SUPPLEMENTARY APPENDIX

# Comprehensive analysis of dose intensity of acute lymphoblastic leukemia chemotherapy

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**Comprehensive analysis of dose intensity of acute lymphoblastic leukemia chemotherapy (supplement)**

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## Supplemental Methods

### Pharmacologic studies

TPMT phenotype was assigned by assessing erythrocyte TPMT activity and by genotyping or sequencing germline DNA for *TPMT* functional variants and used for adjusting thiopurine dosages (Supplement Table S1 legend). Prospective adjustment of thiopurine dosage based on *TPMT* status was the only protocol-specified modification based on germline genetics.

### Statistical analyses

Wilcoxon rank-sum tests were used to compare continuous variables (such as DI or dosages) between two groups. Kruskal-Wallis tests were used to compare variables among three or more groups. Average ANC (log-transformed) for each patient was summarized per phase and compared between treatment groups using a linear mixed effect model with phase as a covariate. Variability is described by the median absolute deviation (MAD). All statistical analyses were conducted using R (version 3.5.0). Nominal P-values without adjusting for multiple testing were presented. In applicable Tables and Figures, we included the total number of statistical tests performed relevant to the specific analysis, and the corresponding statistical significance threshold based on Bonferroni correction for multiple testing. We explored whether estimates of DI for all drugs or of ANC were related to outcome variables as described in the Supplement, with all analyses adjusting for risk group. Patients were censored at time of last follow-up [for those in complete remission (CR)] or at time of coming off therapy for any other reason (second cancer, death, refusal, excessive toxicity, lineage switch, noncompliance, transplant). DI or ANC

were treated in two different ways: leaving DI or ANC as continuous variables, or dividing patient groups into tertiles (Supplement for details). The comparisons between T15 and T16 were not planned a priori but were prompted by our observations of lower DI for some drugs on T16 vs T15.

**Dosages and dose intensity (DI) estimates.**

Prescribed dosages for all chemotherapy were retrieved from protocol databases. All dosages are reported as mg or units per body surface area in $m^2$. Intravenous or intramuscular doses were recorded individually. For oral doses of thiopurines or dexamethasone, data managers could enter doses on a daily, weekly, or per phase basis, with start and stop dates bracketing the dosing period. Each drug entry was linked to a phase of therapy by the data managers in the protocol database. For T15, the phases were (in order): window, induction, consolidation, continuation week 1-6, reinduction I (week 7-9), continuation week 10-16, reinduction II (week 17-20), continuation week 20-47, continuation week 48-95, continuation week 96-120, and (for boys only) continuation week 121-146. For T16, the phases were (in order): induction, consolidation, continuation week 1-6, reinduction I (week 7-9), continuation week 10-16, reinduction II (week 17-20), continuation week 20-37, continuation week 38-69, continuation week 10-101, and continuation week 102-120. Total per-phase dosages were tabulated.

Patients were censored at their "off study" date, no matter when that date fell in a phase, and they were considered to have a proportionally truncated phase. For those patients who came off therapy early due to an event, the denominator for the total cumulative protocol-specified dosage

was truncated at their time off therapy. If the time off therapy came during the middle of a phase, the protocol-indicated day off therapy was used to estimate the percent of that phase the patient would have been eligible to receive, and that percentage was used to individualize the denominator for purposes of estimating DI for that patient and those drugs.

The denominator for expected dosages accounted for the following factors. On T16, patients with a poor early response were to receive 1200 mg/ $m^2$ cyclophosphamide instead of 1000 mg/$m^2$ during induction. On both studies, patients with a poor early response got extra asparaginase, and this was taken into account in their denominator. On both studies, vincristine doses were capped at a fixed dose of 2 mg; this was converted into the patient/phase-specific mg/$m^2$, and this adjusted dosage was used in the denominator for each phase for each patient affected by the cap due to a higher BSA. On T16, patients were randomized (or assigned) to 2500 vs 3500 U/$m^2$ pegaspargase for their doses during continuation and reinductions, and this was taken into account in their denominator.

Where indicated, an alternative DI for mercaptopurine was estimated that accounted for the recommendation that starting dosages for mercaptopurine be tailored based on TPMT status; this adjustment was phase-specific. This entailed multiplying the expected dosage by a correction factor for each patient and phase, based on TPMT status. For this purpose, we estimated a new denominator of expected mercaptopurine dosage for all patients who were treated as TPMT intermediate metabolizers based on genotype or phenotype by multiplying 60/75 = 0.8 for all phases for which the protocol daily mercaptopurine dosage was 75 mg/$m^2$. This applied to all

phases after consolidation for the LR patients, and for all phases after week 19 for the SR patients. No correction factor was needed for other phases because the daily dosage was already 60 mg/m$^2$ or less. There were two patients on the SR arm of T16 who were TPMT poor metabolizers (homozygous for no-activity variants), for whom the recommended starting dosage was 30 mg/m$^2$/week during all phases.

To assess the impact of asparaginase DI on the DI for other drugs, patients on each of the 4 protocol arms (T15 LR, T15 SR, T16 LR, T16 SR) were divided into 3 groups based on their tertile for asparaginase DI (lowest, medium, and highest cumulative DI for asparaginase). The DI for all other drugs given during the phases that overlapped with asparaginase use starting from induction through the last asparaginase of reinduction II or continuation was estimated, and compared among asparaginase DI tertile groups

**Absolute neutrophil count (ANC)**

Per protocol, patients were to have weekly ANCs checked. In practice, ANCs were sometimes more or less frequent. The median number of ANC measures per patient on T15LR, T15SR, T16LR, and T16SR was 95, 112, 74 and 110. To estimate average ANC for each patient and for each phase, we fitted a Bayesian hierarchical regression model with splines within each phase and protocol using Stan.(1)

**Genotyping and ancestry/race**

Germline DNA from blood was genotyped and ancestry was determined using STRUCTURE, and patients were assigned into major race groups as previously described.(2) Germline DNA from blood was genotyped(3) and SNPs were called and imputed, ancestry was estimated using STRUCTURE,(4, 5) and patients were assigned to race groups as described.(6) Those with >90% Northern European ancestry were classified as white; >70% West African ancestry were classified as black; >10% Native American ancestry and greater Native American ancestry than West African ancestry were classified as Hispanic; patients not falling into one of these groups including ancestral Asians were categorized as other.

**Statistical Analyses of Outcomes**

To estimate the cumulative incidence of relapse, the time of relapse was used for those who relapsed; patients were censored at time of last follow-up (for those in CR) or at time of coming off therapy for any other reason (second cancer, death, died in complete remission, refusal, excessive toxicity, lineage switch, noncompliance, transplant). Outcome phenotypes were EFS, cumulative incidence of any relapse, any CNS relapse (isolated plus combined), or isolated CNS relapse was estimated by the method of Kalbfleisch and Prentice. To compare to a prior publication,(7) disease-free survival landmark analysis from end of reinduction II was estimated for purposes of reporting asparaginase DI. Effect of the DI of each drug or ANC on outcomes, adjusted for chemotherapy treatment arms (LR vs SR) was analyzed using the Fine and Gray regression model using R (version 3.5.0).(8)

To explore whether DI for any drug (for any phase or for the entire course) or ANC (for any phase or for the entire course) was related to relapse, DI or ANC were treated in two different ways: a screening analysis, in which DI or ANC were treated as continuous variables, followed by a second analysis, dividing the patient populations into tertiles with respect to each possible predictor. With DI and ANC for each phase treated as a continuous variable, there were many significant associations with outcomes within T15 and within T16, adjusting for risk group; most of these associations had hazard ratios with wide confidence intervals, and there were small numbers in some groups (data not shown). To further test suggestive findings from these screening analyses, those DI and ANC associations with nominal $p < 0.05$ in the continuous variable analysis were divided into tertiles (e.g. lowest third, middle third, or highest third with respect to each DI or ANC variable), and outcomes were compared among the low, medium, and high tertile groups for each DI and ANC variable for both protocols.

Each outcome analysis was repeated using 3 sets of patients: all patients, only those who completed reinduction II, or only those who completed week 120 of therapy.

For those outcomes and predictive DI and ANC variables that were nominally significant ($p < 0.05$) in the screening analysis continuous variables, and suggestive in the tertile analysis (nominal $p < 0.2$), the direction of association was always consistent (e.g. if higher DI for mercaptopurine was positively associated with increased relapse when DI was treated as a continuous variable, the highest tertile for DI for mercaptopurine was also associated with increased relapse) (Suppl Table 10). We focused on outcome analyses with similar findings in both protocols (T15 and T16).

Supplemental Table S1. Details of Remission Induction, Consolidation, and Continuation/reinduction Therapy for Patients on LR or SR arms of Total 15 (T15) and Total 16 (T16)

**A. Remission induction therapy**

| Agents | Dosages and routes | Total dosage | Schedules | Dosages and routes | Total dosage | Schedules |
|---|---|---|---|---|---|---|
| | Total 16 | | | Total 15 | | |
| High-dose Methotrexate | none | | | 1 g/m$^2$ IV over 4 vs 24 hours | 1000 mg/m2 | Day 1 |
| Prednisone | *40 mg/m$^2$ per day PO (t.i.d.) | 1120 mg/m2 | Days 1-28 | 40 mg/m$^2$ per day PO (t.i.d.) | 1120 mg/m2 | Days 5-32 |
| Vincristine | 1.5 mg/m$^2$ IV (max 2 mg) | 6 mg/m2 | Days 1, 8, 15, 22 | 1.5 mg/m$^2$ IV (max 2 mg) | 6 mg/m2 | Days 5, 12, 19, 26 |
| Daunorubicin | 25 mg/m$^2$ IV | 50 mg/m2 | Days 1 and 8 | 25 mg/m$^2$ IV | 50 mg/m2 | Days 5 and 12 |
| Asparaginase | pegaspargase 3,000 units/m$^2$ IV | 3000 or 6000 units/m2 | Day 3, (15)† | E. coli Asparaginase 10,000 units/m$^2$ thrice weekly IM | 60,000 to 90,000 units/m2 | Days 6, 8, 10, 12, 14, 16 (19, 21,23)† |
| Triple intrathecal** | Age-dependent | 2-6 | Days 1, (4), (8), (11), 15, (22) | Age-dependent | 2-4 | Day 1 (intrathecal cytarabine only), 19 (8, 26) |
| Cyclophosphamide | 1000 mg/m$^2$ IV | 1000 - 1200† mg/m2 | Day 22 | 1000 mg/m$^2$ IV | 1000 mg/m2 | Day 26 |
| Cytarabine | 75 mg/m$^2$ IV | 600 mg/m2 | Days 23-26, 30-33 | 75 mg/m$^2$ IV | 600 mg/m2 | Days 27-30, 34-37 |
| Thioguanine (Mercaptopurine for thiopurine methyltransferase intermediate or poor metabolizers) | 60 mg/m$^2$ per dose PO | 840 mg/m2 | Days 22-35 | Mercaptopurine for all; 60 mg/m$^2$ per dose PO | 840 mg/m2 | Days 26-39 |

*Prednisone was substituted by dexamethasone (10 mg/m$^2$ per day on days 1-21, 4 mg/m$^2$ per day on days 22-24, and 2 mg/m$^2$ per day on days 25-28) in patients with early T-cell precursor ALL on T16. †Extra dose of peg-asparaginase or extra three doses of asparaginase given to patients with ≥ 1% residual leukemia cells in the bone marrow on day 15 (Study 16) and on day 19 (Study 15), respectively. †Patients on Total 16 with Day 15 MRD > 5% received cyclophosphamide at 300 mg/m2 IV q 12 hrs x 4 doses instead of a single dose of 1000 mg/m$^2$

**Triple intrathecal treatment (methotrexate 6, 8, 10 or 12 mg; hydrocortisone 12, 16, 20 or 24 mg, and cytarabine 18, 24, 30 or 36 mg for ages <1, 1 to 1.99, 2 to 2.99 and ≥3 years, respectively). Leucovorin rescue (5 mg/m$^2$/dose, max 5 mg) PO was given at 24 and 30 hours after each triple intrathecal treatment during remission induction. In patients presenting with renal function impairment, serum methotrexate level was measured 24 hours after intrathecal therapy and those with delayed methotrexate clearance were rescued with leucovorin until level was no longer measurable. In Study 16, extra triple intrathecal treatment given on days 8 and 22 for patients with Philadelphia chromosome, *KMT2A* rearrangement, hypodiploidy (< 44 chromosomes), or leukocyte >100,000/μL at

presentation; and extra triple intrathecal treatment on days 4, 8, 11, and 22 for patients with T-cell ALL, *TCF3-PBX1*, CNS-2 status, CNS-3 status or traumatic lumbar puncture with blasts. In Study 15, extra triple intrathecal treatment given on days 8 and 26 for patients with CNS-2, CNS-3 or traumatic lumbar puncture with blasts, T-cell ALL with leukocyte >50 x10,000/µL, B-ALL with leukocyte >100,000/µL, Philadelphia chromosome, *KMT2A* rearrangement, or hypodiploidy (< 45 chromosomes).

**B. Consolidation therapy—Total Therapy T15 and T16**

| Agent | Dosage and Route | Total dosage | Schedule |
|---|---|---|---|
| High Dose Methotrexate* | 2.5 g/m$^2$ (or targeted 33µM, low risk), 5.0 g/m$^2$(or targeted 65 µM, standard-risk) | 10,000 or 20,000 mg/m2 | Days 1, 15, 29 and 43 |
| Mercaptopurine | 50 mg/m$^2$/day | 2800 mg/m2 | Days 1 to 56 |
| Triple intrathecal | Age-dependent | 4 | Days 1, 15, 29, and 43 |

* Methotrexate dosage was adjusted according to pharmacokinetic data to achieve a steady-state concentration of 65 µM in standard-risk patients and to 33µM in some low-risk patients (9). Leucovorin, 15 mg/m$^2$ (IV or PO) for standard-risk patients and 10 mg/m$^2$ (PO or IV) for low-risk cases, was initiated at 42 hours after the start of methotrexate infusion and repeated every 6 hours for a total of three doses; for the first methotrexate course on Study 15 or for any patients having prior mucositis, leucovorin rescue was given for five doses. For all courses, leucovorin was adjusted based on plasma methotrexate levels.

