

**Second Meeting of the Subcommittee of the Expert Committee on the  
Selection and Use of Essential Medicines**

Geneva, 29 September to 3 October 2008

**Acute Lymphoblastic Leukemia in Children  
A Brief Review of the Internationally Available Protocols**

The following medicines are available in the first edition of the Essential Medicines List for children.

<b>8.2 Cytotoxic medicines</b>	
<i>Complementary List</i>	
<i>allopurinol</i>	<b>Tablet:</b> 100 mg to 300 mg.
<i>asparaginase</i>	<b>Powder for injection:</b> 10 000 IU in vial.
<i>bleomycin</i>	<b>Powder for injection:</b> 15 mg (as sulfate) in vial.
<i>calcium folinate</i>	<b>Injection:</b> 3 mg/ml in 10-ml ampoule. <b>Tablet:</b> 15 mg.
<i>chlorambucil</i>	<b>Tablet:</b> 2 mg.
<i>cisplatin</i>	<b>Powder for injection:</b> 10 mg; 50 mg in vial.
<i>cyclophosphamide</i>	<b>Powder for injection:</b> 500 mg in vial. <b>Tablet:</b> 25 mg.
<i>cytarabine</i>	<b>Powder for injection:</b> 100 mg in vial.
<i>dacarbazine</i>	<b>Powder for injection:</b> 100 mg in vial.
<i>dactinomycin</i>	<b>Powder for injection:</b> 500 micrograms in vial.
<i>daunorubicin</i>	<b>Powder for injection:</b> 50 mg (as hydrochloride).
<i>doxorubicin</i>	<b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.
<i>etoposide</i>	<b>Capsule:</b> 100 mg. <b>Injection:</b> 20 mg/ml in 5-ml ampoule.
<i>fluorouracil</i>	<b>Injection:</b> 50 mg/ml in 5-ml ampoule.
<i>mercaptopurine</i>	<b>Tablet:</b> 50 mg.

<i>methotrexate</i>	<b><i>Powder for injection:</i></b> 50 mg (as sodium salt) in vial. <b><i>Tablet:</i></b> 2.5 mg (as sodium salt).
<i>procarbazine</i>	<b><i>Capsule:</i></b> 50 mg (as hydrochloride).
<i>vinblastine</i>	<b><i>Powder for injection:</i></b> 10 mg (sulfate) in vial.
<i>vincristine</i>	<b><i>Powder for injection:</i></b> 1 mg; 5 mg (sulfate) in vial.

### **Introduction**

Most children diagnosed with acute lymphoblastic leukaemia (ALL) enrol in a clinical trial or follow a standard treatment protocol.

The following is a *representative description* of different ALL protocols/clinical trials in different centres/countries. Its *not* a detailed account of the treatment.

## The United Kingdom (UK) ALL Protocols

The Medical Research Council (MRC) in the UK usually sponsors research for childhood ALL treatment.

### UKALL2003 Protocol

This protocol consists of three regimens depending on the risk i.e. low risk (regimen A), moderate risk (regimen B) and high risk (regimen C). All medications are available in the EMLc list except that it uses PEG-Asparaginase over E-coli Asparaginase (brief description about the different preparations will be made later).

#### **Summary of Regimen A**

Regimen A consists of the following phases:

Three drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.

Intensification/CNS-directed phase (duration 3 weeks) with **6-mercaptopurine**;

Interim maintenance I (duration 8 weeks) with **dexamethasone** and **6-mercaptopurine**;

Delayed intensification I (duration 7 weeks) with **6-mercaptopurine** in reconsolidation;

Interim maintenance II (**for patients allocated two delayed intensifications**) (duration

8 weeks) with **dexamethasone** and **6-mercaptopurine**;

Delayed intensification II (**for patients allocated two delayed intensifications**)

(duration 7 weeks); with **6-mercaptopurine** in reconsolidation;

Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 112 for girls and end of 164 for boys. Delays accrued during phases I-VI are taken off during the maintenance period.

#### **Summary of Regimen B**

Regimen B consists of the following phases:

Four drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.

