# Epothilones with Clinical Significance in Cancer

Subjects: Oncology

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Epothilone B derivatives such as Ixabepilone and Utidelone are currently used in the clinic for the treatment of advanced breast cancer, their efficacy has been demonstrated in Phase II and III clinical trials.

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## 1. Epothilone B

EPO906 or patupilone is a synthesized version of natural Epothilone B (EpoB) developed by Novartis, with the same structure and, therefore, the same mechanism of action [1]. EPO906 has been part of many preclinical [2][3][4] and clinical studies [5][6][7]. Due to its conserved activity against taxane-resistant cells, it could be an alternative for patients who relapse after chemotherapy based on paclitaxel and platinum derivatives and present high levels of class III beta-tubulin (TUBB3). Clinical trials results recognize the potential of patupilone to improve progression-free survival and pain response in castration-resistant prostate cancer and gynecologic cancer, whose relapse events are accompanied by resistance to docetaxel and cisplatin, respectively. Other tumor pathologies, such as colorectal cancer (CRC) [8] and brain metastases [9], have been evaluated but without significant evidence of efficacy.

In castration-resistant prostate cancer (CRPC), patupilone showed variable results either as first-line therapy (compared to standard docetaxel therapy) or in docetaxel-refractory patients. For instance, a Phase II clinical study was conducted with 45 patients (64% pretreated with taxanes) who received patupilone (2.5 mg/m$^2$) via 5-min bolus i.v. infusion, once per week for 3 weeks, followed by one week of rest (4-week cycle). Decreased patient prostate-specific antigen (PSA) levels by ≥50% was confirmed in only six patients (13%), and the mean time to progression was 1.6 months, which was considered as insignificant [10]. In a second study with 83 participants injected with 10 mg/m$^2$ patupilone by i.v. every 3 weeks, a PSA level decrease of ≥50% was observed in 47% of the patients. Pain responses were observed in 59% of evaluable patients. The median time to PSA level progression was 6.1 months, and the median overall survival (OS) was 11.3 months (95% CI: 9.8 to 15.4), demonstrating antitumor activity and contribution to symptomatic improvement in patients previously treated with docetaxel [11].

The clinical efficacy of patupilone was also evaluated in castration-resistant prostate cancer (mCPRC) patients who had never received chemotherapy, these patients with mCPRC have a poor prognosis, and first-line therapy is

mainly based on docetaxel-based regimens which makes them prone to develop resistance quickly [12]. The treatment based on patupilone + prednisone revealed a better response in view of PSA levels, compared to the classical treatment of docetaxel + prednisone [13] in patients who received intravenous (I.V.) patupilone (10 mg/m$^2$ or docetaxel 75 mg/m$^2$ every 3 weeks.

In ovarian cancer, patupilone has been tested clinically with Phase I and II studies. Novartis Pharmaceuticals evaluated patupilone in a randomized open-label Phase III study (NCT00262990) in 829 patients with interracial differences from 11 different countries. This analysis compared the efficacy of patupilone versus liposomal doxorubicin in patients with epithelial ovarian cancer. The results showed a modest efficacy profile in patients treated with patupilone, but the treatment did not achieve a significant improvement in overall survival compared to the active control [14]. The most frequent toxicity in the patupilone arm was diarrhea (25.6% grade 3 and 4) and mild peripheral neuropathy (6.2% grade 3 and 4), consistent with Phase I and II trials of monotherapy where diarrhea grade 3 was the most common adverse effect present in 8–29% of patients with the highest incidence in patients with colorectal and prostate cancer [15], and is the dose-limiting event in therapeutic schemes.

The safety and toxicity profile of epothilones has been the main problem for bringing these drugs to market, ixabepilone, KOS-862, and ZK-EPO (sagopilone) exhibit a high incidence of myelosuppression, alopecia, severe peripheral neuropathy, and hypersensitivity reactions [16][17]. Despite patupilone (EpoB) showing less toxicity than its derivatives, receiving a good opinion from the European Medicines Agency (EMEA) for the treatment of cancers of the female reproductive system, the effectivity on patients was not significant compared to the control, failing in the Phase III trial [14].

