Science Based Approach

Review of Drug Development Article

and

Recent Example

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
An integrated science-based approach to drug development

Editorial overview
Current Opinion in Immunology 2008, 20:426-430
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Monoclonal Antibodies and related molecules

- Antibody fragments
- Fusion proteins
- Conjugates
- Approximately 2 dozen approved to date
- CTs of this class of therapeutic proteins is accelerating
- Technological advances from fully mouse to fully human has reduced immunogenicity
Concept centers around 3 main aspects

- Target
- Antibody
- Patient

Target – 1st Step

- ‘Exquisite’ target specificity
- Requires extensive knowledge of the target
  - Ability to modulate disease outcome
  - ‘Drugability’
    - Overexpressed in pathogenesis, low or absent in other tissue/organs
    - Often cell surface receptors or their ligands
      - EGF receptors, TNF alpha
Antibody Design – 2nd step

- Must bind with high affinity and specificity
- High throughput screening can do both in parallel
- Now improved understanding / manipulation of Fc portion
  - Protein engineering
  - Glyco-engineering
- IgG1 versus IgG2 and IgG4 (cancer versus immune function)
  - Can In vivo stability issues be overcome with novel approaches
- Combining therapeutic antibodies with drugs/toxins

The Patient – where it really counts

- Addressing safety
- Proof of concept
- Efficacy

Inter-individual genetic heterogeneity or polymorphisms
- Herceptin is only effective against breast Ca that over-expresses the ErbB2
- (or Her-2) target

Disease associated mutations
- Erbitux or Vectibix (anti-ErbB1 or EGF receptors) not effective in patients containing tumours with a mutated K-ras
Trends in therapeutic antibody development

- Now ‘centre stage’
  - Overtaking more traditional (small molecules)
- Demonstrating efficacy in 1st line and long term treatments
- Being used as cocktails but with some increased risk
  - Natalizumab associated with JC virus activation causing Progressive Multifocal Leukoencephalopathy (PML) with other immune modulators

From the Breastcancer.org site

There are three tests for HER2-positive cancer:
- **IHC test** *(IHC stands for ImmunoHistoChemistry)*
  - The IHC test shows if there is too much HER2 receptor protein in the cancer cells.
  - The results of the IHC test can be 0 (negative), 1+ (negative), 2+ (borderline), or 3+ (positive).
- **FISH test** *(FISH stands for Fluorescence In Situ Hybridization)*
  - The FISH test shows if there are too many copies of the HER2 gene in the cancer cells.
  - The results of the FISH test can be "positive" (extra copies) or "negative" (normal number of copies).
- **SPoT-Light HER2 CISH test** *(SPoT stands for Subtraction Probe Technology and CISH stands for Chromogenic In Situ Hybridization)*
  - The SPoT-Light test shows if there are too many copies of the HER2 gene in the cancer cells.
  - The results of the SPoT-Light test can be "positive" (extra copies) or "negative" (normal number of copies).

“Find out which HER2 test you had. This is important. Only cancers that test IHC "3+" or FISH or SPoT-Light "positive" will respond well to therapy that works against HER2. An IHC 2+ test result is called borderline. If you have a 2+ result, you can and should ask to have the tissue tested with the FISH or SPoT-Light test.”
 Posted January 15th, 2009

- The American Society of Clinical Oncology (ASCO) today released its first "Provisional Clinical Opinion" on the use of KRAS gene mutation testing in patients with metastatic colorectal cancer to guide use of the epidermal growth factor receptor (EGFR) inhibitors cetuximab (Erbitux) and panitumumab (Vectibix).
- ASCO's Provisional Clinical Opinion recommends that all patients with metastatic colorectal cancer who are candidates for anti-EGFR therapy have their tumors tested for KRAS gene mutations before receiving these agents.

"Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumour tested for KRAS mutations in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment."

Recent Example

- Large Sponsor with new ‘Antibody Fusion Protein’
- Aggressive development program (5 trials at once)
- Trouble with ‘scale up’
- BGTE worked together as a team ....
Health Products and Food Branch

Synopsis of the response to C&M IR

- All clinical trials to date have been conducted with the Early Process Material EPM (Phase 1 and 2)
- Current Process Material CPM has a significantly higher impurity (5-9% of 6AA + AB fusion protein)
- The variant is not biologically active
- No bioequivalence studies were carried out.
- CPM shows a similar profile to the EPM in terms effect
- In addition mean plasma concentration over time is similar between the two materials - mouse study
- No specific in vitro studies were conducted to evaluate tissue cross reactivity or secondary pharmacodymanics. These studies were performed with EPM

Clinical IR

- Upon review of the impurity profiles for the ‘Antibody Fusion Protein’ produced by the EPM compared with the CPM - BGTD has determined that the products do not appear to be comparable.

  The majority of the submitted supporting data from non-clinical and clinical studies has utilized the EPM.

  Therefore to support the proposed later stage clinical development program, further non-clinical and possible clinical data should be provided utilizing the CPM.
Clinical IR cont’d

According to our review it appears that CPM has been utilized in the following non-clinical studies:

1. In vitro testing
2. Single dose subcutaneous acute ‘disease specific’ mouse model to determine pharmacodynamic activity
3. Single dose subcutaneous acute ‘ordinary’ mouse model to determine pharmacokinetic activity
4. In-silico assessment for immunogenicity
5. An ongoing 52-week primate study for chronic toxicity

BGTD believes that the final data from the 52-week primate toxicity study is required to support the proposed later stage clinical development program. This data should include full toxicity safety data, local tolerance data and immunogenicity data relative to EPM.

As such, it is recommended that you withdraw the current proposed clinical trials until the final data from the 52-week monkey study is available for review.

It is also possible that following review of the chronic toxicity data there may be further recommendations such as to perform a formal bridging clinical trial.

We urge you to consider requesting a pre-CTA meeting prior to re-submitting. If there is no further data to support these submissions and you choose not to withdraw BGTD will issue Non Satisfactory Notices before the default dates.