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Expert Opinion

Discontinued drugs in 2008: oncology drugs

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The failure of drug candidates in clinical development remains a critical issue for the pharmaceutical and biotechnology industries. This article documents those oncology drugs discontinued in 2008 and briefly reviews reasons for termination of development. Source information was derived from a search of the Pharmaprojects database for drugs reaching phase I – III clinical trials.

Keywords: 1D09C3, 4-demethylpenclomedine, ARQ-171, AZD-4992, CNF-1010, DN-101, FCE-28068, FCE-28069, folitixorin calcium, huMy9-6-DM4, INNO-305, mitumprotimut-T, MLN-8054, *N*-acetylcysteine, PD-0325901, phosphomannopentaose sulfate, PI-166, SGX-523, spisulosine, Symadex, tozasertib lactate, vatalanib, zanolimumab

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1. Background

Information presented in the 'discontinued drugs: oncology drugs' series for the past 2 years [1,2] has reported lack of efficacy as the major reason for failure of drug candidates in clinical development for cancer. As has been previously discussed in these reports, high attrition rates in clinical development are a critical problem hampering productivity for the pharmaceutical and biotechnology industries. However, a glimmer of light has perhaps been provided by a recent analysis [3] of drugs entering clinical development during the period 1995 – 2007 indicating a much lower overall clinical development attrition rate of 53% for molecularly targeted protein kinase inhibitors. This current report provides a brief analysis of those candidates for which development was reported to have been terminated in 2008.

2. Discontinued drugs

2.1 General overview

According to the analysis contained in **Table 1**, 24 drugs were dropped from the oncology development pipeline in 2008. One of these molecules, *N*-acetylcysteine, was, however, being developed as a supportive therapy and has not been considered further in this analysis. Of the remaining 23 drugs (exactly the same number as reviewed in the 2007 analysis), 12 were dropped in Phase I, 5 in Phase II and 6 in Phase III. In keeping with previous analysis, a range of therapeutic modalities including small molecules, antibodies and vaccines are represented in terminated candidates from both large pharma and biotech pipelines. **Table 2** summarises the reasons for candidate termination from the 2006, 2007 and 2008 data sets.

2.2 Failures in Phase I

Termination of development was reported for 12 compounds in Phase I development. A broad range of therapeutic modalities were represented in drugs terminated at this stage. Reasons for discontinuation were not disclosed for five drugs: huMy9-6-DM4 (antibody/cytotoxic molecule conjugate), CNF1010 (nanoemulsion derivative of 17-AAG), AZD-4992 (selective oestrogen receptor down regulator), 4-dimethylpenclomedine (aspartate carbamoyltransferase inhibitor) and an undisclosed biological new molecular entity from Lilly. Three drugs were discontinued for financial or strategic reasons. INNO-305, a vaccine comprised of four WT1

Table 1. Discontinued drugs in 2008: oncologic drugs.

Drug name	Originator (licensee)	Indications	Pharmacology description	Target	Development phase reached	Reason	Notes
1D09C3	MorphoSys Eli Lilly	Cancer, lymphoma, Hodgkin's Cancer, lymphoma, non-Hodgkin's Cancer, leukaemia, chronic lymphocytic Cancer, myeloma	MHC class II antagonist Apoptosis agonist	Unspecified	Phase I	Strategic	GPC has discontinued development of 1D09C3, a human mAb against MHC class II-positive B-cell lymphomas and leukaemias, following a strategic pipeline restructuring, refocusing of resources and general concerns over the 'antibody swapping' characteristic of this family of IgG4 antibodies (press release, GPC, 27 Feb 2008). 1D09C3 selectively kills B and T cells and induces apoptosis without the requirement of a fully functioning immune system (press release, GPC, 21 Aug 2003). GPC was also developing antibodies that bind to MHC class II molecules to prevent immune reactions such as transplant rejection and GVHD (anti-MHC II MAbs, immune, GPC; qv) (press release, GPC, 26 Nov 2001) and anti-MHC II peptidomimetics for rheumatoid arthritis and multiple sclerosis (immunosuppressants, GPC; qv) (8th Atlas/Ernst & Young Eur Life Sci Conf (Amsterdam), 2000; direct communication, GPC, 26 Feb 2001)

Source of data: Pharmaprojects, copyright © Informa UK Ltd, 2009 [9].