Patupilone, unlike taxanes, has shown the ability to cross the blood–brain barrier (BBB) and exert antitumor effects in brain tumors. In vitro patupilone evaluated in animal models [18] was able to reduce the proliferative activity of medulloblastoma cell lines at picomolar concentrations (50–200 pM), and it produced an anti clonogenic effect in combination with ionizing radiation (2 or 5 Gy) [19].

In humans, patupilone accumulation in glioblastoma (GBM) tumor tissue is 30 times higher compared to plasma values at 20 min. In this sense, administration of patupilone before and after surgery in recurrent GBM is safe, improving long-term PFS in patients, and could be an alternative for the treatment of central nervous system (CNS) cancers [20]. However, larger clinical trials are needed to ensure the safety and efficacy of this drug.

Patupilone promotes neural regeneration after an injury, inducing concerted polymerization of microtubules at the axon tip, which drives axon growth by inhibiting the migration scar-forming fibroblasts and reactivating neuronal polarization [21].

## 2. Ixabepilone

Ixabepilone, also called aza-epothilone B or BMS 247550 is a semi-synthetic second-generation analogue of the natural product EpoB, which changed the macrolide lactone ring, with nitrogen to give the corresponding

macrolactam [22]. The improvements of the semi-synthetic compound include a higher antitumor activity than epothilones A and B against a broad spectrum of human tumors. It was developed by Bristol-Myers Squibb (BMS, New York, NY, USA), marketed in the USA under the name Ixempra®, and was listed by the FDA in the USA in 2007 for the treatment of metastatic or advanced breast cancer, either as a single agent or together with capecitabine for the treatment of patients with metastatic or locally advanced breast cancers thatshow resistance against anthracycline and taxane treatment [23]. Nevertheless, the Committee for Medicinal Products for Human Use (CHMP) recommended further research evaluating the risk–benefit ratio in the use of the drug due to the high incidence and neurotoxicity with its use.

Early preclinical trials demonstrated that ixabepilone has been shown to induce the activation of selective apoptotic pathways [24]. The compound is effective against multiple cancers, including those tumors resistant to common chemotherapeutic agents, such as against paclitaxel-resistant lines HCT116/VM46 (colorectal cancer), Pat-21 (ovarian carcinoma), Pat-7 (breast), and A2780 Tax (ovarian carcinoma), which express tubulin mutation, as well as to sensitive lines Pat-26 (human pancreatic carcinoma) and M5076 (murine fibrosarcoma) displaying a cytotoxic effect around 2.9 nM ($IC_{50}$) [25] (see **Table 1**). Ixabepilone also shows low susceptibility to multiple resistance mechanisms because it is a poor substrate of P-gp, which is overexpressed in malignant neoplasms of solid tumors, as kidney, colon, liver, ovary, breast, and sarcomas [26]. In this sense, being active against pediatric solid tumor cell lines of osteosarcoma (HOS), Ewing's sarcoma (LD-EWS), and rhabdomyosarcoma (RD), evidencing a similar potency to paclitaxel, vincristine and vinorelbine, the standard tubulin-binding anticancer drugs [27].

**Table 1.** Cytotoxicity of ixabepilone against 21 tumor cell lines.

| Cell Line | Ixabepilone IC50 (nM) | Cell Line | Ixabepilone IC50 (nM) | Cell Line | Ixabepilone IC50 (nM) |
|---|---|---|---|---|---|
| A2780/DDP-S | 2.8 | A2780/DDP-R | 1.8 | A2780/TAX-S | 2.6 |
| A2780/TAX-R | 4.9 | OVCAR-3 | 1.8 | MCF-7 | 2.7 |
| SKBR3 | 2.3 | LNCAP | 1.5 | PC3 | 4.6 |
| HCT116 | 2.6 | HCT116/VM46 | 24.5 | HCT116/VP35 | 2.0 |
| LS174T | 5.8 | MIP | 24.8 | A549 | 5.2 |
| LX-1 | 3.1 | A431 | 1.4 | CCRF-CEM | 6.0 |
| K562 | 2.9 | M109 | 2.9 | MLF | 34.5 |

Median $IC_{50}$: 2.9 nM.

In Phase II studies, ixabepilone was effective against hormone-refractory prostate cancer (HRPC) [28]; non-small cell lung cancer (NSCLC) [29], including NSCLC tumors that have failed in the first-line platinum-based chemotherapy [30]; and other resistant cancers, such as renal [31] and pancreatic carcinomas [32]. However minimal effects have been observed in gynecological cancer [33][34].

