Therapeutic Innovations in Oncology: Targeted Therapies Coming of Age

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- Merck Frosst
- Ortho Biotech
- Pfizer Oncology
- Roche Oncology
- Sanofi-Aventis

Learning Outcome Objectives

At the end of this presentation you will be able to:

- Discuss the difference between traditional anticancer therapy and targeted therapy
- Define targeted anticancer therapy
- Discuss challenges/opportunities in evaluation and use of targeted agents

Cancer Therapeutic Modalities

- Surgery
  - Role in prevention, diagnosis, treatment (removal of the cancer) and palliation
- Radiation
  - Role in treatment (killing of cancer cells) and palliation
- Systemic Therapy
  - Role in prevention, treatment (killing of cancer cells) and palliation

Characteristics of Traditional Antineoplastic Agents

- Cytotoxic
- Nonspecific effect on cell division
- Cause cell death by damaging DNA
- Mechanism of action not always understood in detail

Development of Traditional Antineoplastic Agents

Phase I

- Patients with advanced disease
- Principle aims
  - Toxicity profile
  - Dose limiting toxicity
  - Maximum tolerated dose
  - Dose and schedule for Phase II trials
- Limited pharmacokinetics
- Preliminary evidence of activity

Development of Traditional Antineoplastic Agents

Phase II

- Patients with or without advanced disease
- Tumour type based on
  - In vitro or xenograft information
  - Observed response in Phase I trials
  - Tumour type where there are few active agents
- Principle aims
  - Does agent have activity
  - Is level of activity acceptable
  - Verify toxicity profile
- Combination with other agents
- Expand pharmacokinetic data

Development of Traditional Antineoplastic Agents

Phase III

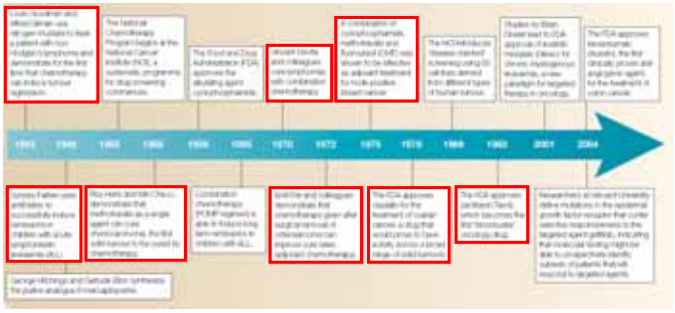
- Comparison with standard agents/regimens

Phase IV

- Expand knowledge base in special populations
  - Patients with impaired organ function
  - Children, elderly
  - Confirm clinical benefit

History of Systemic Cancer Therapy

Chabner BA et al. Nature Reviews Cancer 2005

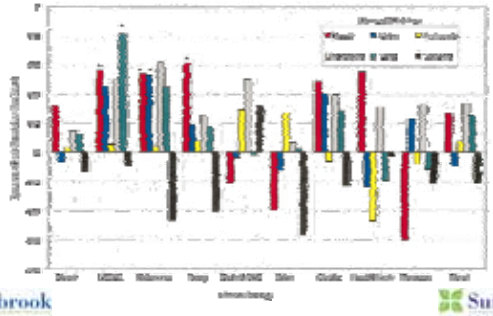


Limitations of Cytotoxic Drug Development

- Animal modules useful but not reliable predictors of activity in humans
- Tumours are genetically heterogenous
  - Response in subsets of patients
  - Subclones of cells are inherently or develop resistant