AML: Acute myelogenous leukaemia; GVHD: Graft-versus-host disease; i.v.: Intravenous; s.c.: Subcutaneous; SERD: Selective oestrogen receptor downregulator.

Table 1. Discontinued drugs in 2008: oncologic drugs (continued).

Drug name	Originator (licensee)	Indications	Pharmacology description	Target	Development phase reached	Reason	Notes
4-Demethyl-penclomedine	Antisoma	Unspecified	Aspartate carbamoyltransferase inhibitor	Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase	Phase I	Unspecified	Xanthus Pharmaceuticals (now Antisoma) has discontinued development of Clomet (4-demethylpenclomedine), the active metabolite of penclomedine (qv), for the treatment of solid tumours potentially without the neurotoxic side effects of penclomedine. It had potential in brain cancer (company web page, Xanthus, 6 Dec 2005; press release, Xanthus, 22 Mar 2007; 5th Rodman & Renshaw Global Healthcare Conf (Monte Carlo), 2008)
Anticancers, Lilly-3	Eli Lilly	Unspecified	Unidentified pharmacological activity	Unspecified	Phase I	Unspecified	Lilly has discontinued development of a biotech new molecular entity for the treatment of cancer after it did not meet critical success factors to continue development
ARQ-171	ArQule (Hoffmann-La Roche)	Unspecified	Transcription factor family E2F activator	E2F transcription factor 1	Phase I	Adverse events	ArQule has discontinued development of ARQ-171, an i.v. transcription factor E2F-1 inhibitor for the treatment of cancer after it was associated with QTc prolongation in a Phase I trial (press release, ArQule, 10 Apr 2008). It was generated through the ARQ-550RP Activated Checkpoint Therapy programme (press release, ArQule, 23 Jul 2004; Form 10-K, ArQule, 2007)

Source of data: Pharmaprojects, copyright © Informa UK Ltd, 2009 [9].

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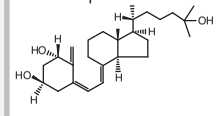
Table 1. Discontinued drugs in 2008: oncologic drugs (continued).

Drug name	Originator (licensee)	Indications	Pharmacology description	Target	Development phase reached	Reason	Notes
AZD-4992	AstraZeneca (Bayer)	Cancer, breast	Oestrogen antagonist	Oestrogen receptor 1	Phase I	Unspecified	AstraZeneca and Bayer Schering Pharma (Bayer) (Schering AG before the acquisition) have discontinued development of AZD-4992, a novel SERD, for the treatment of breast cancer (press release, Schering AG, 15 Sep 2006; Form 20-F, AstraZeneca, 2006; company pipeline, AstraZeneca, 31 Jan 2008). SERDs act by increasing the degradation rate of oestrogen receptor proteins, reducing the amount of interaction with other intracellular signalling pathways involved in hormone treatment resistance. SERDs have the potential to be used as a monotherapy for all stages of breast cancer or in combination for the treatment of hormone-resistant disease
Calcitriol, Transcept 	Transcept Pharmaceuticals	Cancer, prostate Cancer, lung, non-small cell Myelodysplastic syndrome Cancer, pancreatic	Vitamin D receptor agonist Apoptosis agonist	Vitamin D (1, 25-dihydroxyvitamin D3) receptor	Phase III	Strategic	Novacea (now Transcept Pharmaceuticals) has discontinued development of DN-101 (Asentar), a novel formulation of calcitriol, for the treatment of androgen-independent prostate cancer, following discussions leading to a merger with Transcept Pharmaceuticals. Development was previously suspended, but the suspension was lifted (press release, Novacea, 11 Sep 2008). The clinical use of calcitriol had been limited by hypercalcaemia at doses required for antitumour activity, but Novacea believed it had developed a solution to this problem by using a novel dosing regimen (Cowen 7th Ann Global Health Care Conf (London), 2006)

Source of data: Pharmaprojects, copyright © Informa UK Ltd, 2009 [9].

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