Lee KO, Gluckman PD, Lobie PE. (2004). Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone. Proc Natl Acad Sci USA. **101**(42): 15166–71. doi: 10.1073/pnas.0405881101. Epub 2004 Sep 7. PMID: 15353581; PMCID: PMC524067.

43 Murphy N, Knuppel A, Papadimitriou N, Martin RM, Tsilidis KK, Smith-Byrne K, et al. (2020). Insulin-like growth factor-1, insulin-like growth factor-binding protein-3, and breast cancer risk: observational and Mendelian randomization analyses with ~430 000 women. Ann Oncol. **31**(5): 641–649. doi: 10.1016/j.annonc.2020.01.066. PMID: 32169310; PMCID: PMC7221341.

44 Mussa A, Mohd Idris RA, Ahmed N, Ahmad S, Murtadha AH, Tengku Din TADAA, et al. (2022). High-Dose Vitamin C for Cancer Therapy. Pharmaceuticals (Basel). **15**(6): 711. doi: 10.3390/ph15060711. PMID: 35745630; PMCID: PMC9231292.

45 Ngo B, Van Riper JM, Cantley LC, Yun J. (2019). Targeting cancer vulnerabilities with high-dose vitamin C. Nat Rev Cancer. **19**(5): 271–282. doi: 10.1038/s41568-019-0135-7. PMID: 30967651; PMCID: PMC6526932.

46 Nguyen E, Richerolle A, Sánchez-Bellver J, Varennes J, Ségal-Bendirdjian E. (2022). hTERT DNA Methylation Analysis Identifies a Biomarker for Retinoic Acid-Induced hTERT Repression in Breast Cancer Cell Lines. Biomedicines. **10**(3): 695. doi: 10.3390/biomedicines10030695. PMID: 35327497; PMCID: PMC8945736.

47 O'Toole TJ, Sharma S.(2023). Physiology, Somatostatin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30855911.

48 Perry JK, Emerald BS, Mertani HC, Lobie PE. (2006). The oncogenic potential of growth hormone. Growth Horm IGF Res. **16**(5–6): 277–89. doi: 10.1016/j.ghir.2006.09.006. Epub 2006 Nov 13. PMID: 17101287.

49 Pollak MN, Schally AV. (1998). Mechanisms of antineoplastic action of somatostatin analogs. Proc Soc Exp Biol Med. **217**(2): 143–52. doi: 10.3181/00379727-217-44216. PMID: 9452137.

50 Rai U, Thrimawithana TR, Valery C, Young SA. (2015). Therapeutic uses of somatostatin and its analogues: Current view and potential applications. Pharmacol Ther. **152**: 98–110. doi: 10.1016/j.pharmthera.2015.05.007. Epub 2015 May 5. PMID: 25956467.

51 Ramchatesingh B, Martínez Villarreal A, Arcuri D, Lagacé F, Setah SA, Touma F, et al. (2022). The Use of Retinoids for the Prevention and Treatment of Skin Cancers: An Updated Review. Int J Mol Sci. **23**(20): 12622. doi: 10.3390/ijms232012622. PMID: 36293471; PMCID: PMC9603842.

52 Romaniuk-Drapała A, Totoń E, Konieczna N, Machnik M, Barczak W, Kowal D, et al. (2021). hTERT Downregulation Attenuates Resistance to DOX, Impairs FAK-Mediated Adhesion, and Leads to Autophagy Induction in Breast Cancer Cells. Cells. **10**(4): 867. doi: 10.3390/cells10040867. PMID: 33920284; PMCID: PMC8068966.

53 Samanta S. (2022). Melatonin: A Potential Antineoplastic Agent in Breast Cancer. J Environ Pathol Toxicol Oncol. **41**(4): 55–84. doi: 10.1615/JEnvironPatholToxicolOncol.2022041294. PMID: 36374962.