**C. Continuation/reinduction Therapy for Patients on Total 15 (T15) and Total 16 (T16)**

| | **Total 16** | | **Total 15** | |
|---|---|---|---|---|
| **Week** | **Low-risk Patients** | **Standard-risk Patients** | **Low-risk Patients** | **Standard-risk Patients** |
| 1 | Mercaptopurine + Dexamethasone + vincristine | pegaspargase + Mercaptopurine + Dexamethasone + Vincristine + doxorubicin | Mercaptopurine + Dexamethasone + vincristine | Asparaginase + Mercaptopurine + Dexamethasone + Vincristine + doxorubicin |
| 2 | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 3* | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 4 | Mercaptopurine + Dexamethasone + Vincristine | Mercaptopurine + Dexamethasone + Vincristine + Doxorubicin | Mercaptopurine + Dexamethasone + Vincristine | Asparaginase + Mercaptopurine + Dexamethasone + Vincristine + Doxorubicin |
| 5 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 6 | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 7* | Reinduction I pegaspargase + Dexamethasone + Vincristine + Doxorubicin | Reinduction I pegaspargase + Dexamethasone + Vincristine + Doxorubicin | Reinduction I Asparaginase + Dexamethasone + Vincristine + Doxorubicin | Reinduction I Asparaginase + Dexamethasone + Vincristine + Doxorubicin |

| | | | | |
|---|---|---|---|---|
| 8 | Reinduction I Vincristine | Reinduction I Vincristine + Doxorubicin | Reinduction I Asparaginase + Vincristine | Reinduction I Asparaginase + Vincristine + Doxorubicin |
| 9 | Reinduction I pegaspargase + Dexamethasone + Vincristine | Reinduction I pegaspargase + Dexamethasone + Vincristine | Reinduction I Asparaginase + Dexamethasone + Vincristine | Reinduction I Asparaginase + Dexamethasone + Vincristine |
| 10 | Mercaptopurine +Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 11 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine + Vincristine + Doxorubicin | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine + Vincristine + Doxorubicin |
| 12* | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 13 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 14 | Mercaptopurine + Dexamethasone + Vincristine | Mercaptopurine + Dexamethasone + Vincristine + Doxorubicin | Mercaptopurine + Dexamethasone + Vincristine | Asparaginase + Mercaptopurine + Dexamethasone + vincristine + Doxorubicin |
| 15 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 16 | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Asparaginase + Mercaptopurine |
| 17* | Reinduction II pegaspargase + Dexamethasone + Vincristine | Reinduction II pegaspargase + Dexamethasone + Vincristine | Reinduction II Asparaginase + Dexamethasone + Vincristine + doxorubicin | Reinduction II Asparaginase + Dexamethasone + Vincristine |
| 18 | Reinduction II Vincristine | Reinduction II Vincristine | Reinduction II Asparaginase + Vincristine | Reinduction II Asparaginase + Vincristine |
| 19 | Reinduction II pegaspargase + Dexamethasone + Vincristine | Reinduction II pegaspargase + Dexamethasone +Vincristine + high-dose Cytarabine | Reinduction II Asparaginase + Dexamethasone + Vincristine | Reinduction II Asparaginase + Dexamethasone +Vincristine + high-dose Cytarabine |
| 20 | Mercaptopurine + Methotrexate | --- | Mercaptopurine + Methotrexate | --- |
| 21 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |
| 22 | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |
| 23 | Mercaptopurine + Methotrexate | pegaspargase + Mercaptopurine | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine |
| 24 | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine | Mercaptopurine + Dexamethasone + Vincristine | Dexamethasone + Vincristine |
| 25* | Mercaptopurine + Dexamethasone + | pegaspargase + Dexamethasone + | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |

| | | | | |
|---|---|---|---|---|
| 26 | Mercaptopurine + Methotrexate | Mercaptopurine | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |
| 27 | Mercaptopurine + Methotrexate | pegaspargase + mercaptopurine | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine |
| 28 | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine | Mercaptopurine + Dexamethasone + Vincristine | Vincristine + Dexamethasone |
| 29* | Mercaptopurine + Dexamethasone + Vincristine | pegaspargase + Vincristine + Dexamethasone | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |
| 30 | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |
| 31 | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine |
| 32 | Mercaptopurine + Methotrexate | Cyclophosphamide + Cytarabine | Mercaptopurine + Dexamethasone + Vincristine | Dexamethasone + Vincristine |
| 33* | Mercaptopurine + Dexamethasone + Vincristine | Dexamethasone + Vincristine | Mercaptopurine + Methotrexate | Mercaptopurine + Methotrexate |

*Intrathecal therapy

Total 16: For low-risk ALL, triple intrathecal chemotherapy was given to patients with CNS-1 status and leukocyte <100,000/µL on weeks 7, 12, 17, 25, 33, 41, and 49, and to those with CNS-2 status, traumatic lumbar puncture with blasts status, or leukocyte >100 x $10^9$/L at presentation on weeks 3, 7, 12, 17, 25, 29, 33, 37, 41, 45 and 49. For standard-risk ALL, triple intrathecal treatment was given on weeks 7, 12, 17, 25, 29, 33, 37, 41, 45 and 49 and to those with additional leukocyte >100,000/µL at presentation, T-cell immunophenotype, *TCF3-PBX1*, *KMT2A* rearrangement, hypodiploidy <44, CNS-2 status, CNS-3 status, or traumatic lumbar puncture with blasts on weeks 3, 7, 12, 17, 25, 29, 33, 37, 41, 45, 49, 57, 65, 73, 81, 89 and 97.

Total 15: Triple intrathecal treatment was given to low-risk cases with CNS-1 status (no identifiable blasts in CSF) on weeks 7, 12, 17, 24, 32, 40, and 48. Triple intrathecal treatment was given to low-risk cases with CNS-2, traumatic CSF with blasts status, or leukocyte > 100 x $10^9$/L on weeks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48. Triple intrathecal treatment was given to standard-risk cases on weeks 7,12, 17, 24, 28, 32, 36, 40, 44 and 48. Triple intrathecal treatment was given to other standard-risk cases with leukocyte >100 x $10^9$/L, T-cell ALL with leukocyte >50 x $10^9$/L, presence of MLL rearrangement, hypodiploidy <45, or CNS-3 status on weeks 7, 12, 17, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88 and 96.

Mercaptopurine - 75 mg/$m^2$ PO daily for 7 days for low-risk group; 50 mg/$m^2$ PO daily for 7 days between weeks 1 and 19 and 75 mg/$m^2$ after week 19 for standard-risk group. The starting dose for patients with heterozygous deficiency (intermediate metabolizers) of thiopurine methyltransferase was 60 mg/$m^2$ instead of 75 mg/$m^2$. The starting dose for poor metabolizers of thiopurine methyltransferase was 10 mg/m2 thrice weekly instead of 75 mg/m2/day.(10)

Dexamethasone - 8 mg/$m^2$ PO per day in 3 divided doses for 5 days for low-risk group and 12 mg/$m^2$ for standard-risk groups until week 69; 8 mg/$m^2$ on days 1 to 8 and days 15 to 21 during reinduction I (weeks 7 to 9) and reinduction II (weeks 17-19) for both groups; in Study 16, dose was reduced to 6 mg/$m^2$ PO per day in 3 divided doses for 5 days for both groups for weeks 69-101.

Methotrexate – 40 mg/$m^2$ IV; Doxorubicin - 30 mg/$m^2$ IV; Vincristine - 2 mg/$m^2$ IV and 1.5 mg/$m^2$ IV during

reinductions I and II (maximum 2 mg); Cyclophosphamide: 300 mg/$m^2$ IV; Cytarabine: 300 mg/$m^2$ IV

In T16, pegaspargase 2,500 units/$m^2$ or 3,500 units/$m^2$ IV based on randomization. In Study 15, Asparaginase 25,000 units/$m^2$ weekly IM for 19 doses for standard-risk patients and 10,000 units/$m^2$ thrice weekly IM for 9 doses in low-risk patients.

High-dose Cytarabine: 2 gm/$m^2$ IV q 12 hr x 4 doses on days 15 and 16 of Reinduction II in standard-risk group.

For both Total 15 and Total 16, after week 30, low-risk patients received daily mercaptopurine and weekly methotrexate which were interrupted by pulses of dexamethasone, vincristine and mercaptopurine every 4 weeks up to week 101, after which only mercaptopurine and methotrexate were given until week 120 (Total 16 and Total 15 girls; up to week 146 for Total 15 boys).

For Total 15, after week 20, standard-risk patients received three drug pairs given in 4-week blocks: mercaptopurine plus methotrexate in the first and second weeks, cyclophosphamide plus cytarabine in the third week (replaced by mercaptopurine plus methotrexate after week 68), and dexamethasone plus vincristine in the fourth week (replaced by mercaptopurine plus methotrexate after week 101).

For Total 16, after week 30, standard-risk patients received three drug pairs given in 4-week blocks: mercaptopurine plus methotrexate in the first and second weeks, cyclophosphamide plus cytarabine in the third week (replaced by mercaptopurine plus methotrexate after week 68), and dexamethasone plus vincristine in the fourth week (replaced by mercaptopurine plus methotrexate after week 101).Dexamethasone dosage was reduced to 6 mg/$m^2$ daily for 5 days between weeks 69 and 101 for all patients in Study 16.

**D. Dosage Modifications**

The dosage modifications included as instructions in the Total 15 and XVI protocols were as follows.

**<u>Both T15 and T16 Protocols:</u>**

<u>All phases:</u>

Actual body weight was used to calculate body surface area in all patients and used for dosage calculations (with the exception that vincristine dosage was capped at 2 mg).

Vincristine dosage was capped at 2.0 mg; thus, the expected dosage (mg/m2) per phase differed for patients with larger BSA and varied by phase: for induction and reinduction (when the protocol vincristine dosage was 1.5 mg/$m^2$), the 2 mg cap meant that the expected dosage for all patients > 1.33 $m^2$ was < 1. 5 mg/$m^2$ dose; for other phases (when the protocol vincristine dosage was 2 mg/$m^2$), the expected dosage for all patients > 1.0 $m^2$ was < 2 mg/$m^2$/dose. Thus, expected dosages per phase were individualized based on the average BSA per patient per phase, and the dose intensity for each phase was estimated as the administered dosage (mg/$m^2$) divided by the expected dosage (mg/$m^2$), accounting for the impact of capping. For persistent, severe abdominal cramps, gait impairment, severe pain, or SIADH, the vincristine dose could be reduced to 1 mg/$m^2$; only motor paralysis or typhlitis warranted discontinuation of vincristine.

<u>Induction:</u>

Cytarabine and 6-mercaptopurine could be withheld for febrile neutropenia or grade 3 or 4 mucositis. The second daunorubicin could be omitted if total bilirubin was >2 mg/dl and direct

bilirubin >1.4 mg/dl. Oral prednisone could be substituted with methylprednisolone at 20 mg/$m^2$/day IV (t.i.d.) for patients who could not tolerate the oral medication or with oral prednisolone suspension for those who could not swallow tablets. On Total 16, dexamethasone was recommended instead of prednisone for patients with early-T progenitor ALL during induction. Because of heterogeneity in capturing the various formulations used during induction, glucocorticoid doses were not analyzed during this phase.

Consolidation:

Mercaptopurine could be held if ANC < 300/$mm^3$, platelet count < 50,000/$mm^3$ or grade 3 or 4 mucositis was present, or decreased for courses in patients who had prolonged neutropenia. Dosage of high-dose methotrexate during consolidation could be adjusted based on clearance to achieve target steady-state plasma concentrations of 33 uM (LR arm) or 65 uM (SR arm) (9). HDMTX was to be withheld or given at reduced dosages if direct bilirubin if >2 mg/dl and withheld for pre-existing mucositis.

Continuation:

Mercaptopurine and low-dose methotrexate dosages were modified based on myelosuppression and based on TPMT status. (10) Starting dosages were reduced in those who were TPMT intermediate or poor metabolizers. Full dosages could be given if leukocyte > 1000/$mm^3$, ANC > 300/mm3 and platelet count > 50 x $10^9$/L. Patients who missed < 25% of therapy and had persistently high leukocyte (>4 x $10^9$/L) and high ANC (>1000/$mm^3$) were counseled on compliance and thioguanine nucleotide (TGN) levels were measured; after compliance was demonstrated, for those with persistent high leukocyte, mercaptopurine and methotrexate dosages were increased by 30% using a stepwise approach if needed. Patients missing > 25% of therapy who had high TGN levels had mercaptopurine dosage reduced preferentially; without high TGN levels, both mercaptopurine and methotrexate dosages were reduced by 30%; dosages were re-evaluated every 8 to 16 weeks.

Doxorubicin was held if ANC <300/mm3, leukocyte <1000/mm3, or platelet count <50 x $10^9$/L.

Doxorubicin and vincristine dosages were modified for elevated direct bilirubin concentrations or other evidence of biliary obstruction: direct bilirubin 2-4 mg/dl - 50% dosage decrease; direct bilirubin 4-6 mg/dl - 75% dosage decrease; direct bilirubin >6 mg/dl - withheld dose.

L-asparaginase could be withheld in patients with elevated direct bilirubin concentrations, especially if there was evidence of mucositis.

Patients with symptomatic osteonecrosis could have their dexamethasone stopped or reduced, especially if past reinduction II; when dexamethasone was discontinued, the first choice was to replace each week's dosing with one dose of methotrexate 40 mg/m2.

**Total 15—additional dosage modifications**

Window:

Most patients received HDMTX "window" therapy (day -4), (11) but this was withheld for patients who refused or those who were too ill to receive HDMTX at diagnosis.

Continuation:

For patients who developed cerebral thrombosis on the LR arm, dexamethasone was given only in the first week and L-asparaginase in the second and third weeks of reinduction; for the SR arm, dexamethasone was omitted from weeks 4 and 9. Patients with allergic reactions to E. coli L-asparaginase were given erwinase if available; they could receive pegaspargase if it was not possible to give erwinase. Asparaginase could be discontinued for severe pancreatitis. If asparaginase had to be completely discontinued, they generally received methotrexate 40 mg/m2 IV for that week.

**Total 16—additional dosage modifications**

Induction:

Pegaspargase could be withheld in patients with elevated direct bilirubin concentrations, especially if there was evidence of mucositis. Patients who were TPMT poor or intermediate metabolizers (about 10% of all patients) received mercaptopurine during induction instead of thioguanine because of a possible increased risk of hepatic sinusoidal obstruction syndrome.

Continuation:

Patients with symptomatic osteonecrosis could have their dexamethasone stopped or reduced, especially if past reinduction II; when dexamethasone was discontinued, the first choice was to replace each week's dosing with one dose of methotrexate 40 mg/m2. Patients with asymptomatic osteonecrosis with imaging indicating > 30% of a weight-bearing joint affected could have their dexamethasone dose halved, especially if past reinduction II.

Patients with allergy to pegaspargase were occasionally rechallenged (as described). (12) Those that could not be rechallenged received erwinase, if available. Patients who were intolerant to all asparaginase formulations could have asparaginase substituted with methotrexate 40 mg/m2 IV.

Acute hemorrhagic pancreatitis was a contraindication to continue asparaginase treatment. In the case of severe pancreatitis (i.e. abdominal pain of 72 hours or more, amylase level three times or more of the upper limit of normal, and sonographic or CT scan evidence of pancreatitis), asparaginase could be discontinued permanently when the possibility of glucocorticoid- or mercaptopurine-induced pancreatitis was excluded.

Cyclophosphamide, cytarabine, mercaptopurine and methotrexate were held if leukocyte <1000/mm3, platelet count to <50 $x10^9$/L, or ANC <300/$mm^3$.

Mercaptopurine and methotrexate could be reduced if leukocyte and ANC did not increase by at least 2-fold in the week after each dexamethasone pulse.

Doses of cyclophosphamide and cytarabine could be reduced if patient missed 25% of chemotherapy and if the low counts were deemed to be related to this combination.

Table S2. Planned cumulative dosages for all drugs, T15 and T16

| Drug | T15 Low Risk | T16 Low Risk | T15 Standard Risk | T16 Standard Risk |
|---|---|---|---|---|
| Window MTX (mg/m2) | 1000 | 0 | 1000 | 0 |
| Prednisone (mg/m2) | 160 | 160 | 160 | 160 |
| Vincristine (mg/m2) | 61 | 61 | 63 | 63 |
| Daunorubicin (mg/m2) | 50 | 50 | 50 | 50 |
| Asparaginase (U/m2) | 12000 | 13000# | 26750 | 40500# |
| Cytarabine (mg/m2) | 600 | 600 | 12200 | 12200 |
| Thiopurine Induction (mg/m2) | 840 | 840 | 840 | 840 |
| Cyclophosphamide (mg/m2) | 1000 | 1000 | 4600* | 4600* |
| Consol HDMTX (mg/m2) | 10000^ | 10000^ | 20000^ | 20000^ |
| MP.Consol_to_Wk120 (mg/m2) | 62650 | 62650 | 47250 | 47250 |
| Dexamethasone (mg/m2) | 1160 | 1080 | 1620 | 1380 |
| Doxorubicin (mg/m2) | 60 | 30 | 180 | 180 |
| MTX.Cont_to_Wk120 (mg/m2) | 3640 | 3640 | 2720 | 2560 |
| Late MP Boys (mg/m2) | 13650 | 0 | 13650 | 0 |
| Late MTX Boys (mg/m2) | 1040 | 0 | 1040 | 0 |

Window MTX = methotrexate given during the window phase of T15; consol HDMTX = high dose methotrexate given during consolidation; MTX.Cont_to_Wk120 = low dose methotrexate given during continuation till week 120; late MTX Boys= terminal 26 weeks of low dose methotrexate given only to boys in T15; MTX.Cont_to_Wk120 = low dose methotrexate given during continuation till week 120; Asparaginase = pegaspargase equivalents; thiopurine induction (T15 = mercaptopurine; T16 = thioguanine except for TPMT defect patients); MP.Consol_to_Wk120 = mercaptopurine given during consolidation up till week 120 of continuation; late MP Boys = terminal 26 weeks of low dose mercaptopurine given only to boys in T15

# The asparaginase dosage listed for T16 reflects the dosage given to those assigned to the low dose arm of the randomization.
* Patients with poor response on T16 received 200 mg/m2 more of cyclophosphamide during induction than other patients
^ HDMTX dosages were adjusted based on clearance

Table S3. Actual cumulative DIs T15 and T16 all drugs (excludes prednisone in induction, methotrexate window for T15, weeks 120-146 methotrexate and mercaptopurine for T15). P values were calculated using the Wilcoxon rank sum test. Total of 22 comparisons: 11(drugs) x 2(Risk Arms); thus Bonferroni significance threshold= 0.002.

