Treatment of Adolescents and Young Adults with ALL with an Asparaginase-Intensive Pediatric Regimen

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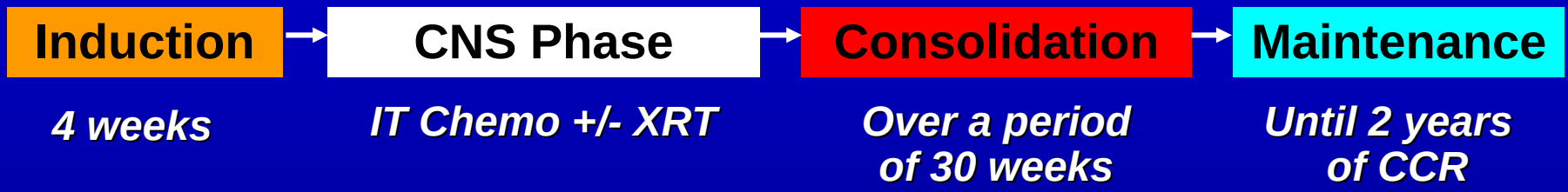
DFCI ALL Consortium

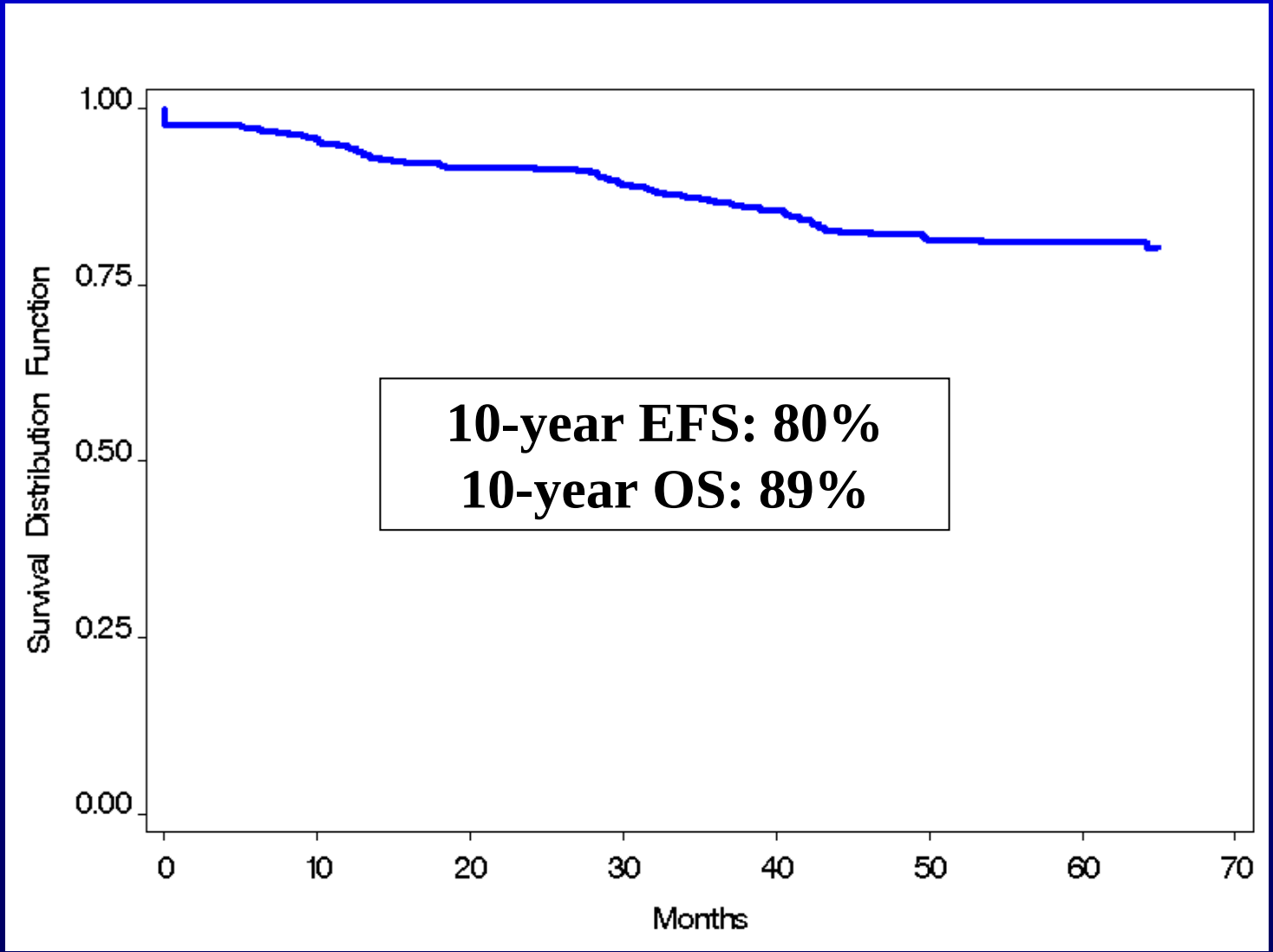
- Randomized, multi-institutional clinical trials since 1973
- Historically, enrolling patients 0-18 years of age
  - Recently expanded to include adults with ALL (up to age 50 years)

