Pathological Response and Circulating Tumor Cell Count Identifies Treated HER2+ Inflammatory Breast Cancer Patients with Excellent Prognosis: BEVERLY-2 Survival Data

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Abstract

Purpose: The BEVERLY-2 single-arm phase II trial assessed the efficacy and safety of combining neoadjuvant chemotherapy with bevacizumab and trastuzumab for the treatment of HER2-positive inflammatory breast cancer (IBC). Here, we report the results of a preplanned survival analysis at 3 years of follow-up, along with the association between outcome and circulating biomarkers and pathologic complete response (pCR).

Experimental Design: Patients received fluorouracil, epirubicin, cyclophosphamide, and bevacizumab (cycles 1–4) and docetaxel, trastuzumab, and bevacizumab (cycles 5–8) before surgery, followed by trastuzumab and bevacizumab for 30 weeks after surgery. Circulating tumor cell (CTC) and endothelial cell (CEC) counts were assessed at baseline, cycle 5, preoperative, and at 1 year.

Introduction

Inflammatory breast cancer (IBC) is a rare, aggressive subtype of breast cancer, characterized by the clinical appearance of rapidly enlarging edematous and erythematous breast (referred to as "peau d’orange"). The disease accounts for 5% of all breast cancer cases and typically presents in younger women who have a higher likelihood of experiencing metastasis when compared with other forms of breast cancer (1–3). Biologically, IBC remains poorly characterized. No consistent gene signature associated with IBC has been validated (4). Recently, it has been shown that IBC is transcriptionally heterogeneous and that all molecular subtypes described in non-IBC are detectable in IBC, albeit with a different frequency (5).

Prognosis of patients with IBC has improved with a combination of treatments that include neoadjuvant chemotherapy, mastectomy and axillary lymph node removal, radiotherapy, and endocrine treatment when appropriate (3). Despite this progress, the prognosis for women with IBC remains poor, with a median overall survival (OS) of approximately 40 to 60 months (6–9). Neoadjuvant chemotherapy and trastuzumab followed by adjuvant trastuzumab is a standard of care for locally advanced HER2-positive primary breast cancer (10). The open-label, single-arm, multicenter phase II BEVERLY-2 study added neoadjuvant and adjuvant bevacizumab to that standard of care regimen for patients diagnosed with non metastatic HER2-positive IBC. As previously reported, a high pCR rate (63.5%) was obtained in the 52 patients enrolled in that study (11).

Results: Fifty-two patients were included. The 3-year disease-free survival (DFS) rate was 68% and overall survival (OS) rate was 90%. pCR (centrally reviewed) was strongly associated with 3-year DFS [80% and 53% in patients with/without pCR, respectively (P = 0.03)]. CTC detection also independently predicted 3-year DFS [81% vs. 43% for patients with <1 vs. ≥1 CTC/7.5 mL at baseline (P = 0.01)]. Patients with no CTCs detected at baseline and with pCR had a high 3-year DFS (95%). CEC changes during treatment had no prognostic value.

Conclusions: Our study suggests that the prognosis of IBC relies on more than the achievement of pCR and highlights the role of early hematogenous tumor dissemination as assessed by CTCs. Combining these two prognostic factors isolates a subgroup of IBC with excellent survival when treated with bevacizumab- and trastuzumab-containing regimens. Clin Cancer Res; 1–7. ©2014 AACR.
Translational Relevance

Inflammatory breast cancer is a rare form of locally advanced breast cancer with a poor prognosis. We report here the preplanned 3-year follow-up survival analysis of the BEVERLY-2 study, studying whether the high pathologic complete response (pCR) rate (63.5%) observed after neoadjuvant chemotherapy, trastuzumab, and bevacizumab would translate into an improved survival. We confirm here the significant impact of pCR on disease-free survival (DFS) after adjuvant trastuzumab and bevacizumab, and highlight the strong independent prognostic value of circulating tumor cells (CTC) detection before the start of the treatment. Importantly, the subgroup of patients without detectable CTCs at baseline and a pCR had an excellent 3-year DFS rate (95%). Circulating endothelial cells had no prognostic value. The early yet frequently observed hematogenous dissemination of cancer cells should therefore be taken into account for prognosis assessment in inflammatory breast cancer and should be considered as a key biologic process to target.

The use of pCR as a prognostic marker for DFS and OS in patients treated by neoadjuvant therapy is supported by several lines of evidence (12, 13), including recent reports in HER2-positive breast cancer (9, 14–16). A noticeable dissociation was however observed in non-IBC with bevacizumab, which increased the pCR rate in the neoadjuvant setting (17, 18) but had no impact on survival in the adjuvant setting of HER2-positive breast cancer (19, 20). To study whether the increased pCR reported in the BEVERLY-2 study would ultimately translate into improved long-term outcomes for the included patients, we report here the results of a preplanned survival analysis after 3 years of follow-up, together with the prognostic value of circulating tumor cell (CTC) and circulating endothelial cell (CEC) count.