Standard BFM consolidation (duration 5 weeks) with **6-mercaptopurine**;

Interim maintenance I (duration 8 weeks) - **dexamethasone and mercaptopurine**;

Delayed intensification I (duration 7 weeks); **6-mercaptopurine** in reconsolidation;

Interim maintenance II (**for patients allocated two delayed intensifications**) (duration 8 weeks) with **dexamethasone and 6-mercaptopurine**;  
Delayed intensification II (**for patients allocated two delayed intensifications**) (duration 7 weeks); **6-mercaptopurine** in reconsolidation;  
Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 114 for girls and end of week 166 for boys. Delays accrued during phases I-VI are taken off the maintenance period.

### **Summary of Regimen C**

Regimen C consists of the following phases:

Completing a four drug induction with dexamethasone as steroid of choice;  
Augmented BFM consolidation (duration 9 weeks); all patients receive 6 mercaptopurine;

Interim Capizzi maintenance I (duration 8 weeks) using PEG asparaginase and escalating doses of IV methotrexate;

Delayed intensification I (duration 8 weeks); **6-mercaptopurine** in reconsolidation; PEG asparaginase;

Interim Capizzi maintenance II (duration 8 weeks) using PEG asparaginase and escalating doses of IV methotrexate;

Delayed intensification II (duration 8 weeks); **6-mercaptopurine** in reconsolidation; PEG asparaginase;

Maintenance chemotherapy with dexamethasone and 6-mercaptopurine to the end of week 118 for girls and end of week 170 for boys. Delays accrued during phases I-VI are taken off the maintenance period.

Ref:

[www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk) via 'projects' then 'UKALL 2003'

### **North America's ALL Protocols**

Most ALL clinical trials in North America are offered by the COG (Children's Oncology Group) which is sponsored by the National Cancer Institute (NCI). The COG came as a merger (in 1999) from two groups: 1. CCG (Children's Cancer Group) and 2. POG (Pediatric Oncology Group). Many children's hospitals still follow the CCG or POG trials that were designed at the time of the merger, and those trials still have the POG or CCG designation; the newest COG trials are designed "AALL".

Ref:

The COG Web site can be found at: <http://www.childrensoncologygroup.org/>

Table 1a: Representative chemotherapy regimens for CCG & POG ALL Protocols (Ref: Pharmacotherapy: A Pathophysiologic Approach, 1999, 4<sup>th</sup> Edition).

Remission Induction		CNS Prophylaxis	Consolidation		Maintenance
Drug and Dose	Timing		Drug and Dose	Days	Drug, Dose, and Timing
<b>Children's Cancer Group 1882 (Pediatric)<sup>27</sup></b>					
PRED (PO) 60 mg/m <sup>2</sup> /d	28 d	Cranial irradiation MTX	<b>Consolidation I</b> CTX (IV) 1 g/m <sup>2</sup>	0, 28	<b>Interim Maintenance</b> VCR (IV) 1.5 mg/m <sup>2</sup> /d, days 0, 10, 20, 30, 40 MTX (IV) 100 mg/m <sup>2</sup> /d, days 0, 10, 20, 30, 40 ASP (IM) 15,000 U/m <sup>2</sup> /d, days 1, 11, 21, 31, 41
VCR (IV) 1.5 mg/m <sup>2</sup> /wk	4 wk		Ara-C (SC/IV) 75 mg/m <sup>2</sup> /d	1-4, 8-11, 29-32, 36-39	
DNR (IV) 25 mg/m <sup>2</sup> /wk	4 wk		MP 60 mg/m <sup>2</sup> PO	0-13, 28-41	
ASP (IM) 6000 U/m <sup>2</sup> /3 × weekly 9 doses			VCR 1.5 mg/m <sup>2</sup> /d	14, 21, 42, 49	
			ASP (IM) 6000 U/m <sup>2</sup> /d	14, 16, 18, 21, 23, 25, 42, 44, 46, 49, 51, 53	
			<b>Reinduction-Reconsolidation I, II</b> VCR 1.5 mg/m <sup>2</sup> /d	0, 7, 14, 42, 49	<b>Maintenance (3-month cycles)</b> VCR (IV) 1.5 mg/m <sup>2</sup> /d, days 0, 28, 56 PDN 60 mg/m <sup>2</sup> /d, days 0-4, 28-32, 56-60 MP 75 mg/m <sup>2</sup> /d, days 0-83 MTX 20 mg/m <sup>2</sup> /d PO, days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77
			DEX 10 mg/m <sup>2</sup> /d PO QD	0-20, then taper	
			DOX 25 mg/m <sup>2</sup> /d	0, 7, 14	
			ASP (IM) 6000 U/m <sup>2</sup>	3, 5, 7, 10, 12, 14, 42, 44, 46, 49, 51, 53	
			CTX (IV) 1 g/m <sup>2</sup>	28	
			Ara-C (SC/IV) 75 mg/m <sup>2</sup> /d	29-32, 36-39	
			TG (PO) 60 mg/m <sup>2</sup> /d	28-41	
<b>POG 8602 (Pediatric)<sup>28</sup> (ALinC14)</b>					
PRED (PO) 40 mg/m <sup>2</sup> /d (Maximum dose 60 mg/d)	1-29	MTX (IT), Ara-C, HCT	MTX (IV) 1 g/m <sup>2</sup> (with leucovorin rescue)	49, 70, 91, 112, 133, 154	<b>Overlapping VCR/PRED Pulse Therapy</b> Weeks 8, 17, 25, 41, 57, 73, 89, 105: VCR (IV) 1.5 mg/m <sup>2</sup> /wk × 2 doses PRED (PO) 40 mg/m <sup>2</sup> /d × 7 days
VCR (IV) 1.5 mg/m <sup>2</sup> /wk	1, 8, 15, 22		Ara-C (IV) 1 g/m <sup>2</sup>	49, 70, 91, 112, 133, 154	
ASP (IM) 6000 U/m <sup>2</sup>	1, 3, 5, 8, 10, 12				<b>Maintenance</b> Weeks 25-156: MP (PO) 75 mg/m <sup>2</sup> /d MTX (IM) 20 mg/m <sup>2</sup> /wk
MP (PO) 75 mg/m <sup>2</sup> /d	29-43				