Correlation of Xenograft Response and Clinical Response

Johnson JI, et al. Br J Cancer 2001



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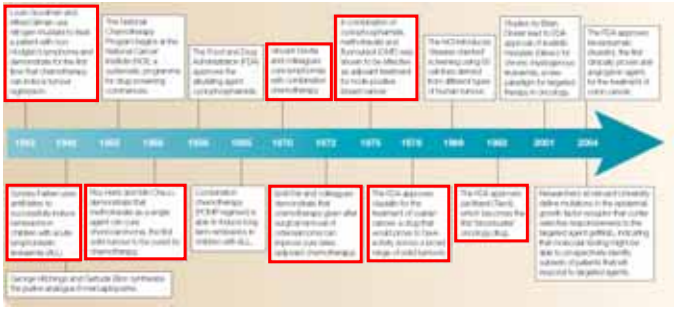
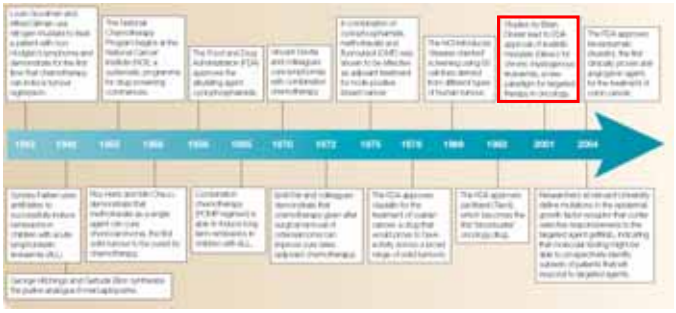
Chabner BA et al. Nature Reviews Cancer 2005



The Acquired Capabilities of Cancer Hanahan B & Weinberg RA. Cell 2000

- Self sufficiency in growth signals
- Insensitivity to growth inhibitory signals
- Evasion of programmed cell death
- Limitless replication capability
- Sustained angiogenesis
- Tissue invasion and metastasis
- Genomic instability

History of Systemic Cancer Therapy Chabner BA et al. Nature Reviews Cancer 2005



What is Targeted Therapy?

"An agent directed against predetermined & well-defined extracellular, transmembrane, or intracellular molecules involved in pathways controlling cellular growth, differentiation, transcription, or angiogenesis"

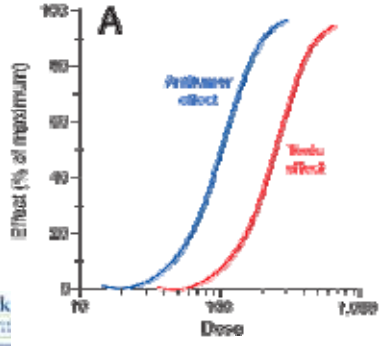
Shaheen PE, et al. Cancer Investigation 2006

Ideal Characteristics of a Targeted Therapy Agent

- High specificity & affinity for target
- Good oral absorption
- Metabolically stable - Long half-life
- No interaction with cytochrome P450
- Favourable toxicity profile

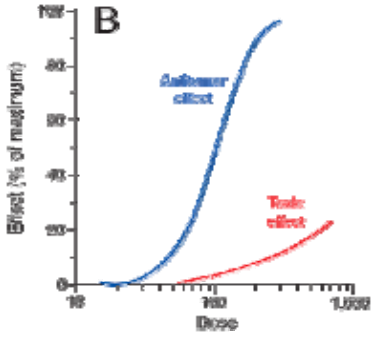
Goal of Targeted Therapy Development

Cytotoxic Drug Dose Response Curve



Goal of Targeted Therapy Development

Targeted Drug Dose Response Curve



Challenges in Development of Targeted Agents

- Cytostatic instead of cytotoxic
- Traditional Phase I study design/endpoints irrelevant
  - Dosing based on body surface area not applicable
  - Wide therapeutic window
  - MTD dose strategy may not applicable
- Not all patients or tumour types express target

Challenges in Development of Targeted Agents

- Biological understanding of target inhibition
- Reliable, sensitive, validated assay for presence of target or pathway activity
- Assay to measure inhibitory effect
- What does target do in normal cells
- When/how should "response" be measured
- Intermittant versus continuous administration/inhibition
- Use alone or in combination

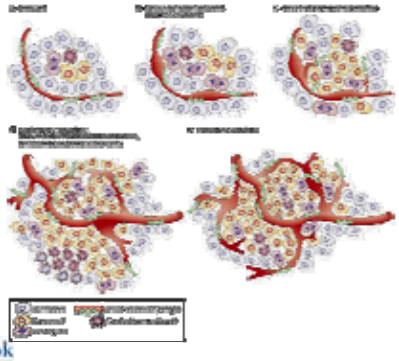
Cytotoxic versus Targeted Drug Development

Fox E et al. Oncologist 2002

	Empirical	Targeted
Discovery	Cell based	Receptor based
MOA	Unknown	Basis for selection
Effect	Cytotoxic	Cytostatic
Specificity	Nonselective	Selective
Dose/schedule	Pulse/cyclical at MTD	Continuous