The treatment with ixabepilone plus capecitabine demonstrates superior efficacy in terms of PFS to capecitabine alone, in patients with anthracycline- or taxane-resistant metastatic breast cancer [35][36], as well as in patients with triple-negative breast cancer (TNBC) where the combination of ixabepilone with capecitabine approximately doubles the median PFS [37], comparable to those observed in non-triple-negative tumor patients [38]. This is particularly advantageous in this patient population because TNBC accounts for 15–20% of all breast cancer and is associated with shorter survival after metastasis development. At present, targeted therapies exist for this type of cancer, and therefore, chemotherapy remains the primary treatment [39]. Controversial results were seen in the Phase II clinical study, where the efficacy of ixabepilone alone or together with ixabepilone plus cetuximab as first-line treatment in patients with advanced/metastatic TNBC showed no significant differences [40]. However, the reported study TITAN, evaluating ixabepilone substitution for paclitaxel after doxorubicin/cyclophosphamide (AC) in adjuvant treatment of early-stage TNBC, revealed similar DFS and OS in patients with operable TNBC compared to AC/paclitaxel treatment, but with less marked adverse effects in contrast to paclitaxel, which could mean an alternative for second-line treatment in these types of patients [41].

Utidelone, UTD1, KOS-862, or Epothilone D is an epothilone derivative generated by genetic engineering of the epothilone gene cluster, increasing the concentration of UTD1 by fermentation in *S. cellulosum.* It was developed and manufactured by Biostar Technologies, Ltd., Beijing, China. UTD1 has revealed strong in vitro and in vivo activity against paclitaxel-sensitive tumors, such as multidrug-resistant human colon, leukemia, and breast tumors [42].

UTD1 is currently an alternative for the treatment of metastatic breast cancer (MBC), especially in breast cancer previously treated with anthracyclines and taxanes [43], as well as for patients with HER2-positive breast cancer [44]. Phase II clinical studies developed in Asia evaluated its efficacy, showing positive results, promising tolerability, and advantageous safety profiles in patients who completed a median of six cycles of therapy alone or in combination with capecitabine. In this regard, combination therapy has shown better results than therapy alone when evaluating the objective response rate (ORR) and PFS. The combination therapy yielded an ORR of 42.4% and a median PFS of 7.9 months, whereas the monotherapy study resulted in an ORR of 28.57% and a median PFS of 5.4 months [43].

Results of a Phase III randomized controlled trial evaluating (OS) in heavily pretreated MBC, refractory to anthracyclines and taxanes, supported the use of UTD1 plus capecitabine as a novel therapeutic regimen for these patients. The evaluation of 405 patients who received UTD1 (30 mg/m$^2$ IV daily, days 1–5, for 90 min) plus capecitabine (1000 mg/m$^2$ orally b.i.d., days 1–14) or capecitabine alone (1250 mg/m$^2$ orally b.i.d., days 1–14) every 21 days, ratified the improvement in OS in the combination group (19.8 months) compared to the monotherapy group (16.0 months), demonstrating that combination therapy with UTD1 remained superior to capecitabine monotherapy [45]. This combination therapy was included in the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2022 recommendations for salvage treatment of triple-negative breast cancer as a level II recommendation, which includes protocols with a relatively high level of evidence, but where a slightly lower expert consensus is used [46].

Similar results were obtained for HER2-positive (human epidermal growth factor receptor 2) breast cancer therapies. The Phase 2 study (NCT04681287) evaluated UTD1 in patients who have been pretreated with trastuzumab and tyrosine kinase inhibitors. Participants received intravenous camrelizumab (200 mg once every 3 weeks), inetetamab (loading dose of 8 mg/kg and then 6 mg/kg, day 1), and UTD1 (30 mg/m$^2$, days 1–5) until the disease progressed or intolerable toxicity occurred. All three drugs showed promising efficacy and an acceptable safety profile, representing a new option for this type of patients [44].

UTD1 has been proposed for use in lung cancer in which chemotherapy is the gold standard treatment in most patients. The Phase II clinical investigation with patients enrolled between 2019 and 2021 (NCT03693547) reported that UTD1 is safe for advanced NSCLC refractory to second-line treatment and could be effective; however, more studies are needed in this specific type of cancer [47].