| | | T15 | | | | | T16 | | | | | P Value T15 vs T16 | T15 minus T16 Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | **Risk Arm** | **N** | **Median** | **5th %-tile** | **95th %-tile** | **MAD** | **N** | **Median** | **5th %-tile** | **95th %-tile** | **MAD** | | |
| Asparaginase | LR | 192 | 0.998 | 0.75 | 1.29 | 0.062 | 254 | 1 | 0.76 | 1.04 | 0.010 | 1 | -0.003 |
| | SR | 173 | 1 | 0.73 | 1.52 | 0.071 | 270 | 1 | 0.42 | 1.14 | 0.035 | 0.77 | -0.003 |
| Cyclophosphamide | LR | 190 | 1 | 0.92 | 1.04 | < 0.01 | 252 | 1 | 0.97 | 1.04 | < 0.01 | 1 | 0.000 |
| | SR | 172 | 0.993 | 0.73 | 1.03 | 0.051 | 269 | 0.851 | 0.51 | 1.02 | 0.192 | <0.0001 | 0.143 |
| Cytarabine | LR | 190 | 0.998 | 0.38 | 1.06 | 0.021 | 253 | 1 | 0.49 | 1.06 | 0.041 | 1 | -0.002 |
| | SR | 172 | 0.96 | 0.35 | 1.02 | 0.077 | 269 | 0.783 | 0.62 | 0.86 | 0.076 | <0.0001 | 0.177 |
| Daunorubicin | LR | 192 | 1 | 0.50 | 1.04 | 0.022 | 254 | 0.988 | 0.49 | 1.02 | 0.017 | 1 | 0.012 |
| | SR | 173 | 1.01 | 0.77 | 1.05 | 0.022 | 270 | 0.989 | 0.50 | 1.02 | 0.016 | 0.0002 | 0.017 |
| Doxorubicin | LR | 189 | 1 | 0.96 | 1.02 | 0.013 | 250 | 1 | 0.97 | 1.03 | 0.013 | 1 | 0.000 |
| | SR | 171 | 0.996 | 0.67 | 1.01 | 0.014 | 265 | 0.898 | 0.66 | 1.01 | 0.142 | 0.15 | 0.098 |
| Vincristine | LR | 192 | 1.04 | 0.88 | 1.12 | 0.054 | 253 | 1.03 | 0.85 | 1.11 | 0.046 | 0.42 | 0.009 |
| | SR | 173 | 1.02 | 0.86 | 1.11 | 0.057 | 269 | 1 | 0.85 | 1.08 | 0.040 | 0.68 | 0.018 |
| Thiopurine Induction | LR | 190 | 0.973 | 0.31 | 1.11 | 0.088 | 230 | 0.968 | 0.42 | 1.09 | 0.1 | 1 | 0.005 |
| | SR | 172 | 0.968 | 0.42 | 1.09 | 0.096 | 243 | 0.949 | 0.46 | 1.04 | 0.105 | 0.53 | 0.018 |
| consol HDMTX | LR | 190 | 1.1 | 0.74 | 1.48 | 0.206 | 250 | 0.997 | 0.90 | 1.03 | 0.018 | <0.0001* | 0.102* |
| | SR | 171 | 0.925 | 0.55 | 1.17 | 0.115 | 266 | 0.921 | 0.67 | 1.04 | 0.087 | 1 | 0.004 |
| Dexamethasone | LR | 190 | 0.916 | 0.61 | 1 | 0.078 | 251 | 0.961 | 0.54 | 1.06 | 0.072 | <0.0001 | -0.046 |
| | SR | 171 | 0.853 | 0.26 | 0.99 | 0.157 | 265 | 0.941 | 0.29 | 1.05 | 0.109 | <0.0001 | -0.089 |
| MP Consol to Wk120 | LR | 191 | 0.821 | 0.49 | 1.1 | 0.166 | 251 | 0.716 | 0.41 | 1.02 | 0.169 | <0.0001 | 0.105 |
| | SR | 171 | 0.818 | 0.47 | 1.05 | 0.162 | 266 | 0.605 | 0.25 | 0.912 | 0.226 | <0.0001 | 0.213 |
| MTX Cont to Wk120 | LR | 190 | 0.896 | 0.64 | 1.26 | 0.132 | 251 | 0.835 | 0.54 | 1.11 | 0.139 | 0.0004 | 0.061 |
| | SR | 165 | 0.91 | 0.64 | 1.28 | 0.151 | 261 | 0.844 | 0.46 | 1.26 | 0.191 | 0.0016 | 0.066 |

DI: dose intensity; MAD: median absolute deviation; consol: consolidation phase; HDMTX: high-dose methotrexate with leucovorin rescue; MP: 6-mercaptopurine; Cont: continuation phase. *Note, although HDMTX had a higher dosage on T15 than on T16, systemic exposures were comparable because dosage for consolidation HDMTX was individualized based on clearance.

Table S4. Mercaptopurine dose intensity by phase T15 vs T16. P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2 (Risk Arms) x 7 (phases)=154 comparisons, thus corrected significance threshold = 0.0003.

| Phase | Risk Arm | T15 | | | | | T16 | | | | | P Value T15 vs T16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Median | 5th %-tile | 95th %-tile | MAD | N | Median | 5th %-tile | 95th %-tile | MAD | |
| Induction | LR | 190 | 0.973 | 0.309 | 1.11 | 0.088 | 253 | 0.968 | 0.422 | 1.09 | 0.102 | 1 |
| | SR | 172 | 0.968 | 0.422 | 1.09 | 0.096 | 269 | 0.948 | 0.447 | 1.05 | 0.113 | 0.55 |
| Consolidation | LR | 190 | 0.87 | 0.426 | 1.13 | 0.2 | 250 | 0.607 | 0.261 | 0.996 | 0.268 | <0.0001 |
| | SR | 171 | 0.854 | 0.469 | 1.11 | 0.204 | 266 | 0.595 | 0.254 | 0.976 | 0.258 | <0.0001 |
| Continuation Wks 1-6 | LR | 190 | 0.912 | 0.572 | 1.07 | 0.131 | 250 | 0.83 | 0.398 | 1.05 | 0.181 | <0.0001 |
| | SR | 171 | 0.901 | 0.494 | 1.07 | 0.154 | 264 | 0.658 | 0.255 | 1 | 0.249 | <0.0001 |
| Continuation Wks 10-16 | LR | 189 | 0.849 | 0.566 | 1.06 | 0.181 | 251 | 0.652 | 0.385 | 0.967 | 0.173 | <0.0001 |
| | SR | 170 | 0.757 | 0.338 | 1.02 | 0.221 | 263 | 0.488 | 0.105 | 0.928 | 0.291 | <0.0001 |
| Continuation Wks 20-120 | LR | 189 | 0.814 | 0.483 | 1.14 | 0.186 | 249 | 0.731 | 0.374 | 1.05 | 0.184 | <0.0001 |
| | SR | 165 | 0.808 | 0.45 | 1.09 | 0.189 | 263 | 0.614 | 0.231 | 0.948 | 0.233 | <0.0001 |

Table S5. Cyclophosphamide dose intensity by phase T15 vs T16. P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2(riskArms) x 7(phases)=154 comparisons, thus corrected significance threshold= 0.0003.

| Phase | Risk Arm | T15 | | | | | T16 | | | | | P Value T15 vs T16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Median | 5th %-tile | 95th %-tile | MAD | N | Median | 5th %-tile | 95th %-tile | MAD | |
| Induction | LR | 190 | 1 | 0.917 | 1.04 | < 0.01 | 252 | 1 | 0.969 | 1.04 | <0.01 | 1 |
| | SR | 171 | 1 | 0.409 | 1.05 | 0.019 | 269 | 1 | 0.895 | 1.02 | 0.009 | 1 |
| Continuation Wks 20-120 | SR | 164 | 0.996 | 0.701 | 1.04 | 0.058 | 263 | 0.8 | 0.387 | 1.02 | 0.239 | <0.0001 |

Table S6. Cytarabine dose intensity by phase T15 vs T16. P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2(riskArms) x 7(phases)=154 comparisons, thus corrected significance threshold= 0.0003.

| Phase | Risk Arm | T15 | | | | | T16 | | | | | P.Value T15 vs T16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Median | 5th %-tile | 95th %-tile | MAD | N | Median | 5th %-tile | 95th %-tile | MAD | |
| Induction | LR | 190 | 0.998 | 0.379 | 1.06 | 0.021 | 253 | 1 | 0.492 | 1.06 | 0.041 | 1 |
| Induction | SR | 172 | 1 | 0.502 | 1.04 | 0.015 | 269 | 0.991 | 0.5 | 1.04 | 0.040 | 1 |
| Reinduction II | SR | 166 | 0.994 | 0.047 | 1.01 | 0.023 | 262 | 0.759 | 0.53 | 0.792 | 0.014 | <0.0001 |
| Continuation Wks 20-120 | SR | 164 | 0.999 | 0.706 | 1.04 | 0.059 | 263 | 0.8 | 0.392 | 1.02 | 0.245 | <0.0001 |

Table S7. Dose intensity (cumulative for protocol) vs TPMT status, all arms and all drugs. P values were calculated using the Wilcoxon rank sum test. Total number of 48 comparisons; thus Bonferroni significance threshold 0.001.

| Drug | Risk Arm | TPMT Deficient | | | | | TPMT Normal | | | | | P Value | Deficient Minus Normal Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Median | MAD | 5th %tile | 95th %tile | N | Median | MAD | 5th %tile | 95th %tile | | |
| Asparaginase (T15) | LR | 32 | 0.997 | 0.051 | 0.843 | 1.39 | 160 | 0.998 | 0.064 | 0.711 | 1.28 | 1 | -0.001 |
| | SR | 30 | 1 | 0.073 | 0.552 | 1.59 | 143 | 1 | 0.071 | 0.778 | 1.5 | 1 | 0.002 |
| Asparaginase (T16) | LR | 34 | 0.999 | 0.010 | 0.728 | 1.04 | 220 | 1 | 0.011 | 0.762 | 1.03 | 1 | -0.002 |
| | SR | 51 | 0.995 | 0.060 | 0.26 | 1.13 | 219 | 1.01 | 0.033 | 0.616 | 1.13 | 0.34 | -0.011 |
| Cyclophosphamide (T15) | LR | 31 | 1 | <0.01 | 0.93 | 1.03 | 159 | 1 | 0 | 0.909 | 1.04 | 1 | <0.001 |
| | SR | 30 | 0.997 | 0.032 | 0.85 | 1.02 | 142 | 0.992 | 0.053 | 0.696 | 1.03 | 1 | 0.005 |
| Cyclophosphamide (T16) | LR | 34 | 1 | 0.007 | 0.979 | 1.03 | 218 | 1 | 0 | 0.968 | 1.03 | 1 | 0 |
| | SR | 51 | 0.898 | 0.154 | 0.547 | 1.01 | 218 | 0.843 | 0.19 | 0.501 | 1.02 | 0.61 | 0.055 |
| Cytarabine (T15) | LR | 31 | 1 | 0.027 | 0.116 | 1.03 | 159 | 0.998 | 0.021 | 0.458 | 1.09 | 1 | 0.002 |
| | SR | 30 | 0.967 | 0.053 | 0.719 | 1.01 | 142 | 0.957 | 0.086 | 0.341 | 1.02 | 1 | 0.011 |
| Cytarabine (T16) | LR | 34 | 1.01 | 0.043 | 0.567 | 1.08 | 219 | 1 | 0.041 | 0.491 | 1.05 | 0.36 | 0.011 |
| | SR | 51 | 0.792 | 0.066 | 0.628 | 0.905 | 218 | 0.782 | 0.078 | 0.616 | 0.857 | 1 | 0.010 |
| Daunorubicin (T15) | LR | 32 | 0.987 | 0.025 | 0.506 | 1.02 | 160 | 1 | 0.022 | 0.502 | 1.04 | 0.94 | -0.013 |
| | SR | 30 | 1.01 | 0.021 | 0.975 | 1.04 | 143 | 1 | 0.021 | 0.75 | 1.04 | 1 | 0.01 |
| Daunorubicin (T16) | LR | 34 | 0.994 | 0.020 | 0.494 | 1.01 | 220 | 0.988 | 0.017 | 0.5 | 1.02 | 1 | 0.005 |
| | SR | 51 | 0.988 | 0.018 | 0.617 | 1 | 219 | 0.99 | 0.015 | 0.5 | 1.02 | 1 | -0.002 |
| Doxorubicin (T15) | LR | 31 | 0.993 | 0.015 | 0.975 | 1.02 | 158 | 1 | 0.013 | 0.96 | 1.01 | 1 | -0.007 |
| | SR | 30 | 0.996 | 0.015 | 0.79 | 1.01 | 141 | 0.996 | 0.013 | 0.672 | 1.01 | 1 | <0.001 |
| Doxorubicin (T16) | LR | 33 | 1 | 0.007 | 0.976 | 1.02 | 217 | 1 | 0.015 | 0.972 | 1.03 | 1 | <0.001 |
| | SR | 50 | 0.836 | 0.132 | 0.664 | 1.01 | 215 | 0.916 | 0.126 | 0.65 | 1.01 | 1 | -0.080 |
| Vincristine (T15) | LR | 32 | 1.05 | 0.061 | 0.793 | 1.13 | 160 | 1.03 | 0.051 | 0.889 | 1.12 | 1 | 0.016 |
| | SR | 30 | 1.01 | 0.078 | 0.875 | 1.12 | 143 | 1.02 | 0.052 | 0.853 | 1.11 | 1 | -0.008 |
| Vincristine (T16) | LR | 34 | 1.03 | 0.045 | 0.954 | 1.1 | 219 | 1.03 | 0.046 | 0.852 | 1.11 | 1 | 0.001 |
| | SR | 51 | 1 | 0.037 | 0.833 | 1.07 | 218 | 1 | 0.042 | 0.857 | 1.08 | 1 | <0.001 |
| Thiopurine Induction (T15) | LR | 31 | 0.947 | 0.093 | 0.035 | 1.11 | 159 | 0.977 | 0.086 | 0.346 | 1.12 | 1 | -0.030 |
| | SR | 30 | 0.957 | 0.114 | 0.364 | 1.07 | 142 | 0.968 | 0.092 | 0.431 | 1.1 | 1 | -0.012 |
| Thiopurine Induction (T16) | LR | 11 | 0.966 | 0.087 | 0.823 | 1.1 | 219 | 0.969 | 0.101 | 0.417 | 1.09 | 0.50 | -0.003 |
| | SR | 25 | 0.84 | 0.16 | 0.428 | 0.994 | 218 | 0.956 | 0.097 | 0.491 | 1.04 | 0.037 | -0.115 |
| consolHDMTX (T15) | LR | 31 | 1.05 | 0.231 | 0.565 | 1.42 | 159 | 1.11 | 0.199 | 0.8 | 1.49 | 0.49 | -0.057 |
| | SR | 30 | 0.927 | 0.11 | 0.704 | 1.12 | 141 | 0.925 | 0.124 | 0.551 | 1.18 | 0.84 | 0.002 |
| ConsolHDMTX (T16) | LR | 33 | 0.992 | 0.012 | 0.931 | 1.02 | 217 | 0.997 | 0.019 | 0.887 | 1.03 | 1 | -0.005 |
| | SR | 50 | 0.907 | 0.102 | 0.505 | 1.01 | 216 | 0.927 | 0.082 | 0.707 | 1.04 | 0.55 | -0.020 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dexamethasone (T15) | LR | 32 | 0.931 | 0.079 | 0.609 | 1 | 158 | 0.91 | 0.082 | 0.642 | 1 | 1 | 0.021 |
| | SR | 30 | 0.858 | 0.165 | 0.323 | 0.992 | 141 | 0.849 | 0.156 | 0.256 | 0.994 | 1 | 0.009 |
| Dexamethasone (T16) | LR | 33 | 0.948 | 0.0638 | 0.657 | 1.05 | 218 | 0.967 | 0.072 | 0.542 | 1.06 | 0.51 | -0.019 |
| | SR | 50 | 0.911 | 0.149 | 0.281 | 1.03 | 215 | 0.95 | 0.096 | 0.299 | 1.06 | 0.50 | -0.040 |
| MP.Consol_to_Wk120 (T15) | LR | 32 | 0.683 | 0.268 | 0.359 | 1.02 | 159 | 0.838 | 0.145 | 0.571 | 1.11 | 0.0005 | -0.155 |
| | SR | 30 | 0.73 | 0.14 | 0.379 | 0.894 | 141 | 0.828 | 0.161 | 0.529 | 1.09 | 0.001 | -0.098 |
| MP.Consol_to_Wk120 (T16) | LR | 33 | 0.6 | 0.226 | 0.306 | 0.914 | 218 | 0.746 | 0.176 | 0.472 | 1.02 | 0.0002 | -0.146 |
| | SR | 50 | 0.484 | 0.245 | 0.172 | 0.788 | 216 | 0.629 | 0.209 | 0.304 | 0.944 | <0.0001 | -0.145 |
| MTX.Cont_to_Wk120 (T15) | LR | 32 | 0.909 | 0.169 | 0.688 | 1.28 | 158 | 0.894 | 0.115 | 0.637 | 1.26 | 0.47 | 0.015 |
| | SR | 28 | 0.922 | 0.11 | 0.682 | 1.23 | 137 | 0.904 | 0.149 | 0.635 | 1.29 | 1 | 0.018 |
| MTX.Cont_to_Wk120 (T16) | LR | 33 | 0.842 | 0.155 | 0.564 | 1.21 | 218 | 0.834 | 0.131 | 0.553 | 1.09 | 0.72 | 0.008 |
| | SR | 49 | 0.85 | 0.276 | 0.314 | 1.31 | 212 | 0.838 | 0.179 | 0.487 | 1.21 | 0.28 | 0.012 |
| Late wk 120-146 MP Boys (T15) | LR | 31 | 0.655 | 0.458 | 0.209 | 1.21 | 155 | 0.868 | 0.238 | 0.472 | 1.53 | 0.096 | -0.213 |
| | SR | 27 | 0.724 | 0.237 | 0.195 | 1.01 | 129 | 0.855 | 0.186 | 0.319 | 1.24 | 0.12 | -0.131 |
| Late wk 120-146 MTX Boys (T16) | LR | 31 | 0.909 | 0.34 | 0.417 | 1.75 | 155 | 0.926 | 0.198 | 0.605 | 1.63 | 0.81 | -0.017 |
| | SR | 27 | 0.906 | 0.107 | 0.425 | 1.03 | 130 | 0.922 | 0.156 | 0.456 | 1.53 | 0.71 | -0.016 |