Ara-C = cytarabine; ASP = asparaginase; CTX = cyclophosphamide; DEX = dexamethasone; DNR = daunorubicin; DOX = doxorubicin; HCT = hydrocortisone, MP = mercaptopurine; MTX = methotrexate; PRED = prednisone; TG = thioguanine; VCR = vincristine.

Table 1a: Intrathecal therapy in paediatric ALL.

Age (yr)	Cytarabine (mg)	Methotrexate (mg)	Hydrocortisone (mg)
≥ 1	16	8	8
≥ 2	20	10	10
3-8	24	12	12
≥ 9	30	15	15

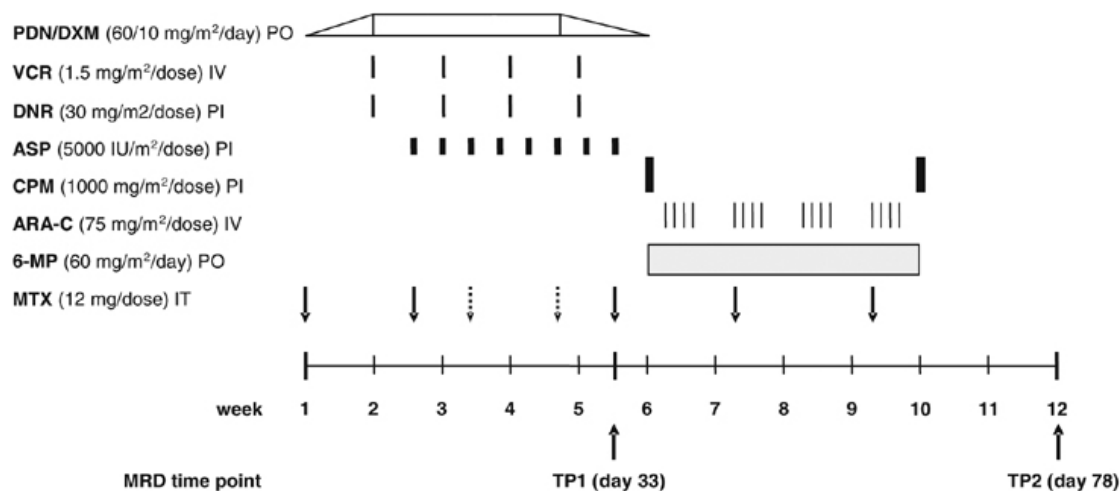
ALL = acute lymphocytic leukemia.