The activity of UTD1 for the treatment of colorectal cancer (CRC) currently being studied. In this regard, UTD1 has exhibited broad antitumor activity in RKO and HCT116 cells, as reported by [48]. UTD1 inhibited CRC cell proliferation, in vitro, with an IC50 of 0.38 µg/mL and 0.77 µg/mL against RKO and HCT116, respectively. These results were also reproducible in RKO xenografts in nude mice, suggesting that UTD1 could be an effective agent in the treatment of CRC in humans. The mechanism of action is similar to that described for other epothilones: induction of microtubule cluster and aster formation, inducing cell cycle arrest in the G2/M phase, and subsequent apoptosis. UTD1 exhibited stronger apoptosis induction effects than paclitaxel and 5-FU, especially in HCT15 cells with ABCB1 overexpression. In CRC cells, UTD1 increased ROS production along with activation of c-Jun N-terminal kinase (JNK), suggesting a mechanism through the ROS/JNK pathway [48].

## References

1. Galmarini, C.M.; Dumontet, C. EPO-906 (Novartis). IDrugs 2003, 6, 1182–1187.
2. O'Reilly, T.; McSheehy, P.M.J.; Wenger, F.; Hattenberger, M.; Muller, M.; Vaxelaire, J.; Altmann, K.-H.; Wartmann, M. Patupilone (epothilone B, EPO906) inhibits growth and metastasis of experimental prostate tumors in vivo. Prostate 2005, 65, 231–240.
3. Becquet, M.; Laborde, L.; Texier, C.; Sterker, D.; Gschwind, H.P.; Pfaar, U.; Wartmann, M.; O'Reilly, T.M.; McSheehy, P.M. Continuous low-dose infusion of patupilone increases the therapeutic index in mouse and rat tumour models. Anticancer Drugs 2018, 29, 691–701.
4. Lin, B.; Catley, L.; LeBlanc, R.; Mitsiades, C.; Burger, R.; Tai, Y.T.; Podar, K.; Wartmann, M.; Chauhan, D.; Griffin, J.D.; et al. Patupilone (epothilone B) inhibits growth and survival of multiple myeloma cells in vitro and in vivo. Blood 2005, 105, 350–357.
5. Smit, W.M.; Sufliarsky, J.; Werner, T.L.; Dizon, D.; Wagnerova, M.; Hirte, H.W.; Delaney, R.; Li, J.; Weber, D.; Schellens, J.H. A phase II study evaluating the safety and efficacy of patupilone in

patients with platinum refractory/resistant ovarian, primary fallopian, or peritoneal cancer. J. Clin. Oncol. 2009, 27, 5563.

