Primary plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling, and clinical outcome with Total Therapy protocols

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Abstract

To determine whether primary plasma cell leukemia (PPCL) remains a high-risk multiple myeloma feature in the context of contemporary therapy and gene expression profiling (GEP), we reviewed records of 1474 patients with myeloma who were enrolled in Total Therapy protocols or treated identically off protocol. 27 patients (1.8%) were classified as having PPCL. As a group, these patients more often had low hemoglobin, high beta-2-microglobulin, high lactate dehydrogenase, low albumin, and cytogenetic abnormalities. Among 866 patients with GEP results, the PPCL group more often had disease that was classified as high risk, and in CD-1 and MF molecular subgroups. Regardless of the therapeutic protocol, patients with PPCL had shorter median overall survival (1.8 years), progression-free survival (0.8 years), and complete response duration (1.3 years) than the remainder whose clinical outcomes had improved markedly with successive protocols. Multivariate analyses of pretreatment parameters showed that PPCL was a highly significant independent adverse feature linked to overall survival, progression-free survival, and complete response duration. In GEP analyses, 203 gene probes distinguished PPCL from non-PPCL; the identified genes were involved the LXR/RXR activation, inositol metabolism, hepatic fibrosis/hepatic stellate-cell activation, and LPS/IL-1-mediated inhibition of RXR function pathways. Different treatment approaches building on these genomic differences may improve the grave outcome of patients with PPCL.

Keywords
plasma cell leukemia; myeloma; total therapy; prognosis; gene expression profiling
Introduction

Plasma cell leukemia is a rare manifestation of symptomatic multiple myeloma (MM), either presenting as primary plasma cell leukemia (PPCL) in the newly diagnosed setting, or as secondary plasma cell leukemia (SPCL) in the relapsed MM setting\(^1\). The definition of PCL is arbitrary and based on one of the following criteria: ≥2,000 circulating plasma cells/μl with >10,000 leukocytes/μl or ≥20% plasma cells with <10,000 leukocytes/μl\(^2\). However, circulating plasma cells can be documented in most patients with untreated MM, and the level of these circulating plasma cells has independent prognostic implications\(^3\). Most studies have shown that PPCL has a dismal prognosis with median survival durations on the order of 6 months\(^4\).

Here, we report the clinical outcomes of patients with PPCL treated with Total Therapy (TT) 1, TT2, and TT3 protocols or in a TT3-like fashion, and we contrast their baseline characteristics and clinical outcomes with non-PPCL patients with MM who were also treated on these protocols\(^5\)–\(^8\). We also used gene expression profiling (GEP) data to examine whether there were genomic features that distinguished PPCL from non-PPCL presentations.

Subjects and methods

Therapeutic schemata of TT trials

Details of TT\(^1\), TT\(^2\), and TT\(^3\)\(^7\)\(^\,\)\(^8\) have been published previously and are briefly described here. TT1 accrued 231 patients and applied VAD (vincristine, doxorubicin, dexamethasone) induction, followed by high-dose cyclophosphamide-based hematopoietic progenitor cell mobilization and EDAP (etoposide, dexamethasone, cytarabine, cisplatin); after tandem transplant with melphalan 200 mg/m\(^2\), interferon maintenance was applied indefinitely. TT2 enrolled 668 patients who were randomized between a control arm and a thalidomide arm. After one cycle of VAD, patients received filgrastim-supported DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin), CAD (cyclophosphamide, doxorubicin, dexamethasone) for hematopoietic progenitor cell collection, and another cycle of DCEP. After tandem melphalan-based transplants, patients received one year of consolidation therapy of DCEP alternating with CAD and, later, with D-PACE (dexamethasone, cisplatin, doxorubicin, etoposide). This was followed by interferon maintenance with high-dose dexamethasone pulsing, limited to the first year of maintenance. TT3 was administered in two successive protocols, TT3A and TT3B\(^8\). TT3A, which enrolled 303 patients, was a phase II trial that added bortezomib to two cycles each of DT (thalidomide)-PACE for induction before and consolidation after tandem transplants; this was followed by maintenance with TD for 3 years, to which bortezomib was added (VTD) in the first year only\(^7\). TT3B enrolled an additional 177 patients to validate the bortezomib pharmacogenomic data generated in TT3A. The two trials were the same except that TT3B used VRD (bortezomib, lenalidomide, dexamethasone) for all 3 years of maintenance therapy\(^8\). Another 94 patients, who had been denied insurance approval for participation in the TT3A trial, were treated off-protocol in a “TT3-like” fashion. Institutional Review Board approval was obtained to gather data from these patients. Prior to protocol enrollment,
patients signed a written informed consent, which was approved by the Institutional Review Board, in keeping with federal and Helsinki Declaration guidelines.

**Patient selection**

We interrogated our TT1, TT2, and TT3 databases for patients who met the criteria for PPCL\(^2\). Among 1 474 subjects in the databases, 27 patients (1.8\%) fulfilled PPCL criteria, of whom 7 were treated with TT1, 12 with TT2, and 8 with TT3.

**Gene expression profiling for PPCL and SPCL**

To discover features of gene expression that may be unique to PPCL and SPCL, we performed unsupervised hierarchical cluster analyses of GEP comparing the following types of samples: (i) bone marrow aspirates of PPCL and non-PPCL; (ii) concomitant bone marrow and blood samples from PPCL; (iii) concomitant bone marrow and blood samples from SPCL; (iv) PPCL and SPCL bone marrow samples and human myeloma cell lines (MMCLs).