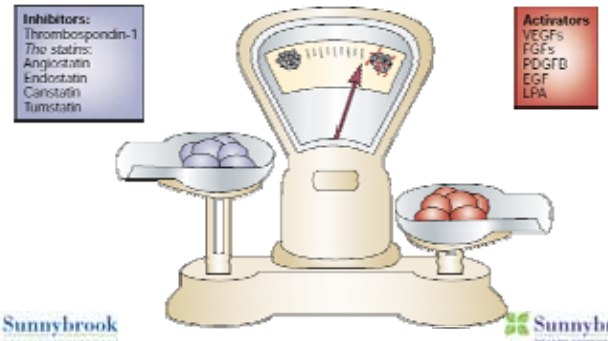
Angiogenesis

Bergers G, et al. Nature Rev Cancer 2002



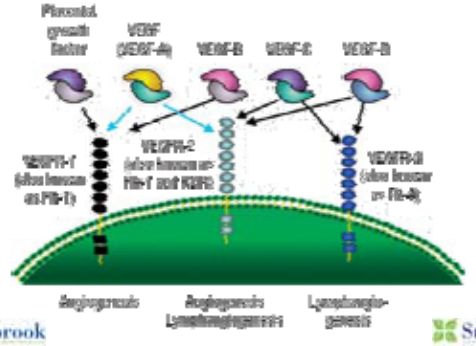
Angiogenic Balance

Bergers G, et al. Nature Rev Cancer 2002



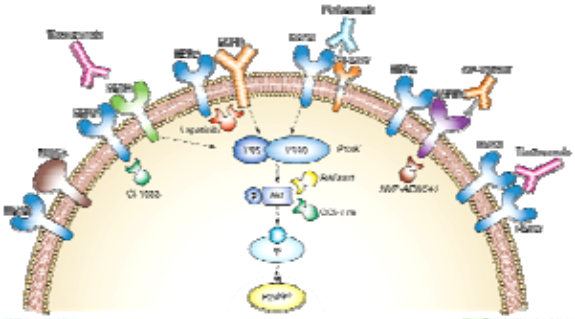
VEGF Family

Viele CS. Oncol Nurs Forum 2005



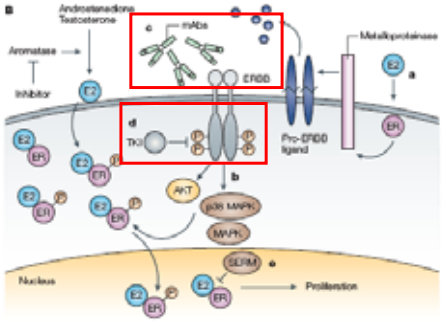
EGFR Family

Nahta R et al. Nature Clin Pract Oncol 2006



Targeted Therapy - EGFR

Hynes NE, ert al. Nature Rev Cancer 2005



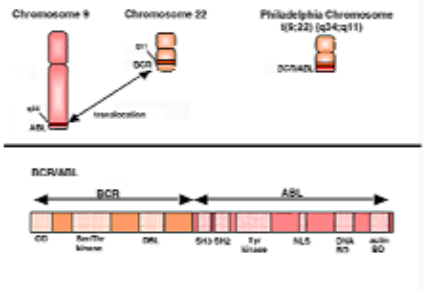
Oral Anticancer Agents

- Imatinib - Gleevec®
- Gefitinib - Iressa®
- Erlotinib - Tarceva®
- Sunitinib - Sutent®
- Sorafenib - Nexavar®
- Lapatinib - Tykerb®

Imatinib

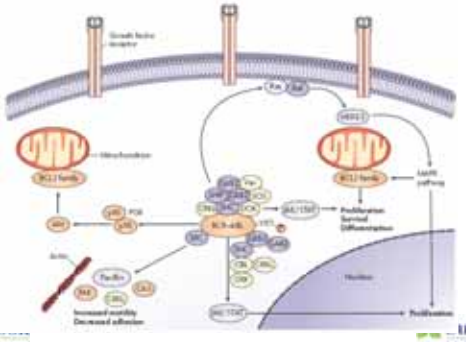
- Competitive inhibitor of Bcr-Abl tyrosine kinase
- Indications
  - Philadelphia chromosome positive CML and ALL
  - CML in blast crisis, accelerated phase or after interferon failure
  - Gastrointestinal Stromal Tumours
- Daily dose - 400 mg