6. Hsin, K.W.; Boyer, M.; Ducreux, M.; Liu, M.; Soo, R.; Yeo, W.; Williams, K.J.; Johri, A. Efficacy of patupilone in advanced local or metastatic gastric cancer: A phase IIa trial. J. Clin. Oncol. 2006, 24, 4069.
7. Nayak, L.; DeAngelis, L.M.; Robins, H.I.; Govindan, R.; Gadgeel, S.; Kelly, K.; Rigas, J.R.; Peereboom, D.M.; Rosenfeld, S.S.; Muzikansky, A.; et al. Multicenter phase 2 study of patupilone for recurrent or progressive brain metastases from non-small cell lung cancer. Cancer 2015, 121, 4165–4172.
8. Moorcraft, S.Y.; Chau, I.; Peckitt, C.; Cunningham, D.; Rao, S.; Yim, K.L.; Walther, A.; Jackson, C.G.; Stamp, G.; Webb, J.; et al. Patupilone in patients with pretreated metastatic/locally recurrent colorectal cancer: Results of the Phase II CINATRA trial. Investig. New Drugs 2013, 31, 1339–1344.
9. Peereboom, D.M.; Murphy, C.; Ahluwalia, M.S.; Conlin, A.; Eichler, A.; Van Poznak, C.; Baar, J.; Elson, P.; Seidman, A.D. Phase II trial of patupilone in patients with brain metastases from breast cancer. Neuro Oncol. 2014, 16, 579–583.
10. Hussain, A.; DiPaola, R.S.; Baron, A.D.; Higano, C.S.; Tchekmedyian, N.S.; Johri, A.R. Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. Ann. Oncol. 2009, 20, 492–497.
11. Chi, K.N.; Beardsley, E.; Eigl, B.J.; Venner, P.; Hotte, S.J.; Winquist, E.; Ko, Y.J.; Sridhar, S.S.; Weber, D.; Saad, F. A phase 2 study of patupilone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: Canadian Urologic Oncology Group study P07a. Ann. Oncol. 2012, 23, 53–58.
12. Schaeffer, E.; Srinivas, S.; Antonarakis, E.S.; Armstrong, A.J.; Bekelman, J.E.; Cheng, H.; D'Amico, A.V.; Davis, B.J.; Desai, N.; Dorff, T. NCCN guidelines insights: Prostate cancer, version 1.2021: Featured updates to the NCCN guidelines. J. Natl. Compr. Cancer Netw. 2021, 19, 134–143.
13. De Souza, P.L.; Mellado, B.; Pfister, C.; Rosenthal, M.; Castellano, D.E.; Weber, D.; Ferrara, S.; Shaik, N.; Tan, E.; Patterson, S.G. Randomized phase II trial of patupilone plus prednisone versus docetaxel plus prednisone in patients with chemotherapy-naïve, metastatic, castrate-resistant prostate cancer (CRPC). J. Clin. Oncol. 2010, 28, 4553.
14. Colombo, N.; Kutarska, E.; Dimopoulos, M.; Bae, D.S.; Rzepka-Gorska, I.; Bidzinski, M.; Scambia, G.; Engelholm, S.A.; Joly, F.; Weber, D.; et al. Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. J. Clin. Oncol. 2012, 30, 3841–3847.

15. Bystricky, B.; Chau, I. Patupilone in cancer treatment. Expert Opin. Investig. Drugs 2011, 20, 107–117.
16. Krause, W.; Klar, U. Differences and similarities of epothilones. Curr. Cancer Ther. Rev. 2011, 7, 10–36.
17. Argyriou, A.A.; Marmiroli, P.; Cavaletti, G.; Kalofonos, H.P. Epothilone-induced peripheral neuropathy: A review of current knowledge. J. Pain Symptom Manag. 2011, 42, 931–940.
18. O'Reilly, T.; Wartmann, M.; Brueggen, J.; Allegrini, P.R.; Floersheimer, A.; Maira, M.; McSheehy, P.M.J. Pharmacokinetic profile of the microtubule stabilizer patupilone in tumor-bearing rodents and comparison of anti-cancer activity with other MTS in vitro and in vivo. Cancer Chemother. Pharmacol. 2008, 62, 1045–1054.
19. Oehler, C.; von Bueren, A.O.; Furmanova, P.; Broggini-Tenzer, A.; Orlowski, K.; Rutkowski, S.; Frei, K.; Grotzer, M.A.; Pruschy, M. The microtubule stabilizer patupilone (epothilone B) is a potent radiosensitizer in medulloblastoma cells. Neuro Oncol. 2011, 13, 1000–1010.
20. Oehler, C.; Frei, K.; Rushing, E.J.; McSheehy, P.M.; Weber, D.; Allegrini, P.R.; Weniger, D.; Lütolf, U.M.; Knuth, A.; Yonekawa, Y.; et al. Patupilone (epothilone B) for recurrent glioblastoma: Clinical outcome and translational analysis of a single-institution phase I/II trial. Oncology 2012, 83, 1–9.
21. Ruschel, J.; Hellal, F.; Flynn, K.C.; Dupraz, S.; Elliott, D.A.; Tedeschi, A.; Bates, M.; Sliwinski, C.; Brook, G.; Dobrindt, K.; et al. Axonal regeneration. Systemic administration of epothilone B promotes axon regeneration after spinal cord injury. Science 2015, 348, 347–352.
22. Hunt, J.T. Discovery of ixabepilone. Mol. Cancer Ther. 2009, 8, 275–281.
23. Mandhare, A.; Biradar, S.; Gurule, A. Azaepothilone B and its derivatives: A patent review. Expert Opin. Ther. Pat. 2016, 26, 891–905.
24. Vahdat, L. Ixabepilone: A novel antineoplastic agent with low susceptibility to multiple tumor resistance mechanisms. Oncologist 2008, 13, 214–221.
25. Lee, F.Y.; Borzilleri, R.; Fairchild, C.R.; Kim, S.H.; Long, B.H.; Reventos-Suarez, C.; Vite, G.D.; Rose, W.C.; Kramer, R.A. BMS-247550: A novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. Clin. Cancer Res. 2001, 7, 1429–1437.
26. Jaramillo, A.C.; Saig, F.A.; Cloos, J.; Jansen, G.; Peters, G.J. How to overcome ATP-binding cassette drug efflux transporter-mediated drug resistance? Cancer Drug Resist 2018, 1, 6–29.
27. Stover, E. In vitro cytotoxicity of the epothilone analog, BMS 247550, in pediatric malignacies. Cantaurus 2002, 10, 31–37.
28. Dawson, N.A. Epothilones in prostate cancer: Review of clinical experience. Ann. Oncol. 2007, 18 (Suppl. S5), v22–v27.

