Changes of Biochemical Markers of Bone Turnover and YKL-40 Following Hormonal Treatment for Metastatic Prostate Cancer Are Related to Survival

Julia S. Johansen,1 Klaus Brasso,2,5 Peter Iversen,2 Børge Teisner,6 Patrick Garnero,7 Paul A. Price,8 and Ib Jarle Christensen3,4

Abstract Purpose: Elevated serum levels of biochemical markers of bone turnover and YKL-40 in patients with metastatic prostate cancer (PC) at the time of diagnosis are associated to poor prognosis. In this study, we evaluated the value of these biomarkers in monitoring the patients during hormonal treatment.

Experimental Design: Serum procollagen type I N-terminal propeptide (PINP), bone-specific alkaline phosphatase (BAP), CTX-I, and YKL-40 were determined by ELISA in a longitudinal study of 106 patients with metastatic PC during treatment with total androgen ablation or parenteral estrogen. Serum samples were collected with 3 months interval. Median observation time was 4.9 years (range, 3.6-6.2). A total of 78 patients died (64 within 7 months following the last blood sampling).

Results: After 6 months treatment, serum PINP, BAP, and YKL-40 decreased (P < 0.0001), but not serum CTX-I compared with baseline values. Univariate Cox analysis showed that serum PINP at 6 months [log transformed and treated as a continuous variable; hazard ratio (HR), 2.2; P < 0.0001], serum BAP (HR, 1.8; P < 0.0001), and serum CTX-I (HR, 2.4; P < 0.0001), but not serum YKL-40 (HR, 1.4; P = 0.16) were associated with survival. Multivariate Cox analysis including the biomarkers 6 months after the start of treatment showed that Soloway score (HR, 3.9; P = 0.013), WHO tumor grade (HR, 3.9; P = 0.004), and serum PINP (HR, 2.2; P < 0.0001) were independent prognostic variables of survival. Scoring the biomarkers during treatment as time-dependent covariates in univariate Cox regression analysis showed that increases in serum PINP (HR, 2.0; P < 0.0001), BAP (HR, 2.1; P < 0.0001), and YKL-40 (HR, 2.1; P < 0.0001) were predictors of early death.

Conclusions: Serial monitoring of serum PINP, BAP, CTX-I, and YKL-40 in metastatic PC patients during hormonal treatment provided information of prognosis.

Prostate cancer (PC), the most frequent cancer in males, is responsible for ~27,350 deaths in the United States in 2006 (1). The optimal management of patients with metastatic PC is still a question open for debate (2). The ongoing discussions reflect the fact that once patients have developed metastatic disease and the PC has become hormone refractory, the prognosis is poor (3). Bone is the most common site of PC spread and accounts for up to 80% of all PC metastases, and 85% to 100% of those who die from PC have bone metastases (3). High frequency and poor prognosis of patients with metastatic PC emphasize the need for good biomarkers of treatment response, disease progression, and short survival to optimize treatment of PC patients.

Several biomarkers (defined as physical signs or laboratory measurements that occur in association with a pathologic process or that have putative and/or prognostic utility) of bone resorption [e.g., urine N-telopeptide of type I collagen (NTX-I), serum or urine C-telopeptide of type I collagen (CTX-I)] and bone formation [e.g., serum bone-specific alkaline phosphatase (BAP), osteocalcin, the amino (NH2)- and carboxy (COOH)-terminal extension propeptides of type I procollagen (PINP and PICP)] are increased in PC patients with bone imaging, diagnosis, and prognosis.
metastasis (5–12). Recently, three large studies of PC patients with bone metastases showed that high serum CTX-I and NTX-I (8), urine NTX-I (9, 10, 12), serum BAP (8–10, 12), and PINP (8) were predictors of short survival. In PC patients with bone metastases treated with the bisphosphonate zoledronic acid, high urine NTX-I and serum BAP in the most recent sample before an event were associated with a risk of skeletal morbidity, bone lesion progression, and death (10).