Philadelphia Chromosome



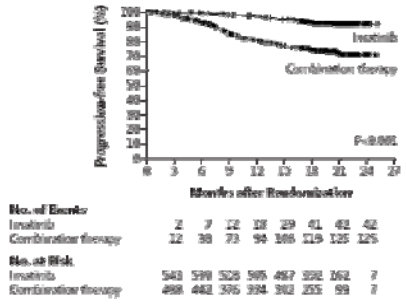
Bcr-Abl Signalling in CML

Weisberg E, et al. Nature Rev Cancer 2007



Imatinib Clinical Activity

IRIS Study O'Brien SG, et al. N Engl J Med 2003

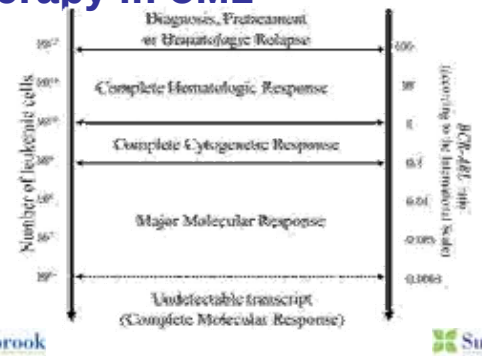


Imatinib Clinical Activity

IRIS Study O'Brien SG, et al. N Engl J Med 2003

Response	Initial Treatment		Crossover Treatment	
	Imatinib (N=553)	Interferon Alfa plus Cytarabine (N=553)	From Imatinib to Interferon Alfa plus Cytarabine (N=11)	From Interferon Alfa plus Cytarabine to Imatinib (N=318)
	percent (95% CI)			
Complete hematologic	95.3 (93.2–96.9)	55.5 (51.3–59.7) †	27.3 (6.0–61.0)	82.4 (77.7–86.4)
Major cytogenetic	85.2 (81.9–88.0)	22.1 (18.7–25.8) †	0 (0–28.5)	55.7 (50.0–61.2)
Complete cytogenetic	73.8 (69.9–77.4)	8.5 (6.3–11.1) †	0 (0–28.5)	39.6 (34.2–45.2)
Partial cytogenetic	11.4 (8.9–14.3)	13.6 (10.8–16.7)	0 (0–28.5)	16.0 (12.2–20.5)

Measuring Response to Therapy in CML



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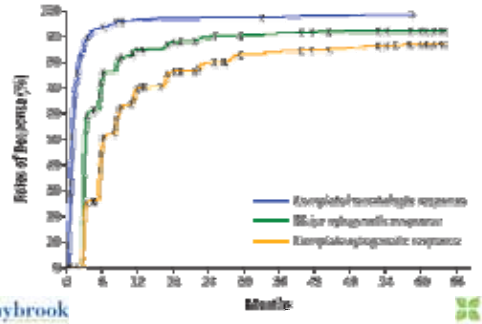
IRIS Study Druker BJ, et al. N Engl J Med 2006



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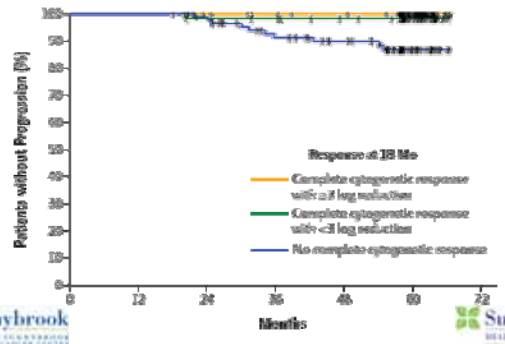
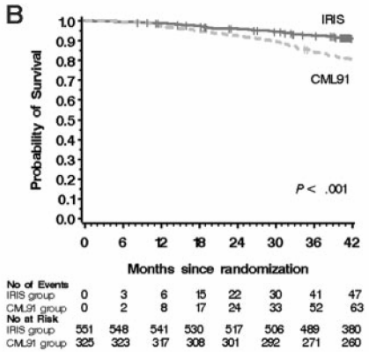


