

Pipeline Insight: Hematological Malignancies - Pursuit for the next blockbuster intensifies

Description: Introduction

Unmet needs across the hematological malignancies remain high, with most traditional therapies conferring low levels of specificity and high toxicity. Pipeline candidates classified as molecular targeted therapies, cytotoxic therapies and immunotherapeutic agents, may offer attractive therapeutic additions and Datamonitor's insight into their clinical and commercial potential is provided.

Scope

Research and analysis of the hematological malignancies pipeline with in-depth clinical and commercial assessment of Phase III candidates Seven major pharmaceutical market sales forecasts to 2016 for key pipeline candidates incorporating product specific assumptions and events Segmentation and examination of product pipeline by developmental phase, class, indication and developer Insight and analysis of the hematological malignancies market potential including commercial opportunity and disease epidemiology

Highlights

180 different pipeline candidates have been identified of which 22 are in late-phase development. These existing candidates have a forecast sales potential of up to \$3.61 billion in the seven major pharmaceutical markets by 2016. Agents holding strong commercial potential include Novartis' Gleevec-follow-on, Tasigna (nilotinib), and Genzyme's already approved purine analog Clolar (clofarabine) which is in development for acute myeloid leukemia. Other notable candidates include the anti-idiotypic therapeutic vaccines and Biogen Idec's anti-CD23 MAb, lumiliximab. Over 50% of the products are being investigated in acute and/or chronic leukemia. However, as an individual hematological subtype, NHL attracts the greatest attention from developers with 53 (29%) products in the pipeline despite the malignancy being comparatively well served by existing treatment regimens.

Reasons to Purchase

Acquire a detailed appreciation and impartial perspective of the entire hematological malignancies developmental pipeline Identify the key products in late-phase development based on sales forecasts to 2016

and Datamonitor's drug assessment methodology Consider, assess and react to opportunities and risks influencing the future potential of products in the hematological malignancies pipeline

**Table Of
Contents:**

CHAPTER 1 EXECUTIVE SUMMARY	3
Scope of the analysis	3
Datamonitor insight into the hematological malignancies market	4
Key metrics	6
Datamonitor pipeline assessment summary	10
CHAPTER 2 PIPELINE OVERVIEW AND DYNAMICS	24
Pipeline overview	24
Products in late-phase development for hematological malignancies	24
Products in Phase II development for hematological malignancies	27
Products in Phase I development for hematological malignancies	36
Pipeline by developmental phase and class	43
There are 180 different products in the clinical developmental pipeline for hematological malignancies	43
Segmentation of products by developmental phase reflects high attrition rate in oncology drug development	44
Segmentation of products by class reflects shift in oncology drug development away from cytotoxics	49
Pipeline by indication	52
Over 50% of the pipeline products are being investigated in leukemia	52
The 22 late-phase pipeline products target eight different hematological malignancies	55
Pipeline by company	57
Developmental pipeline dominated by small pharma/biotech players	57
Only 17 (12%) companies/institutes have more than two candidates in the developmental pipeline for hematological malignancies	58
Novartis has six candidates in clinical development	59
Biogen Idec draws on the success of Rituxan	61
CHAPTER 3 HEMATOLOGICAL MALIGNANCIES - MARKET POTENTIAL	64
A diverse range of disease subtypes	64
Genetic basis of cancer evolution	64
Tumorigenesis is the result of co-operative accumulated mutations	66
Existing pharmacotherapy approaches provide limited treatment benefit	66
Cytotoxic drugs lack specificity	67
Hormonal or endocrine therapy provides incremental benefit in selected tumors	67
Optimizing current treatment strategies is paramount	67
The emergence of targeted treatment heralds a revolution in cancer pharmacotherapy	67
Dynamic cancer market offers significant commercial opportunity	68
Ongoing sales growth drives the market	68