We identified within our database 32 patients who met the definition of PCL (13 PPCL, 19 SPCL) and who had GEP data from blood samples (Supplementary Table 1A), including those treated in TT clinical trials (7 PPCL, 4 SPCL), non-TT trials (0 PPCL, 4 SPCL), and off-protocol (6 PPCL, 11 SPCL). GEP data from baseline bone marrow samples was also available for 11 of the 13 PPCL cases and for 10 of the 19 SPCL cases. For the purposes of comparing GEP of bone marrow from patients with or without PPCL, we selected PPCL and non-PPCL patients who had GEP data from baseline bone marrow samples and were enrolled in TT2, TT3a, TT3b, TT4, and TT5 or were treated with a TT3-like regimen (Supplementary Table 1B).

**Procurement of plasma cells for GEP and GEP analyses**

Gene expression profiling was performed with the Affymetrix U133Plus2.0 microarray platform (Santa Clara, CA) using methods previously described\(^9\). Plasma cells were enriched by anti-CD138 immunomagnetic bead selection of mononuclear cell fractions of bone marrow aspirates and peripheral blood samples in a central laboratory. All samples applied to microarray contained more than 85\% plasma cells as determined by 2-color flow cytometry (CD38\(^+\) and CD45\(^-/dim\)) performed after selection. To maintain consistency and ensure faithful assessment of the MM transcriptome, we eliminated samples with high degree of contamination of either myeloid cells or normal plasma cells as assessed by gene expression signatures.

**Response evaluation and analysis**

Patient work-up was standardized, as reported previously\(^7\). To define onset and frequency of complete response (CR), in keeping with European Group for Blood and Marrow Transplant\(^10\) and recently revised IMWG criteria\(^11\), we conducted serial serum and urine analyses for myeloma protein, along with bone marrow examinations. Imaging studies included magnetic resonance imaging (MRI) and, since 2003, positron emission tomography (PET). In cases of suspected PPCL, additional peripheral blood studies included...
multiparameter flow cytometry of DNA and cytoplasmic immunoglobulin, as well as phenotype analysis (CD138, CD16, CD45)\textsuperscript{12}.

Kaplan-Meier plots were used to portray overall survival (OS), progression-free survival (PFS), timing of CR onset, and CR duration (CRD)\textsuperscript{13}. For OS, events included death from any cause; for PFS and CRD, events included progression, relapse, or death from any cause. OS, PFS, and CR onset were measured from enrollment, while CRD was measured from CR onset.

**Results**

**Features linked to PPCL**

Baseline characteristics that distinguished patients with PPCL from patients without PPCL included higher frequencies of low albumin and hemoglobin; of elevated serum levels of beta-2-microglobulin (B2M), creatinine, and lactate dehydrogenase (LDH); of cytogenetic abnormalities (CA) overall and, specifically, of chromosome 13 deletion (CA-13) and hypodiploidy (CA-hypodiploidy) (Table 1). The remaining CA group ("other CA") was under-represented in the PPCL subset.

GEP was introduced in 2000, and data are available for 866 of all 1 474 patients in the protocols that were analyzed, including 16 of the 27 with PPCL. GEP-defined high-risk disease, defined by the 70-gene model (GEP-70)\textsuperscript{9}, was noted in 44% of patients with PPCL and 16% of those without PPCL ($P=0.008$). Similarly, GEP-defined high-risk disease, defined by the 80-gene model (GEP-80)\textsuperscript{14}, pertained to 31% of patients with PPCL and only 7% of non-PPCL patients ($P=0.005$). Among patients with PPCL, CD-1 and MF molecular subgroups were overrepresented and HY underrepresented\textsuperscript{15}. PET data, available at baseline for 724 patients, revealed a higher incidence of extramedullary disease (EMD) in the PPCL group than in the non-PPCL group (21% versus 6%; $P=0.05$). No differences in distribution were noted with regard to TT trial.

Logistic regression analysis was used to identify parameters associated with PPCL (Table 2). PPCL was linked to low albumin and hemoglobin levels; high B2M, LDH, and creatinine levels; and CA-13 and CA-hypodiploidy cytogenetic groups. Among GEP variables, GEP-70 and GEP-80 high-risk designation and CD1 and MF molecular subgroups were overrepresented in the PPCL group. B2M $\geq 5.5$ mg/L and CA were the only standard variables independently linked to PPCL among 1 408 patients. For the subset of 630 patients with added imaging and GEP data, CD-1 and MF subgroups, CA-13, and high B2M were independently linked to PPCL.

**Clinical outcomes**

Timing of onset and eventual rate of CR were virtually identical for patients with or without PPCL; however, for patients with PPCL, median OS (1.8 years), PFS (0.8 years), and CRD (1.3 years) (for all treatment groups combined) were inferior to those of the non-PPCL group as a whole (8.8 years, 5.4 years, 7.6 years, respectively) (Figure 1). Significant advances in clinical outcomes were observed among non-PPCL patients with the transitions...
from TT1 to TT2 to TT3, but such advances were not observed in PPCL patients (not shown due to small sample size).

We next examined the baseline variables linked to OS and PFS (Table 3). Among the 1394 patients for whom complete clinical data were available, multivariate modeling identified low albumin (<3.5 g/dL), high B2M (≥5.5 mg/L), high LDH (≥190 U/L), presence of CA-13, and PPCL as independently linked to inferior OS and PFS. CA-hypodiploidy and advanced age (≥65 years) were associated only with shorter OS. In the subset of 597 patients with GEP and imaging data, GEP-70 high-risk designation, GEP-defined TP53 deletion, high B2M, presence of any CA, presence of ≥3 PET-defined focal lesions, and PPCL were associated with shorter OS and PFS. In both multivariate models, the presence of thalidomide (TT2, TT3A, TT3B, TT3-like) was associated with improved OS and PFS; presence of bortezomib (TT3A, TT3B, TT3-like) was significantly associated only with improved OS. CRD was shorter with high B2M, CA, and PPCL; female gender and the presence of thalidomide and bortezomib were associated with extended CRD (Table 4). For the patients with added information on GEP and imaging data, GEP-70 high-risk designation and PPCL were adverse risk features, and the presence of bortezomib was linked to longer CRD.

