UNIVERSITY OF BIRMINGHAM

MRC Hubs for Trials Methodology Research
Midlands Hub

Review of predictive biomarkers in European Medicines Agency (EMA) drugs

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10 February 2012

Objectives

- What predictive biomarkers are included in drug indications and contraindications in Europe?
- How many are there?
- In what therapeutic areas?
- What is the supporting evidence?

What is a biomarker?

"Biological Marker (Biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Controlled Clinical Trials 22:485–502 (2001)

What is a predictive biomarker?

- “a marker that predicts the differential efficacy (benefit) of a particular therapy based on marker status”

  Sargent DJ, JCO (2005) vol. 23, no.9, 2020-2027

- “measured at baseline to identify patients who are likely or unlikely to benefit from a specific treatment”

  Simon R, Cur Breast Cancer Rep (2009) 1:216-221

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Review of EMA drugs

- Updated and extended since October 2010
- Database created January 2012: one entry for each drug and marketing status
- **1st stage of sifting** – indications or contraindications potentially include a predictive biomarker
- **2nd stage of sifting**
  - potential Biomarker-Indication-Drug (B-I-D) combinations
  - based on full EMA documentation, additional internet searches and clinical advice

HER2 expression – breast cancer - trastuzumab

Review of EMA drugs

Inclusion criteria

- predictive biomarker
  - associated with the indicated drug
  - differential effectiveness and/or toxicity
- included in the EMA therapeutic indication or contraindication

Exclusion criteria

- diagnostic and screening biomarkers
- prognostic biomarkers - unless they are also predictive
- biomarkers used for dose adjustments
- biomarkers associated with another treatment
- non-therapeutic substances

SIFTING: 1st STAGE

808 entries in the database

643 entries excluded
did not potentially include a predictive biomarker

165 entries potentially include a predictive biomarker

SIFTING: 2nd STAGE

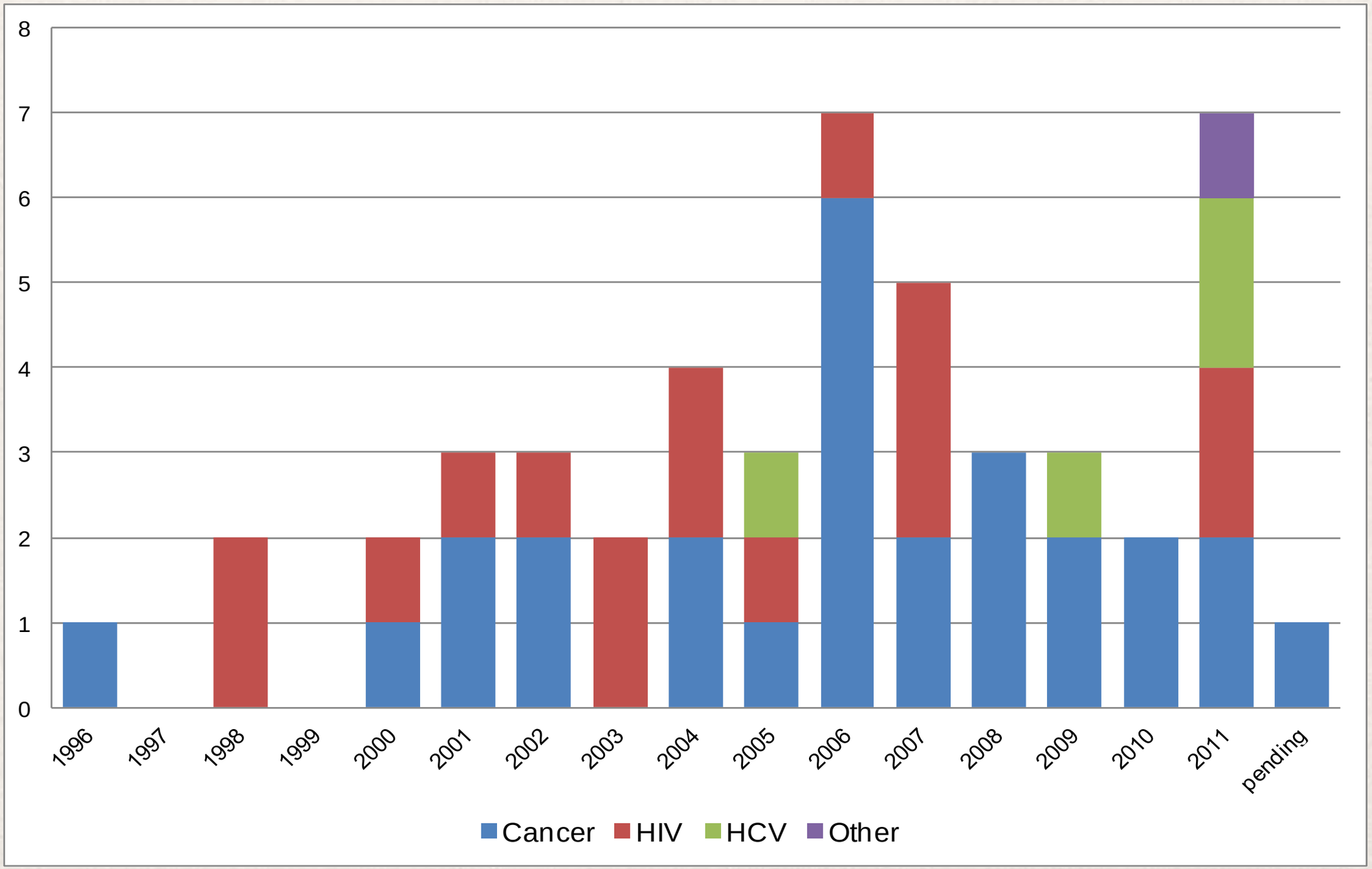
181 potential B-I-D combinations identified
(within 165 entries)

