Therapeutic Advances in Paediatric ALL

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Incidence of Paediatric Diseases in NZ

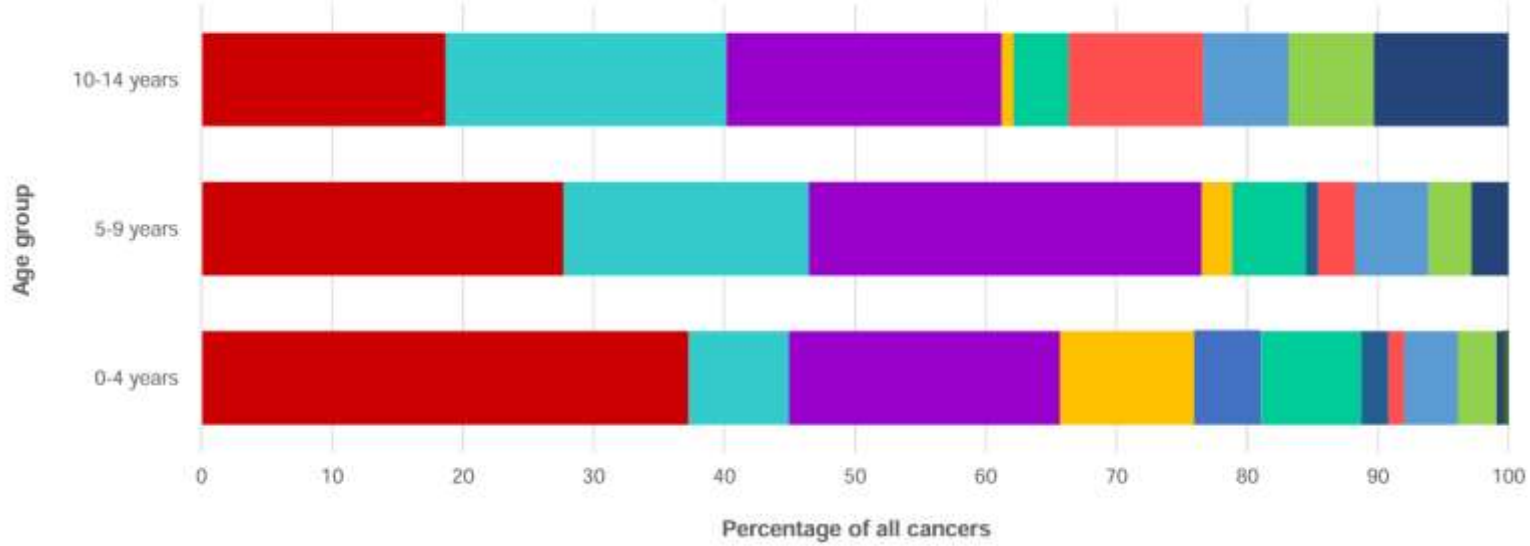
	Incidence per 10,000 per year
Asthma	1450
Pertussis (<1 year)	466
Pertussis (1-4 years)	254
Autistic Spectrum Disorder	170
All Cancer	149
Invasive pneumococcal disease (all ages)	107
Leukaemia	51
Rheumatic Fever	46
Non-CF Bronchiectasis	37
Lymphoma	13

Provided by Dr Peter Bradbeer

Paediatric and AYA ALL in NZ

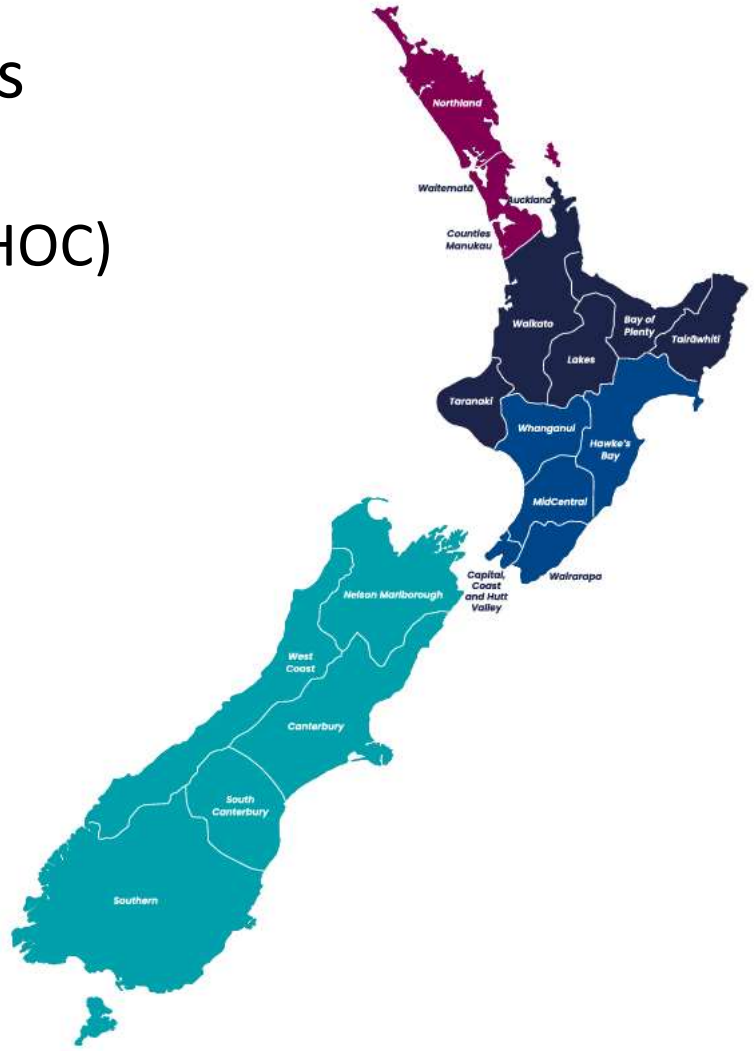
- 37 patients per year (0-14 years)
  - 24% of childhood cancer presentations (2019)
- 10 patients per year (15-19 years)
- 8 patients per year (19-24 years)

Figure 1. Proportional distribution of childhood cancer in Aotearoa, New Zealand 2015 – 2019 by diagnostic group and age at diagnosis



Distribution of Paediatric Cancer Care in NZ

- 2 Paediatric Haematology and Oncology Centres
  - Starship Blood and Cancer – Auckland (SBCC)
  - Christchurch Haematology and Oncology Centre (CHOC)
- Shared Care Model
  - 70 to 75% of patients in SBCC catchment
  - 25 to 30% of patients in CHOC catchment
    - Hub and spoke model of care
    - Total of 14 shared care centres around NZ