54 Schilbach K, Bidlingmaier M. (2015). Growth hormone binding protein - physiological and analytical aspects. Best Pract Res Clin Endocrinol Metab. **29**(5): 671–83. doi: 10.1016/j.beem.2015.06.004. Epub 2015 Jun 27. PMID: 26522453.

55 Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018. **379**(22): 2108–2121. doi:10.1056/NEJMoa1809615

56 Seoane S, Martinez-Ordoñez A, Eiro N, Cabezas-Sainz P, Garcia-Caballero L, Gonzalez LO, et al. (2019). POU1F1 transcription factor promotes breast cancer metastasis via recruitment and polarization of macrophages. J Pathol. **249**(3): 381–394. doi: 10.1002/path.5324. Epub 2019 Aug 27. PMID: 31292963.

57 Seraphin G, Rieger S, Hewison M, Capobianco E, Lisse TS. (2023). The impact of vitamin D on cancer: A mini review. J Steroid Biochem Mol Biol. **231**: 106308. doi: 10.1016/j.jsbmb.2023.106308. Epub 2023 Apr 11. PMID: 37054849; PMCID: PMC10330295.

58 Subramani R, Lopez-Valdez R, Salcido A, Boopalan T, Arumugam A, Nandy S, et al. (2014). Growth hormone receptor inhibition decreases the growth and metastasis of pancreatic ductal adenocarcinoma. Exp Mol Med. **46**(10): e117. doi: 10.1038/emm.2014.61. PMID: 25301264; PMCID: PMC4221692.

59 Subramani R, Nandy SB, Pedroza DA, Lakshmanaswamy R. (2017). Role of Growth Hormone in Breast Cancer. Endocrinology. **158**(6): 1543–1555. doi: 10.1210/en.2016-1928. PMID: 28379395.

60 Talib WH, Alsayed AR, Abuawad A, Daoud S, Mahmod AI. (2021). Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. Molecules. **26**(9): 2506. doi: 10.3390/molecules26092506. PMID: 33923028; PMCID: PMC8123278.

61 Tartarone A, Lerose R, Aieta M. (2016). Somatostatin Analog Therapy in Small Cell Lung Cancer. Semin Nucl Med. **46**(3): 239–42. doi: 10.1053/j.semnuclmed.2015.12.004. PMID: 27067504.

62 Tratnjek L, Jeruc J, Romih R, Zupančič D. (2021). Vitamin A and Retinoids in Bladder Cancer Chemoprevention and Treatment: A Narrative Review of Current Evidence, Challenges and Future Prospects. Int J Mol Sci. **22**(7): 3510. doi: 10.3390/ijms22073510. PMID: 33805295; PMCID: PMC8036787.

63 Vacas E, Muñoz-Moreno L, Valenzuela PL, Prieto JC, Schally AV, Carmena MJ, et al. (2016). Growth hormone-releasing hormone induced transactivation of epidermal growth factor receptor in human triple-negative breast cancer cells. Peptide. **86**: 153–161. doi: 10.1016/j.peptides.2016.11.004. Epub 2016 Nov 2. PMID: 27816751.

64 van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ. (2019). The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review. Nutrients. **11**(5): 977. doi: 10.3390/nu11050977. PMID: 31035414; PMCID: PMC6566697.

65 Wakle KS, Mokale SN, Sakle NS. (2024). Emerging perspectives: unraveling the anticancer potential of vitamin D3. Naunyn Schmiedebergs Arch Pharmacol. **397**(5): 2877–2933. doi: 10.1007/s00210-023-02819-5. Epub 2023 Nov 23. PMID: 37994947.

66 Wang L, Wang C, Choi WS. (2022). Use of Melatonin in Cancer Treatment: Where Are We? Int J Mol Sci. **23**(7): 3779. doi: 10.3390/ijms23073779. PMID: 35409137; PMCID: PMC8998229.

67 Wang Y, Jamieson SMF, Perry JK. (2023). Targeting growth hormone in cancer: future perspectives. Endocr Relat Cancer. **30**(9): e230033. doi: 10.1530/ERC-23-0033. PMID: 37310137.

