treatment of various types of cancer, including breast, ovarian and non-small cell lung cancer.[34]

2. Patent Portfolio

a) Process

The synthetic procedure, disclosed in the basic patent family, while allowing for the production of larger amounts of docetaxel was however still far from being optimal since it involved an unselective reaction step with a consequent substantial loss of product. A company, which has to produce material for the various clinical studies and for a possible launch, therefore needs to address this issue as can be seen by the large number of successive patents in this area. E.g. EP 0336841 A1[35] disclosed an optimized synthesis which is no longer based on a late-stage reaction with poor selectivity, but introduces the synthetic fragment (A) (side-chain: Formula 1) as complete building block. Hence, any difficult reaction step potentially involving a loss of material is carried out before the valuable core (baccatin III) (B, Formula 2) extracted from the natural source is brought into play. This improved process found by the Rhone-Poulenc group demonstrates therefore a significant advantage, both from the technical (less difficult) and the economic (less material loss) point of view.

Successive patents[36] in the period from 1989 to 1994 deal with several alternative preparations of the fragment (A). Moreover, research was also directed towards the improvement of joining the two

34 O. Esposito, M. Bonfill, E. Moyano, M. Onrubia, M.H. Mirjalili, R.M. Cusidó, J. Palazón, *Biotechnological Production of Taxol and Related Taxoids: Current State and Prospects*, 9 Anti-Cancer Agents in Medicinal Chemistry 109, 110, (2009).

35 Filed in October 1989, French priority: FR 8804513, (06 April 1988).

36 WO 91/13066, WO 93/04038, WO 93/17997, WO 94/07847, WO 94/22813 and WO 94/24103.

fragments (A) and (B) together and 6 further patent families[37] originated from this work.

A final process patent discloses the stable crystal form (docetaxel trihydrate) which is necessary to allow for a storage stable form to be delivered to the patient (WO 96/01815).[38] Docetaxel trihydrate is actually the form which is packaged into the vials which are marketed.[39]

Hence, process research contributed to the patent portfolio around docetaxel with 14 patent families as listed by their international applications.

b) Formulation

Another problem to be dealt with after the discovery of a potential drug during preclinical and clinical studies and also after marketing is the identification of a suitable formulation. Safety problems or simply the desire to identify a more user friendly dosage form can drive research in this area. In the case of docetaxel patents from 1990 to about 1999 regard certain aspects of injectable dosage forms. Taxane products have low water solubility and traditionally for clinical use taxane formulations were obtained by addition of ethanol and a surfactant.[40] This formulation could cause "manifestations of alcohol poisoning during treatment".[41]

The FR 9108527 patent family addressed the ethanol issue and disclosed novel stable injectable taxane compositions with low ethanol

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37 WO 93/01179, WO 93/18210, WO 94/07876, WO 94/07877, WO 94/07879 and WO 94/10169.

38 The corresponding EP 0770070 filed in 1995 will expire in 2015, the corresponding US 6022985 was filed in 1997 but can be followed only until its issue date in 2000.

39 L. Zaske, M.A. Perrin, C. Daiguebonne, O. Guillou, *Docetaxel (Taxotere® Trihydrate) Forms: Crystal Structure Determination from XRPD & XRSCD data*, 443-444 Mat. Sci. Forum 411, (2004).

40 John Zhikong He, *Docetaxel*, IP Front Line, http://www.ipfrontline.com/depts/article.aspx?id=24725&deptid=5 (last visited March 11, 2012).

41 Reported in US 5,714,512.

content. Marketing authorisation in the major markets was obtained for this new formulation (single vial). Patents of this family will expire in Europe,[42] Canada[43] and Australia in July 2012, while expiry in the U.S.,[44] where a paediatric extension was granted, will be in January 2013.[45]

The successive patent family EP 0671912 B1 protects a formulation in a twin compartment system which solves the problem of gelling observed upon dilution of the previously known composition. The date of expiry of these patents is in November 2013 except in the U.S. equivalent where paediatric extension was granted until May 2014.[46] No opposition has been filed against this patent, which it is still in force. However, this formulation compared to the challenged single vial composition appears less practical.

c) Combination Therapy

Between 1993 and 2009 research activities had also been directed towards the identification of combination therapies (see figure 2).