Intensive R&D produces a rich developmental pipeline	69
Epidemiology - Hematological Malignancies	70
Cancer epidemiology - an expanding patient base	70
Leukemia	73
Lymphoma	77
Multiple myeloma	81
Myelodysplastic syndrome	83
Disproportionate increase in prevalence results from improvements in diagnosis and treatment	86
Significant areas of unmet need persist	88
The need for more sophisticated pharmacotherapy	88
Long-term control of advanced tumors is suboptimal	88
Novel strategies required to reduce relapse rates in early-stage disease	89
Toxicity of existing treatments jeopardizes quality of life and rates of treatment uptake	89
Improvements in diagnostics and prognostic analysis will enhance cost-effectiveness of treatment	90
Enhanced preventative strategies will ease the disease burden	90
Clinical and strategic threats to the commercialization of cancer drugs	91
Progressively rising R&D costs threaten industry productivity	91
High attrition rates can be mitigated by improved strategic decision-making	92
Lengthening drug approval process - a consequence of increased regulatory demands	92
Pharmacoeconomic pressures drive payers to implement restrictive pricing and reimbursement policies	92
Therapeutic and generic competition reduces periods of market exclusivity	93
Segmentation of market will require changes in clinical trial methodology	94
CHAPTER 4 R&D APPROACH	95
Classification of pipeline products	95
Molecular targeted therapies	95
Angiogenesis inhibitors	95
Single-target signal transduction inhibitors	99
Multi-targeted inhibitors	99
Cell cycle and apoptosis targeted inhibitors	101
Epigenetic modulators	103
Cytotoxic Therapies	104
Antimetabolites	104
Mitotic inhibitors	105
DNA-interactive chemotherapeutic agents	105
Immunotherapeutic agents	110
Antibody-based technologies are an effective anticancer approach	110
Active, specific immunotherapy	111
Evolution in oncology clinical trial design	112

Patient selection is increasingly significant in the era of targeted treatment	113
Clinical trials must have sufficient follow-up to establish true clinical benefit	114
Diversity of targeted treatments will require an evolution in clinical trial design	114
Most oncology clinical trials designate multiple endpoints	115
Survival	115
Quality of life	115
Tumor response rates	116
Toxicity	116
Time to tumor progression	116
Modification of accelerated approval process may impact significantly on approval times for hematologic oncology drugs	117
CHAPTER 5 MOLECULAR TARGETED THERAPIES ANALYSIS AND FORECASTS	120
Overview of molecular targeted therapies for hematological malignancies	120
Pipeline summary	120
Late-phase pipeline of molecular targeted therapies	121
Phase II pipeline of molecular targeted therapies	122
Phase I pipeline of molecular targeted therapies	125
Comparative forecasts	127
Definition of current comparator therapy	130
Novartis's Gleevec/Glivec (imatinib)	130
Tasigna (Nilotinib, AMN-107; Novartis)	133
Drug overview	133
Clinical trial data	133
Tasigna enters preregistration in the US and EU for Gleevec-resistant CML	133
Promising Phase II interim data reported	134
Tasigna appears effective in CML patients who have failed or are intolerant to both Gleevec and Sprycel	138
Only one BCR-ABL mutation is insensitive to Tasigna	139
Datamonitor comments	140
Tasigna ready to challenge Bristol-Myers Squibb's already approved Sprycel	140
Novartis looking to expand its leading role in the CML therapy market	140
Forecasts to 2016	141
Datamonitor drug assessment summary	142
Ceflatonin (Myelostat; ChemGenex Pharmaceuticals)	143
Drug overview	143
Clinical trial data	144
Ceflatonin receives Fast Track status for chronic myeloid leukemia	145
Ceflatonin aims to restore Gleevec sensitivity in CML patients	145
ChemGenex looking to expand Ceflatonin into the AML/APL market	147

Datamonitor comments	148
Despite convincing clinical benefit, Ceflatonin will face strong competition from Bristol-Myers Squibb's Sprycel and Novartis's Tasigna	148
Forecasts to 2016	149
Datamonitor drug assessment summary	150
Sarasar (Lonafarnib; Schering-Plough)	151
Drug overview	151
Clinical trial data	152
Main focus of Sarasar development in MDS, where greatest antitumor activity is shown	152
Farnesyl transferase inhibitors predominately in hematological disorders	153
Mild toxicity in the majority of patients, although grade 3 events do occur	153
Datamonitor comments	154
Sarasar's chances for approval will be delayed beyond 2007	154
Sarasar racing against Johnson & Johnson's Zarnestra as the first farnesyl transferase inhibitor to reach the market	154
Presence in oncology market will aid commercialization of Sarasar	155
Forecasts to 2016	155
Datamonitor drug assessment summary	157
Torisel (Temsirrolimus; Wyeth)	158
Drug overview	158
Torisel inhibits a key pathway in tumor cell proliferation	158
Clinical trial data	159
Torisel showing promise in mantle cell lymphoma	159
Torisel also making headway in other NHL subtypes	161
Datamonitor comments	163
Torisel will have to face Velcade in the MCL market	163
Prior commercialization of Mylotarg and Neumega will provide Wyeth with valuable insight into the oncology market	164
Forecasts to 2016	164
Datamonitor drug assessment summary	165
Zarnestra (Tipifarnib; Janssen/Johnson & Johnson)	166
Drug overview	166
Clinical trial data	167
Following rejection of NDA, the FDA requires Phase III data for Zarnestra in AML before regulatory approval can be considered	168
Results from Phase III studies have yet to be announced	168
Zarnestra has demonstrated a favorable profile in a variety of Phase II studies	169
Single-agent Zarnestra demonstrates antitumor activity in relapsed/refractory aggressive NHL	171