## The Berlin-Frankfurt-Munster (BFM) ALL Protocols

The BFM study group is conducting an International clinical trial 'AIEOP-BFM ALL 2000' for childhood acute lymphoblastic leukemia.

**Outline of induction** (see reference below for diagram)



This is a randomized, multicenter study, the results of which have been published this year (2008), used the following regimens.

***Prednisone prephase therapy:*** Patients receive oral prednisone on days 1-7 and one dose of methotrexate (MTX) intrathecally (IT) on day 1.

***Induction/consolidation therapy, protocol I:*** Patients are randomized to 1 of 2 treatment arms.

***Arm I:*** Patients receive prednisone (PRED) on days 8-28.

***Arm II :*** Patients receive dexamethasone (DEXA) on days 8-28.

Patients in both arms also receive vincristine (VCR) and daunorubicin hydrochloride (DNR) once weekly in weeks 2-5; asparaginase (ASP) on days 12-33; cyclophosphamide (CPM) on days 36 and 64; cytarabine (ARA-C) in weeks 6-9; mercaptopurine (MP) on days 36-63; and MTX IT on days 1, 12, 33, 45, and 59.\*

[Note: \*Patients with CNS disease also receive MTX IT on days 18 and 27.]

***Extracompartment therapy, protocol M:*** Patients receive MP on days 1-56 and MTX on days 8, 22, 36, and 50.

***Reintensification therapy:***

**Arm I (standard reinduction therapy, protocol II):** SR and IR patients receive DEXA on days 1-22; VCR and doxorubicin hydrochloride (DOX) in weeks 2-5; ASP on days 8, 11, 15, and 18; CPM on day 36; ARA-C and thioguanine (TG) on days 36-49; and MTX IT on days 38 and 45.\* Patients then proceed to maintenance therapy.

[Note: \*Patients with CNS disease also receive MTX IT on days 1 and 18.]

**Arm II (reduced-intensity reinduction therapy, protocol III):** SR patients receive DEXA on days 1-15; VCR and DOX on days 1 and 8; ASP on days 1, 4, 8, and 11; CPM on day 15; ARA-C and TG on days 15-28; and MTX IT on days 17 and 24.\* Patients then proceed to maintenance therapy.

[Note: \*Patients with CNS disease also receive MTX on day 1. ]

**Arm III (reduced-intensity reinduction/second delayed reinduction therapy [double reintensification therapy]):** IR patients receive reduced-intensity reintensification therapy as in arm II. After a 10-week interim maintenance phase, treatment repeats once for a second delayed course of reintensification therapy. Patients then proceed to maintenance therapy.

**Arm IV (standard reintensification therapy):** HR patients receive two sequences of the following HR therapy elements (i.e., in this order: 1, 2, 3, 1, 2, 3) following reintensification therapy as in arm I. Patients then proceed to maintenance therapy.

**Element HR-1:** Patients receive DEXA on days 1-5; VCR on days 1 and 6; ARA-C twice on day 5; MTX and CPM every 12 hours on days 2-4 (5 doses); ASP on days 6 and 11; and MTX/ARA-C/PRED IT on day 1.

**Element HR-2:** Patients receive DEXA on days 1-5; vindesine on days 1 and 6; DNR on day 5; MTX and ifosfamide every 12 hours on days 2-4 (5 doses); ASP on days 6 and 11; and MTX/ARA-C/PRED IT on day 1.\*

[Note: \*HR patients with CNS disease also receive IT therapy on day 5.]

**Element HR-3:** Patients receive DEXA on days 1-5; ARA-C every 12 hours on days 1-2 (4 doses); etoposide five times daily on days 3-5; ASP on days 6 and 11; and MTX/ARA-C/PRED IT on day 1.

**Arm V (extended reintensification therapy [triple protocol III]):** HR patients receive HR therapy elements 3, 2, and 1 as in arm IV following reintensification therapy as in arm II repeated the therapy element twice with

4-week interim maintenance phases in between. Patients then proceed to maintenance therapy.

***Interim maintenance/maintenance therapy:*** Patients receive MTX once weekly and MP daily until week 104.

***Radiotherapy:*** HR patients or patients with T-cell acute lymphoblastic leukemia or CNS disease undergo CNS radiotherapy.