Genomic analyses

The availability of GEP data from paired bone marrow and peripheral blood samples offered the opportunity to examine their relationships. Nine of 11 patients with PPCL, and 6 of 10 patients with SPCL clustered together (Figure 2). Human multiple myeloma cell lines (MMCLs), which are often derived from SPCL, constituted a cluster that was clearly separated from both PPCL and SPCL (Figure 3). PPCL may be a subentity of myeloma that is grows and proliferates independently of the bone marrow microenvironment, or PPCL may result from overcrowding of extensively involved bone marrow space with leakage into the peripheral blood. Unsupervised hierarchical clustering of bone marrow samples from PPCL and non-PPCL patients revealed that most PPCL samples represent a tight uniform cluster, suggesting that they are a separate molecular entity among myeloma samples. Interestingly, the PPCL were overrepresented in the MF and CD1 molecular subgroups (Figure 4). We next studied differential gene expression in bone marrow samples from PPCL patients compared with non-PPCL patients. There were 203 differentially expressed probes (false discovery rate [FDR] of 0.01) (Supplemental Table 3). A list of these probes, along with gene symbols, chromosomal locations, means, P-values, and q-values is provided in Supplementary Tables 2A and 2B. Ingenuity pathway analysis identify probe sets primarily involved with lipid metabolism pathways (Supplemental Figure 1, Supplementary Tables 4A–D).

Discussion

With the successive TT protocols from TT1 to TT3, advances in OS, PFS, and CRD were observed for non-PPCL patients but not for PPCL patients. Thus, although both groups of patients experienced similar timing of onset and frequency of CR, our results confirm the dismal prognosis associated with PPCL, which was retained after adjusting for GEP and...
imaging variables. Not surprisingly, EMD was overrepresented in the PPCL group and was linked to standard and GEP variables associated with high-risk disease, facilitating the bone marrow egress of malignant plasma cells. Vicinity of most blood and bone marrow samples (17 of 21) in PPCL and SPCL suggest that further gene alterations do not occur after myeloma cells have exited the bone marrow.

GEP results revealed a tight PPCL cluster within non-PPCL cases, which suggests that unique genomic features characterize the PPCL group, even though MF and CD-1 molecular subgroup designations were frequently seen among PPCL and non-PPCL cases. This was further supported by the underrepresentation of genes associated with high-risk disease among the genes that distinguished PPCL from non-PPCL. The PPCL-distinguishing genes belonged predominantly to the lipid-metabolism pathway, but the significance of these interesting findings has not yet been elucidated. Because normal plasma cells constitute a very minute fraction of circulating hematopoietic cells and largely confined to the bone marrow, we had expected PPCL cases to show preferential loss of stroma-homing receptors, but this was not observed. The lack of PPCL or SPCL cases among the MMCL cluster is interpreted as the latter having acquired further stroma-independence features. The cell-membrane LPS receptor CD14, the TNF receptor-associated factor 2 (TRAF2), and the chemokine C-C motif ligand 2 (CCL2), which are all normally expressed in monocytes and macrophages but not plasma cells, were also among the 203 genes that distinguished PPCL from non-PPCL. This raises the possibility that myeloid differentiation of myeloma cells allows for leukemic presentation.

The surprisingly dismal performance of patients with traditionally defined PPCL even with a Total Therapy approach strongly supports our current practice of including such patients in trials that target high-risk MM and for quantifying CD138-positive cells in all newly diagnosed patients. Due to the rarity of PPCL, we also advocate a national, if not international, effort toward researching the basis for its poor prognosis and advancing its therapy. In our program, patients presenting with PPCL are offered Total Therapy 5 (TT5), which emphasizes greater dose density and reduced dose intensity, resulting in shorter treatment-free intervals (required for recovery from toxicities) in an effort to guard against high-grade disease relapse.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**Conflict of Interest**

Dr. Shaughnessy is a founder of and has an ownership stake in Signal Genetics, LLC, a biotechnology company that has licensed technology from the University of Arkansas for purposes of commercial development. He holds patents, or has submitted patent applications, on the use of GEP in cancer medicine. Dr. Shaughnessy receives royalties related to patent licenses from Genzyme Novartis and Signal Genetics. He has received research funding from Celgene, Millennium, and Novartis. He has advised Celgene, Genzyme, Millennium, and Novartis and has received speaking honoraria from Celgene, ArrayBioPharma, Centocor Ortho Biotech, Genzyme, Millennium, and Novartis. Dr. Barlogie has received research funding from Celgene and
Novartis. He is a consultant to Celgene and Genzyme and has received speaking honoraria from Celgene and Millennium. Dr. Barlogie is a co-inventor on patents and patent applications related to use of GEP in cancer medicine. Dr. Usmani is a consultant to Celgene, Millennium, and Onyx. He has received research funding from Onyx and speaking honoraria from Celgene.