Zarnestra holding promise in juvenile myelomonocytic leukemia	172
Initiation of Phase II trials in large granular lymphocyte leukemia and multiple myeloma	173
Mild toxicity is particularly significant since Zarnestra's main indication is for elderly AML patients where quality of life is a major issue	173
Datamonitor comments	173
Schering-Plough's Sarasar catching up with Zarnestra as the first farnesyl transferase inhibitor to reach the market	173
Johnson & Johnson limiting Zarnestra's target population in the short term	174
Johnson & Johnson's experience will be invaluable to Zarnestra	175
Forecasts to 2016	175
Datamonitor drug assessment summary	177
Alvocidib (Flavopiridol; Sanofi-Aventis)	178
Drug overview	178
Clinical trial data	179
Continuous infusion dosing schedules fail to demonstrate clinical activity	180
Modified dosing regimen drives further development in CLL	182
Datamonitor comments	183
Given alvocidib's checkered history, Sanofi-Aventis may face an uphill struggle communicating the drug's potential	183
Alvocidib may show more promise as part of a combination regimen	183
Presence in oncology field will aid commercialization of alvocidib	183
Enzastaurin (LY317615; Eli Lilly)	184
Drug overview	184
Clinical trial data	184
Enzastaurin looking to make its mark in the B-Cell Lymphoma market	185
Enzastaurin holding promise as a maintenance therapy in mantle cell lymphoma	186
Datamonitor comments	186
Eli Lilly adopt a risky strategy for enzastaurin in DLBCL	186
Termination of Phase III trial for enzastaurin in glioma may hamper its potential in other indications	187
Forecasts to 2016	188
Datamonitor drug assessment summary	189
Lestaurtinib (CEP-701; Cephalon)	190
Drug overview	190
Clinical trial data	191
Lestaurtinib emerging as a promising agent for AML patients harboring Flt-3 activating mutations	191
Datamonitor comments	193
Lestaurtinib may be the first in its class to reach the market	193
Cephalon's recent acquisition of Trisenox will provide invaluable experience of the leukemia market	194

Forecasts to 2016	194
Datamonitor drug assessment summary	195
Genasense (Oblimersen; Genta)	196
Drug overview	196
Clinical trial data	197
FDA reject Genasense for use in combination with chemotherapy in CLL	197
Early-phase benefits of Genasense in AML require confirmation in Phase III clinical trial	198
Disappointing Phase III trial results in multiple myeloma means status of further development is unclear	199
Promise shown in combination with Rituxan in NHL, but randomized trials have yet to be initiated	200
Datamonitor comments	201
Approval of Genasense is looking increasingly unlikely	201
Termination of agreement with Sanofi-Aventis is a major setback for Genta	202
Forecasts to 2016	202
Datamonitor drug assessment summary	204
CHAPTER 6 CYTOTOXIC THERAPIES ANALYSIS AND FORECASTS	206
Overview of cytotoxic therapies for hematological malignancies	206
Pipeline summary	206
Late-phase pipeline of cytotoxic therapies	207
Phase II pipeline of cytotoxic therapies	208
Phase I pipeline of cytotoxic therapies	210
Comparative forecasts	210
Clolar/Evoltra (Clofarabine; Genzyme/Bioenvision)	212
Drug overview	212
Clinical trial data	213
FDA and EMEA approve Clolar for ALL but further data in AML are required	215
Clolar and cytarabine appears to be an active and well tolerated regimen for elderly AML patients for which a Phase III trial has recently been initiated	215
Single-agent Clolar may provide an important treatment option for AML patients with adverse cytogenetics who are unsuitable for standard chemotherapy	217
Despite further data now required for approval, Clolar demonstrates activity in pediatric AML	219
Datamonitor comments	220
While approval in AML will significantly broaden Clolar's label, increased economic constraints on healthcare systems may restrict its uptake	220
Forecasts to 2016	222
Datamonitor drug assessment summary	223
Dacogen (decitabine; MGI Pharma)	224
Drug overview	224
Clinical trial data	225