ALL Overall Survival

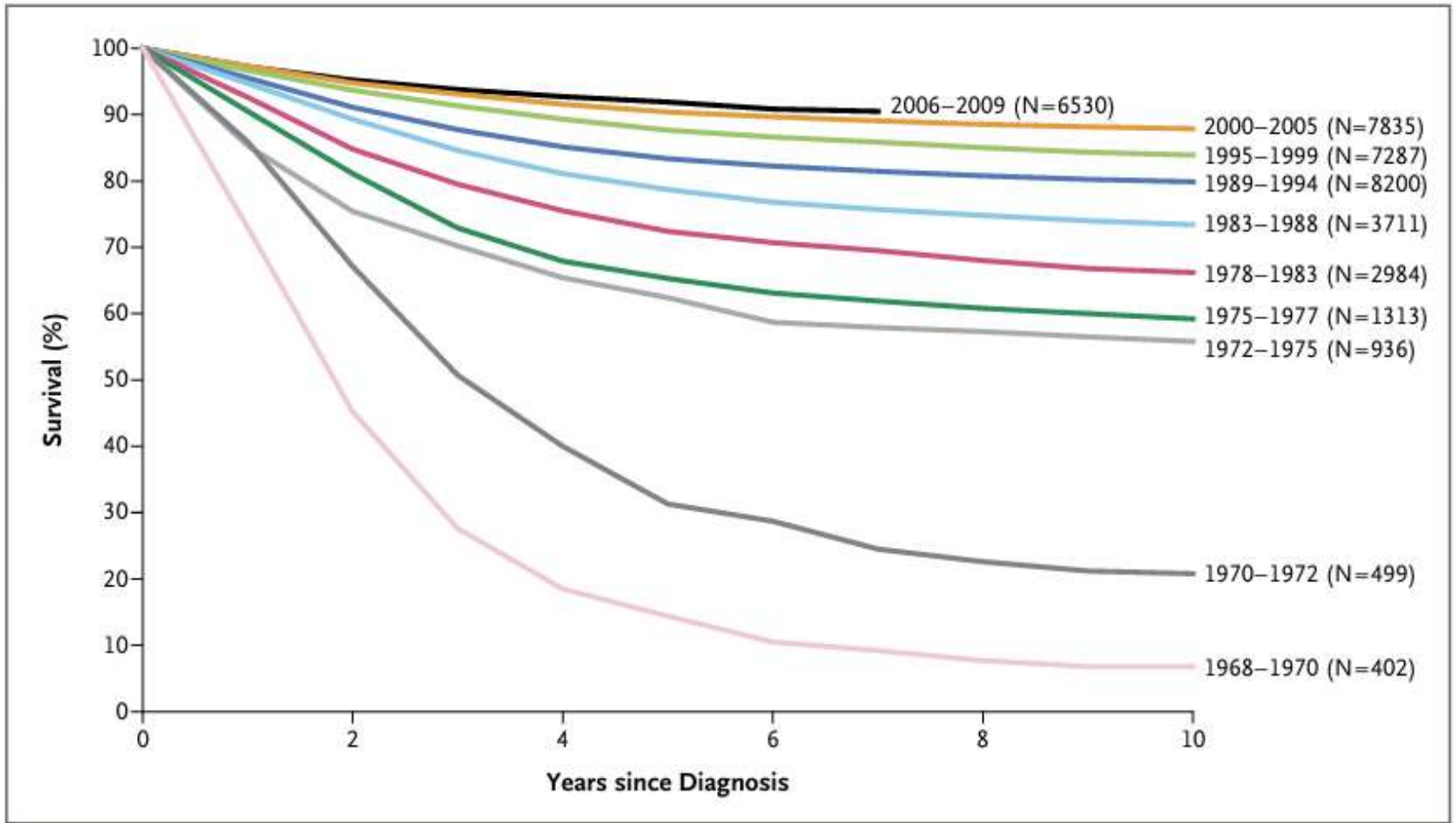
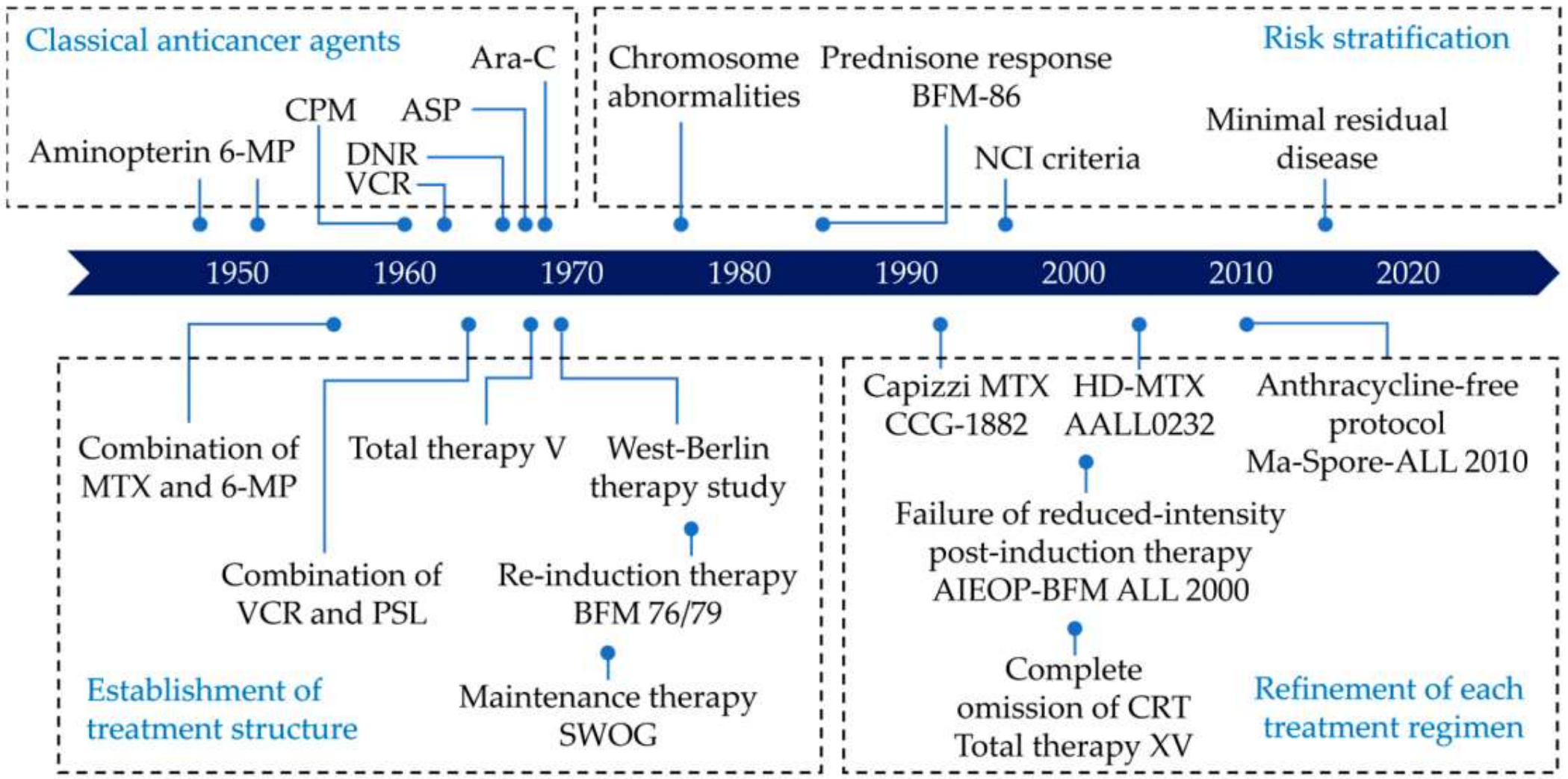


Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Development of ALL Treatment



Key Clinical Prognostic Factors

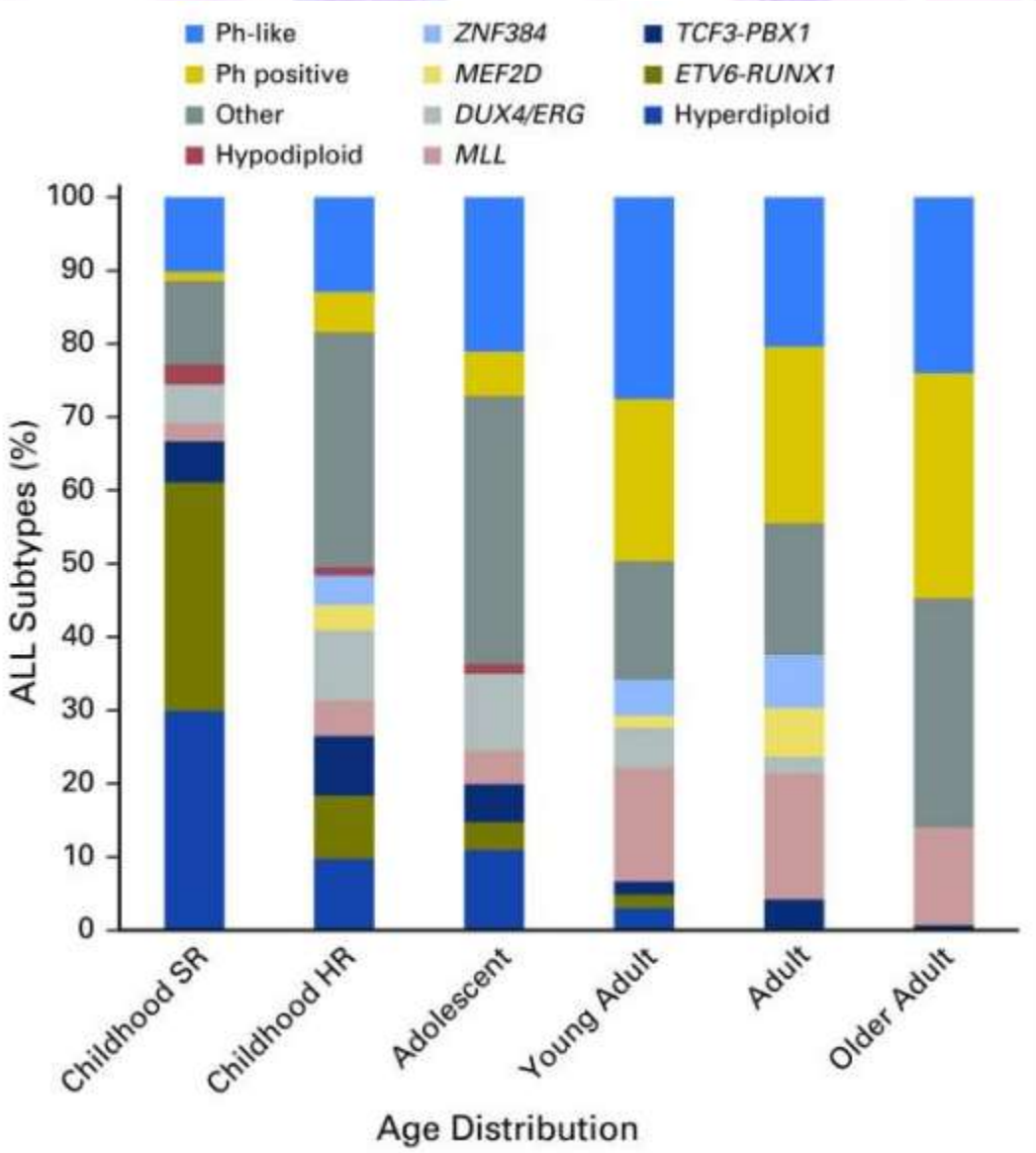
Age	• > 1, < 10 years – favorable • ≤ 1 and ≥ 10 years – unfavorable
White Blood Cell Count	• <50,000/µL – favorable • ≥50,000/µL – unfavorable
Immunophenotype	• B-precursor – favorable • T-cell – requires more intensive therapy
Gender	• Female – favorable • Male – historically required longer treatment
Extramedullary Disease	• Absent – favorable • Present – unfavorable