Materials and Methods

Study design and participants

Full details of the study design, inclusion criteria, and patient characteristics have been published previously (11). In summary, women enrolled into our phase II trial had histologically confirmed IBC and were aged ≥18 years. The trial was a single-arm, open-label, multicentre, nonrandomized, Simon (two-stage) trial. All patients had a centrally reviewed HER-2 positive IBC, defined as T4d (any N), stage II or stage III according to the PEV (Poussée Evolutive) classification (21), or as the presence of tumor emboli in the lymph vessels of the superficial derma on skin biopsy sampling.

All enrolled patients provided written informed consent before screening procedures that were specific for this study. Written informed consent was also required for the translational research studies. The study was approved by the ethical board (Comité de Protection des Personnes Sud Méditerranée I) and registered (NCT00717405 and EUDRACT 2008-000783-16).

Treatment

The treatment included four planned stages. No pretreatment sentinel lymph node biopsy was performed. During stage 1, patients received four three-weekly cycles of neoadjuvant treatment with intravenous fluorouracil (500 mg/m²), epirubicin (100 mg/m²), cyclophosphamide (500 mg/m²), and bevacizumab (15 mg/kg), followed by four cycles of docetaxel (100 mg/m²), bevacizumab (15 mg/kg), and trastuzumab (initially at a loading-dose of 8 mg/kg, and then a dose of 6 mg/kg once every 3 weeks from cycle 5). All treatments were given on day 1 of the cycle. Stage 2 consisted of mastectomy and axillary node dissection surgery. Bevacizumab was stopped 4 weeks before surgery and resumed (for a further 30 weeks) once the wound was healed entirely, during or after radiotherapy. Patients continued receiving trastuzumab maintenance (6 mg/kg) during the perioperative period, which continued for another 30 weeks following surgery (42 weeks in total). In stage 3, patients received 4 to 6 weeks adjuvant radiotherapy treatment as required (administered according to standard practice) in combination with trastuzumab, and bevacizumab every three weeks. Selected patients with hormone receptor–positive tumors received endocrine therapy. The final stage (stage 4) of the trial consisted of a 5-year follow-up after the last patient inclusion.

Translational research assessments

CTIC and CEC counts were measured in blood samples using CellSearch (Janssen Diagnostics). Additional blood samples (2 × 7.5 mL) were taken from each patient: (i) before the first bevacizumab administration during the neoadjuvant period of the study (baseline); (ii) before the first trastuzumab administration during the neoadjuvant period (cycle 5); (iii) before surgery (cycle 8); (iv) during the adjuvant period before the reintroduction of bevacizumab (postoperative assessment); and (v) at the final visit at the end of adjuvant treatment (1-year follow-up). HER2 status of CTC and changes during neoadjuvant treatment have been previously reported (22).

Endpoints and statistical analysis

Efficacy analyses were done on all enrolled patients (intent-to-treat population, n = 52) and safety analyses were done on all patients who received at least one dose of treatment (safety population, n = 52). Efficacy during the neoadjuvant phase was assessed by pCR using Sataloff and Chevallier criteria as described previously (11). Tissue blocks for each patient were examined by central review and pCR was defined as a total or near total treatment effect with loss of nodal involvement (Sataloff classification TA and NA or NB or Chevallier classification Ch1 and Ch2; ref. 23). The BEVERLY-2 study was powered to detect a pCR rate of 40% or more, as previously reported (11). Patients who did not undergo surgery, or who had insufficient tissue for assessment were regarded as failures.

Long-term efficacy outcomes were DFS, recurrence-free interval (RFI), and OS. DFS was defined as time to local recurrence following first administration of neoadjuvant treatment, local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause. RFI was defined as the time from first treatment administration until a local or regional recurrence or the occurrence of distant metastases. OS was defined using death from any cause. DFS, RFI and OS were analyzed using the Kaplan–Meier method.
CTC count was correlated to patients’ characteristics using Fisher’s exact test, \( \chi^2 \), and Wilcoxon test, when appropriate. On the basis of the current knowledge about prognostic factors in IBC, we tested whether pCR, baseline CTC and CEC count, SBR grade, lymphovascular invasion (assessed at baseline on prechemotherapy biopsy), lymph node involvement, tumor size, and hormone receptor impacted patients survival by univariate Cox regression analysis. Independent prognostic factors in univariate analysis were further analyzed with a multivariate Cox regression model built using stepwise selection of variables, with \( P \leq 0.15 \) as the entry threshold (to be part of the initial model) and \( P \leq 0.10 \) as the retention threshold (to be kept in the model).

Safety (adverse events coded according to the MedDRA guidelines and their intensity graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0) and cardiac safety according to the New York Heart Association classification were additional secondary endpoints. Data analyses were performed using SAS version 9.1.