RESULTS

133 combinations excluded
125 – diagnostic/ screening biomarker or part of the disease definition
3 – non-therapeutic substance
3 - associated with another medicine licensed in combination
2 - biomarker mentioned in the indication, but not used to stratify patients

48 B-I-D combinations included
34 biomarkers
39 drugs

Inclusion of predictive biomarkers by year



CANCER

Biomarker		Indication	Drug	
BRAF V600 mutation	p	Melanoma	vemurafenib	Zelboraf
CD-33	r	Acute Myeloid Leukemia	gemtuzumab ozogamicin	Mylotarg
DPD deficiency	a	Colorectal Neoplasms; Colonic Neoplasms; Stomach Neoplasms; Breast Neoplasms	Capecitabine	Xeloda
DPD deficiency	a	Stomach Neoplasms	tegafur / gimeracil / oteracil	Teysuno
EGFR expression	a	Colorectal Neoplasms	cetuximab	Erbitux
EGFR expression	a	Non-Small-Cell Lung Carcinoma	erlotinib	Tarceva
EGFR mutation	a	Non-Small-Cell Lung Carcinoma	erlotinib	Tarceva
EGFR mutation	a	Non-Small-Cell Lung Carcinoma	gefitinib	Iressa
EpCAM	a	Cancer, Ascites	catumaxomab	Removab
estrogen receptor	a	Breast Neoplasms	toremifene	Fareston
estrogen receptor	a	Breast Neoplasms	fulvestrant	Faslodex
FIP1L1-PDGFR	a	Hypereosinophilic Syndrome	imatinib	Glivec
HER2	a	Breast Neoplasms	trastuzumab	Herceptin
HER2	a	Stomach Neoplasms	trastuzumab	Herceptin
HER2	a	Breast Neoplasms	lapatinib	Tyverb
Kit (CD 117)	a	Gastrointestinal Stromal Tumors	imatinib	Glivec
Kit (D816V)	w	Systemic Mastocytosis	imatinib	Glivec
KRAS mutation	a	Colorectal Neoplasms	cetuximab	Erbitux
KRAS mutation	a	Colorectal Neoplasms	panitumumab	Vectibix
PDGFR	a	Myelodysplastic-Myeloproliferative Diseases	imatinib	Glivec
Philadelphia chromosome	a	Precursor Cell Lymphoblastic Leukemia-Lymphoma	imatinib	Glivec
Philadelphia chromosome	a	Precursor Cell Lymphoblastic Leukemia-Lymphoma	dasatinib	Sprycel
Philadelphia chromosome	a	Chronic Myelogenous Leukemia	imatinib	Glivec
Philadelphia chromosome	a	Chronic Myelogenous Leukemia	dasatinib	Sprycel
Philadelphia chromosome	a	Chronic Myelogenous Leukemia	nilotinib	Tasigna
receptor positive	w	Breast Neoplasms	zoledronic acid	Zometa
t(15;17) translocation	a	Acute Promyelocytic Leukemia	arsenic trioxide	Trisenox