T-ALL

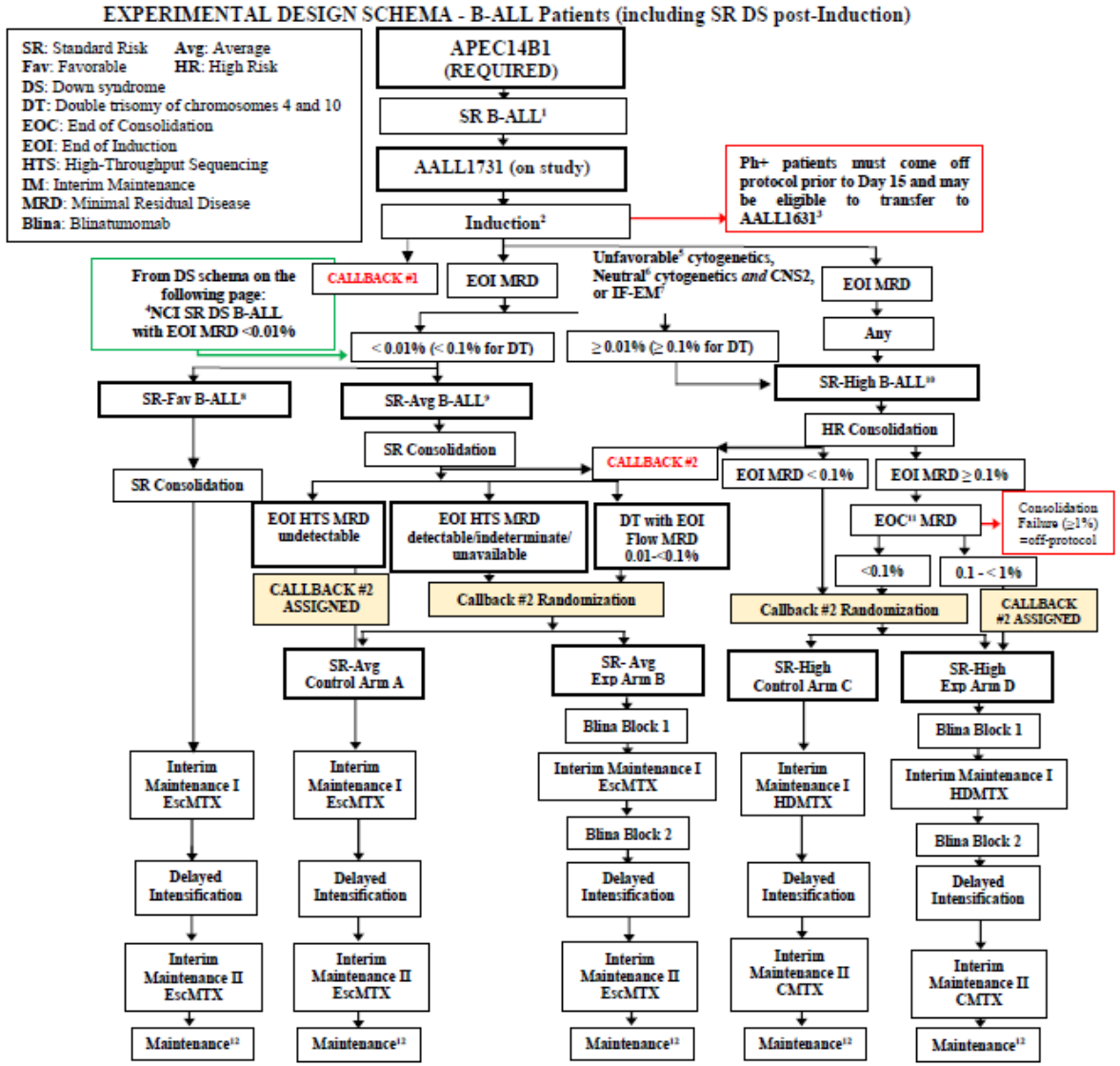
- 12-15% of all newly diagnosed paediatric ALL
- T-ALL patients have higher rates of CNS disease
- Most important prognostic marker: Disease response to treatment
  - Slower pattern of disease regression compared with B-ALL
  - Patients with EOI MRD positivity but EOC MRD negative have favourable outcomes
- Other factors such as age and presenting WBC are not independently prognostic
- Cytogenetics are not prognostic (currently)

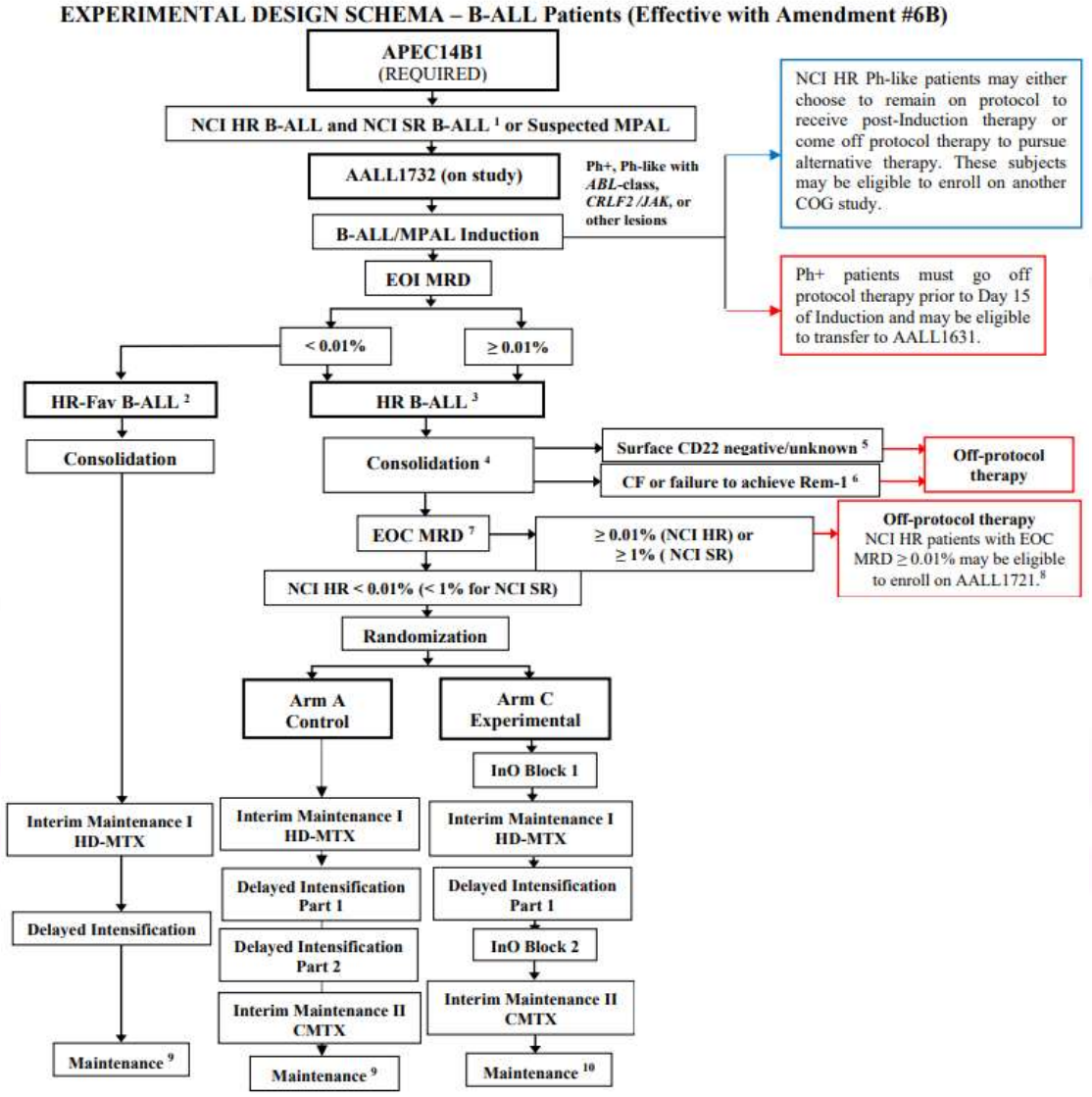
Cytogenetics

- Assists in diagnosis
- Monitoring of residual disease
- Early detection of relapse
- Guide precision medicine