Table S8. Mercaptopurine Dose Intensity in T15 by Phase and Risk. The P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2(risk groups) x 7 (phases); thus Bonferroni significance threshold 0.0003.

| Phase | Standard Risk (SR) | | Low Risk (LR) | | Low Minus Standard Median | P Value |
|---|---|---|---|---|---|---|
| | Median | MAD | Median | MAD | | |
| Consolidation | 0.854 | 0.204 | 0.87 | 0.2 | 0.016 | 0.90 |
| Continuation Wks 1 - 6 | 0.901 | 0.154 | 0.912 | 0.131 | 0.011 | 0.89 |
| Continuation Wks 10 - 16 | 0.757 | 0.221 | 0.849 | 0.181 | 0.092 | 0.0004 |
| Continuation Wks 20-47* | 0.829 | 0.178 | 0.813 | 0.144 | -0.016 | 0.102 |
| Continuation Wks 48-95 | 0.815 | 0.173 | 0.813 | 0.194 | -0.001 | 1 |
| Continuation Wks 96-120 | 0.827 | 0.243 | 0.822 | 0.236 | -0.005 | 0.39 |

* phase immediately following end of asparaginase (Elspar) phase.

Table S9. Mercaptopurine Dose Intensity in T16 by Phase and Risk. The P values were calculated using the Wilcoxon rank sum test. Total = 11(drug)x2(protocol)x7(phase) = 154 comparisons, thus Bonferroni significance threshold 0.0003.

| Phase | Standard Risk (SR) | | Low Risk (LR) | | LR median Minus SR Median | P Value |
|---|---|---|---|---|---|---|
| | Median | MAD | Median | MAD | | |
| Consolidation | 0.597 | 0.258 | 0.607 | 0.268 | 0.011 | 0.68 |
| Continuation Wks 1-6 | 0.658 | 0.249 | 0.83 | 0.181 | 0.172 | <0.0001 |
| Continuation Wks 10-16 | 0.488 | 0.291 | 0.652 | 0.173 | 0.164 | <0.0001 |
| Continuation Wks 20-37* | 0.41 | 0.265 | 0.692 | 0.194 | 0.281 | <0.0001 |
| Continuation Wks 38-69 | 0.571 | 0.268 | 0.715 | 0.199 | 0.143 | <0.0001 |
| Continuation Wks 70-101 | 0.644 | 0.265 | 0.742 | 0.217 | 0.098 | 0.003 |
| Continuation Wks 102-120 | 0.682 | 0.264 | 0.745 | 0.237 | 0.062 | 0.030 |

* phase immediately following end of asparaginase (pegaspargase) phase.

Table S10. Cumulative dose intensity for all drugs on T16 by risk arms (LR vs SR). P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2(risk groups), thus Bonferroni significance threshold 0.002.

| Drug | Standard Risk (SR) | | | | | Low Risk (LR) | | | | | P Value | LR Minus SR Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Median | 5th %tile | 95th %tile | MAD | N | Median | 5th %tile | 95th %tile | MAD | | |
| Asparaginase | 254 | 1 | 0.761 | 1.04 | 0.010 | 270 | 1 | 0.422 | 1.14 | 0.035 | 1 | -0.004 |
| Cyclophosphamide | 252 | 1 | 0.969 | 1.04 | 0 | 269 | 0.851 | 0.508 | 1.02 | 0.192 | <0.0001 | 0.149 |
| Cytarabine | 253 | 1 | 0.492 | 1.06 | 0.041 | 269 | 0.783 | 0.619 | 0.86 | 0.076 | <0.0001 | 0.217 |
| Daunorubicin | 254 | 0.988 | 0.495 | 1.02 | 0.017 | 270 | 0.989 | 0.5 | 1.02 | 0.016 | 1 | -0.001 |
| Doxorubicin | 250 | 1 | 0.972 | 1.03 | 0.013 | 265 | 0.898 | 0.66 | 1.01 | 0.142 | <0.0001 | 0.102 |
| Vincristine | 253 | 1.03 | 0.853 | 1.11 | 0.046 | 269 | 1 | 0.847 | 1.08 | 0.040 | 0.01 | 0.272 |
| Thiopurine.Induction | 230 | 0.968 | 0.42 | 1.09 | 0.1 | 243 | 0.949 | 0.459 | 1.04 | 0.105 | 0.38 | 0.019 |
| consolHDMTX | 250 | 0.997 | 0.899 | 1.03 | 0.018 | 266 | 0.921 | 0.666 | 1.04 | 0.087 | <0.0001 | 0.075 |
| Dexamethasone | 251 | 0.961 | 0.538 | 1.06 | 0.072 | 265 | 0.941 | 0.287 | 1.05 | 0.109 | 0.02 | 0.020 |
| MP.Consol_to_Wk120 | 251 | 0.716 | 0.411 | 1.02 | 0.169 | 266 | 0.605 | 0.254 | 0.912 | 0.226 | <0.0001 | 0.111 |
| MTX.Cont_to_Wk120 | 251 | 0.835 | 0.545 | 1.11 | 0.139 | 261 | 0.844 | 0.461 | 1.26 | 0.191 | 1 | -0.009 |

Table S11. Cumulative dose intensity for all drugs on T15 by risk arms (LR vs SR). P values were calculated using the Wilcoxon rank sum test. Total number of comparisons = 11(drugs) x 2(risk groups); thus Bonferroni significance threshold 0.002.

| Drug | Standard Risk (SR) | | | | | Low Risk (LR) | | | | | P Value | LR Minus SR Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Median | 5th %tile | 95th %tile | MAD | N | Median | 5th %tile | 95th %tile | MAD | | |
| Asparaginase | 192 | 0.998 | 0.748 | 1.29 | 0.0623 | 173 | 1.002 | 0.732 | 1.521 | 0.071 | 1 | -0.004 |
| Cyclophosphamide | 190 | 1 | 0.917 | 1.04 | 0 | 172 | 0.993 | 0.728 | 1.03 | 0.051 | 1 | 0.007 |
| Cytarabine | 190 | 0.998 | 0.379 | 1.06 | 0.0214 | 172 | 0.96 | 0.346 | 1.017 | 0.077 | 0.0003 | 0.039 |
| Daunorubicin | 192 | 1 | 0.501 | 1.04 | 0.022 | 173 | 1.006 | 0.768 | 1.046 | 0.022 | 1 | -0.006 |
| Doxorubicin | 189 | 1 | 0.961 | 1.02 | 0.013 | 171 | 0.996 | 0.674 | 1.014 | 0.014 | 1 | 0.004 |
| Vincristine | 192 | 1.04 | 0.879 | 1.12 | 0.054 | 173 | 1.018 | 0.858 | 1.111 | 0.057 | 0.055 | 0.018 |
| Thiopurine Induction | 190 | 0.973 | 0.309 | 1.11 | 0.088 | 172 | 0.968 | 0.422 | 1.093 | 0.096 | 1 | 0.005 |
| consolHDMTX | 190 | 1.1 | 0.741 | 1.48 | 0.206 | 171 | 0.925 | 0.553 | 1.169 | 0.115 | <0.0001 | 0.174 |
| Dexamethasone | 190 | 0.916 | 0.614 | 1 | 0.0783 | 171 | 0.853 | 0.263 | 0.995 | 0.157 | <0.0001 | 0.063 |
| MP Consol_to_Wk120 | 191 | 0.821 | 0.488 | 1.1 | 0.166 | 171 | 0.818 | 0.471 | 1.048 | 0.162 | 1 | 0.003 |
| MTX Cont_to_Wk120 | 190 | 0.896 | 0.635 | 1.26 | 0.132 | 165 | 0.91 | 0.639 | 1.278 | 0.151 | 0.82 | -0.014 |
| Late MP Boys | 87 | 0.866 | 0.401 | 1.47 | 0.274 | 98 | 0.836 | 0.316 | 1.198 | 0.207 | 0.40 | 0.03 |
| Late MTX Boys | 87 | 0.926 | 0.598 | 1.7 | 0.212 | 100 | 0.922 | 0.426 | 1.395 | 0.136 | 0.40 | 0.004 |

Table S12. Selected outcomes. Listed are all outcomes (cumulative incidence or CI of any relapse, CNS relapse, isolated CNS relapse, event free survival (EFS)) for those predictor dose intensity (DI) or absolute neutrophil count (ANC) variables with a p value < 0.05 (adjusting for risk group, when the variable was treated continuously (p value continuous)) AND had a corresponding p value (p value tertile) that was p < 0.2 when the predictor variable was used to divide patients into tertiles with respect to the DI or ANC variable. Highlighted in bold are the only variables (DI for mercaptopurine, albeit different phases) that replicated in both protocols. Total number of comparisons = 12(drugs or ANC measures) x 2 (protocols) x 7(phases) x 4(outcomes) x 3(durations of follow-up)=2016 comparisons. Bonferroni significance threshold 0.0000348.

| **Outcome** | **DI/ANC variable** | **HR** | **Patients completed ?** | **p value continuous** | **p value tertile (if p < .2)** | **Protocol** |
|---|---|---|---|---|---|---|
| CI of any relapse | DI MP wk 10-16 | 1.29 | any time of tx | 0.0079 | 0.097 | T15 |
| CI any CNS relapse | DI MTX wk 48-95 | 0.73 | any time of tx | 0.0205 | 0.053 | T15 |
| CI any CNS relapse | ANC wk 20-120 | 0.0111 | any time of tx | < 0.0001 | 0.055 | T15 |
| EFS | DI MP wk 10-16 | 1.35 | Reind II | 0.0012 | 0.045 | T15 |
| CI of any relapse | DI MP wk 10-16 | 1.31 | Reind II | 0.0066 | 0.11 | T15 |
| CI of any relapse | ANC wk 20-120 | 0.062 | Reind II | 0.042 | 0.04 | T15 |
| CI any CNS relapse | ANC wk 20-120 | 0.001 | Reind II | 0.0002 | 0.08 | T15 |
| CI isolated CNS | ANC wk 20-120 | 0.018 | Reind II | 0.0088 | 0.16 | T15 |
| **EFS** | **DI MP entire course** | **1.27** | **completed wk 120** | **0.0489** | **0.03** | **T15** |
| **EFS** | **DI MP wk 10-16** | **1.45** | **completed wk 120** | **0.0032** | **0.008** | **T15** |
| **CI of any relapse** | **DI MP wk 10-16** | **1.45** | **completed wk 120** | **0.007** | **0.03** | **T15** |
| EFS | ANC wk 10-16 | 32.1 | completed wk 120 | 0.0261 | 0.048 | T15 |
| EFS | ANC wk 1-6 | 17.2 | completed wk 120 | 0.04 | 0.1 | T15 |
| EFS | DI VCR Reind I | 0.73 | any time of tx | 0.0063 | 0.087 | T16 |
| CI of any relapse | DI dex wk 1-6 | 0.81 | any time of tx | 0.0035 | 0.18 | T16 |
| CI any CNS relapse | DI mtx wk 20-37 | 1.15 | any time of tx | 0.0135 | 0.04 | T16 |
| CI isolated CNS | DI mtx wk 20-37 | 1.18 | any time of tx | 0.004 | 0.04 | T16 |
| CI isolated CNS | DI HDMTX | 0.6 | any time of tx | 0.029 | 0.14 | T16 |
| EFS | DI VCR wk 70-101 | 0.83 | Reind II | 0.014 | 0.14 | T16 |
| CI of any relapse | DI dex wk 1-6 | 0.8 | Reind II | 0.0024 | 0.18 | T16 |
| CI any CNS relapse | DI mtx wk 20-37 | 1.15 | Reind II | 0.0137 | 0.16 | T16 |
| CI isolated CNS | DI dex reind II | 0.75 | Reind II | 0.035 | 0.17 | T16 |
| CI isolated CNS | DI mtx wk 20-37 | 1.18 | Reind II | 0.004 | 0.04 | T16 |
| CI isolated CNS | ANC wk 1-6 | 3689 | Reind II | 0.0056 | 0.16 | T16 |
| EFS | DI dox wk 1-6 | 0.825 | completed wk 120 | 0.025 | 0.024 | T16 |
| EFS | DI dex wk 1-6 | 0.795 | completed wk 120 | 0.0042 | 0.07 | T16 |
| **CI of any relapse** | **DI MP wk 38-69** | **1.27** | **completed wk 120** | **0.0324** | **0.07** | **T16** |
| CI of any relapse | DI dox wk 1-6 | 0.812 | completed wk 120 | 0.0309 | 0.089 | T16 |
| CI of any relapse | DI dex wk 1-6 | 0.774 | completed wk 120 | 0.0022 | 0.054 | T16 |
| CI isolated CNS | DI HDMTX | 0.018 | completed wk 120 | 0.0448 | 0.12 | T16 |

Table S13. Correlation between mercaptopurine DI vs ANC by phase. All correlations were positive (higher DI predicted higher ANC). Total of 20 comparisons, 10 (phases) x 2(protocols), thus Bonferroni significance threshold=0.003.

| Phase | Risk | T15 Estimate | T15 P Value | T16 Estimate | T16 P Value |
|---|---|---|---|---|---|
| Induction | Low | 0.137 | 0.061 | 0.107 | 0.63 |
| Consolidation | Low | 0.364 | 7.8E-07 | 0.447 | <0.0001 |
| Continuation Wks 1-6 | Low | 0.390 | 6.4E-07 | 0.377 | <0.0001 |
| Continuation Wks 10-16 | Low | 0.331 | 1.8E-05 | 0.319 | <0.0001 |
| Continuation Wks 20-120 | Low | 0.341 | 1.3E-15 | 0.249 | <0.0001 |
| Induction | Standard | 0.148 | 0.054 | 0.189 | 0.36 |
| Consolidation | Standard | 0.406 | 1.1E-07 | 0.379 | <0.0001 |
| Continuation Wks 1-6 | Standard | 0.473 | 4.2E-09 | 0.274 | <0.0001 |
| Continuation Wks 10-16 | Standard | 0.400 | 9.8E-07 | 0.326 | <0.0001 |
| Continuation Wks 20-120 | Standard | 0.406 | 3.5E-19 | 0.147 | <0.0001 |

Estimate = correlation coefficient; p value from Spearman's correlation test.

Figure S1. Overall schema of therapy on Total 15 (T15) and Total 16 (T16). DAUNO = daunorubicin; DOXO = doxorubicin; CYCLO = cyclophosphamide; ARA-C = cytarabine; VCR = vincristine; DEX = dexamethasone; MTX = methotrexate; MP = mercaptopurine; PRED = prednisone; L-ASP = native E.Coli asparaginase (Elspar); TG = thioguanine; PEG-ASP = pegylated E.Coli asparaginase (Oncaspar). Widths of bars reflect duration of therapy; heights of bars reflect dosage.