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	Biomarker		Indication	Drug	
HIV	**CCR5 tropism**	a	HIV Infections	maraviroc	Celsentri
	HLA-B*5701	a	HIV Infections	abacavir	Kivexa (abacavir / lamivudine); Trizivir (abacavir / lamivudine / zidovudine); Ziagen (abacavir)
	viral resistance	w	HIV Infections	amprenavir	Agenerase
	viral resistance	a	HIV Infections	tipranavir	Aptivus
	viral resistance	a	HIV Infections	efavirenz / emtricitabine / tenofovir disoproxil	Atripla
	viral resistance	a	HIV Infections	rilpivirine hydrochloride	Edurant
	viral resistance	a	HIV Infections	emtricitabine	Emtriva
	viral resistance	a	HIV Infections	emtricitabine / rilpivirine / tenofovir disoproxil	Eviplera
	viral resistance	a	HIV Infections	enfuvirtide	Fuzeon
	viral resistance	a	HIV Infections	lopinavir / ritonavir	Kaletra
	viral resistance	a	HIV Infections	darunavir	Prezista
	viral resistance	a	HIV Infections	atazanavir sulphate	Reyataz
	viral resistance	a	HIV Infections	fosamprenavir calcium	Telzir
	viral resistance	a	HIV Infections	nelfinavir	Viracept
	viral resistance	a	HIV Infections	nevirapine	Viramune
	viral resistance	a	HIV Infections	tenofovir disoproxil fumarate	Viread
HCV	**HCV genotype**	a	Hepatitis C	telaprevir	Incivo
	HCV genotype	a	Hepatitis C	boceprevir	Victrelis
	HCV genotype	a	Hepatitis C	ribavirin	Rebetol; Ribavirin BioPartners; Ribavirin Mylan (previously Ribavirin Three Rivers); Ribavirin Teva; Ribavirin Teva Pharma B.V.
	HCV genotype	w	Hepatitis C	interferon alfa-2b	Viraferon
Other	**NADPH reductase deficiency**	a	Methemoglobinemia	methylthioninium chloride	Methylthioninium chloride Proveblue

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Other	**NADPH reductase deficiency**	a	Methemoglobinemia	methylthioninium chloride	Methylthioninium chloride Proveblue

Supporting evidence: Before update – initial review

- 135 studies
- **Design**
  - Often unclear (56 studies)
  - Most frequent:
    - enrichment (targeted) design (58 studies)
    - subgroup analysis (19 studies)
  - 1 stratified design (SATURN, erlotinib for NSCLC)
  - 1 marker-strategy design (PREDICT-1, abacavir for HIV infection)

Supporting evidence: current data collection on studies

- Main/ supportive
- Phase
- Design
- Power calculation
- Participant numbers
- Participant characteristics vs. indication
- Biomarker assay

Supporting evidence: two cases

1) **EGFR expression – non small cell lung carcinoma (NSCLC) – erlotinib**

   - 2005 licensed - locally advanced or metastatic NSCLC after failure of chemotherapy
   - 2010 extension – maintenance in locally advanced or metastatic NSCLC stable after 4 cycles of platinum-based chemotherapy

2) **PDGFR gene rearrangements – myelodysplastic/myeloproliferative diseases (MDS/MPD) – imatinib**