We have recently reported elevated serum PINP in most patients with PC and bone metastasis and elevated serum BAP, CTX-I, and YKL-40 in approximately half of the patients compared with healthy subjects (11). The three biomarkers of bone remodeling were related to the burden of PC in the skeleton determined by the Soloway score (11). All four biomarkers at the time of diagnosis and before endocrine therapy were prognostic predictors of survival. Serum PINP in combination with serum YKL-40, performance status, WHO grade, and Soloway score were independent prognostic parameters of poor prognosis (11).

Serum YKL-40 is a new biomarker with a prognostic value of survival in patients with other solid tumors and hematological malignancies (13). YKL-40 may play a role in proliferation and differentiation of cancer cells and protect them from apoptosis, although in vivo proof is yet to be obtained. YKL-40 is a growth factor for fibroblasts and chondrocytes (14, 15), acts synergistically with insulin-like growth factor-1 (15), is regulated by tumor necrosis factor-α (16, 17), requires sustained activation of NF-κB (17), binds to collagen types I, II, and III, and modulates the rate of type I collagen fibril formation (18).

In the present retrospective, longitudinal study of PC patients with bone metastases, we have evaluated if serial measurement of serum PINP, BAP, CTX-I, and YKL-40 may provide an early assessment of response to endocrine therapy and if these biomarkers can be used to predict death during follow-up.

Patients and Methods

Patients and treatments. Retrospective, longitudinal study included 106 men (median age, 72; range, 54-89 years) with metastatic PC (stage T1-4, Nx, M+, Soloway score 1-3) and a WHO performance status of 0 to 2. The patients were enrolled from five Danish hospitals and included in the Scandinavian Prostate Cancer Group-5 study of patients with metastatic PC (19). The patients were included between November 1993 and June 1996 and randomized to treatment with either total androgen ablation (either bilateral orchietomy or castration) or triptorelin 3.75 mg/mo combined with the antiandrogen flutamide 250 mg thrice daily or parenteral estrogen [i.m. injections of 240 mg estradiol valerate every second week] in the first 8 weeks (5 doses), followed by a maintenance dose of 240 mg/mo]. The choice between orchietomy and castration was at the discretion of the clinician and patient. Staging was based on histologic and/or cytologic findings and digital rectal examination, and assessment of bone metastases at diagnosis was based on plain X-ray skeletal surveys and radioisotopic bone imaging. The extent of osseous dissemination was graded according to Soloway et al. (20). Patients previously given systemic therapy had PC, previously diagnosed with another malignant disease, myocardial or cerebral infarction within the past month, with previous or present liver disease, or not believed capable of following the study rules were excluded.

The patients were followed in the outpatient clinic every 3 months until death or January 31, 2000. The median follow-up time was 4.9 years (range, 3.6-6.2 years). Time to death was measured from the date of starting treatment. A total of 78 (74%) patients died in the follow-up period, and 64 within 7 months following the last blood sampling. The study was done in accordance with the Helsinki II declaration. The patients were informed about the possibility of withdrawing from the study at any time. The Central Ethics Committee and The Danish Board of Health approved the study.

Healthy controls. The reference range of serum BAP in 126 healthy men >25 years was provided by Quidel. The reference range of serum CTX-I in 115 healthy men aged 41 to 80 years was provided by Synarc Laboratory. The reference range of serum PINP and YKL-40 was determined in 93 healthy men >25 years (median age, 51; range, 26-73). They were all healthy, were not taking any medicine, and had no signs or symptoms of cancer, joint, liver, metabolic, or hormonal disease.