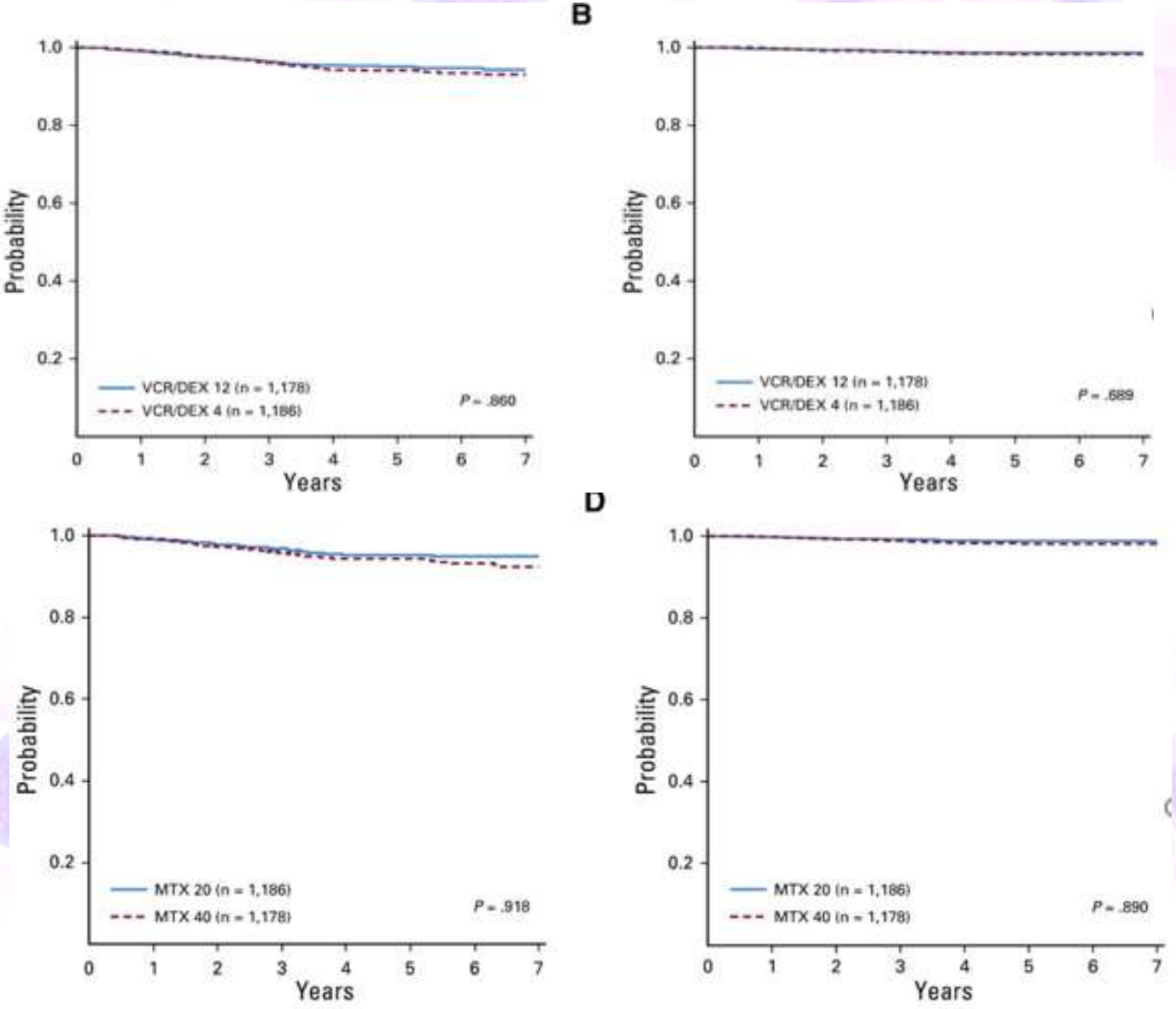
Current Schema for Treatment





AALL0932 – Std Risk

- Maintenance
  - Vincristine/Dexamethasone q4weeks vs q12 weeks
    - DFS & OS
  - Oral methotrexate 20mg/m^2 vs 40mg/m^2
    - DFS & OS
- Outcomes
  - 5-year EFS 92%
  - 5-year OS 98.5%
    - Changes to q12 weekly dosing of vinc/dex
    - Mtx dosing remains at 20mg/m^2



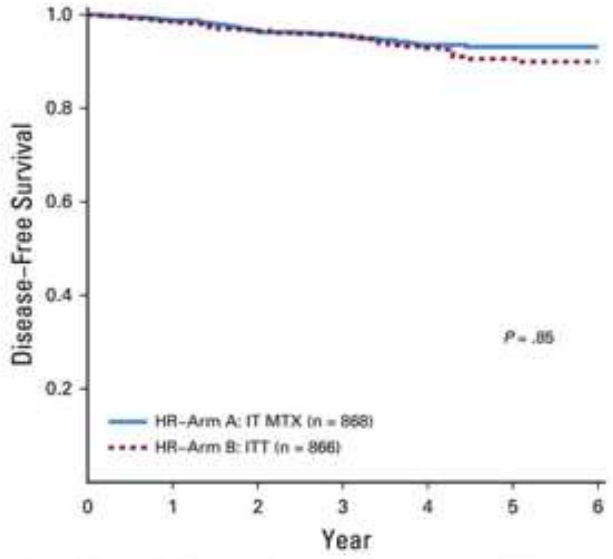
AALL0232 – High Risk

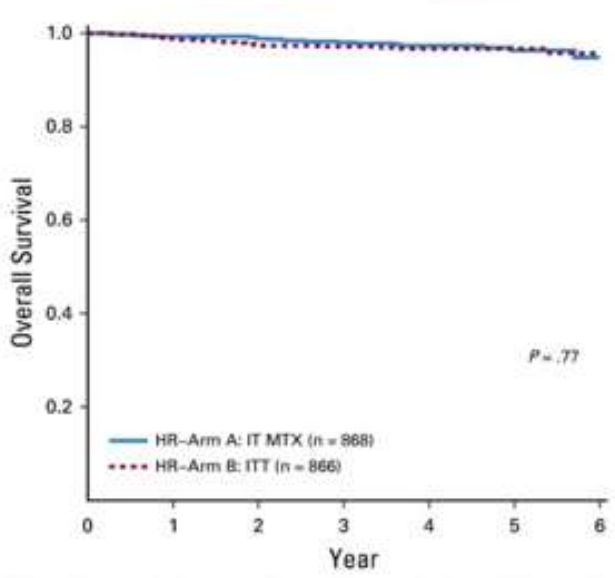
- Dexamethasone vs Prednisone in Induction
  - Dexamethasone 10mg/m^2/day for 14 days vs 60 mg/m^2/day of prednisone for 28 days
    - Dexamethasone – higher risk of febrile neutropenia (NS)
    - Dexamethasone – higher risk of osteonecrosis in > 10 years of age (S)
  - SOC – prednisone ≥ 10 years, dexamethasone < 10 years