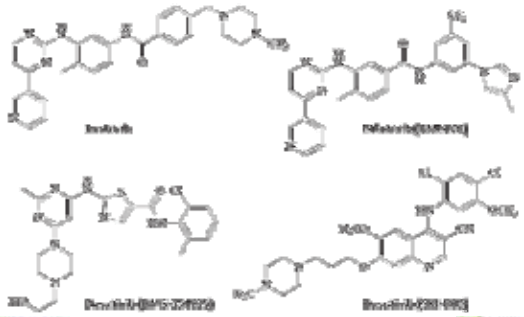
Imatinib & Survival in CML

Roy L, et al. Blood 2006



New TKIs for CML

Weisberg E, et al. Nature Rev Cancer 2007



Resistance to Imatinib

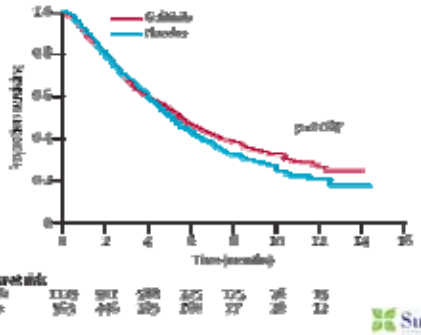
- Bcr-Abl point mutations which affect binding of imatinib
- Different point mutations have different prognostic outcomes
- Point mutations are both pre-existing and are acquired
- Mutations to second generation inhibitors have been identified

Gefitinib

- Selective inhibitor of epidermal growth factor receptor tyrosine kinase
- Indications (NOC/c)
  - Locally advanced or metastatic NSCLC
  - EGRF positive or unknown
  - Failure to platinum based & paclitaxel chemotherapy
- Daily dose - 250 mg

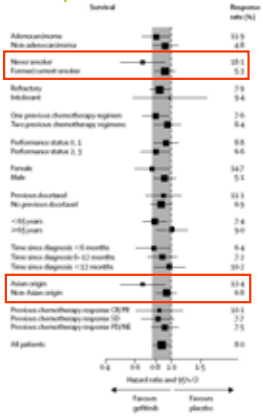
Gefitinib Clinical Activity

ISEL Study Thatcher , et al. Lancet 2005



Gefitinib Clinical Activity

ISEL Study Thatcher , et al. Lancet 2005

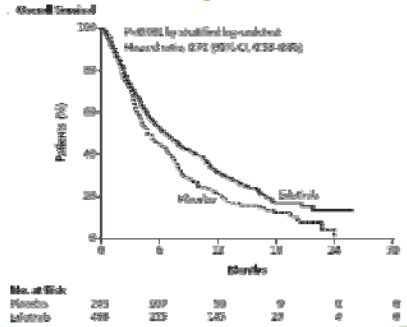


Erlotinib

- Selective inhibitor of epidermal growth factor receptor tyrosine kinase
- Indications
  - Monotherapy for patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen
  - EGFR expression positive or unknown
- Daily dose - 150 mg

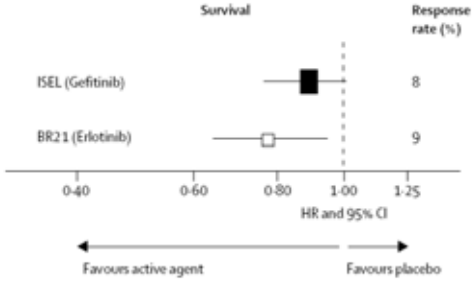
Erlotinib Clinical Activity

Shepherd FA, et al. N Engl J Med 2005



Gefitinib vs Erlotinib

ISEL Study Thatcher , et al. Lancet 2005



Sunitinib

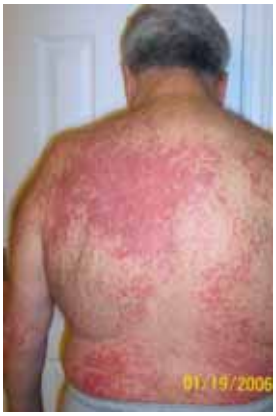
- Multitargeted tyrosine kinase inhibitor
  - Platelet-derived endothelial growth factor receptors, vascular endothelial growth factor receptors and others
- Indications
  - Gastrointestinal stromal tumour (GIST) after imatinib failure
  - Metastatic renal cell carcinoma clear cell histology, after interferon failure