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Figure 1.
Clinical outcomes for PPCL and non-PPCL patients enrolled in TT1, TT2, or TT3. While clinical outcomes improved in non-PPCL patients with successive TT protocols (TT1, TT2, and TT3), PPCL patients as a group continued to have significantly inferior OS (A) and PFS (B), CRD* (C) and Cumulative Incidence of CR (D). Because of small sample size, PPCL outcomes are not shown according to TT protocol. *Note: Seven patients enrolled in TT1 that achieved CR after disease progression were excluded from CRD but were included in time-to-CR analyses. Blue, PPCL; red, TT1 non-PCL; green, TT2 non-PCL; yellow, TT3A/TT3B/TT3 like non-PCL.
Figure 2.
Unsupervised hierarchical clustering of GEP results (with 54,675 probes) from paired blood and bone marrow samples of PPCL (n=11) and SPCL (n=10) patients. Paired blood (pink text) and bone marrow (green text) samples from 15 of 21 patients (9 of 11 PPCL, 6 of 10 SPCL) clustered next to each other, as indicated by the red branches. Paired samples that did not cluster next to each other are indicated by symbols of same colors (e.g., solid blue circles to the left of blood and bone marrow samples of patient 30715). Analyses used. We also performed hierarchical clustering for PPCL and SPCL samples separately. In these separate analyses, 9 of 11 PPCL pairs and 7 of 10 SPCL pairs clustered next to each other (data not shown).
Figure 3.
Unsupervised hierarchical clustering of GEP results of bone marrow samples from non-PCL patients (n=1,018), blood samples from PPCL patients (n=13) and SPCL patients (n=19), and MMCL samples (n=15), applying 54,675 probes. The color bar indicates sample group (light gray, non-PCL; blue, PPCL; aqua, SPCL; red, MMCL).
Figure 4.
Unsupervised hierarchical clustering of baseline bone marrow samples from PPCL patients (n=20) and non-PPCL patients (n=1,096) for the 203 probe sets distinguishing PPCL and non-PPCL at the 0.01 level of FDR. Sample types are categorized by PPCL status (first color bar below the heatmap; blue, non-PPCL; red, PPCL) and patient molecular subgroup (second color bar below the heatmap; red, CD-1; blue, CD-2; green, HY; purple, LB; orange, MF; yellow, MS; brown, PR).
Table 1
Baseline characteristics for all patients enrolled in TT1, TT2, TT3A, or TT3B or receiving TT3-like regimen

| Factor                          | Overall     | Non-PCL     | PPCL        | P-value |
|---------------------------------|-------------|-------------|-------------|---------|
| Age ≥ 65 years                  | 312/1474 (21%) | 305/1447 (21%) | 7/27 (26%) | 0.541   |
| Female                          | 581/1474 (39%) | 571/1447 (39%) | 10/27 (37%) | 0.798   |
| White                           | 1293/1474 (88%) | 1267/1447 (88%) | 26/27 (96%) | 0.240   |
| Albumin <3.5 g/dL               | 367/1458 (25%) | 354/1431 (25%) | 13/27 (48%) | 0.005   |
| R2M ≥ 3.5 mg/L                  | 625/1453 (43%) | 602/1426 (42%) | 23/27 (85%) | <.001   |
| R2M ≥ 5.5 mg/L                  | 315/1453 (22%) | 298/1426 (21%) | 17/27 (63%) | <.001   |
| CRP ≥ 8 mg/L                    | 528/1440 (37%) | 518/1413 (37%) | 10/27 (37%) | 0.968   |
| Creatinine ≥ 2 mg/dL            | 133/1450 (9%) | 127/1424 (9%) | 6/26 (23%) | 0.026   |
| Hb < 10 g/dL                    | 424/1464 (29%) | 410/1437 (29%) | 14/27 (52%) | 0.008   |
| LDH ≥ 190 U/L                   | 401/1458 (28%) | 387/1431 (27%) | 14/27 (52%) | 0.004   |
| CA                              | 480/1448 (33%) | 458/1421 (32%) | 22/27 (81%) | <.001   |
| CA-hypodiploidy                 | 241/1448 (17%) | 228/1421 (16%) | 13/27 (48%) | <.001   |
| CA-13 or CA-hypodiploidy        | 186/1448 (13%) | 173/1421 (12%) | 13/27 (48%) | <.001   |
| Other CA                        | 1148/1448 (79%) | 1137/1421 (80%) | 11/27 (41%) | <.001   |
| GEP deTP53                      | 81/866 (9%) | 79/850 (9%) | 2/16 (13%) | 0.655   |
| GEP-70 high risk                | 140/866 (16%) | 133/850 (16%) | 7/16 (44%) | 0.008   |
| GEP-80 high risk                | 67/866 (8%) | 62/850 (7%) | 5/16 (31%) | 0.005   |
| GEP CD-1 subgroup               | 62/866 (7%) | 57/850 (7%) | 5/16 (31%) | 0.004   |
| GEP CD-2 subgroup               | 124/866 (14%) | 121/850 (14%) | 3/16 (19%) | 0.490   |
| GEP HY subgroup                 | 265/866 (31%) | 265/850 (31%) | 0/16 (0%) | 0.007   |
| GEP LB subgroup                 | 116/866 (13%) | 115/850 (14%) | 1/16 (6%) | 0.710   |
| GEP MF subgroup                 | 62/866 (7%) | 57/850 (7%) | 5/16 (31%) | 0.004   |
| GEP MS subgroup                 | 114/866 (13%) | 113/850 (13%) | 1/16 (6%) | 0.709   |
| GEP PR subgroup                 | 123/866 (14%) | 122/850 (14%) | 1/16 (6%) | 0.714   |
| Extramedullary disease (PET)    | 45/724 (6%) | 42/710 (6%) | 3/14 (21%) | 0.050   |
| Number of PET focal lesions ≥3  | 282/724 (39%) | 276/710 (39%) | 6/14 (43%) | 0.762   |
| Number of MRI focal lesions ≥7  | 422/1097 (38%) | 416/1079 (39%) | 6/18 (33%) | 0.652   |
| TT1                             | 231/1474 (16%) | 224/1447 (15%) | 7/27 (26%) | 0.175   |
| TT2 (both arms)                 | 668/1474 (45%) | 656/1447 (45%) | 12/27 (44%) | 0.927   |
| TT3 (TT3A, TT3B, TT3-like)      | 575/1474 (39%) | 567/1447 (39%) | 8/27 (30%) | 0.313   |