- High Dose Methotrexate vs. Capizzi Methotrexate
  - HDMtx > Capizzi
  - 5-year EFS (80% *v* 75%; *P* = .008) and OS (88.9 ± 1.2% *v* 86.1 ± 1.4%; *P* = .025) rates

AALL1131 – High Risk

- Triple intrathecals vs. Single intrathecal
  - Assess if Triple IT's would further decrease CNS relapse rates without increasing neurological toxicities

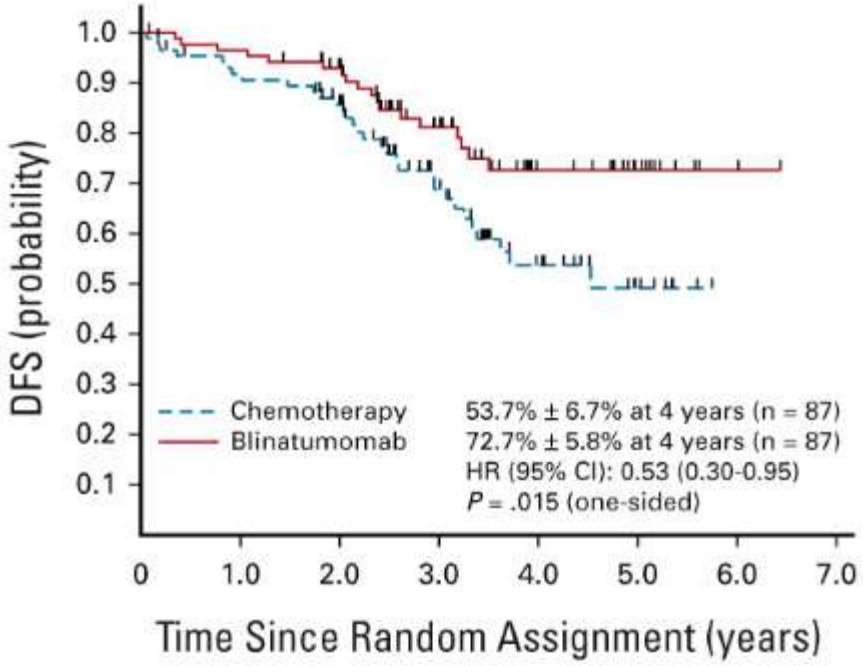


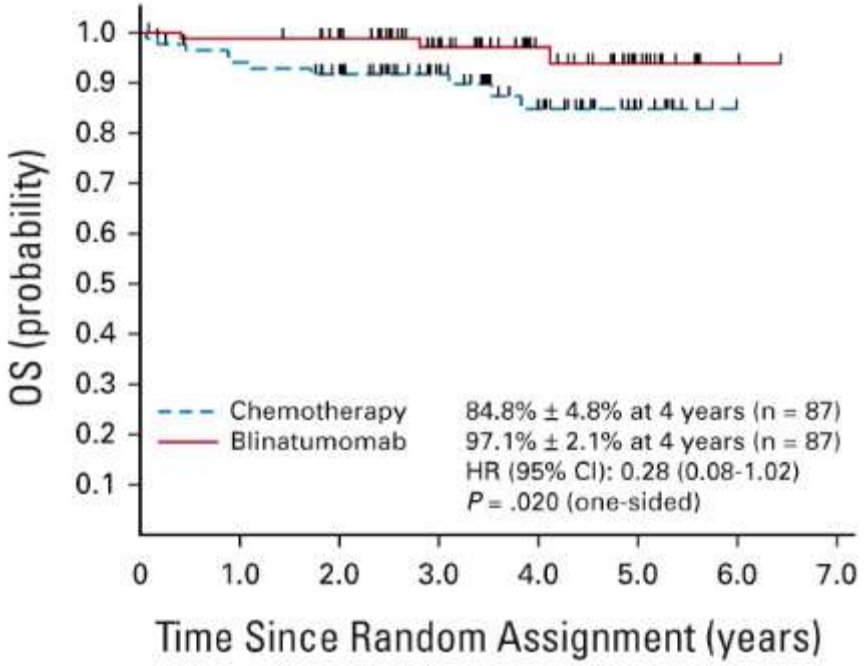


  - 5yr DFS was not improved with triple intrathecals

AALL1331 – Relapsed/Refractory

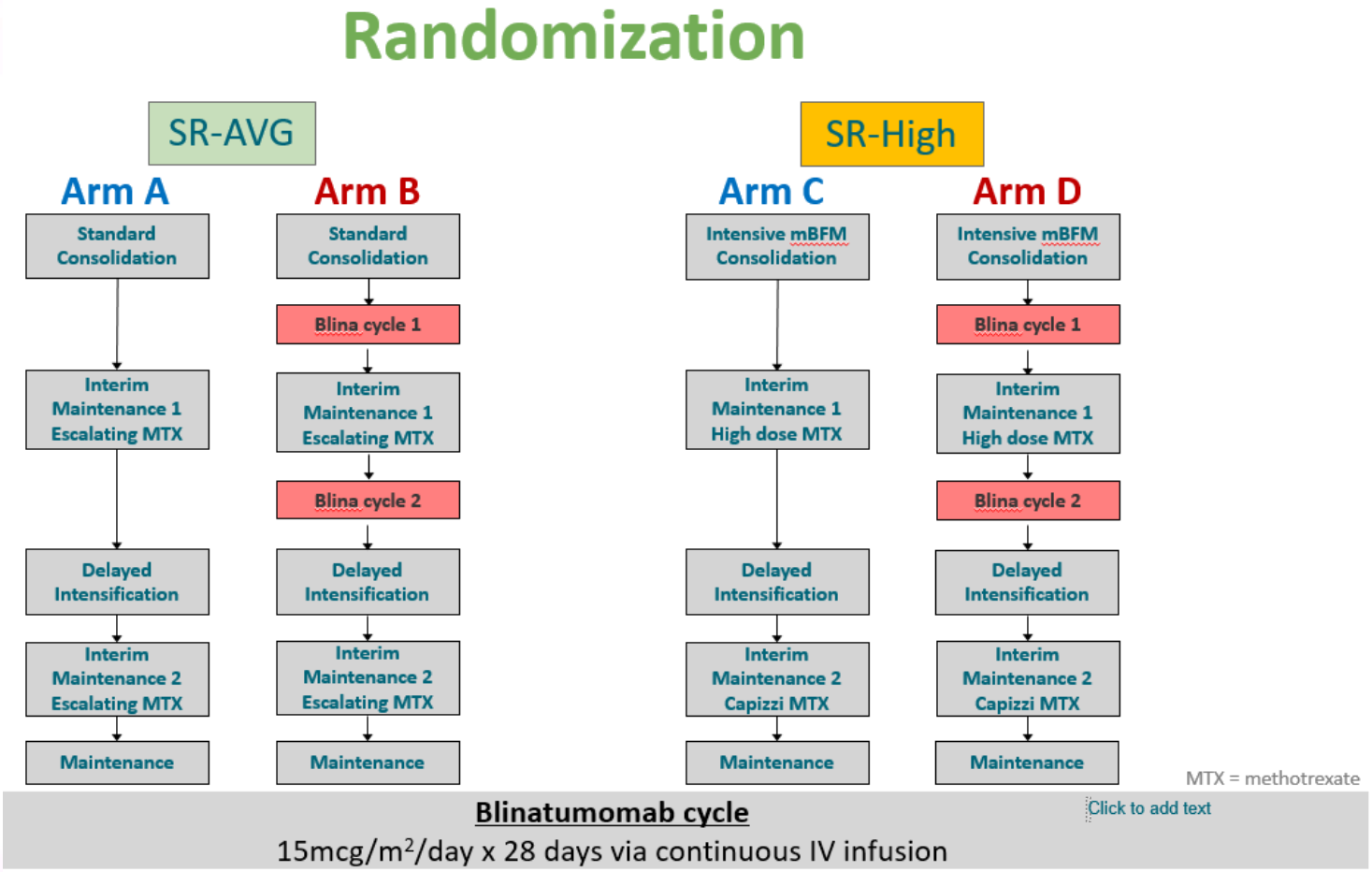
- Approx. 10-15% relapse.
  - 5-year OS ~35-50%
- Blinatumomab
  - Established that blinatumomab in addition to chemotherapy was superior to