Biomarkers. Nonfasting blood samples were collected at the time of inclusion, after 4 weeks of treatment, and then every 3 months until death or January 31, 2000. Serum was only available for measurement of CTX-I from 73 patients at 6 months. Urine was not collected. Serum was collected between 8:00 a.m. and 1:00 p.m. and separated from blood cells within 3 h after venipuncture by centrifugation at 3,000 rpm for 10 min. Serum was stored in aliquots at −80°C until analysis. Serum PINP was determined in an in-house ELISA, which measures both molecular forms of PINP (21). The detection threshold is 0.5 μg/L, intra- and interassay variations are <5.3%. The median serum PINP in controls is 49 μg/L [range, 24-143 μg/L; cut-point, 66 μg/L (95th percentile)]. Serum BAP was determined by ELISA (Quidel; ref. 22). The sensitivity is 0.7 units/L intra- and interassay variations are <5.8% and 7.6%. The median serum BAP in controls is 23 units/L (range, 15-41 units/L; cut-point, 41 units/L). Serum CTX-I was determined by a two-site immunoassay (Roche Diagnostic; ref. 23).

The sensitivity is 0.01 μg/L and intra- and interassay variations are <4% and 6%. The median serum CTX-I in controls is 0.300 μg/L [range, 0.07-0.72 μg/L; cut-point, 0.638 μg/L (95th percentile)]. Serum YKL-40 was determined by ELISA (Quidel; ref. 24). The sensitivity is 20 μg/L and intra- and interassay variations are <3.6% and 5.3%. The median serum YKL-40 in controls is 47 μg/L (range, 20-184 μg/L; 95th percentile is 104 μg/L). Serum YKL-40 increases with age in controls, and the age-adjusted 95th percentile is set as cut-point.

Statistical analyses. The SAS software package (version 9.1; SAS Institute) was used. Rank statistics were used for estimation of correlation coefficients and paired tests. The end point for survival analysis was death of all causes. Serum PINP, BAP, CTX-I, and YKL-40 at 6-months were analyzed using the landmark method, i.e., from time of most recent sample to death. The Kaplan-Meier method was used to estimate survival probabilities. The log-rank test was used to test for equality of strata. The Cox proportional hazards model was applied for multivariate analysis. The assumption of proportional hazards was verified graphically. Serum PINP, BAP, CTX-I, and YKL-40 were log-transformed and treated as continuous variables for the uni- and multivariate Cox analyses of survival.

Analysis of repeated measurements was done using time-dependent covariates in the Cox proportional hazards model. Samples taken at 3-month intervals were available and entered into the Cox regression model with updated values scored by the log of the actual level. Only the updated covariates were used in this analysis that is the biomarker levels. Patients without an updated measurement within 7 months after the latest update were removed from the risk set and only reentered if a measurement subsequently was available. P values <5% were considered significant.

Results

Early changes in the biomarkers. At baseline, all four biomarkers were elevated (P < 0.001) in the patients with metastatic PC compared with healthy men (Table 1). After
6 months of treatment with either total androgen ablation or parenteral estrogen serum PINP, BAP, and YKL-40 decreased significantly, but not serum CTX-I (Table 1). Serum PINP and BAP at baseline and after 6 months of treatment were correlated ($R_{T0} = 0.85; R_{T6} = 0.85; P < 0.0001$). Serum CTX-I correlated with PINP at baseline and 6 months ($R_{T0} = 0.84; R_{T6} = 0.73; P < 0.0001$) and with BAP ($R_{T0} = 0.67; R_{T6} = 0.63; P < 0.0001$). Neither serum PINP, BAP, nor CTX-I correlated with YKL-40 at baseline and after 6 months. Significant correlations were found between the baseline and 6 months value for all biomarkers (PINP: $R = 0.78$; BAP: $R = 0.72$; CTX-I: $R = 0.68$; and YKL-40: $R = 0.67; P < 0.0001$).

The differences between the baseline level and the level after 6 months of treatment were not different between the three treatment groups for serum PINP ($P = 0.24$), BAP ($P = 0.63$), and YKL-40 ($P = 0.20$). The median difference between the baseline and 6 months concentration for serum CTX-I was -0.12 (range, -2.26 to 0.41) for the group treated with parenteral estrogen and significantly different ($P = 0.01$) from the differences in serum CTX in the group treated with bilateral orchectomy and antiandrogen flutamide (median difference, 0.12; range, -0.59 to 0.64) and the group treated with triptorelin and the antiandrogen flutamide (median difference, 0.10; range, -2.78 to 0.61).