n/N (%): n, number with factor; N, number with valid data for factor

Bold text and values indicate statistical significance

* Fisher exact test, otherwise chi-square test
Table 2

Univariate and multivariate logistic regression analysis of variables linked to PPCL (all TT studies combined)

| Variable                                | N    | With factor | Without factor | OR (95% CI)  | P - value |
|-----------------------------------------|------|-------------|----------------|--------------|-----------|
| Age ≥ 65 years                          | 1474 | 7/312 (2%)  | 20/1162 (2%)   | 1.31 (0.55, 3.13) | 0.5420    |
| Female                                  | 1474 | 10/581 (2%) | 17/893 (2%)    | 0.90 (0.41, 1.98) | 0.7985    |
| Caucasian                               | 1474 | 26/1293 (2%)| 1/181 (1%)     | 3.69 (0.50, 27.39) | 0.2011    |
| Albumin < 3.5 g/dL                      | 1458 | 13/367 (4%) | 14/1091 (1%)   | 2.83 (1.32, 6.07)  | 0.0077    |
| B2M ≥ 3.5 mg/L                          | 1453 | 23/625 (4%) | 4/828 (0%)     | 7.87 (2.71, 22.87) | 0.0002    |
| B2M ≥ 5.5 mg/L                          | 1453 | 17/315 (5%) | 10/1138 (1%)   | 6.44 (2.92, 14.20) | <.0001    |
| CRP ≥ 8 mg/L                            | 1440 | 10/528 (2%) | 17/912 (2%)    | 1.02 (0.46, 2.24)  | 0.9678    |
| Creatinine ≥ 2 mg/dL                    | 1450 | 6/131 (5%)  | 20/1317 (2%)   | 3.06 (1.21, 7.77)  | 0.0183    |
| Hb < 10 g/dL                            | 1464 | 14/424 (3%) | 13/1040 (1%)   | 2.70 (1.26, 5.79)  | 0.0108    |
| LDH ≥ 190 U/L                           | 1458 | 14/401 (3%) | 13/1057 (1%)   | 2.91 (1.35, 6.24)  | 0.0062    |
| CA                                      | 1448 | 22/480 (5%) | 5/968 (1%)     | 9.25 (3.48, 24.59) | <.0001    |
| CA-13                                   | 1448 | 13/241 (5%) | 14/1207 (1%)   | 4.86 (2.25, 10.48) | <.0001    |
| CA-hypodiploidy                         | 1448 | 13/186 (7%) | 14/1262 (1%)   | 6.70 (3.10, 14.49) | <.0001    |
| CA-13 or CA-hypodiploidy               | 1448 | 16/300 (5%) | 11/1148 (1%)   | 5.82 (2.67, 12.69) | <.0001    |
| Other CA                                | 1448 | 11/1148 (1%)| 16/300 (5%)    | 0.17 (0.08, 0.37)  | <.0001    |
| GEP delTP5                              | 866  | 2/81 (2%)   | 14/785 (2%)    | 1.39 (0.31, 6.25)  | 0.6640    |
| GEP-70 high risk                        | 866  | 7/140 (5%)  | 97/262 (1%)    | 4.19 (1.54, 11.45) | 0.0052    |
| GEP-80 high risk                        | 866  | 5/67 (7%)   | 11/799 (1%)    | 5.78 (1.95, 17.15) | 0.0016    |
| GEP CD-1 subgroup                       | 866  | 5/62 (8%)   | 11/804 (1%)    | 6.32 (2.12, 18.83) | 0.0009    |
| GEP CD-2 subgroup                       | 866  | 3/124 (2%)  | 13/742 (2%)    | 1.39 (0.39, 4.95)  | 0.6111    |
| GEP LB subgroup                         | 866  | 1/116 (1%)  | 15/750 (2%)    | 0.43 (0.06, 3.26)  | 0.4111    |
| GEP MF subgroup                         | 866  | 5/62 (8%)   | 11/804 (1%)    | 6.32 (2.12, 18.83) | 0.0009    |
| GEP MS subgroup                         | 866  | 1/114 (1%)  | 15/752 (2%)    | 0.43 (0.06, 3.32)  | 0.4223    |
| GEP PR subgroup                         | 866  | 1/123 (1%)  | 15/743 (2%)    | 0.40 (0.05, 3.04)  | 0.3744    |
| PET EMD                                 | 724  | 3/45 (7%)   | 11/679 (2%)    | 4.34 (1.17, 16.15) | 0.0286    |
| PET focal lesions ≥ 3                   | 724  | 6/282 (2%)  | 8/442 (2%)     | 1.18 (0.40, 3.44)  | 0.7623    |
| MRI focal lesions ≥ 7                   | 1097 | 6/422 (1%)  | 12/675 (2%)    | 0.80 (0.30, 2.14)  | 0.6523    |
**Multivariate model excluding GEP, PET, MRI**

|                  | N   | With factor | Without factor | OR (95% CI) | P - value |
|------------------|-----|-------------|----------------|-------------|-----------|
| B2M ≥ 5.5 mg/L   | 1408| 17/304 (6%) | 9/1104 (1%)    | 5.11 (2.22, 11.77) | 0.0001    |
| CA               | 1408| 21/471 (4%) | 5/937 (1%)     | 6.40 (2.36, 17.37)  | 0.0003    |

**Multivariate model including GEP, PET, MRI**

|                  | N   | With factor | Without factor | OR (95% CI) | P - value |
|------------------|-----|-------------|----------------|-------------|-----------|
| B2M ≥ 5.5 mg/L   | 630 | 10/138 (7%) | 3/492 (1%)     | 8.54 (2.11, 34.57) | 0.0027    |
| CA-13            | 630 | 9/114 (8%)  | 4/516 (1%)     | 5.63 (1.53, 20.68) | 0.0092    |
| GEP CD-1 subgroup| 630 | 4/42 (10%)  | 9/588 (2%)     | 9.62 (2.06, 44.93) | 0.0040    |
| GEP MF subgroup  | 630 | 4/43 (9%)   | 9/587 (2%)     | 6.07 (1.41, 26.09) | 0.0152    |

HR, hazard ratio; 95% CI, 95% confidence interval; P-value from Wald chi-square test in Cox regression.