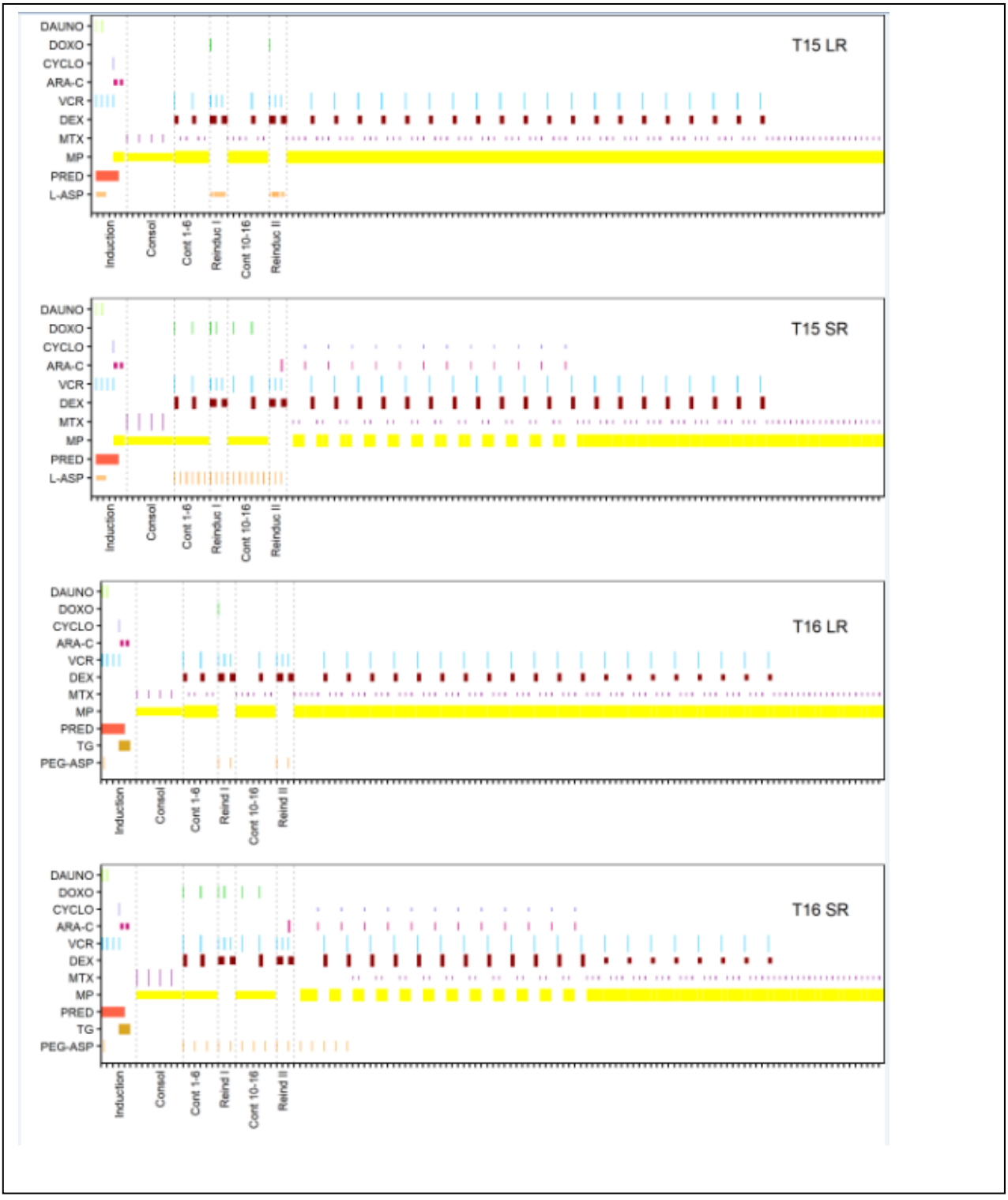


Figure S2. Consort diagrams indicating number of patients and reasons for exclusion from dose intensity (DI) analysis for Total 15 (T15) and Total 16 (T16) clinical trials.

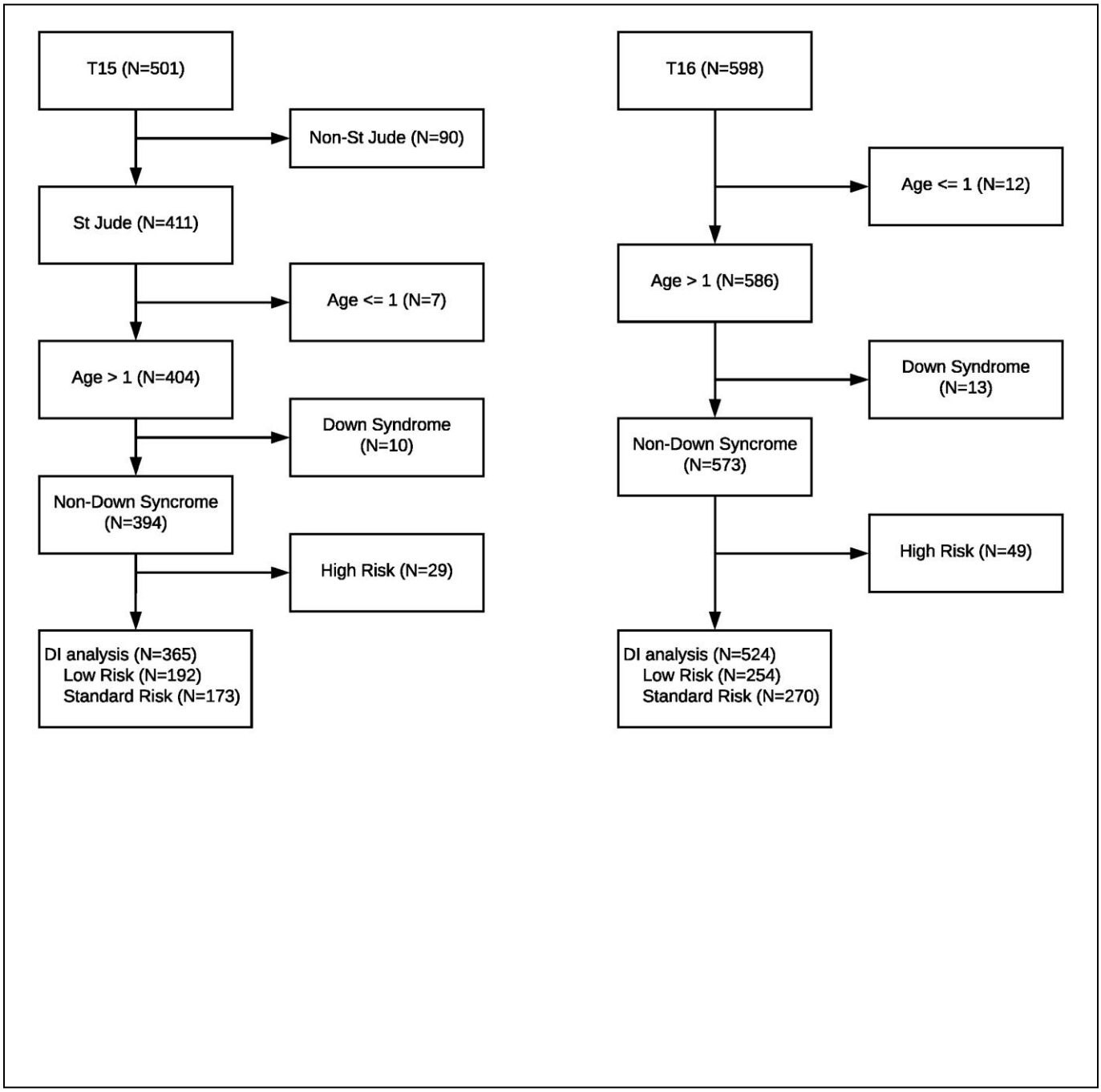
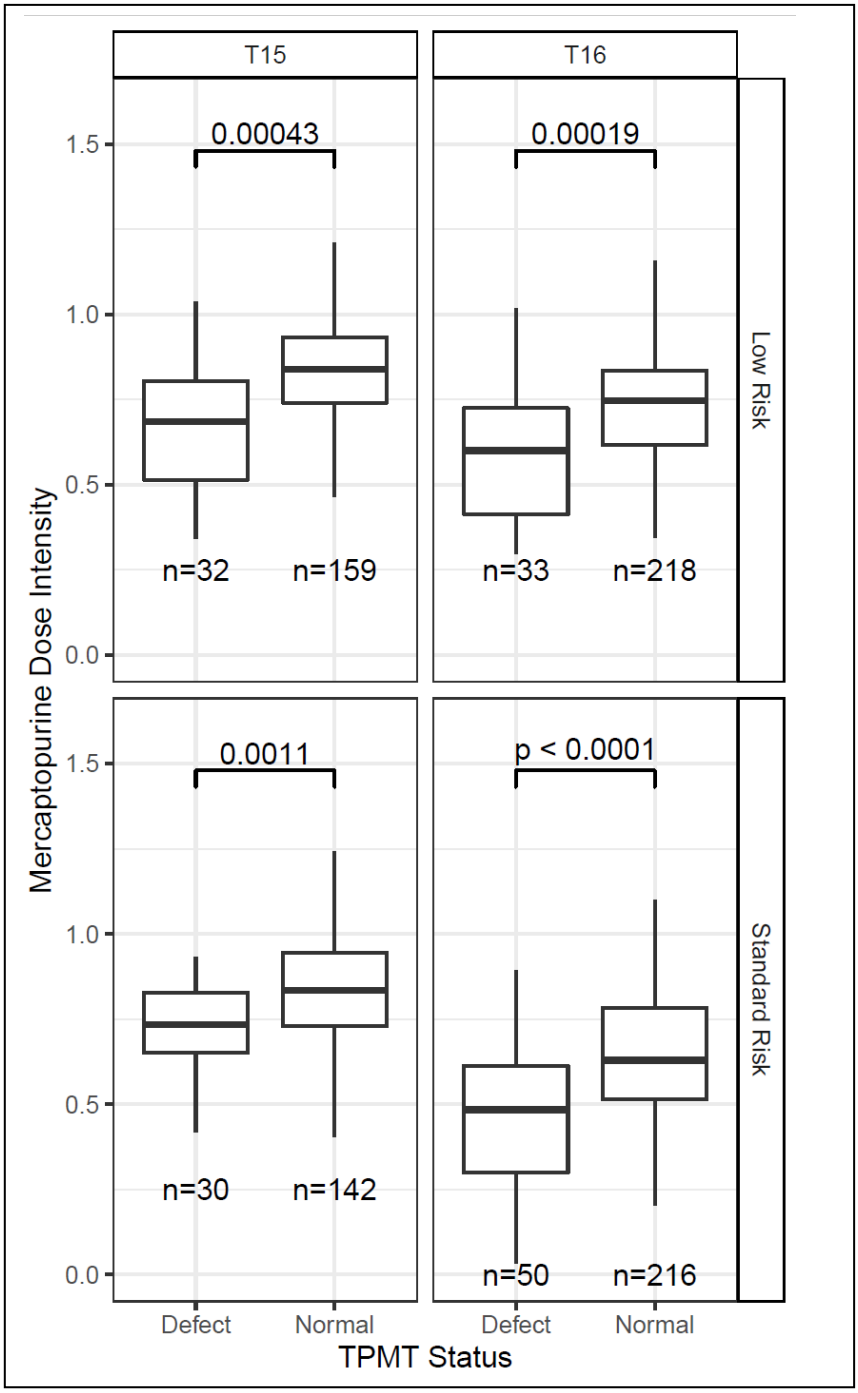
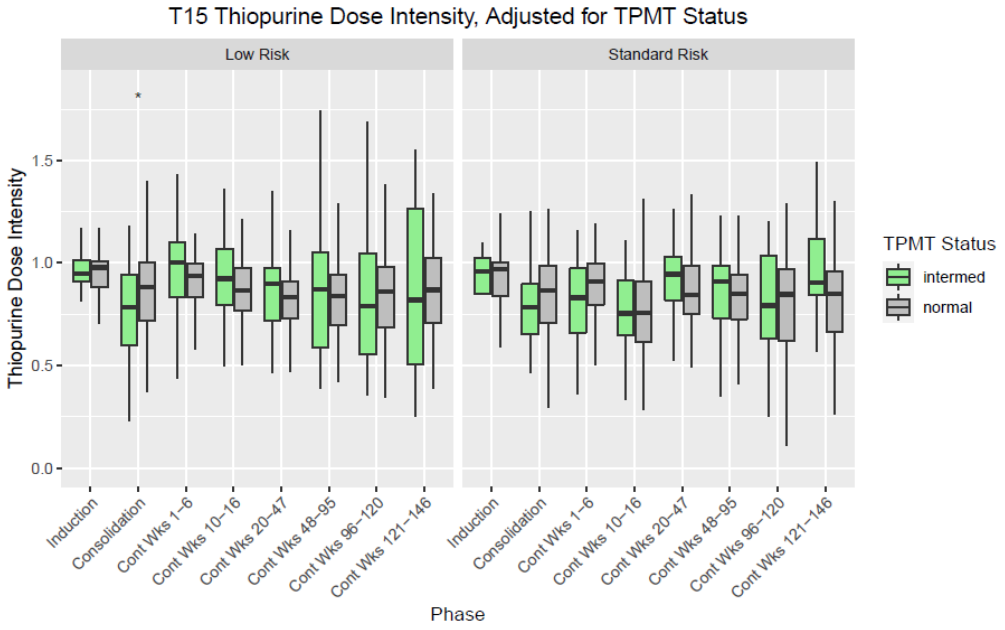
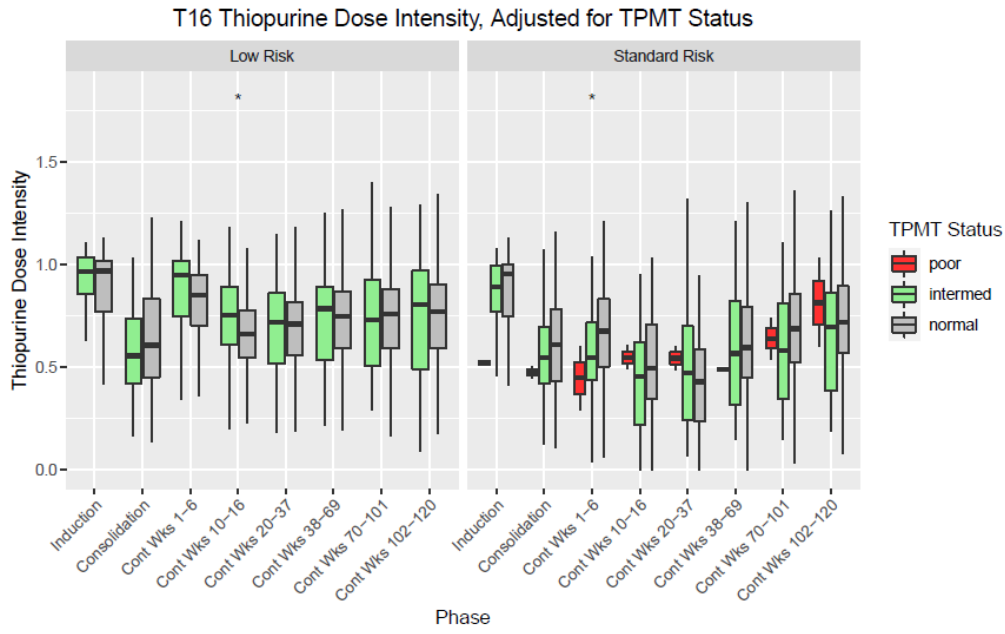


Figure S3. Cumulative dose intensity (DI) for entire course of therapy for mercaptopurine by TPMT status. Defect = those patients classified as intermediate or poor metabolizers for TPMT; normal = patients classified as normal metabolizers for TPMT. Boxes represent quartiles; whiskers represent nonoutlier ranges. Nominal P values from Wilcoxon rank sum test. Total of 4 comparisons, thus corrected significance threshold=0.01.