Sunitinib

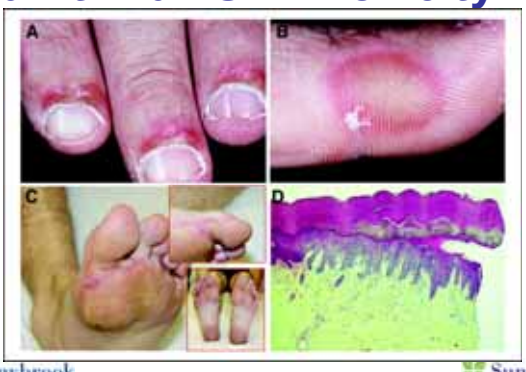
Dosing

- Starting dose: 50 mg qd, 4 weeks on/2 weeks off
  - Reduce off period to 1 week if well tolerated
- DL 2: 50mg qd, 2 weeks on/1 week off
- DL 3: 37.5 mg qd, 4 weeks on/1 week off
  - If tolerated 37.5 mg continuously
- DL 4: 25 mg qd, 4 weeks on/1 week off
  - If tolerated 25 mg continuously

Sunitinib - Rash



Sunitinib - Skin Toxicity



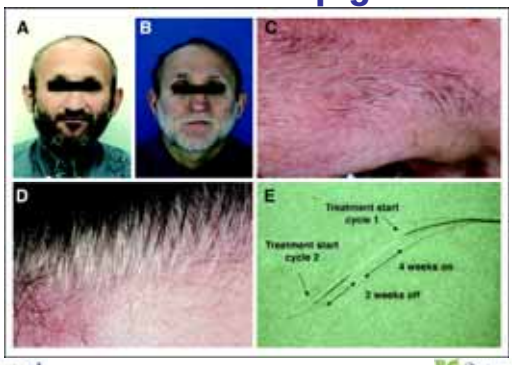
Faivre, S. et al. J Clin Oncol 2006

Sunitinib - Skin Toxicity PPE

Grade 2

Grade 3

Sunitinib - Hair Depigmentation



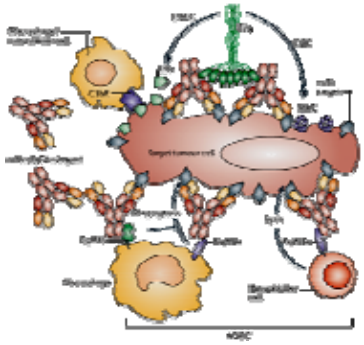
Faivre, S. et al. J Clin Oncol 2006

Monoclonal Antibodies

- Alemtuzumab - MabCampath®
- Bevacizumab - Avastin®
- Ibritumomab - Zevalin®
- Rituximab - Rituxin®
- Trastuzumab - Herceptin®

Targeted Therapy - MoAb

Imai K & Takaoka A Nature Reviews Cancer 2006



Targeted Therapy - MoAb

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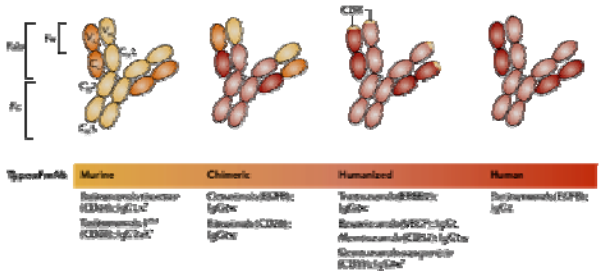
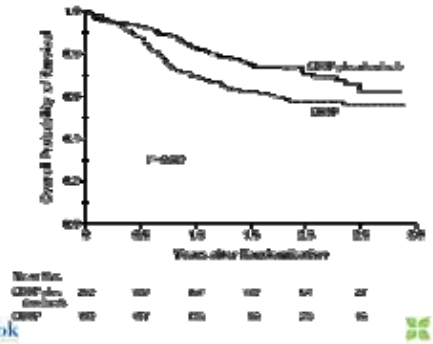


Rituximab

- Chimeric mouse-human monoclonal antibody
- Binds to CD20 antigen expressed on B-lymphocytes and > 90% of B-cell lymphomas
- Treatment of CD20 positive low grade, follicular or diffuse large B-cell NHL
- 375 mg/m² day 1 of each CHOP cycle
- Maintenance - 375 375 mg/m² day 1 q 3 monthly