Bold text and values indicate statistical significance.

Multivariate model used stepwise selection with entry level 0.1, and variable remains if it meets the 0.05 level.

Multivariate P-value greater than 0.05 indicates variable forced into model with significant variables chosen with stepwise selection.

Note: Also looked at GEP only and Imaging only, however, no imaging vars entered MV model and GEP only MV (n=771) differed from the GEP + Imaging MV model (n=630) in that CA-13 enters instead of CA.
Table 3

Univariate and multivariate regression analysis of baseline parameters associated with OS and PFS (all TT studies combined)

| Univariate model | n/N (%) | OS from enrollment | P-value | PFS from enrollment | P-value |
|------------------|---------|--------------------|---------|---------------------|---------|
| Age ≥ 65 years   | 312/1474 (21%) | 1.44 (1.21, 1.72) | <.001   | 1.19 (1.01, 1.39) | 0.034   |
| Female           | 581/1474 (39%)  | 0.91 (0.79, 1.06) | 0.247   | 0.91 (0.80, 1.05) | 0.196   |
| Caucasian        | 1293/1474 (88%) | 1.01 (0.81, 1.26) | 0.949   | 1.06 (0.87, 1.30) | 0.552   |
| Albumin < 3.5 g/dL | 367/1458 (25%) | 1.49 (1.26, 1.75) | <.001   | 1.38 (1.19, 1.61) | <.001   |
| B2M ≥ 3.5 mg/L   | 625/1453 (43%)  | 1.70 (1.46, 1.97) | <.001   | 1.53 (1.34, 1.75) | <.001   |
| B2M ≥ 5.5 mg/L   | 315/1453 (22%)  | 2.02 (1.71, 2.38) | <.001   | 1.82 (1.56, 2.12) | <.001   |
| CRP ≥ 8 mg/L     | 528/1440 (37%)  | 1.37 (1.18, 1.59) | <.001   | 1.24 (1.08, 1.42) | 0.002   |
| Creatinine ≥ 2 mg/dL | 133/1450 (9%)   | 1.90 (1.52, 2.37) | <.001   | 1.79 (1.46, 2.20) | <.001   |
| Hb < 10 g/dL     | 424/1464 (29%)  | 1.51 (1.29, 1.76) | <.001   | 1.50 (1.30, 1.73) | <.001   |
| LDH ≥ 190 U/L    | 401/1458 (28%)  | 1.67 (1.43, 1.96) | <.001   | 1.53 (1.33, 1.77) | <.001   |
| CA               | 480/1448 (33%)  | 2.03 (1.75, 2.36) | <.001   | 1.67 (1.45, 1.92) | <.001   |
| CA-13            | 241/1448 (17%)  | 2.24 (1.87, 2.68) | <.001   | 1.76 (1.48, 2.08) | <.001   |
| CA-hypodiploidy  | 186/1448 (13%)  | 2.18 (1.79, 2.66) | <.001   | 1.80 (1.50, 2.16) | <.001   |
| CA-13 or CA-hypodiploidy | 300/1448 (21%) | 2.10 (1.78, 2.49) | <.001   | 1.70 (1.45, 1.99) | <.001   |
| Other CA         | 1148/1448 (79%) | 0.48 (0.40, 0.56) | <.001   | 0.59 (0.50, 0.69) | <.001   |
| GEP delTP53      | 81/866 (9%)     | 2.20 (1.62, 2.99) | <.001   | 1.64 (1.23, 2.20) | <.001   |
| GEP-70 high risk | 140/866 (16%)   | 3.96 (3.12, 5.04) | <.001   | 2.95 (2.36, 3.68) | <.001   |
| GEP-80 high risk | 67/866 (8%)     | 3.89 (2.84, 5.32) | <.001   | 2.85 (2.12, 3.83) | <.001   |
| GEP CD-1 subgroup | 62/866 (7%)   | 0.95 (0.62, 1.45) | 0.804   | 0.89 (0.62, 1.29) | 0.551   |
| GEP CD-2 subgroup | 124/866 (14%) | 0.80 (0.57, 1.12) | 0.188   | 0.95 (0.73, 1.25) | 0.724   |
| GEP HY subgroup  | 265/866 (31%)   | 0.66 (0.51, 0.85) | 0.001   | 0.76 (0.61, 0.93) | 0.009   |
| GEP LB subgroup  | 116/866 (13%)   | 0.66 (0.46, 0.94) | 0.021   | 0.66 (0.49, 0.89) | 0.006   |
| GEP MF subgroup  | 62/866 (7%)     | 1.54 (1.07, 2.24) | 0.022   | 1.57 (1.13, 2.17) | 0.007   |
| GEP MS subgroup  | 114/866 (13%)   | 1.27 (0.94, 1.72) | 0.122   | 1.21 (0.92, 1.58) | 0.175   |
| GEP PR subgroup  | 123/866 (14%)   | 2.08 (1.60, 2.72) | <.001   | 1.75 (1.37, 2.23) | <.001   |
| PET EMD          | 45/724 (6%)     | 2.17 (1.43, 3.28) | <.001   | 1.78 (1.21, 2.62) | 0.004   |
| PET focal lesions ≥3 | 282/724 (39%) | 1.69 (1.31, 2.18) | <.001   | 1.35 (1.09, 1.68) | 0.007   |
### Univariate model