DFCI ALL Consortium Trials



- **Consolidation (week 7)**
  - **Asparaginase: 20-30 weeks**
    - **Goal: Maintain continuous asparagine depletion**
    - **E.coli ASP 25,000 IU/m2/week**
      - **PEG ASP 2500 IU/m2 every 2 weeks**
  - **Vincristine/steroid pulses every 3 weeks**
    - ***SR*: weekly methotrexate, daily 6MP**
    - ***HR*: doxorubicin every 3 weeks**

DFCI ALL Consortium Trials (1996-2000)



DFCI Protocol 95-01 (1996-2000)

DFCI ALL Consortium: Adolescents

- 844 patients treated between 1991-2000
- Median follow-up 6.5 years

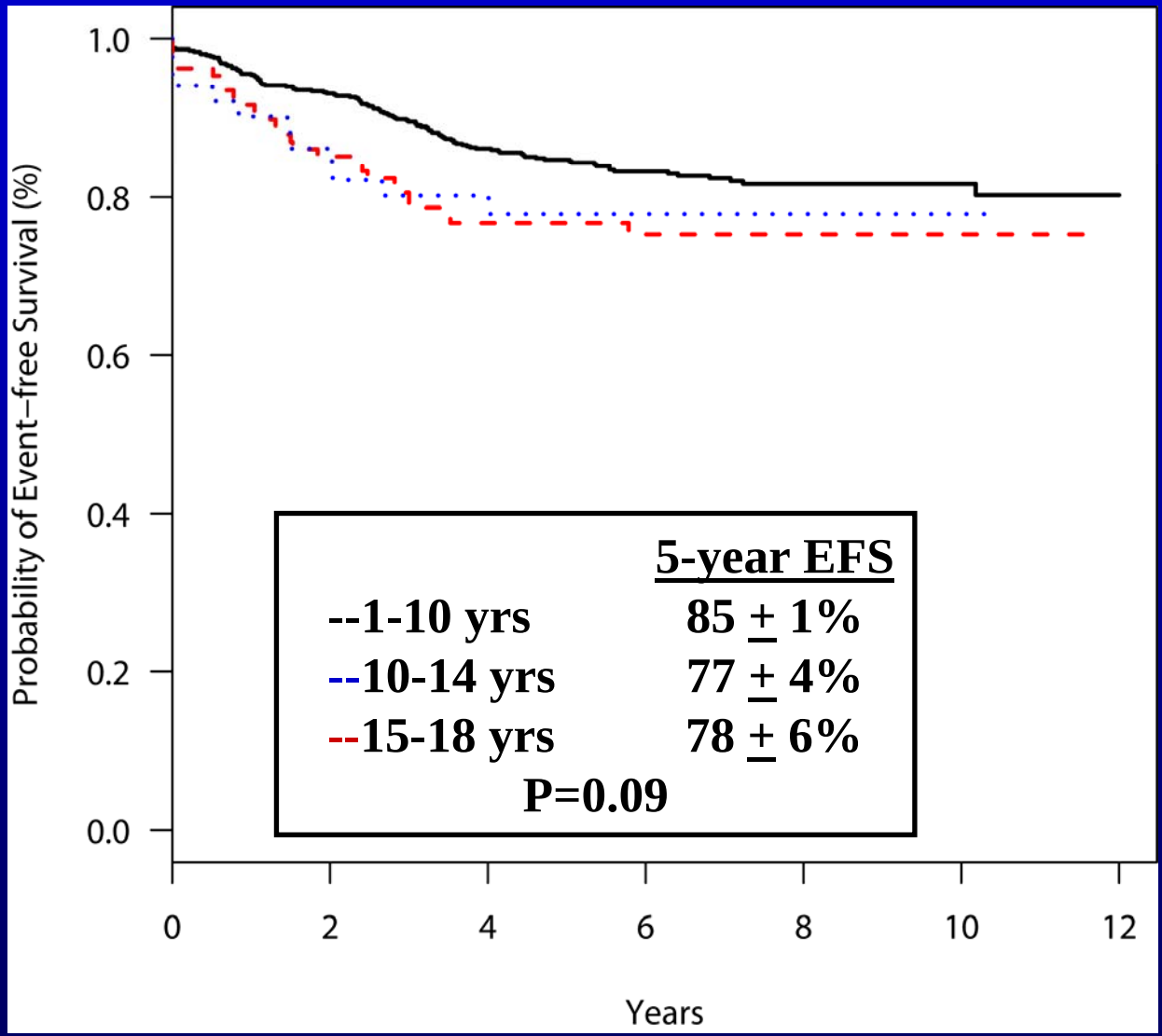
	1-10 yrs	10-14 yrs	15-18 yrs	p-value
N	685	108	51	
T-cell	7%	14%	29%	<0.001
WBC (median)	9,900	10,050	6,500	0.18
TEL/AML1	28%	24%	0%	0.05