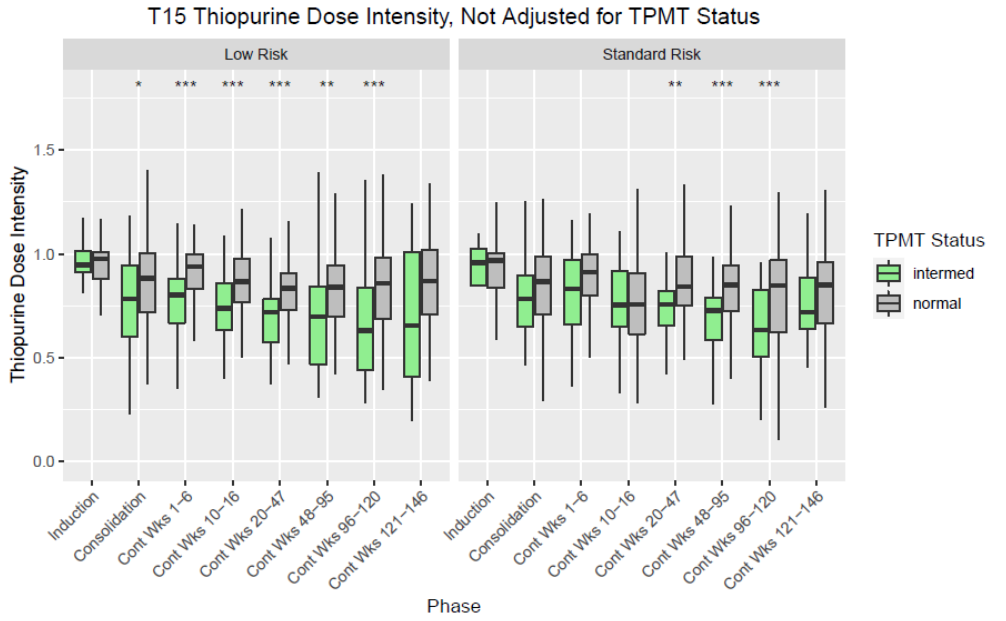


Supplemental Figure S4. Mercaptopurine dose intensity (DI) by phase and by TPMT status, using a denominator that was tailored based on TPMT status for expected mercaptopurine dosages; T15 upper graph and T16 lower graph. Boxes depict quartiles; depicted are nonoutlier ranges. Significant differences by TPMT status are indicated by *, **, and *** (nominal p values < 0.05, 0.01 and 0.001, respectively) Total of 32 comparisons, thus Bonferroni significance threshold=0.002.



Supplemental Figure S5. Mercaptopurine dose intensity (DI) by phase and by TPMT status, using a common denominator for expected mercaptopurine dosages, regardless of TPMT status; T15 upper graph, T16 lower graph. Boxes depict quartiles; depicted are nonoutlier ranges. Significant differences by TPMT status are indicated by *, **, and *** (nominal p values < 0.05, 0.01 and 0.001, respectively) Total of 32 comparisons test. Bonferroni significance threshold=0.002.



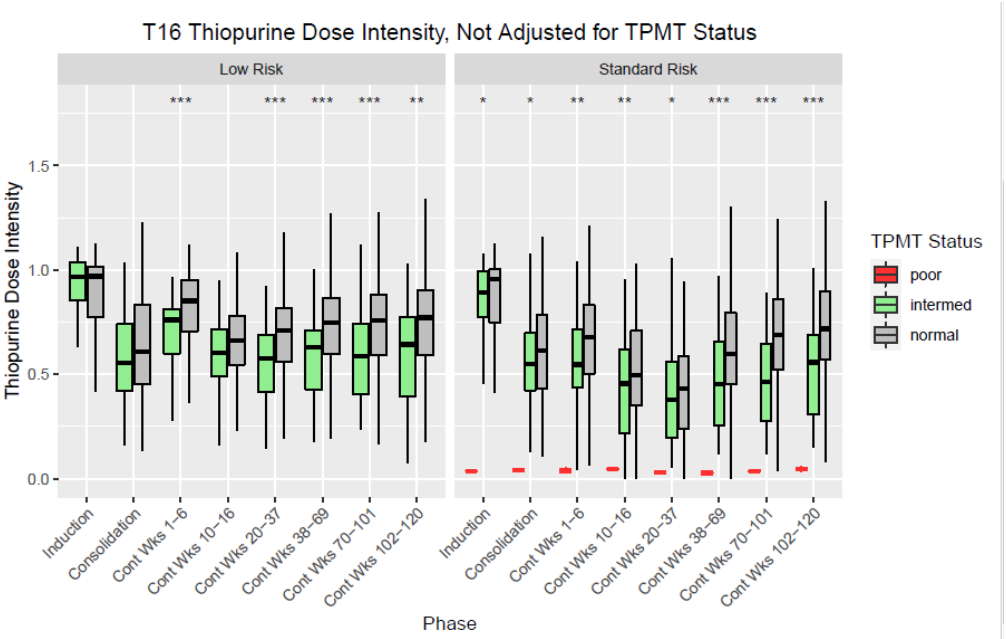
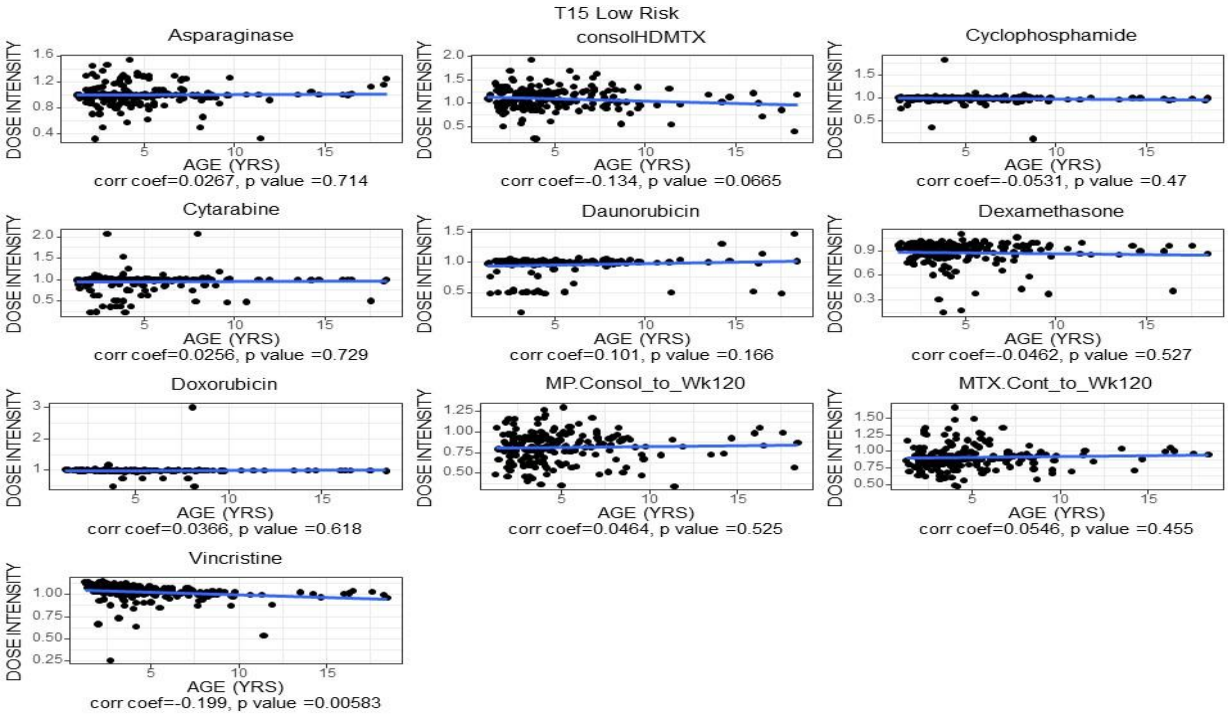
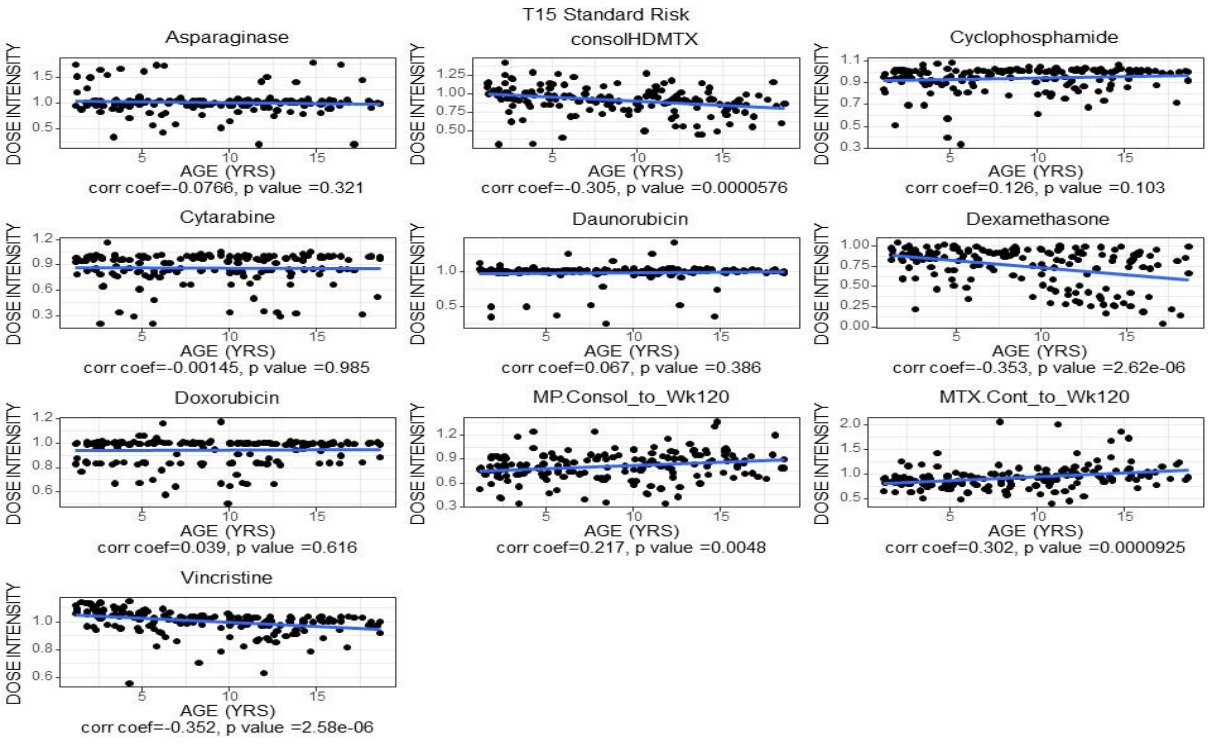
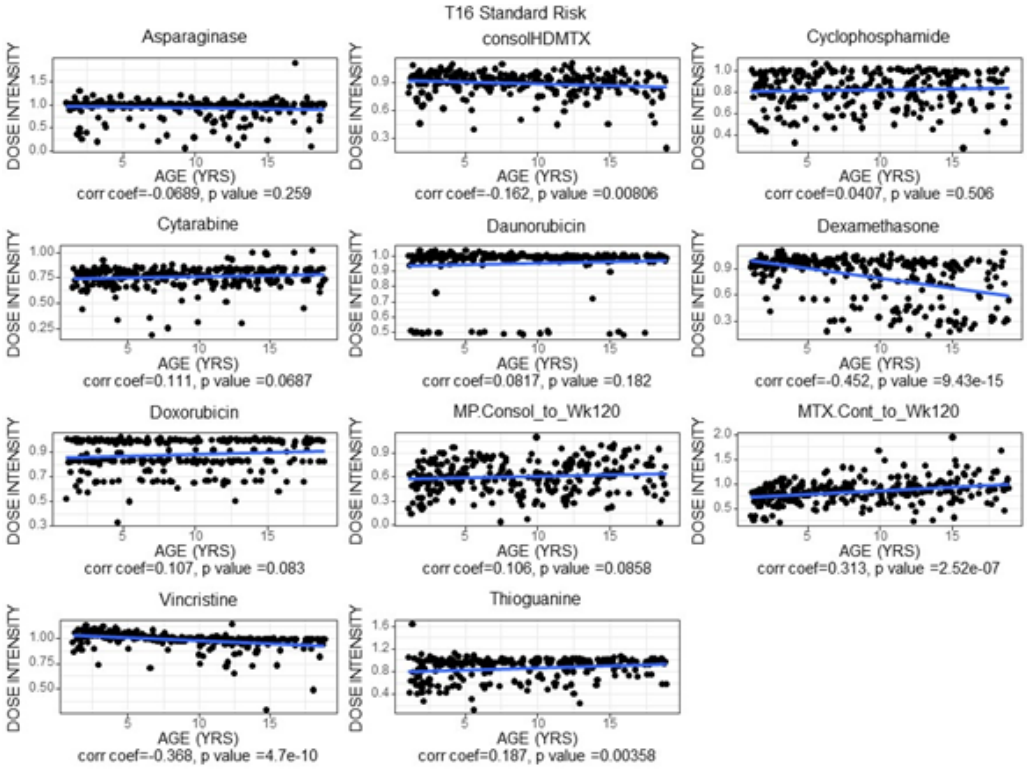



Figure S6. Cumulative dose intensity (DI) for each drug by age. Includes nonoutlier data, where every dot represents a patient. Correlation coefficients and P values were calculated using Pearson's correlation. A total of 40 comparisons, thus Bonferroni significance threshold=0.001.




T16 Standard Risk
Asparaginase
DOSE INTENSITY
AGE (YRS)
corr coef=-0.0689, p value =0.259
consolHDMTX
corr coef=-0.162, p value =0.00806
Cyclophosphamide
corr coef=0.0407, p value =0.506
Cytarabine
corr coef=0.111, p value =0.0687
Daunorubicin
corr coef=0.0817, p value =0.182
Dexamethasone
corr coef=-0.452, p value =9.43e-15
Doxorubicin
corr coef=0.107, p value =0.083
MP.Consol_to_Wk120
corr coef=0.106, p value =0.0858
MTX.Cont_to_Wk120
corr coef=0.313, p value =2.52e-07
Vincristine
corr coef=-0.368, p value =4.7e-10
Thioguanine
corr coef=0.187, p value =0.00358

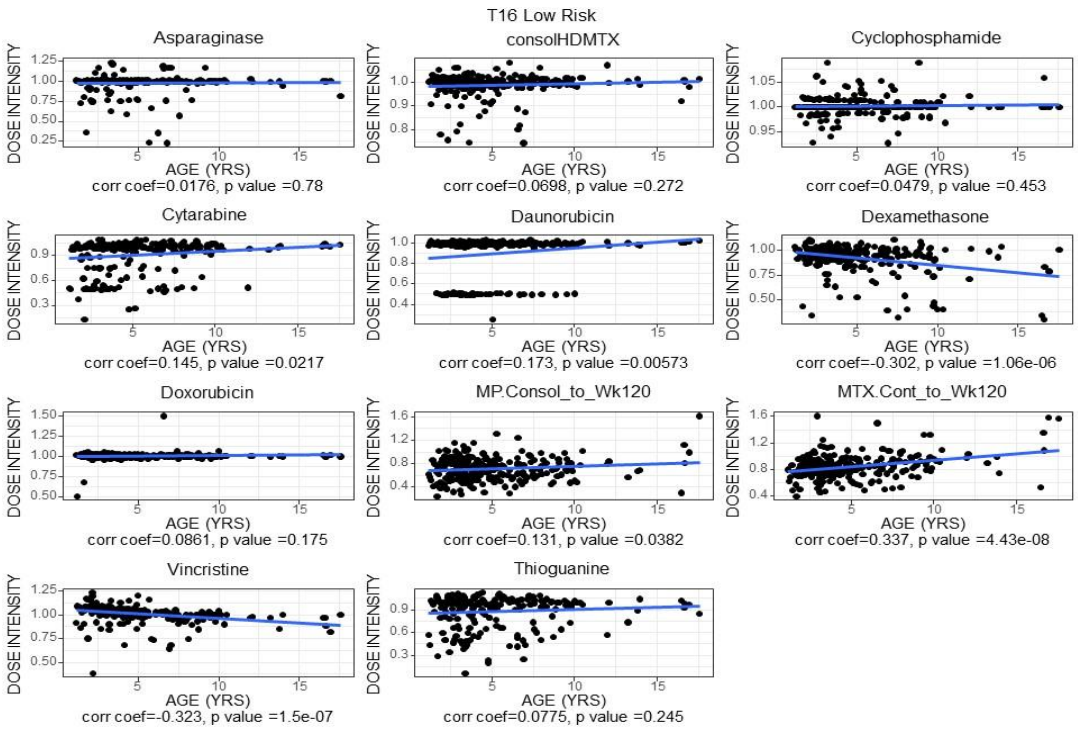

T16 Low Risk
Asparaginase
DOSE INTENSITY
AGE (YRS)
corr coef=0.0176, p value =0.78
consolHDMTX
corr coef=0.0698, p value =0.272
Cyclophosphamide
corr coef=0.0479, p value =0.453
Cytarabine
corr coef=0.145, p value =0.0217
Daunorubicin
corr coef=0.173, p value =0.00573
Dexamethasone
corr coef=-0.302, p value =1.06e-06
Doxorubicin
corr coef=0.0861, p value =0.175
MP.Consol_to_Wk120
corr coef=0.131, p value =0.0382
MTX.Cont_to_Wk120
corr coef=0.337, p value =4.43e-08
Vincristine
corr coef=-0.323, p value =1.5e-07
Thioguanine
corr coef=0.0775, p value =0.245

Figure S7. Cumulative incidence of any relapse in those who completed 120 weeks of therapy based on tertiles for dose intensity (DI) for mercaptopurine (red = highest tertile for DI, blue = middle tertile for DI, green = lowest tertile for DI. For T15 (upper graph), DI is for mercaptopurine during weeks 10-16; for T16 (lower graph), DI is for weeks 38-69. P values adjusted for risk group but not for multiple comparisons.