However, clinical studies of product combinations can be quite complex due to potential drug interaction.[47]

About 10 patent applications regarding combination therapies with further anticancer agents and antibiotics have been filed.[48] For example, patent application WO 03/097164 A1[49] covers the use of doc-

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42 EP 0593601 B1 and EP 0593656 B1.
43 CA 2102777 and CA 2102778.
44 US 5,698,582, US 5,714,512 and US 5,750,561.
45 See Zhikong He *supra* note 40.
46 See Zhikong He *supra* note 40.
47 Jan I. Drayer, James P. Burns, *From Discovery to Market: The Development of Pharmaceuticals*, in BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY, 251, 280-282, (Manfred E. Wolff ed., 1995).
48 WO 94/10995, WO 96/22101, EP 0827745, EP 1093811, EP 1295597, WO 03/097164, WO 2004/037258, EP 1537871, FR 2887454, WO 2010/067027, EP 1169059 B1.
49 Filed on 15 May 2003.

etaxel in combination with doxorubicin and cyclophosphamide (further anticancer agents) in adjuvant therapy of breast and ovarian cancer. The application was restricted to breast cancer during proceedings because of lack of support for the treatment of ovarian cancer and then refused on ground of obviousness. The applicant appealed the decision.[50] This combination has been approved either by FDA and EMA and it is the current primary treatment for breast cancer.[51]

The binary combination of docetaxel and cyclophosphamide is covered by EP 0827745 B1.

Another application WO 02/076484[52] regards the combination of Taxotere and the CDK-inhibitor flavopiridol. Clinical trials for such combinations are ongoing or being evaluated.

Of these patents 3 have been revoked,[53] 3 were not granted and 1 is under appeal.

d) New Uses

In addition, new uses for docetaxel have been identified: the treatment of parasitic diseases (as covered by WO 95/01790) and the treatment of hepatoma (WO 01/15675). Further research which accompanied the already marketed drug was directed towards the identification of biological markers allowing for the prediction of docetaxel response, resistance or sensitivity (WO 00/39590, WO 2006/062811 and WO 2009/140304). Hence, these patents are more related to diagnostic

50 Appeal T 1902/09 ongoing. See EPO register: document of July 24, 2012 found at https://register.epo.org/espacenet/application?number=EP03738122&lng=en&tab=doclist (last visited Aug. 28, 2012).

51 John Crown, Michael O'Leary, Wei-Song Ooi, Docetaxel and Paclitaxel in the Treatment of Breast Cancer: A Review of Clinical Experience, 9 (suppl. 2) The Oncologist 24, 30, (2004).

52 Filed in March 2002.

53 E.g. EP 0827745 B1: binary combination (docetaxel/cyclophosphamide), or EP 1169059 B1 (docetaxel/ Rhumab HER2) revoked by the BundesPatentGericht (BPatG) [Federal Patent Court]: BPatG Mar. 1, 2011, BECK-RECHTSPRECHUNG (BeckRS), 14402, 2011 (Ger.).

procedures and allow for better determination of the target patient population.

e) Derivatives

The research around docetaxel did not diminish the efforts in basic research to find new innovative drugs. Attempts to improve various aspects (for example the anti-tumoural activity) of docetaxel resulted in nine patent families dealing with novel derivatives of taxoids.[54] This research work successfully led to the marketing of Jevtana (cabazitaxel), approved in the U.S. in June 2010. Cabazitaxel was first disclosed in the patent WO 96/30335 (oral formulation WO 00/41482). Despite attempts to switch to the new therapy, docetaxel is still part of the widely used first line therapy. Cabazitaxel currently finds more use in retreatment of patients previously treated with a docetaxel-containing regime.[55] For some types of cancer there is currently no data (no studies done) at hand which proves an added benefit of cabazitaxel over docetaxel, while for others it has been demonstrated that the life time is significantly improved for cases of refractory cancer.[56]

3. Use of Procedural Provisions: Supplementary Protection Certificates (SPCs)/Patent Term Extension

In Europe, Supplementary Protection Certificates can be requested from the national patent offices under Regulation (EC) 496/2009

54 WO 92/09589, WO 93/23389, WO 94/08984, WO 94/11547, WO 94/20484, WO 95/01969, WO 95/11247, WO 96/03395 and WO 97/23473.

55 Institute for Quality and Efficiency in Health Care, IQWiG Reports – Commission No. A11-24 Cabazitaxel – Benefit assessment according to § 35a Social Code Book V, (Jan. 12, 2012), found at https://www.iqwig.de/download/A11-24_Extract_Cabazitaxel_Benefit_assessment_35a_Social_Code_Book_V.pdf, (last visited Sept. 11, 2012).

56 *Id*.