Barry et al, J Clin Oncol 25:813, 2007

DFCI: Outcome By Age Group

	1-10 yrs	10-14 yrs	15-18 yrs	p-value
N	685	108	51	
IF/ID	6/2	3/1	1/2	
CR	99%	96%	94%	0.01
Relapse	14%	20%	14%	0.18
CR Death	2%	0%	2%	0.40
2nd Malig	0.3%	0.9%	0%	
CCR	571 (83%)	82 (76%)	40 (78%)	0.17

DFCI Consortium: EFS by Age



DFCI Consortium: EFS by Age and Phenotype

5-year EFS	1-10 yrs	10-14 yrs	15-18 yrs	p-value
B-precursor	85 ± 1	75 + 5	77 ± 7	0.05
T-ALL	82 ± 5	87 ± 9	79 ± 11	0.88

Outcome of Older Adolescents by Pediatric Treatment Regimen

Study	Years	N	5-year EFS
DFCI 91-01/95-01	1991-2000	51	78%
CCG 1961	1996-2002	262	68%
FRALLE 93	1993-1999	77	67%
BFM 90	1990-1995	141	64%
DCOG 6-9	1984-1999	47	69%

DFCI Consortium: Asparaginase Toxicity

	1-10 yrs	10-14 yrs	15-18 yrs	p-value
N	685	108	51	
Allergy	15%	10%	10%	0.38
Pancreatitis	3%	9%	4%	0.02
Thrombosis	2%	14%	10%	<0.01

Barry et al, J Clin Oncol 15:813, 2007

DFCI Consortium: Asparaginase Toxicity

	1-10 yrs	15-18 yrs	p-value
N	685	51	
Allergy	15%	10%	0.41
Pancreatitis	3%	4%	0.67
Thrombosis	2%	10%	<0.01

DFCI Consortium: Other Toxicities

- **Infections: No difference by age (p=0.99)**

Adolescent Outcome: Summary

- Relatively favorable EFS
  - 15-18 years: 5 yr EFS 78%
- Reasonably well-tolerated
  - Increased risk of:
    - Asparaginase-related TE complications
  - No increased risk:
    - Asparaginase-related pancreatitis or allergy
    - Infections
  - Increased risk of Osteonecrosis in younger adolescents?
    - ?Peak risk from age 10-14 years old

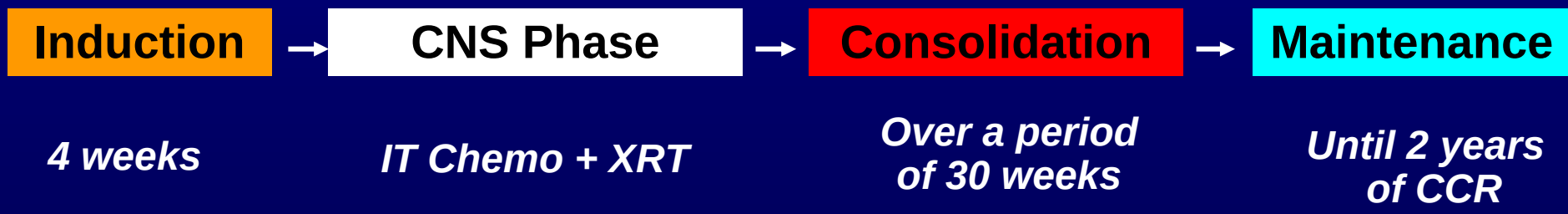
- **Could relatively favorable results for adolescents be extended to young adults with ALL?**

Protocol 01-175: Adult ALL Pilot

- Pilot of DFCI ALL Consortium Pediatric Regimen in Adults with ALL
- Eligibility
  - Newly diagnosed ALL (excluding mature B-cell)
  - Age 18-50 years
  - No prior chemotherapy
- Objective: Determine feasibility of administering Pediatric DFCI regimen in adults