Elderly AML is an attractive indication for horizontal expansion of Dacogen 226

Dacogen as a maintenance therapy in AML 226

Dacogen plus Zolinza may be an effective combination 227

Datamonitor comments 227

Dacogen would fulfill a high unmet need in unfavorable risk AML 227

Dacogen may face competition from Vidaza, another approved DNA demethylating agent in development for AML 228

Dacogen will compete with Mylotarg in the relapsed elderly AML market 228

Forecasts to 2016 229

Datamonitor drug assessment summary 230

Cloretazine (VNP40101M; Vion Pharmaceuticals) 231

Drug overview 231

Clinical trial data 232

Cloretazine will enjoy the advantages of Orphan Drug and Fast Track status for AML 232

Cloretazine and cytarabine appears a feasible combination for second-line AML 233

Single agent Cloretazine appears effective in elderly poor risk AML 234

High-risk MDS patients may also benefit from Cloretazine monotherapy 235

Cloretazine and Temodar in hematological malignancies appears to be a rational combination 236

Vion discontinues Cloretazine development in CLL to focus on AML 237

Datamonitor comments 237

Given persistent high unmet needs and the lack of a gold-standard in relapsed/refractory AML, Cloretazine demonstrates promise 237

Vion should seek a collaborative agreement with a more experienced oncology partner 238

Forecasts to 2016 239

Datamonitor drug assessment summary 240

Pixantrone (BBR-2778; Cell Therapeutics) 241

Drug overview 241

Clinical trial data 242

Use of pixantrone for aggressive NHL 243

Use of pixantrone for indolent NHL 246

Datamonitor comments 248

Problems associated with trying to replace genericized drugs must be overcome 248

Patient recruitment to trials and physician awareness may be an uphill struggle 248

Pixantrone set to benefit from co-licensing agreement with Novartis 249

Forecasts to 2016 250

Datamonitor drug assessment summary 251

Marqibo (Sphingosomal vincristine; Hana Biosciences) 252

Drug overview 252

Clinical trial data 253

Despite an FDA non-approvable letter and recommendation to initiate a Phase III study in NHL, to date no such trial has been initiated 253

Relapsed aggressive NHL 254

Marqibo as a replacement for vincristine in the R-CHOP regimen for first-line NHL appears to be a promising possibility 256

Marqibo is a potential candidate for the treatment of relapsed/refractory Hodgkin's disease 257

Trials in ALL may hold promise for Marqibo 258

Datamonitor comments 259

Hana Biosciences face a difficult strategic development plan for Marqibo in NHL and shifting the focus to ALL may offer a quicker route to market 259

CHAPTER 7 IMMUNOTHERAPEUTIC AGENTS ANALYSIS AND FORECASTS 260

Overview of immunotherapeutic agents for hematological malignancies 260

Pipeline summary 260

Late-phase pipeline of immunotherapeutic agents 261

Phase II pipeline of immunotherapeutic agents 262

Phase I pipeline of immunotherapeutic agents 264

Comparative forecasts 267

Definition of current comparator therapy 270

Biogen Idec/Genentech/Roche's Rituxan/MabThera (rituximab) 270

Ceplene (Histamine dihydrochloride; Epicept) 272

Drug overview 272

Clinical trial data 272

Ceplene enters preregistration in Europe as a maintenance therapy in first remission in patients with AML 272

Ceplene plus IL-2 prolongs leukemia-free survival but no significant difference in overall survival observed 274

Datamonitor comments 274

FDA requests additional Phase III trial despite primary endpoints being met 274

EpiCept's lack of oncology experience may hamper Ceplene's market success 275

Forecasts to 2016 275

Datamonitor drug assessment summary 277

Galiximab (Anti-CD80 MAb; Biogen Idec) 278

Drug overview 278

Clinical trial data 279

Randomized Phase III trial will compare survival of galiximab plus Rituxan with Rituxan alone in relapsed/refractory follicular NHL patients 279

Phase II results show galiximab and Rituxan can be safely combined and can produce promising response rates in follicular NHL patients 280