**Biomarkers after 6 months of treatment and survival.** In the original paper, no difference was found in overall survival in the two treatment groups (19). In the present study of 106 patients, their survival was independent of treatment; thus, all patients were evaluated together for survival analysis. No interaction between treatment, the biomarkers, and survival could be shown. The serum concentrations of the biomarkers after 6 months of treatment were log transformed and treated as continuous variables in uni- and multivariate analysis.

Serum samples were available at 6 months from 102 patients for PINP, BAP, and YKL-40 determination and from 73 patients for CTX-I determination. Serum BAP is closely associated to PINP and, therefore, not included in the multivariate analysis. The ratio of the 6-month level to baseline level was not significant for any of the

### Table 1. Changes in serum PINP, BAP, CTX-I, and YKL-40 levels in patients with metastatic prostate carcinoma after 6 mo of treatment with total androgen ablation or parenteral estrogen

<table>
<thead>
<tr>
<th>Serum PINP ($\mu$g/L)</th>
<th>Serum BAP (units/L)</th>
<th>Serum CTX-I ($\mu$g/L)</th>
<th>Serum YKL-40 ($\mu$g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>At 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>167 (32-3,412)</td>
<td>115 (31-6,136)</td>
<td>0.45 (0.09-5.19)</td>
<td>141 (20-2,080)</td>
</tr>
<tr>
<td>(32-3,412)</td>
<td>(9-2,420)</td>
<td>(0.09-5.19)</td>
<td>(20-2,080)</td>
</tr>
<tr>
<td>55 (9-2,420)</td>
<td>29 (10-840)</td>
<td>0.50 (0.04-2.38)</td>
<td>88 (20-1,176)</td>
</tr>
</tbody>
</table>

NOTE: Values are medians (range). Serum samples were available from 102 patients for PINP, BAP, and YKL-40 determination and from 73 patients for CTX-I determination.

### Table 2. Univariate and multivariate Cox regression analyses of the four biomarkers at 6 mo after treatment start and the clinical parameters at start of treatment in patients with metastatic prostate carcinoma

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINP</td>
<td>2.2 (1.6-2.9)</td>
<td>&lt;0.0001</td>
<td>2.4 (1.3-4.4)</td>
<td>0.006</td>
<td>1.7 (1.3-2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BAP</td>
<td>1.8 (1.4-2.3)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td>Not included, see results</td>
<td></td>
</tr>
<tr>
<td>CTX-I</td>
<td>2.4 (1.6-3.8)</td>
<td>&lt;0.0001</td>
<td>0.8 (0.4-1.7)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKL-40</td>
<td>1.4 (0.9-2.2)</td>
<td>0.16</td>
<td>1.2 (0.7-2.1)</td>
<td>0.42</td>
<td>1.0 (0.7-1.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.0 (1.0-1.1)</td>
<td>0.11</td>
<td>1.6 (0.8-3.2)</td>
<td>0.21</td>
<td>2.1 (1.2-3.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>T-category</td>
<td></td>
<td></td>
<td>1.2 (0.5-3.4)</td>
<td>0.67</td>
<td>0.8 (0.3-1.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>WHO grade 1 versus 2</td>
<td>0.7 (0.2-2.0)</td>
<td>0.51</td>
<td>0.8 (0.3-1.9)</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade 3 versus 2</td>
<td>2.4 (1.0-6.3)</td>
<td>0.06</td>
<td>2.1 (1.2-3.7)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO score 1 versus 2</td>
<td>3.9 (1.6-9.7)</td>
<td>0.004</td>
<td>1.1 (0.5-2.5)</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO score 3 versus 2</td>
<td>0.5 (0.2-1.1)</td>
<td>0.08</td>
<td>0.4 (0.2-0.8)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soloway score 1 versus 2</td>
<td>4.4 (1.4-14.0)</td>
<td>0.011</td>
<td>3.1 (1.2-7.8)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Serum samples at 6 mo was only available for CTX-I analysis from 73 patients (51 deaths), and therefore, only these patients were used in the calculation for the left and middle column. The right column gives the results when serum CTX was removed from the calculation in 102 patients (74 deaths) with available serum PINP, BAP, and YKL-40 concentrations at 6 mo. The serum levels of PINP, BAP, CTX-I, and YKL-40 were log transformed and treated as continuous variables.
biomarkers (PINP: $P = 0.78$; BAP: $P = 0.30$; CTX-I: $P = 0.47$; YKL-40: $P = 0.77$).