Protocol 01-175: Adult ALL Pilot Trial

- **Treatment: same as HR arm of DFCI Childhood ALL Protocol 00-01**
  - **Including: 30 weeks of E.coli asparaginase during consolidation**
  - **Note: Ph+ ALL to SCT in 1st CR (imatinib pre-SCT)**



Protocol 01-175: Phases of Treatment

- **Remission Induction: 4 weeks**
  - IT-chemo days 1, 15, 29
  - VCR, Pred, Dox, HD-MTX, E.coli ASP x 1, + imatinib if Ph+
- **CNS: 3 weeks**
  - IT-chemo MAH X 4 + 18 Gy Cranial XRT
  - VCR, Dox, 6-MP
- **Consolidation: 30 weeks**
  - VCR/dexamethasone every 3 weeks, standard-dose 6MP
  - Doxorubicin (cumulative dose 300 mg/m^2)
  - IT-chemo every 18 weeks
  - Weekly E.coli ASP x 30 weeks
- **Continuation: until 2 years CCR**
  - VCR/dexamethasone every 3 weeks
  - Daily 6MP, weekly MTX (standard dose)
  - IT-chemo q18 weeks

Protocol 01-175: Adult ALL Pilot

- Open for accrual: 2002-2008
- 11 participating sites
- N=94 evaluable patients

Protocol 01-175: Presenting Characteristics

- Median age: 28 years (range 18-50)
- 61% male, 39% female
- 75% B-precursor, 25% T-cell
- Median WBC at diagnosis: 15.5 K (range 1.0-3600)
- Philadelphia Chromosome: 22%

Protocol 01-175: Summary

- **The administration of an asparaginase-intensive pediatric regimen in adults with ALL is feasible, with acceptable toxicity**
- **Encouraging preliminary EFS/OS**
  - **This approach *may* lead to better survival rates for adults with ALL**
  - **Longer follow-up is needed**

DFCI Consortium Adult ALL: Follow-up Trial

- Continue to treat adults per DFCI ALL Pediatric Regimen
- Pilot IV PEG asparaginase during consolidation
  - 15 doses given every 2 weeks

Asparaginase dosing in AYA population

- ASP dosed by BSA
  - E.coli ASP 25,000 IU/m2/week
- High interpatient variability in ASP enzyme levels
- ?optimal ASP dose
  - ?optimal dose varies by patient subgroup (age)

Protocol 00-01: Asparaginase Randomization

R → E.coli L-ASP 25,000 IU/m^2 IM x 30 weeks

R → E.coli L-ASP 12,500* IU/m^2 IM x 30 weeks

ASP levels I I I I I I I I I ...

1 2 3 4 5 6 7 8 9 … 30 weeks

*increase/decrease dose to maintain asparagine depletion (Nadir ASP level 0.1-0.14 IU/ml)

Protocol 00-01: ASP Enzyme levels

- Measured every 3 weeks
- Nadir level (1 week after last dose)
- Validated biochemical assay performed in central laboratory
- Lower limit of quantitation: 0.025 IU/mL
- Inter-day Accuracy: 99.7%

Note: Serum asparagine measurements are “gold standard”, but not performed due to technical limitations

ASP Enzyme Levels

- **Asp Enzyme Level ≥ 0.01 IU/mL considered "therapeutic"**
  - **Previously correlated with serum asparagine depletion**

Protocol 00-001

- Open for Accrual: 2000-2005
- 385 randomized patients
  - Fixed : 196
  - Individualized: 189
- Asparaginase samples: 2545 analyzed

Asparaginase Enzyme Levels by Age: Summary

- **Fixed Dose Arm: Patients 10-18 years old have higher median nadir ASP levels (7 days after dose of E.coli ASP) compared with younger patients ($p<0.01$)**
- **Individualized Dose Arm: Lower median dose in patients 10-18 years old compared to younger patients**

⟶ Adolescents may achieve adequate ASP depletion with lower doses of asparaginase

AYA ALL: Conclusions

- Biologically higher risk disease
- Relatively favorable outcomes when treated with ASP-intensive pediatric regimen
- Therapy reasonably well-tolerated in AYA patients
  - Increased risk for ASP-related TE complications ?pancreatitis
  - Majority of patients able to tolerate 26+ weeks of ASP
- Pilot trial of DFCI Pediatric Regimen in adults
  - Appears feasible
  - Encouraging preliminary outcome results
- Optimal ASP dose in AYA patients to be determined
  - May be adequately treated with lower doses than younger children

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DFCI ALL Consortium

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