68 Wennbo H, Törnell J. (2000). The role of prolactin and growth hormone in breast cancer. Oncogene. **19**(8): 1072–6. doi: 10.1038/sj.onc.1203349. PMID: 10713692.

69 Xu XQ, Emerald BS, Goh EL, Kannan N, Miller LD, Gluckman PD, et al. (2005). Gene expression profiling to identify oncogenic determinants of autocrine human growth hormone in human mammary carcinoma. J Biol Chem. **280**(25): 23987–4003. doi: 10.1074/jbc.M503869200. Epub 2005 Apr 20. PMID: 15845533.

70 Yan HZ, Wang HF, Yin Y, Zou J, Xiao F, Yi LN, et al. (2021). GHR is involved in gastric cell growth and apoptosis via PI3K/AKT signalling. J Cell Mol Med. **25**(5): 2450–2458. doi: 10.1111/jcmm.16160. Epub 2021 Jan 25. PMID: 33492754; PMCID: PMC7933969.

71 Yang R, Han Y, Guan X, Hong Y, Meng J, Ding S, et al. (2023). Regulation and clinical potential of telomerase reverse transcriptase (TERT/hTERT) in breast cancer. Cell Commun Signal. **21**(1): 218. doi: 10.1186/s12964-023-01244-8. PMID: 37612721; PMCID: PMC10463831.

72 Zasowska-Nowak A, Nowak PJ, Ciałkowska-Rysz A. (2021). High-Dose Vitamin C in Advanced-Stage Cancer Patients. Nutrients. **13**(3): 735. doi: 10.3390/nu13030735. PMID: 33652579; PMCID: PMC7996511.

73 Zhang W, Qian P, Zhang X, Zhang M, Wang H, Wu M, et al. (2015). Autocrine/Paracrine Human Growth Hormone-stimulated MicroRNA 96-182-183 Cluster Promotes Epithelial-Mesenchymal Transition and Invasion in Breast Cancer. J Biol Chem. **290**(22): 13812–29. doi: 10.1074/jbc.M115.653261. Epub 2015 Apr 14. PMID: 25873390; PMCID: PMC4447958.

74 Zhang X, Pandey V, Bhardwaj V, Zhu T, Lobie PE. (2023). Autocrine/paracrine growth hormone in cancer progression. Endocr Relat Cancer. **31**(1): e230120. doi: 10.1530/ERC-23-0120. PMID: 37877767.

75 Zhou N, Wei ZX, Qi ZX. (2019). Inhibition of autophagy triggers melatonin-induced apoptosis in glioblastoma cells. BMC Neurosci. **20**(1): 63. doi: 10.1186/s12868-019-0545-1. PMID: 31870319; PMCID: PMC6929316.

76 Zhu X, Li Y, Xu G, Fu C. (2020). Growth hormone receptor promotes breast cancer progression via the BRAF/MEK/ERK signaling pathway. FEBS Open Bio. **10**(6): 1013–1020. doi: 10.1002/2211-5463.12816. Epub 2020 May 6. PMID: 32069380; PMCID: PMC7262926.

77 Zonta YR, Martinez M, Camargo IC, Domeniconi RF, Lupi Júnior LA, Pinheiro PF, et al. (2017). Melatonin Reduces Angiogenesis in Serous Papillary Ovarian Carcinoma of Ethanol-Preferring Rats. Int J Mol Sci. **18**(4): 763. doi: 10.3390/ijms18040763. PMID: 28398226; PMCID: PMC5412347.

78 Zuo L, Yang X, Lu M, Hu R, Zhu H, Zhang S, et al. (2016). All-Trans Retinoic Acid Inhibits Human Colorectal Cancer Cells RKO Migration via Downregulating Myosin Light Chain Kinase Expression through MAPK Signaling Pathway. Nutr Cancer. **68**(7): 1225–33. doi: 10.1080/01635581.2016.1216138. Epub 2016 Aug 26. PMID: 27564600.