Figure 1 illustrates the survival plots when the patients were grouped by tertiles according to serum PINP, BAP, and YKL-40 ($n = 102$) and serum CTX-I ($n = 73$) at 6 months of treatment. Significantly shorter survival was found between the three groups of patients according to increasing level for serum PINP. Patients with normal or a small increase in serum BAP and CTX-I had similar survival, whereas patients with serum BAP and CTX-I in the highest tertile had shorter survival compared with the other groups. There was no difference in survival stratifying serum YKL-40 by tertiles.

**Changes in the biomarkers during follow-up and prediction of early death.** Serum PINP, BAP, and YKL-40 were measured in 106 patients during follow-up with time intervals of ~3 months. Seventy-eight (74%) died in this period. A total of 784 serum samples were collected during follow-up. The median number of samples collected from each patient was 6 (range, 1-24 samples; 2-4 samples, 38%; 5-8 samples, 30%; 9-12 samples, 13%; ≥13 samples, 20%). Serum CTX-I was only measured at baseline and 6 months in 73 patients.

The changes in serum PINP and BAP were closely associated with a rank correlation of 0.80. The changes in serum YKL-40 were not as closely related to the markers of bone formation with rank correlation of 0.18 and 0.11, respectively. In patients with blood samples collected a few months before death, increases in all biomarkers were often observed.

Serum PINP, BAP, and YKL-40 were analyzed in Cox regression analysis including each biomarker as a time-dependent covariate and updated at each 3 months examination. If no update exists after 7 months, the patient is removed from the risk set and reentered if a subsequent measurement is available. Univariate analysis showed that the ratio of last available serum PINP to the previous measurement (logarithmically transformed and treated as a continuous variable) was significantly associated with early death within 7 months following this measurement [hazard ratio (HR), 2.0: $P < 0.0001$]. Similar findings were found for serum BAP (HR, 2.1; $P < 0.0001$) and YKL-40 (HR, 2.1; $P < 0.0001$). In multivariate Cox analysis, serum PINP and YKL-40 were independent prognostic variables (HR, 1.6; $P < 0.0001$; and HR, 1.4; $P = 0.003$, respectively; Table 3).

**Discussion**

The biomarkers of bone formation and serum YKL-40 decreased in patients with metastatic PC after 6 months of treatment with total androgen ablation or parenteral estrogen compared with pretreatment level, probably reflecting the
Table 3. Univariate and multivariate Cox regression analyses of updated serum PINP, BAP, and YKL-40 values to predict death within the following 7 mo in 106 patients with metastatic PC during hormonal treatment

<table>
<thead>
<tr>
<th>Ratio of the concentration in the last sample/previous sample</th>
<th>Univariate analysis*</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Serum BAP*</td>
<td>2.1 (1.8-2.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum PINP*</td>
<td>2.0 (1.8-2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum YKL-40*</td>
<td>2.1 (1.9-2.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P = 106; 64 deaths.
† The serum levels of PINP, BAP, and YKL-40 were log transformed. The log of the ratio of the concentration in the last serum sample compared with the concentration in the previous sample was used as continuous variables in the calculations.