29. Shipley, D.; Spigel, D.R.; Burris, H.A.; Waterhouse, D.M.; Webb, C.D.; Gian, V.; Hart, L.L.; Greco, F.A.; Hainsworth, J.D. Phase II trial of ixabepilone and carboplatin with or without bevacizumab in patients with previously untreated advanced non-small cell lung cancer. J. Clin. Oncol. 2010, 28, 7601.

30. Vansteenkiste, J.; Lara, P.N.; Le Chevalier, T.; Breton, J.-L.; Bonomi, P.; Sandler, A.B.; Socinski, M.A.; Delbaldo, C.; McHenry, B.; Lebwohl, D. Phase II clinical trial of the epothilone B analog, ixabepilone, in patients with non-small-cell lung cancer whose tumors have failed first-line platinum-based chemotherapy. J. Clin. Oncol. 2007, 25, 3448–3455.

31. Huang, H.; Menefee, M.; Edgerly, M.; Zhuang, S.; Kotz, H.; Poruchynsky, M.; Huff, L.M.; Bates, S.; Fojo, T. A phase II clinical trial of ixabepilone (Ixempra; BMS-247550; NSC 710428), an epothilone B analog, in patients with metastatic renal cell carcinoma. Clin. Cancer Res. 2010, 16, 1634–1641.

32. Rocha Lima, C.M.; Lin, E.H.; Kim, G.P.; Giguere, J.K.; Marshall, J.; Zalupski, M.; Papageorgio, C.; Auber, M.L.; Kaleta, R.; McHenry, M.B.; et al. A phase 2 trial of ixabepilone plus cetuximab in first-line treatment of metastatic pancreatic cancer. Gastrointest. Cancer Res. 2012, 5, 155–160.

33. McCourt, C.K.; Deng, W.; Dizon, D.S.; Lankes, H.A.; Birrer, M.J.; Lomme, M.M.; Powell, M.A.; Kendrick, J.E.; Saltzman, J.N.; Warshal, D.; et al. A phase II evaluation of ixabepilone in the treatment of recurrent/persistent carcinosarcoma of the uterus, an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2017, 144, 101–106.

34. Roque, D.M.; Siegel, E.R.; Buza, N.; Bellone, S.; Silasi, D.-A.; Huang, G.S.; Andikyan, V.; Clark, M.; Azodi, M.; Schwartz, P.E.; et al. Randomised phase II trial of weekly ixabepilone ± biweekly bevacizumab for platinum-resistant or refractory ovarian/fallopian tube/primary peritoneal cancer. Br. J. Cancer 2022, 126, 1695–1703.

35. Thomas, E.S.; Gomez, H.L.; Li, R.K.; Chung, H.-C.; Fein, L.E.; Chan, V.F.; Jassem, J.; Pivot, X.B.; Klimovsky, J.V.; de Mendoza, F.H. Ixabepilone Plus Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment. J. Clin. Oncol. 2007, 25, 5210–5217.

36. Sparano, J.A.; Vrdoljak, E.; Rixe, O.; Xu, B.; Manikhas, A.; Medina, C.; Da Costa, S.C.; Ro, J.; Rubio, G.; Rondinon, M.; et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J. Clin. Oncol. 2010, 28, 3256–3263.