Ref:

1. Leukemia (2008) **22**, 771–782; doi:10.1038/leu.2008.5; published online 31 January 2008
2. <http://www.cancer.gov/clinicaltrials/ALL-BFM-2000>

## Hong Kong ALL Protocol (HKALL97)

The Hong Kong Paediatric Haematology and Oncology Study Group commenced a new clinical study in 1997 that adopted a German Berlin-Frankfurt-Muenster 95 (BFM95) protocol aimed at improving treatment outcome. This study aimed to determine the outcome of children with ALL who received a treatment protocol that included either one or two delayed intensifications.

**Table 2. Chemotherapy protocol of HKALL97 and HKALL93<sup>s</sup> studies\***

	HKALL97 (present) study	HKALL93 study <sup>s</sup>
Induction	Week 1-5 <ul style="list-style-type: none"> <li>• Prednisolone 60 mg/m<sup>2</sup> D1-29</li> <li>• Vincristine 1.5 mg/m<sup>2</sup> D8, 15, 22, 29</li> <li>• L-Asparaginase 5000 IU/m<sup>2</sup> IV from D11 Q3D x 8 doses</li> <li>• Daunorubicin 30 mg/m<sup>2</sup> IV weekly D8, 15, 22, 29 (standard risk: only D8, D15)</li> </ul>	Week 1-4 <ul style="list-style-type: none"> <li>• Prednisolone 40 mg/m<sup>2</sup> D1-28</li> <li>• Vincristine 1.5 mg/m<sup>2</sup> D1, 8, 15, 22</li> <li>• L-Asparaginase 6000 U/m<sup>2</sup> SC from D4 Q3D x 9 doses</li> </ul>
Early intensification	Week 5-9 <ul style="list-style-type: none"> <li>• Cyclophosphamide 1 g/m<sup>2</sup> D36, 64</li> <li>• Ara-C 75 mg/m<sup>2</sup> IV daily on D38-41, 45-48, 52-55, 59-62</li> <li>• 6-Mercaptopurine 60 mg/m<sup>2</sup> po D36-62</li> </ul>	Week 6 <ul style="list-style-type: none"> <li>• Prednisolone 40 mg/m<sup>2</sup> D1-5</li> <li>• Etoposide 100 mg/m<sup>2</sup> IV D1-5</li> <li>• Daunorubicin 45 mg/m<sup>2</sup> IV D1, 2</li> <li>• Ara-C 100 mg/m<sup>2</sup> IV Q12H D1-5</li> <li>• Thioguanine 80 mg/m<sup>2</sup> po D1-5</li> </ul>
Consolidation	Week 12-20 <p><i>Standard risk</i></p> <ul style="list-style-type: none"> <li>• Methotrexate 2 g/m<sup>2</sup> IV Q2W x 4</li> </ul> <p><i>Intermediate risk</i></p> <ul style="list-style-type: none"> <li>• Methotrexate 5 g/m<sup>2</sup> IV Q2W x 4</li> </ul> <p><i>High risk</i></p> <ul style="list-style-type: none"> <li>• Three 6-day intensive blocks including CNS RT 1200 cGy</li> </ul>	Week 8-18 <p><i>Standard risk</i></p> <ul style="list-style-type: none"> <li>• 6-Mercaptopurine intrathecal methotrexate</li> </ul> <p><i>Intermediate risk</i></p> <ul style="list-style-type: none"> <li>• Methotrexate 8 g/m<sup>2</sup> or 6 g/m<sup>2</sup> IV Q2W x 3</li> </ul> <p><i>High risk</i></p> <ul style="list-style-type: none"> <li>• 6-Mercaptopurine + CNS RT 1800 cGy</li> </ul>
Late intensification	Week 22-29 (re-Induction) <p><i>Standard and intermediate risks</i></p> <ul style="list-style-type: none"> <li>• Dexamethasone 10 mg/m<sup>2</sup> po D1-21</li> <li>• Vincristine 1.5 mg/m<sup>2</sup> IV D8, 15, 22, 29</li> <li>• L-Asparaginase 10 000 units/m<sup>2</sup> IV D11, 2 times/week x 4 doses</li> <li>• Cyclophosphamide 1 g/m<sup>2</sup> D36</li> <li>• Ara-C 75 mg/m<sup>2</sup> IV daily on D38-41, 45-48</li> <li>• 6-Thioguanine 40 mg/m<sup>2</sup> po D36-49</li> </ul> <p><i>High risk</i></p> <ul style="list-style-type: none"> <li>• Repeat late intensification at week 37-44</li> </ul>	Week 20 <p><i>All risks</i></p> <ul style="list-style-type: none"> <li>• As early intensification</li> </ul> <p><i>High risk: week 35-42</i></p> <ul style="list-style-type: none"> <li>• Dexamethasone 10 mg/m<sup>2</sup> po D1-10</li> <li>• Vincristine 1.5 mg/m<sup>2</sup> IV D1, 8, 15, 22</li> <li>• L-Asparaginase 6000 unit/m<sup>2</sup> IV 3 times/week from D4 x 9 doses</li> <li>• Cyclophosphamide 600 mg/m<sup>2</sup> IV D1 of week 39 and 41</li> <li>• Ara-C 75 mg/m<sup>2</sup> IV D1-4 in week 39-42</li> <li>• Thioguanine 60 mg/m<sup>2</sup> po week 39-42</li> </ul>
Maintenance	<ul style="list-style-type: none"> <li>• 6-Mercaptopurine 50 mg/m<sup>2</sup> po daily</li> <li>• Methotrexate 20 mg/m<sup>2</sup> po weekly</li> <li>• Dexamethasone 6 mg/m<sup>2</sup> po D1-7 and vincristine 1.5 mg/m<sup>2</sup> IV D1, 8 every 10 week</li> <li>• Treatment of up to 2 years from diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• 6-Mercaptopurine 75 mg/m<sup>2</sup> po daily</li> <li>• Methotrexate 20 mg/m<sup>2</sup> po weekly</li> <li>• Prednisolone 40 mg/m<sup>2</sup> po D1-5 and vincristine 1.5 mg/m<sup>2</sup> IV D1 every 4 week</li> <li>• Treatment of up to 2 years from diagnosis</li> </ul>