ALL1731 – Standard Risk

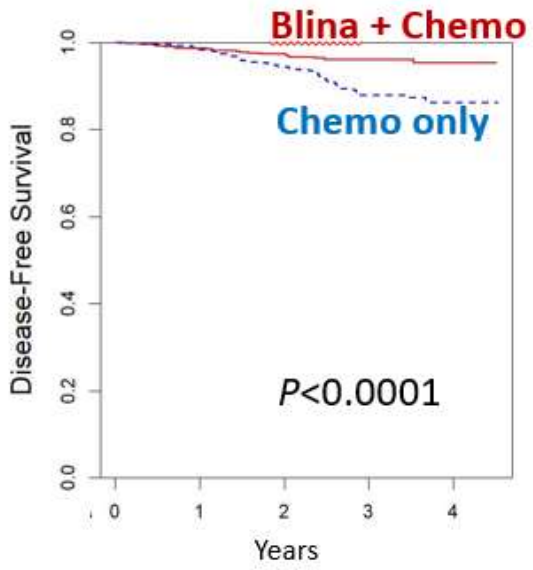
- Blinatumomab brought into the upfront setting



AALL1731 – Standard Risk

- Interim data analysis – early termination of randomisation
- Blinatumomab significantly improved DFS

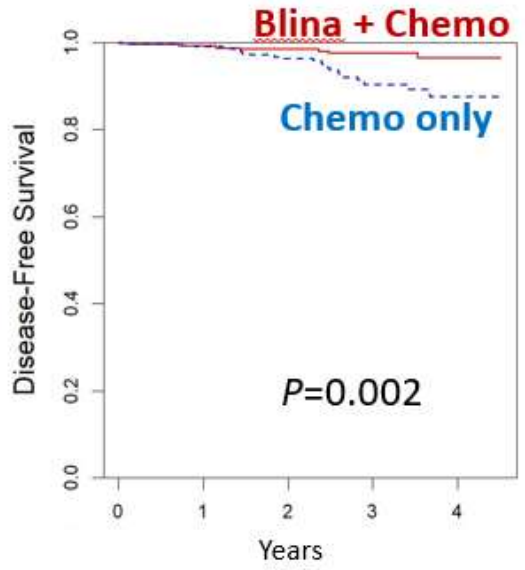
Overall cohort



3-yr DFS 87.9 vs 96%

Hazard ratio (HR) 0.39

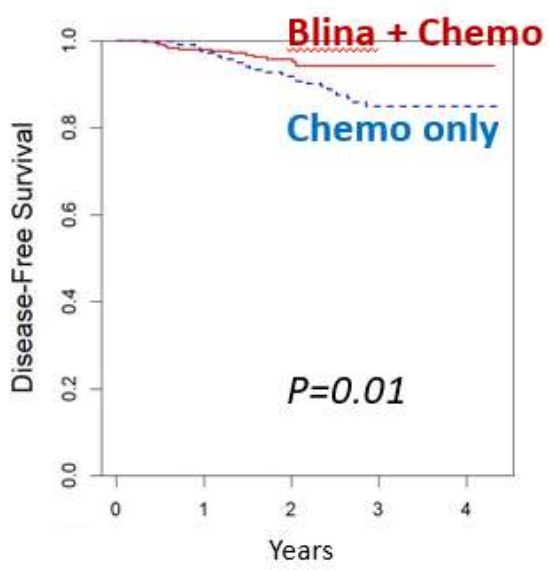
SR-Avg



3-yr DFS 90.2 vs 97.5%

HR 0.33

SR-High

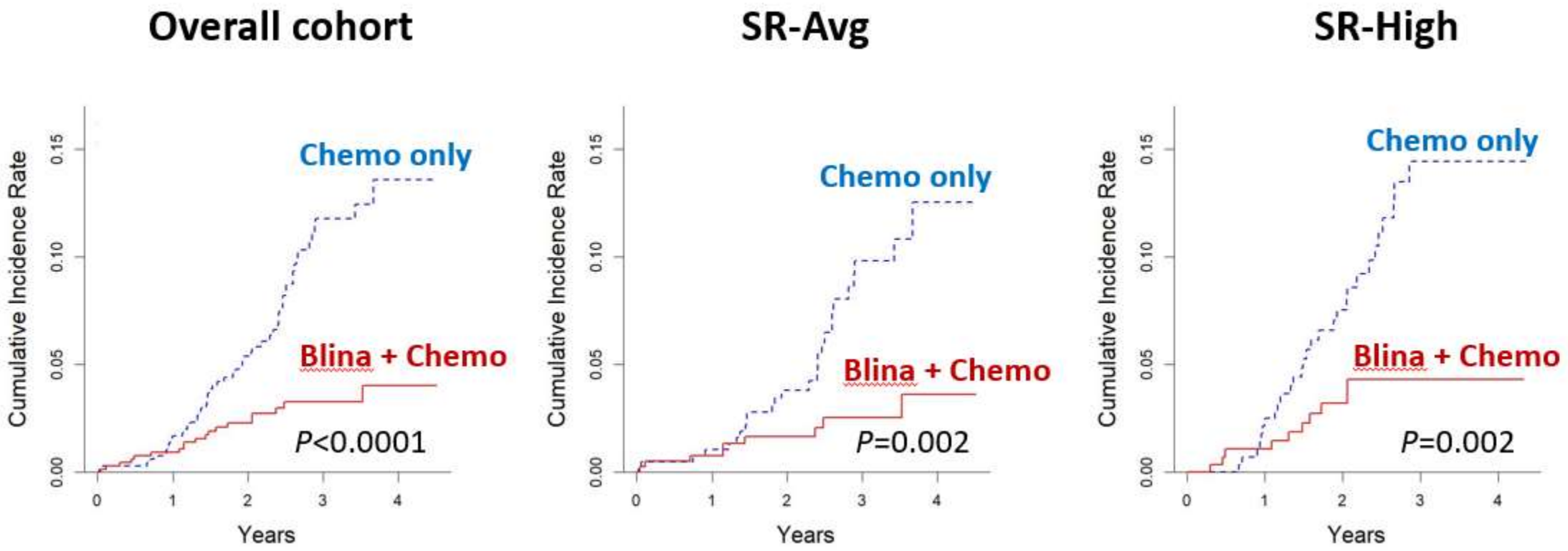


3-yr DFS 84.8 vs 94.1%

HR 0.45

AALL1731 – Standard Risk

- Blinatumomab also reduced relapse



AALL1731 – Standard Risk

- Low incidence of blinatumomab specific toxicities

	Blina Cycle 1 (N=624)		Blina Cycle 2 (N=552)	
	Grade 2+	**Grade 3+**	Grade 2+	**Grade 3+**
Cytokine release syndrome	18 (2.9%)	**2 (0.3%)**	9 (1.6%)	**0 (0.0%)**

- Anecdotal experience
  - Most frequent adverse effect seen is seizures
  - Expected incidence is 4%

Blinatumomab

- Dosing
  - 15mcg/m^2/day for 28 days (cap at 28mcg/day)
  - Day 1 dexamethasone – 5mg/m^2 single dose

- Administration