|                         | n/N (%) | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------------------|---------|-------------|---------|-------------|---------|
| MRI focal lesions ≥7    | 422/1097 (38%) | 1.49 (1.24, 1.79) | <.001   | 1.34 (1.14, 1.57) | <.001   |
| PCL                     | 277/474 (2%) | 3.07 (2.02, 4.65) | <.001   | 4.64 (3.13, 6.87) | <.001   |
| TT1                     | 231/474 (16%) | 1.51 (1.27, 1.80) | <.001   | 1.95 (1.66, 2.28) | <.001   |
| Thalidomide (in TT2+thal, TT3A, TT3B, TT3-like) | 898/1474 (61%) | 0.70 (0.60, 0.81) | <.001   | 0.52 (0.45, 0.59) | <.001   |
| Bortezomib (in TT3A, TT3B, TT3-like) | 575/1474 (39%) | 0.76 (0.63, 0.90) | 0.002   | 0.54 (0.46, 0.63) | <.001   |
| Lenalidomide (in TT3B)  | 117/1474 (12%) | 0.85 (0.62, 1.15) | 0.292   | 0.63 (0.48, 0.83) | 0.001   |

### Multivariate Model Excluding GEP, PET, MRI

|                         | n/N (%) | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------------------|---------|-------------|---------|-------------|---------|
| Ages ≥65 yr             | 295/1394 (21%) | 1.28 (1.07, 1.54) | 0.008 | NS          | NS      |
| Albumin < 3.5 g/dL      | 354/1394 (25%) | 1.30 (1.09, 1.55) | 0.003 | 1.33 (1.13, 1.55) | <.001   |
| B2M ≥5.5 mg/L           | 302/1394 (22%) | 1.54 (1.28, 1.85) | <.001 | 1.56 (1.32, 1.84) | <.001   |
| LDH ≥190 U/L            | 387/1394 (28%) | 1.41 (1.19, 1.67) | <.001 | 1.38 (1.19, 1.61) | <.001   |
| CA-13                   | 232/1394 (17%) | 1.75 (1.39, 2.20) | <.001 | 1.67 (1.40, 2.00) | <.001   |
| CA-hypodiploidy         | 179/1394 (13%) | 1.33 (1.04, 1.71) | 0.024 | NS          | NS      |
| PPCL                    | 26/1394 (2%) | 1.84 (1.20, 2.83) | 0.005 | 2.70 (1.80, 4.07) | <.001   |
| Thalidomide (in TT2+thal, TT3A, TT3B, TT3-like) | 855/1394 (61%) | 0.63 (0.53, 0.73) | <.001 | 0.57 (0.48, 0.68) | <.001   |
| Bortezomib (in TT3A, TT3B, TT3-like) | 546/1394 (39%) | NS          | NS      | 0.70 (0.57, 0.86) | <.001   |

### Multivariate Model Including GEP, PET, MRI

|                         | n/N (%) | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------------------|---------|-------------|---------|-------------|---------|
| B2M ≥5.5 mg/L           | 130/597 (22%) | 1.72 (1.25, 2.38) | <.001 | 1.77 (1.34, 2.35) | <.001   |
| CA                      | 210/597 (35%) | 1.65 (1.21, 2.25) | 0.002 | 1.40 (1.07, 1.82) | 0.014   |
| GEP delTP53             | 61/597 (10%) | 2.45 (1.70, 3.55) | <.001 | 2.00 (1.41, 2.83) | <.001   |
| GEP-70 high-risk        | 101/597 (17%) | 3.01 (2.12, 4.27) | <.001 | 2.54 (1.86, 3.46) | <.001   |
| PET focal lesions ≥3    | 236/597 (40%) | 1.69 (1.26, 2.27) | <.001 | 1.57 (1.21, 2.03) | <.001   |
| PPCL                    | 11/597 (2%) | 2.15 (1.06, 4.37) | 0.034 | 2.80 (1.45, 5.44) | 0.002   |
| Thalidomide (in TT2+thal, TT3A, TT3B, TT3-like) | 504/597 (84%) | 0.62 (0.43, 0.88) | 0.008 | 0.59 (0.41, 0.85) | 0.004   |
| Bortezomib (in TT3A, TT3B, TT3-like) | 408/597 (68%) | NS          | NS      | 0.57 (0.41, 0.80) | 0.001   |

HR, hazard ratio; 95% CI, 95% confidence interval; P-value from Wald chi-square test in Cox regression

NS-Not Significant, multivariate results not statistically significant at 0.05 level; all univariate P-values were reported, regardless of significance.

Bold text and values indicate statistical significance.