Rituximab Clinical Activity

Coiffier B, et al. N Engl J Med 2002

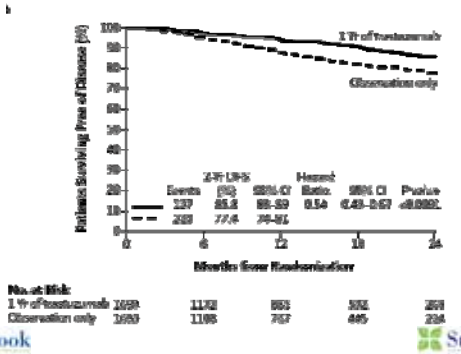


Trastuzumab

- Humanized monoclonal antibody
- Binds to HER2-neu
- Treatment of HER2-neu postive breast cancer
- 8 mg/m^2 LD followed by 6 mg/m^2 MD q 3 weekly x 1 year

Trastuzumab Clinical Activity

Piccart-Gebhart MJ, et al. N Engl J Med 2005



Bevacizumab

- Humanized monoclonal antibody
- Binds to VEGF
- First line treatment on metastatic colorectal cancer in combination with fluorouracil containing regimen
- 5mg/m^2 day 1 of chemotherapy cycle

Bevacizumab Clinical Activity

Hurwitz H, et al. N Engl J Med 2004

End Point	IFL plus Placebo	IFL plus Bevacizumab	P Value
Median survival (mo) Hazard ratio for death	15.6	20.3 0.66	<0.001
One-year survival rate (%)	63.4	74.3	<0.001
Progression-free survival (mo) Hazard ratio for progression	6.2	10.6 0.54	<0.001
Overall response rate (%) Complete response Partial response	34.8 2.2 32.6	44.8 3.7 41.0	0.004
Median duration of response (mo) Hazard ratio for relapse	7.1	10.4 0.62	0.001

Clinical Pharmacology Developments in Oncology

- Traditional Systemic Pharmacology
  - Improved analytical methodology
  - Population pharmacokinetic modeling
- Pharmacodynamic Endpoints
  - Patient survival, tumour regression, Partial versus complete response
  - Confounding affect of use of multiple agents
  - Measurement of drug action in blood or tumour
    - DNA adducts in peripheral blood lymphocytes
    - Incorporation of nucleotide analogs into DNA
    - PCR to measure Bcr-Abl gene in CML
  - Novel imaging techniques (PET) for drug, metabolite or surrogate markers

Clinical Pharmacology Developments in Oncology

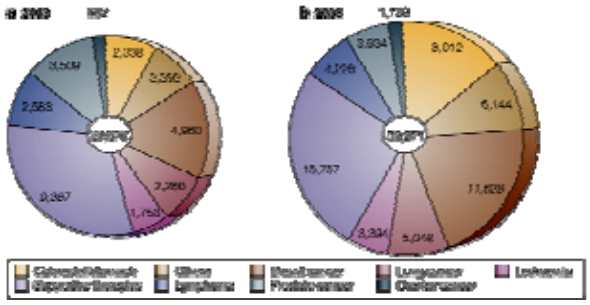
- Pharmacogenetic Determinants
  - Polymorphisms in drug ADME
    - Dihydropyrimidine dehydrogenase & Tiopurine methyltransferase, Methylenetetrahydrofolate reductase
    - Cytochrome P450
    - UDP-glucuronosyltransferases
    - Transporter proteins
    - Role of single nucleotide polymorphisms in drug metabolizing genes
  - Tumour regulatory genes
    - Methylguanine methyltransferase, Thymidylate synthase,
    - Microarray technology
- Integrated modeling

Challenges and Opportunities of Targeted Therapies

- Optimizing therapy
  - Selection of patients
    - Tumour gene expression profile
    - Patient genetic profile
  - Individualizing therapy
    - Pharmacogenetic covariates of drug metabolism, Therapeutic drug monitoring
- Evaluation of response
- Monitoring toxicity
- Use of targeted agents in combination with "traditional" antineoplastic agents
- Pharmacoeconomics

Global Oncology Market Sales

Anonymous. Nature Rev Drug Discovery Suppl. 2005



Sales in US $ Million

Make A Difference For Your Patient