\* D denotes day, IV intravenous, Q3D every 3 days, SC subcutaneous, Ara-C cytarabine arabinoside, po orally, Q12H every 12 hours, Q2W every 2 weeks, CNS RT radiation therapy of the central nervous system

### Reference:

Improved outcome of acute lymphoblastic leukaemia treated by delayed intensification in Hong Kong children: HKALL97 study. Hong Kong Med J 2006;12:33-9.

## **A brief description of some of the discrepancies between protocols in relation to some medicines:**

### **Dexamethasone versus Prednisolone**

Some trials showed that dexamethasone is more effective than prednisolone, but associated with more toxicity (e.g. increased severity of infections). Whereas, other trials showed it to be effective and safe.

Ref:

1. Journal of Clinical Oncology, Vol 23, No 27 (September 20), 2005: pp. 6489-6498
2. Br J Haematol 2005; 129 (6): 734-45.

### **Mercaptopurine versus Thioguanine**

Associated with remission deaths Despite many literature that thioguanine is no longer recommended for use in ALL in children as it is associated with more toxicity and prolonged myelosuppression, there are countries that still continue to use it.

Ref:

1. The Lancet 2006 , Volume 368 , Issue 544 , Pages 1304 – 1306.
2. Blood, 15 October 2003, Vol. 102, No. 8, pp. 2736-2740.

### **E. coli Asparaginase versus PEG-Asparaginase**

There are different types of L-asparaginase available for use in the treatment of children with ALL, with Escherichia coli (E. coli) L-asparaginase the most commonly used. PEG-L-asparaginase is an alternative form of L-asparaginase in which the E. coli enzyme is modified by the covalent attachment of polyethylene glycol. PEG-L-asparaginase has a much longer serum half-life than native E. coli L-asparaginase, allowing it to produce asparagine depletion with less frequent administration. In another randomized trial in which patients with standard-risk ALL were randomly assigned to receive PEG-L-asparaginase versus native E. coli asparaginase in induction and each of two delayed intensification courses, the use of PEG-L-asparaginase was associated with more rapid blast clearance and a lower incidence of neutralizing antibodies.

Ref:

1. J Clin Oncol 1993; 11 (9): 1780-6.
2. Blood 2002; 99 (6): 1986-94.