The effect of endocrine therapy on osteoblast activity. Serum PINP, BAP, and CTX-I after 6 months of treatment were prognostic parameters of overall survival. Serum PINP at 6 months in combination with baseline WHO grade and Soloway score were independent parameters of short survival. These observations suggest that serum PINP, BAP, and CTX-I at 6 months after start of hormonal treatment of PC patients with bone metastasis may identify a subgroup of patients that is less likely to benefit from this treatment. The study has not evaluated the relationship between these three biomarkers of bone remodeling and quality of life and progression in bone metastasis.

Urine samples were not available in the present study, and the bone resorption marker, serum CTX-I, was only determined 6 months after the start of therapy. In contrast to bone formation markers, serum CTX-I was unchanged at this time point. In patients with localized PC, hormonal therapy increases the bone resorption markers urinary NTX-I (25–27), urinary CTX-I (27), and serum ICTP (28) within 9 weeks to 6 months, whereas no effect was observed on the bone formation markers serum BAP, osteocalcin, and PICP. Thus, short-term hormonal therapy in men with PC leads to a general skeletal increase of bone resorption, which could mask its beneficial effects in reducing bone metastases activity when assessed by a systemic biochemical marker. These opposite effects of hormonal therapy are likely to explain the absence of significant change of serum CTX-I after 6 months in our study of PC patients with skeletal metastasis.

Others have found that the most recent biomarker assessments of urine NTX-I and BAP, taken <6 months before disease progression or death, have greater predictive value of disease progression and time to death than values at diagnosis or start of treatment with bisphosphonates (9, 10). In multivariate analysis, higher levels of serum BAP but not urine NTX-I were associated with shorter overall survival (12). We found that the increases in serum PINP, BAP, and YKL-40 in PC patients with bone metastases during hormonal treatment were predictive parameters of death within the following 7 months. Serum PINP and BAP are closely correlated (both reflect osteoblast activity), but PINP seems to be a more general marker of extracellular matrix building. Others have also reported that serum PINP has prognostic value in metastatic PC and breast cancer (8, 29). The applied PINP ELISA should enable the measurement of α1-chains of PINP irrespective of the molecular forms because the trimeric structure of PINP is labile at body temperature, and thermal transition from trimeric to monomeric α1-chains is an ongoing in vivo process (30). The ELISA technology applied in the present study measures the sum of the α1-chains of PINP irrespective of the molecular form. This is important because the ratio of the trimeric and monomeric PINP varies between individual serum samples (30, 31). It has been proposed that when PC cells invade bone matrix, signaling between these cells causes the release of bone morphogenic proteins from bone matrix to trigger bone formation. New bone formation causes a positive feedback that allows further release of these growth factors, not only from bone matrix but also from the carcinoma cells within the matrix. This cascade compound further stimulates bone formation and proliferation, which leads to osteosclerosis. As more cancer cells invade bone, this cascade leads to increased intra-osseous pressure and periosteal elevation in bone, which causes bone pain and fractures (32).

YKL-40 is produced by cancer cells, including PC (National Center for Biotechnology Information databases; ref. 13) and tumor-associated macrophages (33). High serum YKL-40 at diagnosis is an independent prognostic biomarker of short survival in patients with different types of adeno- and squamous cell cancer, glioblastoma (13), and acute myelogenous leukemia (34). In patients operated for colorectal cancer (35) and stages I-II melanoma (36), significant associations are observed during follow-up between serum YKL-40 (updated continuous covariate) and relapse-free and overall survival, and serum YKL-40 is independent of clinical and histologic parameters (35, 36). Patients operated for high-grade gliomas and no radiographic evidence of disease had lower serum YKL-40 during follow-up than patients with signs of disease (37). High-serum YKL-40 (time-dependent covariate) during follow-up in patients with glioblastoma multiforme and anaplastic astrocytoma is associated with short survival (37).

To conclude, we found that serum PINP, BAP, CTX-I, and YKL-40 could be of value in the monitoring of patients with metastatic PC treated with hormonal therapy. High serum values of these biomarkers combined were related to poor prognosis. This could suggest that a score based on the levels of these biomarkers could be helpful; however, this should be validated in an independent patient cohort.

**Acknowledgments**

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References

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