Multivariate model used stepwise selection with entry level 0.1, and variable remains if it meets the 0.05 level.
Multivariate P-value greater than 0.05 indicates variable forced into model with significant variables chosen with stepwise selection.
Table 4

Univariate and multivariate regression analysis of baseline variables associated with duration of CR (measured from onset of CR; all TT studies combined)

| Univariate                         | n/N (%)       | CR Duration | P-value |
|------------------------------------|---------------|-------------|---------|
|                                    | n/N (%)       | HR (95% CI) |         |
| Age ≥65 years                      | 157/783 (20%) | 1.10 (0.85, 1.43) | 0.473   |
| Female                             | 305/783 (39%) | 0.81 (0.65, 1.01) | 0.059   |
| Caucasian                          | 702/783 (90%) | 1.05 (0.75, 1.48) | 0.775   |
| Albumin < 3.5 g/dL                 | 167/774 (22%) | 1.07 (0.82, 1.38) | 0.627   |
| B2M ≥3.5 mg/L                      | 304/771 (39%) | 1.41 (1.14, 1.74) | 0.001   |
| B2M ≥5.5 mg/L                      | 142/771 (18%) | 1.99 (1.57, 2.53) | <.001   |
| CRP ≥8 mg/L                        | 280/769 (36%) | 1.14 (0.92, 1.41) | 0.241   |
| Creatinine ≥2 mg/dL                | 55/771 (7%)   | 1.96 (1.41, 2.73) | <.001   |
| Hb < 10 g/dL                       | 200/779 (26%) | 1.41 (1.13, 1.77) | 0.003   |
| LDH ≥190 U/L                       | 212/774 (27%) | 1.43 (1.15, 1.79) | 0.002   |
| CA                                 | 229/775 (30%) | 1.61 (1.30, 2.01) | <.001   |
| CA-13                              | 115/775 (15%) | 1.69 (1.29, 2.21) | <.001   |
| CA-hypodiploidy                    | 86/775 (11%)  | 1.70 (1.26, 2.29) | <.001   |
| CA-13 or CA-hypodiploidy           | 148/775 (19%) | 1.64 (1.29, 2.10) | <.001   |
| Other CA                           | 627/775 (81%) | 0.61 (0.48, 0.78) | <.001   |
| GEP delTP53                        | 41/499 (8%)   | 1.42 (0.88, 2.28) | 0.150   |
| GEP-70 high risk                   | 70/499 (14%)  | 2.95 (2.10, 4.13) | <.001   |
| GEP-80 high risk                   | 35/499 (7%)   | 2.71 (1.73, 4.23) | <.001   |
| GEP CD-1 subgroup                  | 51/499 (10%)  | 1.22 (0.78, 1.90) | 0.388   |
| GEP CD-2 subgroup                  | 59/499 (12%)  | 0.93 (0.58, 1.48) | 0.758   |
| GEP HY subgroup                    | 144/499 (29%) | 0.75 (0.54, 1.05) | 0.092   |
| GEP LB subgroup                    | 74/499 (15%)  | 0.50 (0.31, 0.81) | 0.005   |
| GEP MF subgroup                    | 35/499 (7%)   | 1.76 (1.09, 2.83) | 0.020   |
| GEP MS subgroup                    | 64/499 (13%)  | 1.23 (0.81, 1.87) | 0.325   |
| GEP PR subgroup                    | 72/499 (14%)  | 1.57 (1.09, 2.26) | 0.015   |
| PET EMD                            | 23/446 (5%)   | 1.93 (1.07, 3.48) | 0.030   |
| PET focal lesions ≥3               | 175/446 (39%) | 1.25 (0.90, 1.74) | 0.184   |
| MRI focal lesions ≥7               | 256/626 (41%) | 1.17 (0.92, 1.50) | 0.205   |
| PCL                                | 11/783 (1%)   | 4.20 (2.16, 8.16) | <.001   |
| TT1                                | 87/783 (11%)  | 2.40 (1.85, 3.12) | <.001   |
| Thalidomide (in TT2r-thal, TT3A, TT3B, TT3-like) | 550/783 (70%) | 0.48 (0.39, 0.60) | <.001   |
| Bortezomib (in TT3A, TT3B, TT3-like) | 349/783 (45%) | 0.48 (0.38, 0.62) | <.001   |
| Lenalidomide (in TT3B)             | 120/783 (15%) | 0.69 (0.46, 1.03) | 0.066   |

Multivariate Model Excluding GEP, PET, MRI

|            | N (%)       | HR (95% CI) | P-value |
|------------|-------------|-------------|---------|
| Female     | 297/754 (39%) | 0.74 (0.59, 0.92) | 0.007   |
| B2M ≥5.5 mg/L | 138/754 (18%) | 1.99 (1.56, 2.54) | <.001   |
| CA         | 226/754 (30%) | 1.65 (1.31, 2.08) | <.001   |

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### Multivariate Model Excluding GEP, PET, MRI

|                          | N (%) | HR (95% CI) | P-value |
|--------------------------|-------|-------------|---------|
| PPCL                     | 10/754 (1%) | 2.08 (1.02, 4.27) | 0.045  |
| Thalidomide (in TT2+thal, TT3A, TT3B, TT3-like) | 528/754 (70%) | 0.61 (0.47, 0.78) | <.001  |
| Bortezomib (in TT3A, TT3B, TT3-like) | 332/754 (44%) | 0.58 (0.43, 0.78) | <.001  |

### Multivariate Model Including GEP, PET, MRI

|                          | n/N (%) | HR (95% CI) | P-value |
|--------------------------|---------|-------------|---------|
| Female                   | 144/388 (37%) | 0.66 (0.45, 0.97) | 0.034  |
| B2M ≥ 5.5 mg/L           | 71/388 (18%) | 2.35 (1.57, 3.53) | <.001  |
| GEP-70 high-risk         | 54/388 (14%) | 2.71 (1.77, 4.14) | <.001  |
| PPCL                     | 7/388 (2%) | 3.92 (1.65, 9.27) | 0.002  |
| Bortezomib (in TT3A, TT3B, TT3-like) | 276/388 (71%) | 0.48 (0.33, 0.69) | <.001  |

HR, hazard ratio; 95% CI, 95% confidence interval; P-value from Wald chi-square test in Cox regression. Bold text and values indicate statistical significance.

Multivariate model used stepwise selection with entry level 0.1, and variable remains if it meets the 0.05 level. Multivariate P-value greater than 0.05 indicates variable forced into model with significant variables chosen with stepwise selection.