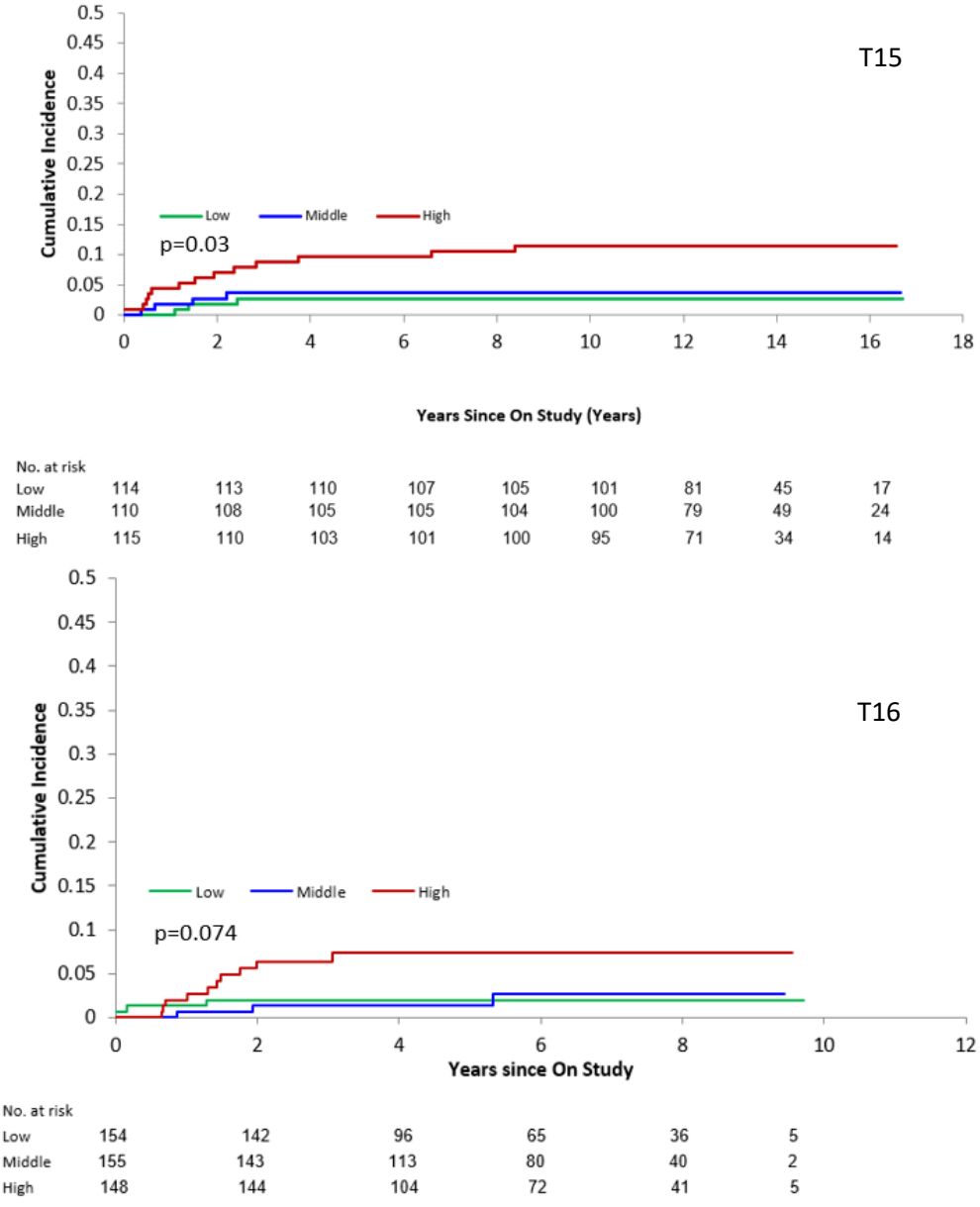
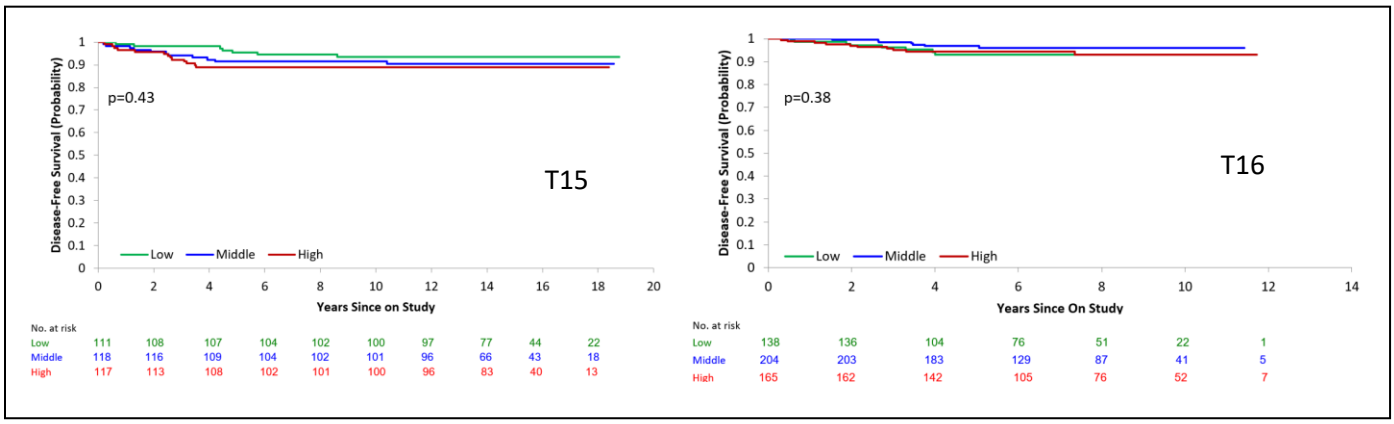
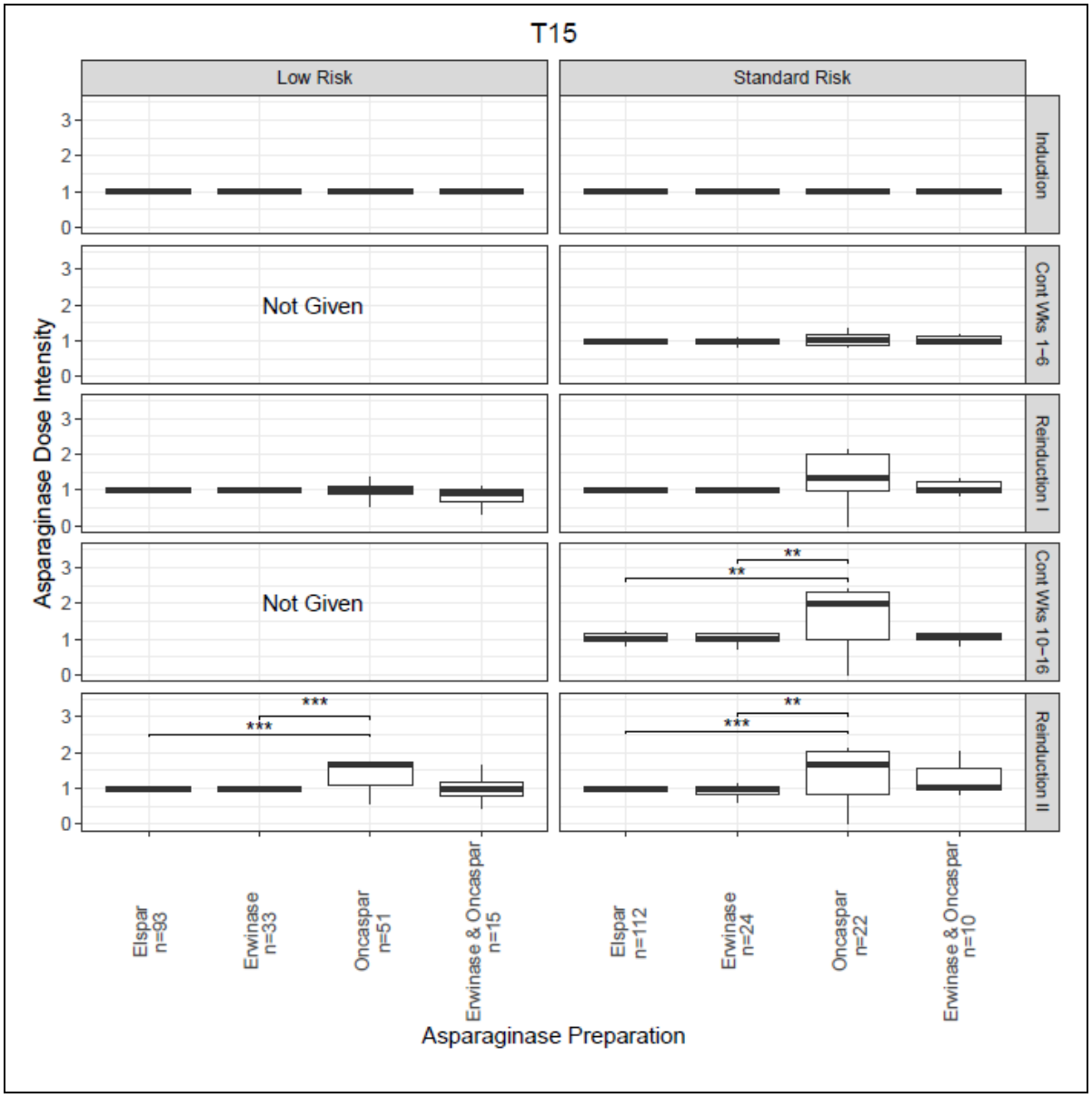
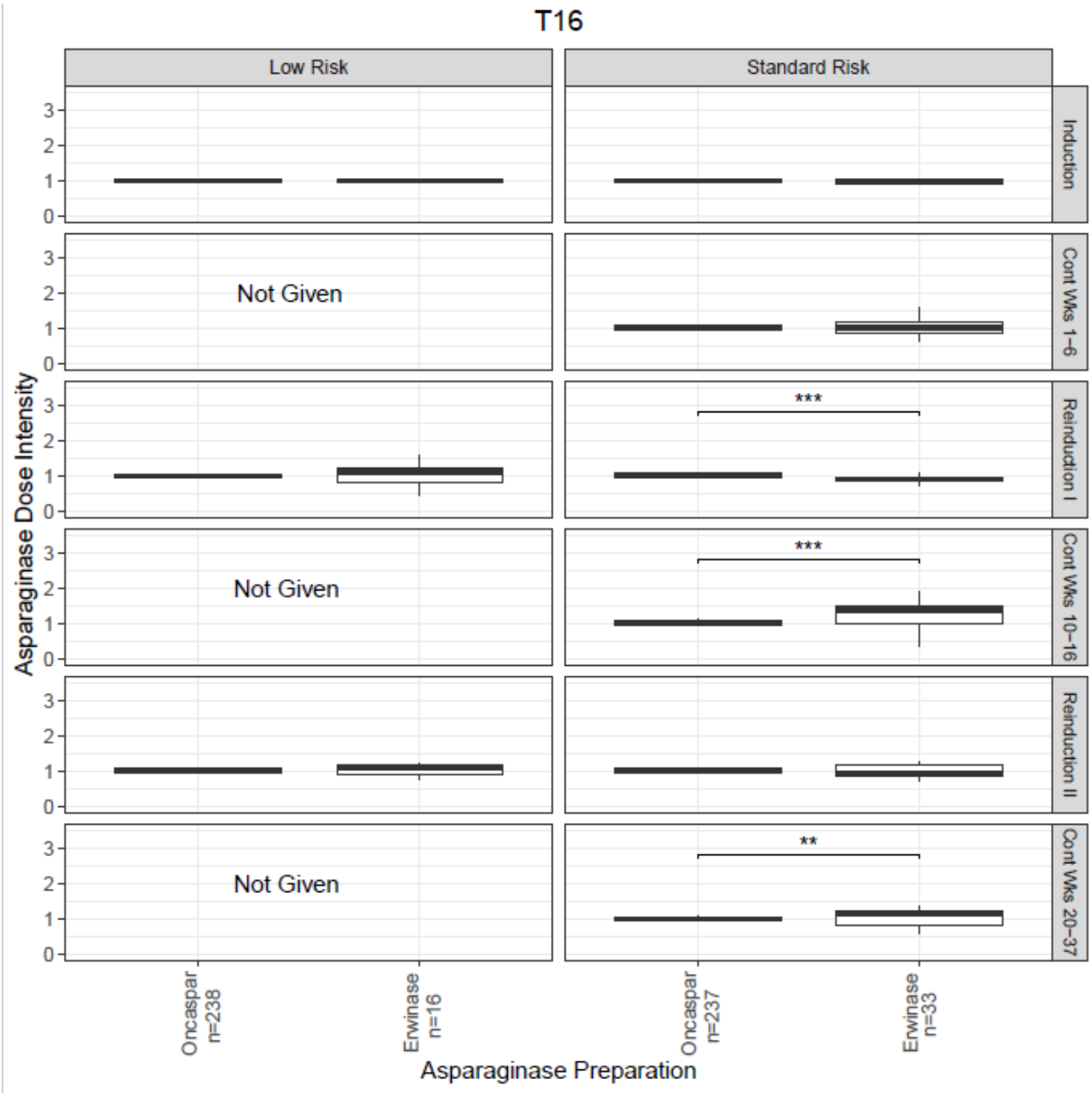


Figure S8. Disease-free survival from end of reinduction II based on cumulative asparaginase dose intensity (DI) including all phases tertile groups. P values adjust for risk arm but not for multiple comparisons (red = highest, blue = middle, green = lowest tertile for asparaginase DI.