37. Rugo, H.S.; Roche, H.; Thomas, E.; Chung, H.C.; Lerzo, G.L.; Vasyutin, I.; Patel, A.; Vahdat, L. Efficacy and Safety of Ixabepilone and Capecitabine in Patients With Advanced Triple-negative Breast Cancer: A Pooled Analysis From Two Large Phase III, Randomized Clinical Trials. Clin. Breast Cancer 2018, 18, 489–497.

38. Perez, E.A.; Patel, T.; Moreno-Aspitia, A. Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer. Breast Cancer Res. Treat. 2010, 121, 261–271.

39. Partridge, A.H.; Rumble, R.B.; Carey, L.A.; Come, S.E.; Davidson, N.E.; Di Leo, A.; Gralow, J.; Hortobagyi, G.N.; Moy, B.; Yee, D.; et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. 2014, 32, 3307–3329.
40. Trédan, O.; Campone, M.; Jassem, J.; Vyzula, R.; Coudert, B.; Pacilio, C.; Prausova, J.; Hardy-Bessard, A.-C.; Arance, A.; Mukhopadhyay, P.; et al. Ixabepilone Alone or With Cetuximab as First-Line Treatment for Advanced/Metastatic Triple-Negative Breast Cancer. Clin. Breast Cancer 2015, 15, 8–15.
41. Yardley, D.A.; Arrowsmith, E.R.; Daniel, B.R.; Eakle, J.; Brufsky, A.; Drosick, D.R.; Kudrik, F.; Bosserman, L.D.; Keaton, M.R.; Goble, S.A.; et al. TITAN: Phase III study of doxorubicin/cyclophosphamide followed by ixabepilone or paclitaxel in early-stage triple-negative breast cancer. Breast Cancer Res. Treat. 2017, 164, 649–658.
42. Zhang, P.; Sun, M.; Qiu, R.; Tang, L.; Dou, G.; Xu, B. Phase I clinical and pharmacokinetic study of UTD1, a genetically engineered epothilone analog in patients with advanced solid tumors. Cancer Chemother. Pharmacol. 2011, 68, 971–978.
43. Zhang, P.; Tong, Z.; Tian, F.; Wang, Y.; Yang, J.; Li, W.; Di, L.; Liu, W.; Tang, L.; Qiu, R. Phase II trial of utidelone as monotherapy or in combination with capecitabine in heavily pretreated metastatic breast cancer patients. J. Hematol. Oncol. 2016, 9, 1–9.
44. Yan, M.; Lv, H.; Niu, L.; Zhang, M.; Zeng, H.; Zhao, S.; Wang, J.; Sun, H.; Chen, S. Anti-HER2 antibody inetetamab plus camrelizumab and utidelone for pretreated HER2-positive advanced breast cancer: A single-arm, multicenter, phase 2 study. J. Clin. Oncol. 2022, 40, e13030.
45. Xu, B.; Sun, T.; Zhang, Q.; Zhang, P.; Yuan, Z.; Jiang, Z.; Wang, X.; Cui, S.; Teng, Y.; Hu, X.C.; et al. Efficacy of utidelone plus capecitabine versus capecitabine for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer: Final analysis of overall survival in a phase III randomised controlled trial. Ann. Oncol. 2021, 32, 218–228.
46. Jiang, Z.; Li, J.; Chen, J.; Liu, Y.; Wang, K.; Nie, J.; Wang, X.; Hao, C.; Yin, Y.; Wang, S. Chinese society of clinical oncology (CSCO) breast cancer guidelines 2022. Transl Breast Cancer Res 2022, 3, 13.
47. Shi, Y.; Chen, G.; Zhao, Y.; Zhao, J.; Lin, L. 31P Efficacy and safety of utidelone in treatment-refractory advanced non-small cell lung cancer. Ann. Oncol. 2022, 33, S45–S46.
48. Li, F.; Huang, T.; Tang, Y.; Li, Q.; Wang, J.; Cheng, X.; Zhang, W.; Zhang, B.; Zhou, C.; Tu, S. Utidelone inhibits growth of colorectal cancer cells through ROS/JNK signaling pathway. Cell Death Dis. 2021, 12, 338.