



#### How a Drug is Developed for Blood Cancers

- Preclinical rationale laboratory studies
- Pharmacology and manufacturing
- Animal studies toxicity and efficacy
- Human studies
  - Phase I
  - Phase II
  - Phase III
  - Phase IV

#### Blood Cancer Drug Development: Unique Challenges

- Many different diseases
  - Treatment approaches vary from observation to bone marrow transplantation
- Why do we need new treatments?
  - Increase the cure rate
  - Improve survival
  - Minimize toxicity/side effects
- Relatively rare diseases
  - Requires multicenter or even international collaborations
- Many existing agents have significant activity

Cost of developing a drug may exceed several hundred million \$ Increasing interest in "small diseases" as progress can be made

### **Phase I Trials**

- History
  - First in human
  - Goal: define maximum tolerated dose of potentially active agents
  - PRIMARY ENDPOINT: TOXICITY
  - Generally single-arm studies in patients with refractory disease
  - Often around 20 patients
- Blood cancer issues
  - Uncommon for first-in-human studies to be done in blood cancers
  - "Disease-specific" phase I more common
  - Novel biological agents require new trial designs
    - "Biologically active" dose more appropriate than maximum tolerated dose
  - Primary endpoint: remains toxicity

#### **Phase II Trials**

- Very common in oncology
  - May study a variety of doses and schedules
  - Goal: determine activity in disease
  - PRIMARY ENDPOINT: EFFICACY
  - Common to have many correlative scientific studies
  - Often single-arm studies in patients with either newly diagnosed or refractory disease
  - Usually between 20 and 80 patients
- Randomized phase II
  - Becoming more common
  - Necessary when "historical control" group does not exist
  - May explore different agents or combinations to determine optimal regimens for the ultimate phase III trial
  - Primary endpoint: efficacy, but two arms not directly compared

#### **Phase III Trials**

- Randomized trials to definitively evaluate efficacy
  - Single dose and schedule, determined by phase II
  - Large (>100 patients) with substantial statistical power
  - PRIMARY ENDPOINT: EFFICACY
  - Very few correlative scientific studies
- Placebo rarely utilized in oncology
  - Standard of care generally is control arm
  - Numerous examples in lymphoma of importance of randomized phase III trials
  - FDA may allow a single-arm trial if there is no clear standard of care (relevant particularly to rare diseases)

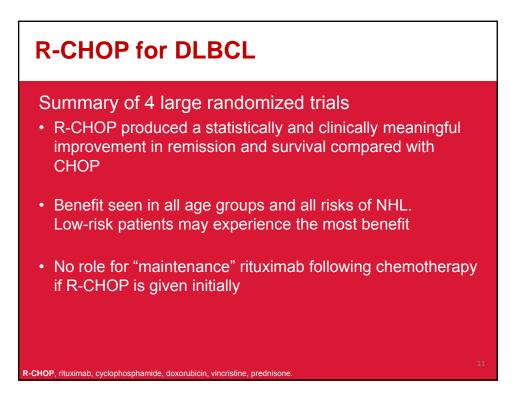
#### Lessons in Blood Cancers From Phase III Trials

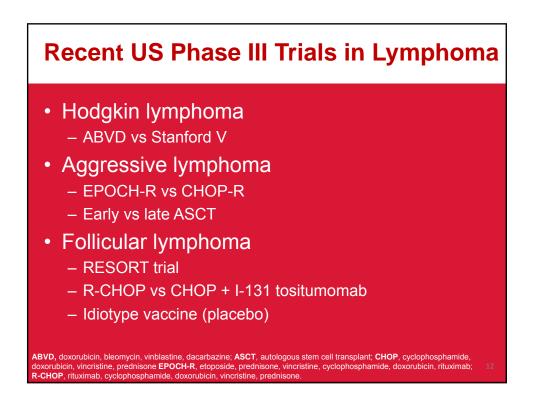
- CHOP is the standard for aggressive NHL
  - High priority lymphoma study
  - CHOP vs MACOP-B vs m-BACOD vs ProMACE-CytaBOM
  - Equivalent outcomes except for toxicity
- ABVD is the standard for advanced stage Hodgkin lymphoma
- Abbreviated CHOP with radiation is sufficient for localized aggressive NHL
  - CHOP x 3 + XRT vs CHOP x 8
  - Superior outcomes in combined modality arms

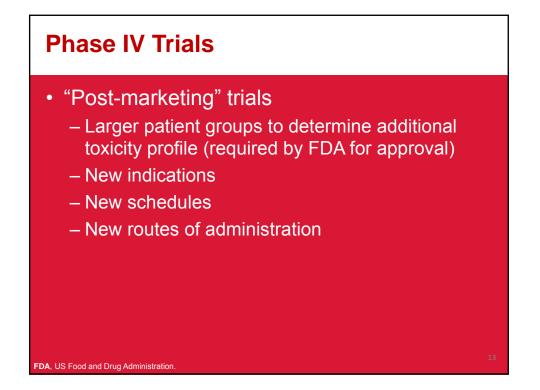
ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; m-BACOD, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, methotrexate, leucovorin; NHL, non-Hodgkin lymphoma; ProMACE-CytaBOM, 9 cyclophosphamide, doxorubicin, etoposide cytarabine, bleomycin, vincristine, methotrexate and prednisone; XRT, radiotherapy.