  - Requires 24-72 hour initial admission for monitoring
  - Alternating use of 72 hour and 96 hour infusion bags
  - CADD pumps
  - Overage in infusion bag (30mL)

- Future studies looking at subcutaneous blinatumomab

Blinatumomab Access in NZ

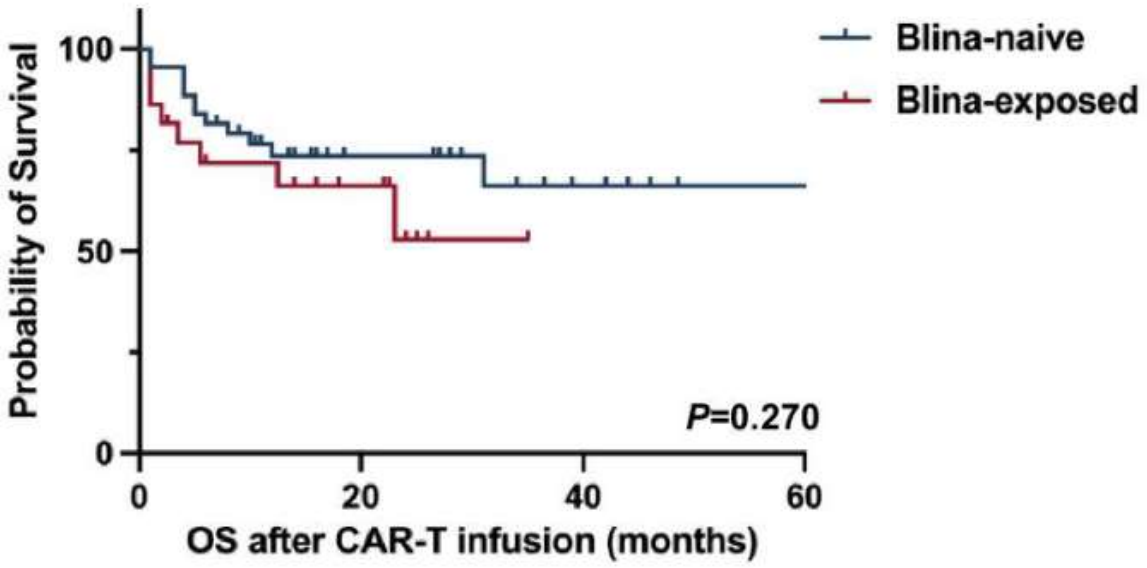
- Considered Standard of Care for Standard and High Risk ALL
  - Up to the age of 25 years
- Funding/Access challenges for the AYA cohort

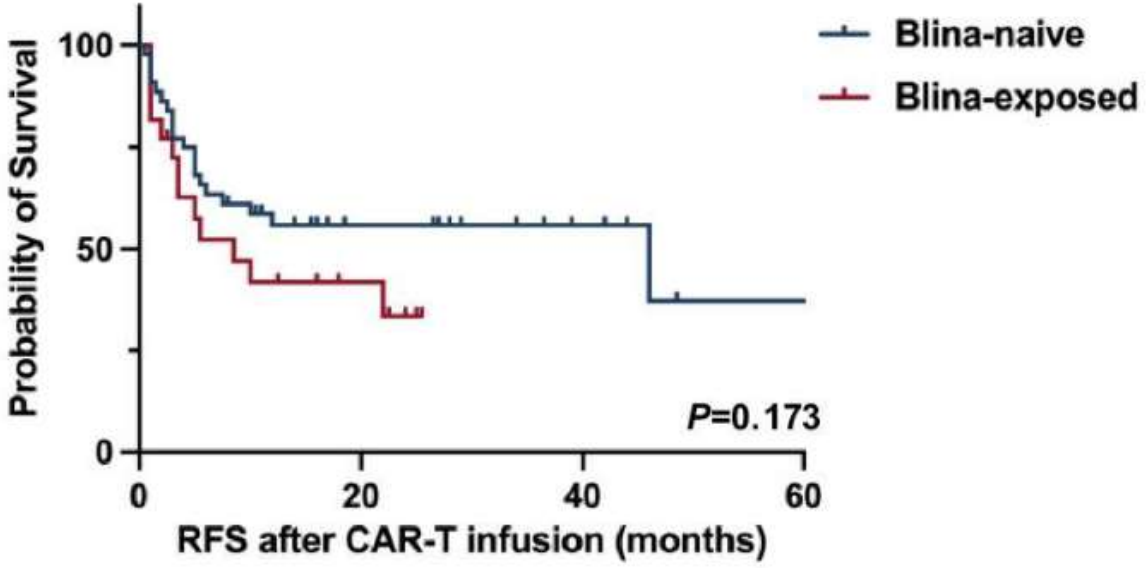
What Next……

- What does the next clinical trial look like
- Can we de-intensify chemotherapy?
  - Reduce steroid exposure
  - Remove asparaginase
  - Remove specific phases of treatment
  - Long term effects
- What does relapsed/refractory therapy look like with upfront blinatumomab therapy?
  - Do you use blinatumomab again?
- Greater risk of CNS related relapse?
  - What does next steps look like for these patients

What Next……

- What does CAR-T Therapy look like with blinatumomab in the up-front setting?





Acknowledgements

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