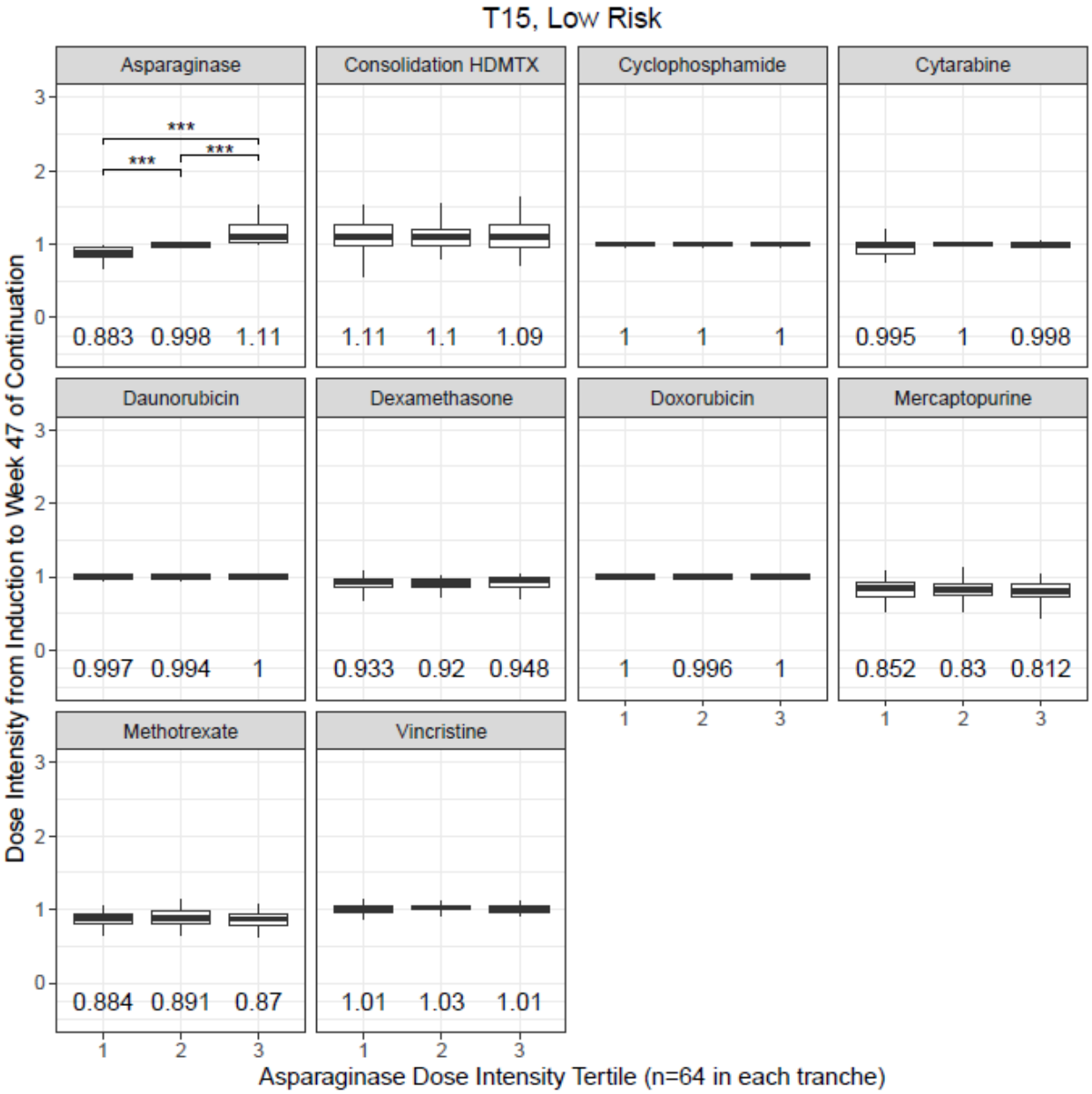


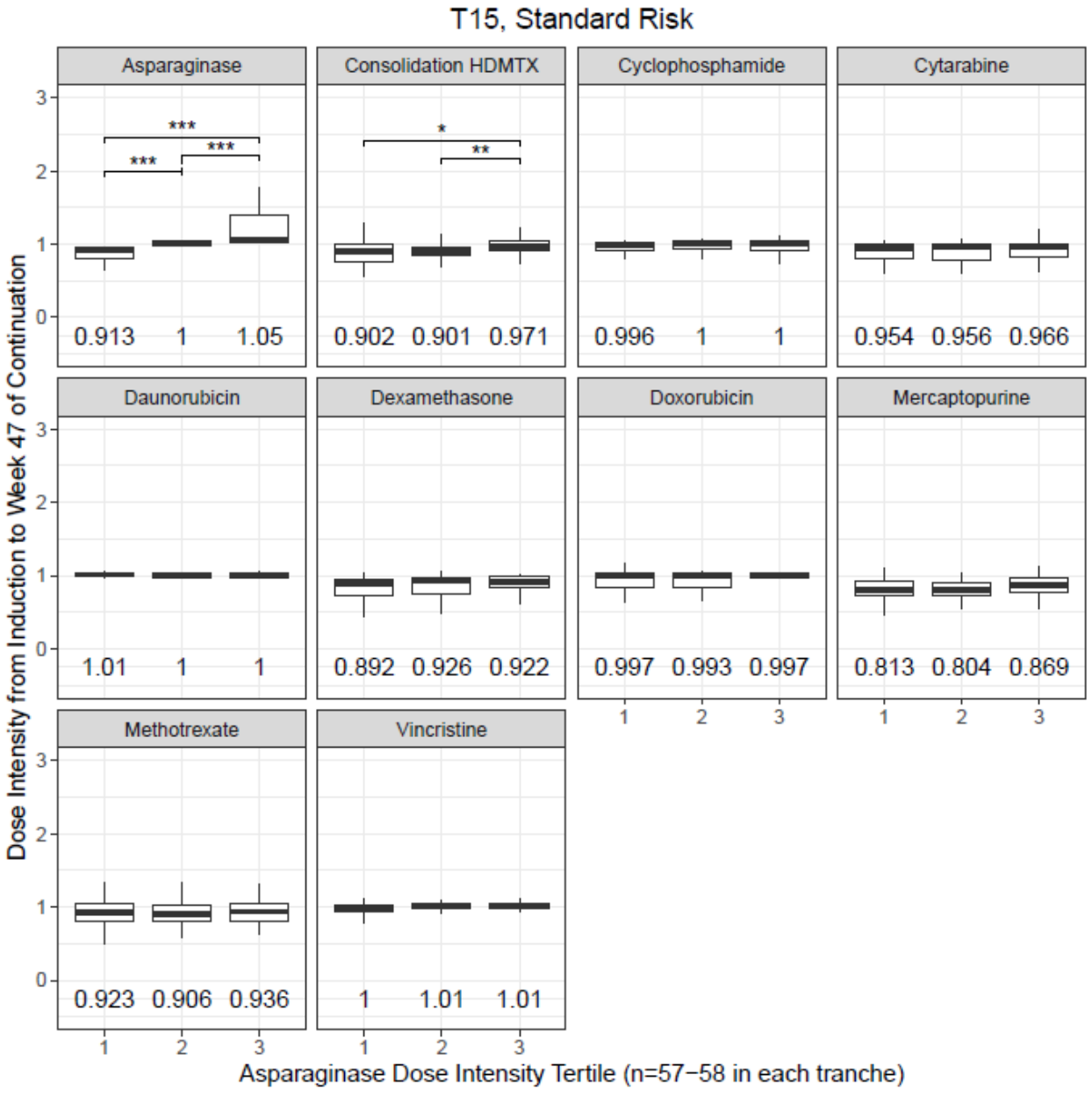
Supplemental Figure S9: Asparaginase dose intensity (DI) (quartiles and nonoutlier ranges) was largely maintained or even increased upon formulation switching for both T15 and T16; *, **, and *** denotes differences between groups of with p values < 0.05, 0.01 and 0.001, respectively. For T15, patients are divided into those who never had allergy (Elspar), and those who had allergy but whose only substituted product was Erwinase , whose only substituted product was Oncaspar (depending on drug availability), and those who received a combination of Oncaspar and Erwinase (depending on drug availability). For T16, patients are divided into those who were never switched from Oncaspar versus those who had allergy to Oncaspar and were switched to Erwinase; the former group includes 34 patients who had a reaction to Oncaspar but were not switched (usually because they were almost done with therapy). A total of 54 comparisons, thus Bonferroni significance threshold = 0.0009.

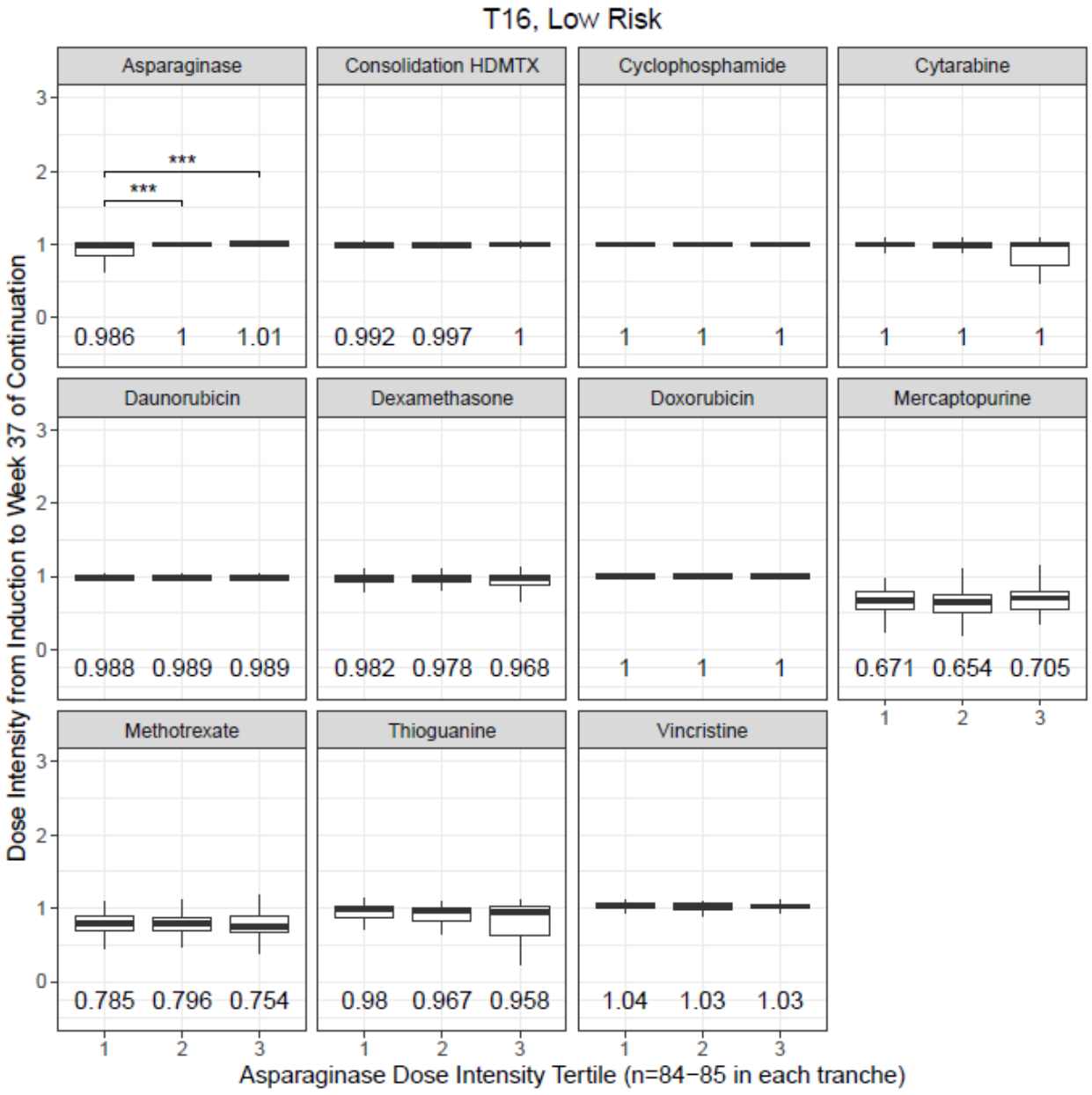


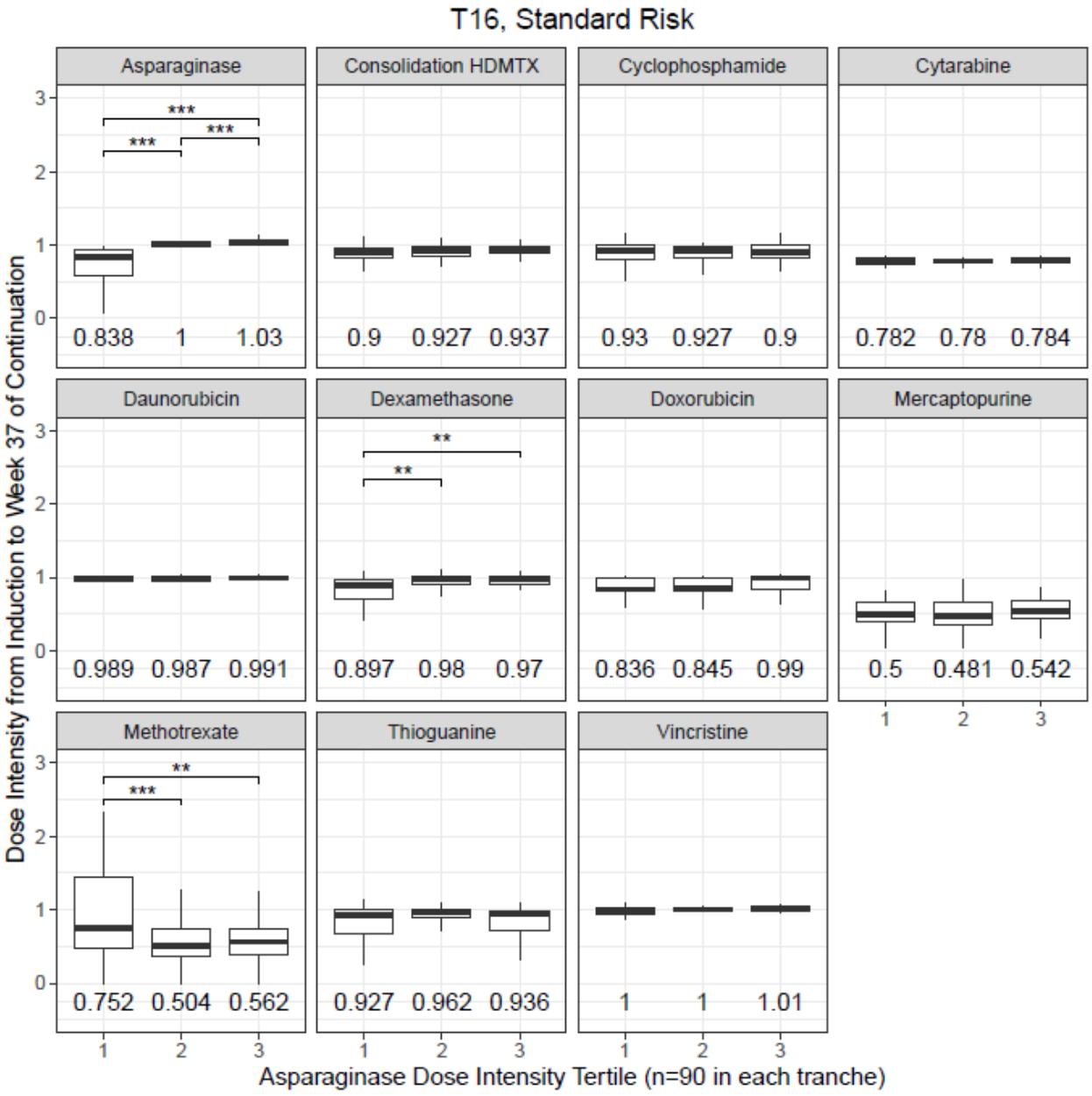

T16
Low Risk
Standard Risk
Induction
Cont Wks 1–6
Reinduction I
Cont Wks 10–16
Reinduction II
Cont Wks 20–37
Not Given
Not Given
Not Given
***
***
**
Asparaginase Dose Intensity
0
1
2
3
Oncaspar n=238
Erwinase n=16
Oncaspar n=237
Erwinase n=33
Asparaginase Preparation

Supplementary Figure S10: Cumulative drug dose intensity (DI) (quartiles, nonoutlier ranges) based on asparaginase DI tertile for T15 and T16, LR and SR arms. Patients were divided into 3 groups based on their asparaginase DI (lowest, medium, highest tertile with respect to asparaginase DI), to explore whether dosages of other drugs were affected by asparaginase DI. The numbers inside the panels indicate the median values. Significant differences by tertile are indicated by *, **, and *** (p values < 0.05, 0.01 and 0.001, respectively, using the Wilcoxon rank sum test). A total of 10 (drugs)x4(protocol/riskArms)x3=120 comparisons. Bonferroni significance threshold=0.0004.




T15, Standard Risk
Asparaginase
Consolidation HDMTX
Cyclophosphamide
Cytarabine
Daunorubicin
Dexamethasone
Doxorubicin
Mercaptopurine
Methotrexate
Vincristine
Dose Intensity from Induction to Week 47 of Continuation
Asparaginase Dose Intensity Tertile (n=57−58 in each tranche)
0.913 1 1.05
0.902 0.901 0.971
0.996 1 1
0.954 0.956 0.966
1.01 1 1
0.892 0.926 0.922
0.997 0.993 0.997
0.813 0.804 0.869
0.923 0.906 0.936
1 1.01 1.01


T16, Low Risk
Asparaginase
Consolidation HDMTX
Cyclophosphamide
Cytarabine
Daunorubicin
Dexamethasone
Doxorubicin
Mercaptopurine
Methotrexate
Thioguanine
Vincristine
***
***
0.986 1 1.01
0.992 0.997 1
1 1 1
1 1 1
0.988 0.989 0.989
0.982 0.978 0.968
1 1 1
0.671 0.654 0.705
0.785 0.796 0.754
0.98 0.967 0.958
1.04 1.03 1.03
Dose Intensity from Induction to Week 37 of Continuation
Asparaginase Dose Intensity Tertile (n=84−85 in each tranche)


T16, Standard Risk
Asparaginase
Consolidation HDMTX
Cyclophosphamide
Cytarabine
Daunorubicin
Dexamethasone
Doxorubicin
Mercaptopurine
Methotrexate
Thioguanine
Vincristine
Dose Intensity from Induction to Week 37 of Continuation
Asparaginase Dose Intensity Tertile (n=90 in each tranche)
0.838 1 1.03
0.9 0.927 0.937
0.93 0.927 0.9
0.782 0.78 0.784
0.989 0.987 0.991
0.897 0.98 0.97
0.836 0.845 0.99
0.5 0.481 0.542
0.752 0.504 0.562
0.927 0.962 0.936
1 1 1.01

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