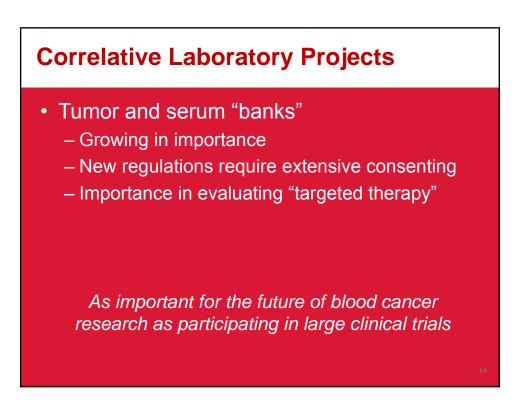
#### Lessons in Oncology From Phase III Trials

 Role of high-dose chemotherapy and autologous stem cell support in high-risk breast cancer









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#### **Who Conducts Clinical Trials?**

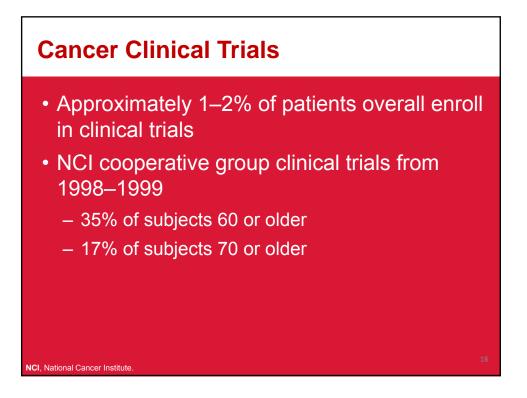
- Sponsor (organizer)
  - National Cancer Institute
  - Cooperative groups (CALGB/Alliance, SWOG, ECOG)
  - Pharmaceutical companies
  - Groups of academic and treatment centers
  - Individual academic and treatment centers
- Investigator (local center)
  - Academic centers/medical colleges
  - Large hospitals
  - Small hospitals and clinics
  - Small clinical practices
- · Virtually all "blood cancer expert" MDs are doing trials

#### **Advantages to Research**

- Access to novel agents
- · "Cutting-edge" care
- Standardization of staging and follow-up
- Team approach to care
  - Dedicated trials nurse; data manager; other MDs
  - Attention to details
- Altruism
- Reasonable expectations
  - Full understanding of rationale and goals of trial
  - Reassurance that you can leave trial if new information becomes available
  - Results of clinical research
    - Patience....



- All clinical research is performed at large academic medical centers
- Use of placebo and deviation from standard care
- Clinical research increases the cost of care
- All treatments on clinical trials are free



# Why Don't Patients Enroll in Clinical Trials?

- Possibilities
  - Lack of awareness (patient and MD)
  - Nature of treatment
  - Feeling that they are not end stage and don't need trial
  - Fear of unproven treatments
  - Excluded by comorbid illnesses
  - Complexities of study design and need for procedures
  - Concern about perception of benefit
  - Insufficient financial, logistic, social support
  - Distance
  - MD financial incentives/disincentives

#### Slow Accrual To Cancer Clinical Trials Causes Patients To Die Unnecessarily

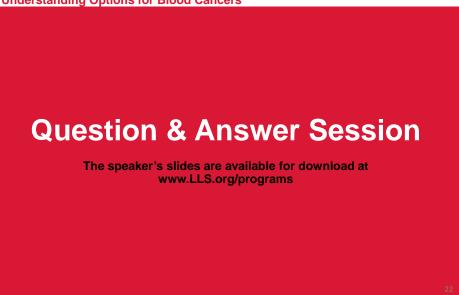
- US national CHOP vs CHOP-R study in DLBCL
  - 600 patients, accrued nationally over 3 years
  - To complete 1 year earlier, would have needed 100 more patients/year nationally
  - Amounts to about 1-2 patients/per center
- 20% improvement in cure rates
  - During 1 year, 20,000 DLBCL pts diagnosed in US
  - Completing study 1 year earlier would have saved estimated 4000 lives

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-R, rituximab, cyclophosphamide, doxorubicin, vincristine, 20 prednisone; DLBCL, diffuse large B-cell lymphoma.

## Is a Clinical Trial Right for You?

- Ask your doctor
  - Do they participate?
  - If not, can they refer you to someone who does to discuss?
  - Most blood cancer expert centers are involved
- Reach out
  - LLS (www.LLS.org), other organizations
  - Internet/clinicaltrials.gov
  - Company websites
- Clinical trials should be at least <u>considered</u> for <u>every</u> situation

#### Clinical Trials or Standard Treatment? Understanding Options for Blood Cancers



#### **Clinical Trials or Standard Treatment? Understanding Options for Blood Cancers** The Leukemia & Lymphoma Society (LLS) offers: · Live, weekly Online Chats are moderated by an oncology social worker and provide a friendly forum to share experiences. ≻WEBSITE: www.LLS.org/chat • Co-Pay Assistance Program offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist. ≻WEBSITE: www.LLS.org/copay >TOLL-FREE PHONE: (877) LLS-COPAY • For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist. ≻EMAIL: infocenter@LLS.org >TOLL-FREE PHONE: (800) 955-4572

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