   - 2006 licensed
   - Orphan designation

Supporting evidence

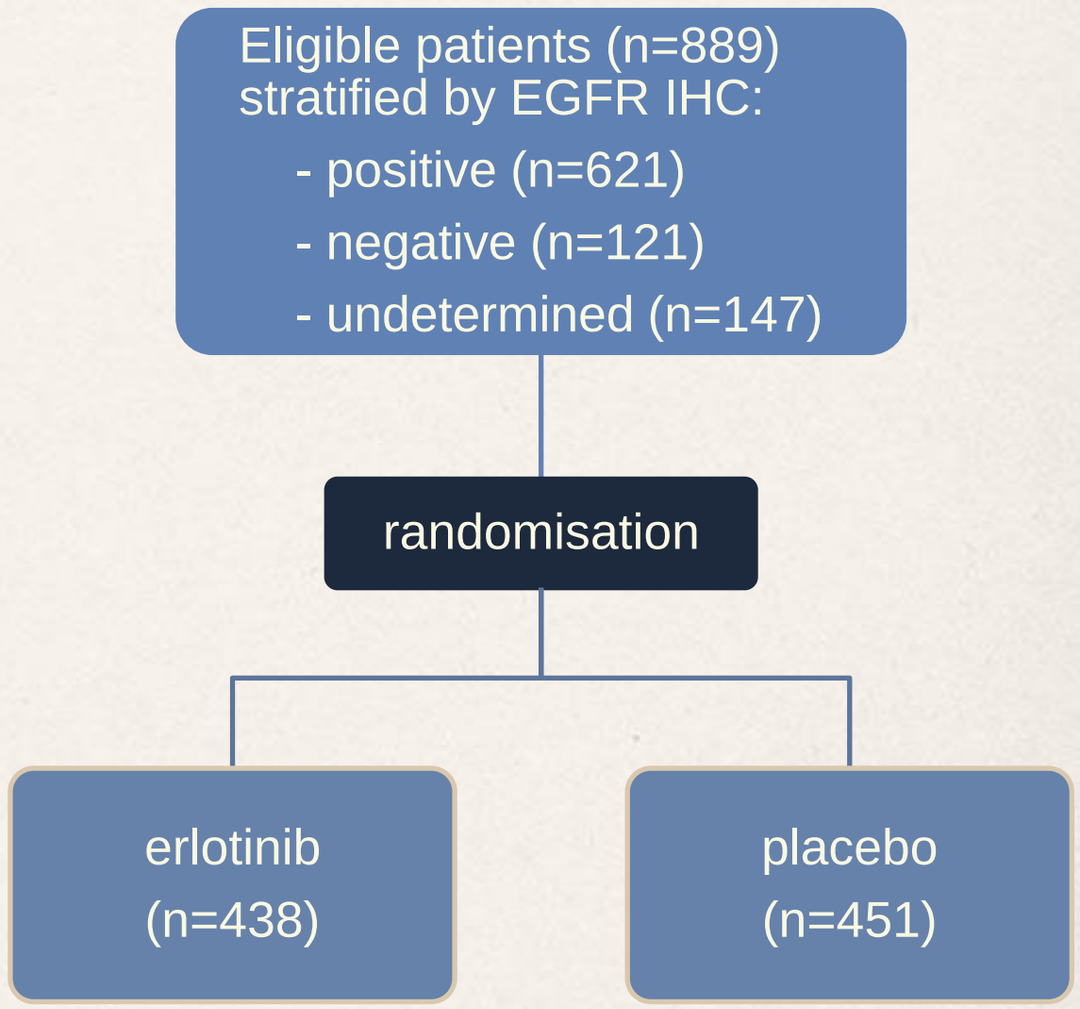
	study name	biomarker/ study design	primary outcome(s)	power calculation	N	biomarker known
EGFR - erlotinib – NSCLC (original)	**BR.21**	**subgroup (prospective)** RCT; phase III; double blind	overall survival	582 events to detect a 33% improvement in median survival (HR =0.75, initially 0.67) with erlotinib, using a two-sided 5% level test of significance and 90% power, assuming a median survival of 4 months for placebo	731	326 (45%)
	Perez-Soler 2004 (A248-1007)	**enrichment** uncontrolled; phase II	response rate	not reported	57	57 (100%)
EGFR - erlotinib – NSCLC (extension)	**SATURN (BO18192)**	**stratified** RCT; phase III; double blind	progression free survival in (1) overall population (2) EGFR+	5% significance level (1) overall population: 80% power at a 2-sided 3% significance level (HR=0.8), 731 events (2) 2% for the **EGFR IHC positive** (assuming 50% of all patients) at a 2-sided significance level of 2% would have 85% power to detect a HR of 0.7 (360 events expected) and 66% power for a HR of 0.75 (365 events expected)	889	742 (83%)
PDGFR – imatinib – MDS/MPD	**Heinrich 2008 (B2225)**	**enrichment** uncontrolled; phase II	tumor response (based on blood counts and bone marrow analyses)	none	7	7 (100%)
	Cortes 2003	**none** uncontrolled	not reported	not reported	10	10 (100%)
	Apperley 2002 Pardanani 2002	**none** case study	not reported	N/A	2	2 (100%)
	Magnusson 2002 Garcia 2003 Grand 2004 Levine 2005 Wittman 2004 Pitini 2007 Safley 2004 Trempat 2003 Vizmanos 2004 Wilkinson 2003	**none** case study	not reported	N/A	1	1 (100%)

SATURN: stratified design

- population: patients with non-small-cell lung cancer; non-progressive after first-line chemotherapy

- is erlotinib more effective in EGFR+ patients?

- two primary analyses: progression free survival in the overall population and in patients with EGFR IHC positive tumors



Limitations

- Definition of a predictive biomarker
- Only drugs reviewed
- Only EMA - drugs licensed after 1995
- Dose adjustment biomarkers were not considered relevant

Conclusions

- On average about 3 new B-I-D combinations every year – a lot?
- Also in rare diseases
- Therapeutic areas – limited to cancer, HIV infection, HCV infection and methemoglobinemia
- Study designs – mainly enrichment (targeted) design and subgroup analyses – can have serious limitations
- Further work: examine evidence in more detail