Datamonitor comments 281

Biogen Idec in a strong position to successfully market galiximab alone	281
Biogen-Idec will need to effectively demonstrate the value of a combination of galiximab and Rituxan to payers	281
Forecasts to 2016	282
Datamonitor drug assessment summary	283
Lumiliximab (Anti-CD23 MAb; Biogen Idec)	284
Drug overview	284
Clinical trial data	285
Lumiliximab receives Fast Track and Orphan Drug designation for relapsed CLL	285
The addition of lumiliximab to the FCR regimen may produce a higher response rate without additional toxicity	286
Datamonitor comments	288
Lumiliximab on course to become an established addition to the standard treatment for CLL	288
Biogen Idec should look to investigate Lumiliximab as a maintenance therapy	289
Cluster of Differentiation (CD) drugs have become Biogen Idec's specialty	289
Forecasts to 2016	290
Datamonitor drug assessment summary	291
Ofatumumab (HuMax-CD20; Genmab/GlaxoSmithKline)	292
Drug overview	292
Clinical trial data	293
Genmab hoping ofatumumab will demonstrate a preferred efficacy profile over Rituxan in the clinic	293
Ofatumumab receives Fast Track status for CLL and enters a Phase III trial	294
Genmab initiate a pivotal Phase III trial in follicular NHL	296
Datamonitor comments	297
Ofatumumab may offer hope for Rituxan-insensitive patients	298
Approval of other MAbs being developed by Biogen Idec for NHL and CLL may restrict ofatumumab's potential even further	299
GlaxoSmithKline will offer invaluable experience to Genmab and aid commercialization of ofatumumab	299
Forecasts to 2016	300
Datamonitor drug assessment summary	302
Zanolimumab (HuMax-CD4; Merck Serono/Genmab)	303
Drug overview	303
Clinical trial data	304
Zanolimumab's Orphan Drug and Fast Track status reflects the high unmet needs in CTCL	304
Zanolimumab may also hold promise for PTCL patients	306
Datamonitor comments	307
The T-cell lymphoma market offers zanolimumab a limited commercial potential	307
Depletion of CD4+ T-cells by zanolimumab may render the patient susceptible to opportunistic infections	307

Forecasts to 2016	308
Datamonitor drug assessment summary	309
BIOVAXID (Accentia Biopharmaceuticals)	310
Drug overview	310
Clinical trial data	311
BIOVAXID inches closer to approval in the US and European markets for follicular NHL	311
Phase III trial initiated in February 2000 is ongoing and continues to show favorable survival benefits of BIOVAXID	312
Possible association between a specific negative chromosomal translocation following vaccination and disease free survival in follicular NHL	313
Phase II results of BIOVAXID in mantle cell lymphoma are promising	313
Datamonitor comments	314
BIOVAXID competing with FavId and MyVax for first-to-market status	314
BIOVAXID's price-tag should reflect the anticipated competition and current treatment costs	314
Forecasts to 2016	315
Datamonitor drug assessment summary	316
FavId (Id-KLH; Favrilite)	317
Drug overview	317
Clinical trial data	318
FavId receives Fast Track status by the FDA for follicular NHL	318
Single-agent FavId demonstrates an objective response in indolent B-cell NHL	321
Favrilite initiates FavId Phase III trial in DLBCL NHL	322
Datamonitor comments	323
FavId competing with BIOVAXID and MyVax to reach the market first	323
Favrilite's lack of commercial experience will be a barrier to optimizing market penetration	323
Forecasts to 2016	324
Datamonitor drug assessment summary	325
MyVax (GTOP-99; Genitope)	326
Drug overview	326
Clinical trial data	327
MyVax received Fast Track status for follicular NHL while Phase III clinical trial approaches completion	328
Phase II clinical trials show greater number of immune responses among previously untreated patients	328
Genitope initiates Phase I/II trial for MyVax in chronic lymphocytic leukemia	329
Follow-up Phase II data of MyVax in mantle cell and diffuse large B-cell lymphoma warrants further investigation	329
Datamonitor comments	331
Despite competition from BIOVAXID and FavId, MyVax increases its commercial potential by targeting an earlier stage treatment	331

With trials ongoing in CLL, MyVax may ultimately emerge as the most adaptable anti-idiotypic vaccine	331
Forecasts to 2016	331
Datamonitor drug assessment summary	333
Comparison of anti-idiotypic vaccines	335
APPENDIX	338
List of tables	338
List of figures	348
Methodology	353
Datamonitor forecast methodology	353
Datamonitor drug assessment summary	354
Abbreviations	356
Contributing experts	358
Key opinion leader interview transcripts	358
Bibliography	359
About Datamonitor	371
About Datamonitor Healthcare	371
Datamonitor Healthcare's therapy area capabilities	372
About the Disease analysis team	372
Disclaimer	374