**Results**

**Initial analysis**

Overall, 52 patients with HER2-positive IBC were enrolled in this study. All patients had clinical IBC symptoms (2). Mean age was 50.6 years; 26 of 48 (54%) patients with available data were SBR grade 3 and 18/51 (35.3%) had hormone receptor–positive tumors. The study flow chart is displayed in Fig. 1. In total, 33 of 52 patients [63.5%; 95% confidence interval (CI), 49.4–77.5] had a pCR by central review; the combination treatment was therefore determined as effective (11). CTC positivity (\( \geq 1 \) CTC/7.5 mL) rate before the start of treatment was 35% and dropped to 7% before surgery. CTC positivity at baseline was not associated with any of the patients’ clinical and pathologic characteristics (Supplementary Table S1). Overall, 24 of 52 (46%) patients had at least one positive CTC value during the baseline to presurgical period, without any association between pCR and CTC status (at a given time) or kinetics (during treatment).

**Adjuvant treatment**

Three to 4 weeks after surgery, \( \geq 1 \) CTC/7.5 mL were detected in 5 (13.2%) of 38 patients assessed. The mean CTC count at that time point was 0.3 CTC/7.5 mL (range, 0–7; median, 0). The median CEC count was 21 CEC/4 mL (range, 0–1,794) in the 39 patients with CEC data. Forty-eight of the 52 enrolled patients entered the adjuvant treatment phase. All received adjuvant radiotherapy and 13 patients received adjuvant endocrine therapy. Four patients did not receive any bevacizumab; the median relative dose intensity of bevacizumab received was 84.7% (range, 9.6–103.7). One patient did not receive any adjuvant trastuzumab; the median relative dose intensity of trastuzumab received was 93.4% (range, 24.2–106.8). Adverse events occurring in >5% of patients during the adjuvant phase are shown in Supplementary Table S2. Fourteen patients (29.2%) had at least one grade 3–4 adverse event. At the end of adjuvant treatment, \( \geq 1 \) CTC/7.5 mL were detected in 6 (20.7%) of 29 patients assessed. The mean CTC count at the end of adjuvant treatment in these 29 patients was 0.3 CTC/7.5 mL (range, 0–3; median, 0). The median CEC count was 20 CEC/4 mL (range, 1–431) in the 27 patients with CEC data. An exploratory analysis showed that, 3 to 4 weeks after surgery, CTCs were detected in one out of 25 patients with pCR (4%) and in four of 13 patients with no pCR (31%; \( P = 0.03 \), Fisher exact test; \( P = 0.02 \), Wilcoxon test). After 1 year of adjuvant therapy, no significant difference was seen in the 29 patients assessed.

**Follow-up analysis**

At the time of this analysis, 5 patients had died and 16 experienced disease recurrence. At the 3-year follow-up, the DFS
rate was 68% (95% CI, 53–79; Fig. 2A), while the OS rate was 90% (95% CI, 77–96; Fig. 2B). Three-year DFS was longer in patients with a pCR compared with those who did not achieve pCR [80%; (95% CI, 61–90) vs. 53% (95% CI, 29–72), respectively]. Univariate analysis showed that SBR grade (P = 0.02), lymphovascular invasion (P = 0.05) and pCR (P = 0.03) were the clinical and pathologic characteristics associated with DFS (Table 1).

We then analyzed the impact of CTC detection on DFS: 3-year DFS in patients with ≥1 CTC/7.5 mL at baseline was significantly lower (43%; 95% CI, 20–64) than for patients with no CTC detected at baseline (81%; 95% CI, 62–91; HR, 3.69; 1.34–10.21; P = 0.012; Fig. 3; Table 1). For all other time points, there was no significant association between CTC and DFS other than that observed at baseline. Detection of CTC at any point during neoadjuvant stages (i.e., at baseline or at cycle 5 or 8) was associated with a significant reduction in DFS; patients with at least one positive CTC sample had a DFS of 54% (95% CI, 32–71), compared with a DFS of 83% (95% CI, 61–93) in patients where no CTC were detected during neoadjuvant stages (HR, 3.62; 95% CI, 1.15–11.39; P = 0.018). At time of analysis, patients with no CTC detected during neoadjuvant stages had a 96% OS rate versus 83% for those with at least one CTC value ≥1. The low number of deaths (n = 5) precluded, however, any formal statistical comparison. Only SBR grade and baseline CTC status were found to be independent prognostic factors (Table 1). Using previously reported thresholds (11), no impact of CEC count on DFS or OS was observed at univariate analysis.

In an exploratory analysis, we sought to define a subgroup with excellent prognosis by combining CTC with pCR. As shown in Fig 4, those patients with baseline CTC <1/7.5 mL and a pCR had excellent prognosis [3-year DFS was 95% (95% CI, 71–99)] while those with baseline CTC ≥1/7.5 mL and no response were at a high risk of relapse [3-year DFS was 38% (95% CI, 9–67)].

Discussion

This preplanned 3-year follow-up analysis of the BEVERLY-2 study shows a good 3-year DFS rate of 68%, and an excellent OS rate of 90%. This adds further evidence of the effectiveness of the proposed treatment, made of a combination of neoadjuvant fluorouracil, epirubicin, cyclophosphamide, docetaxel, bevacizumab, and trastuzumab, followed by adjuvant bevacizumab, trastuzumab, and eventual hormone therapy in patients with primary HER2-positive IBC. Adjuvant trastuzumab and bevacizumab dose intensities observed in our study were similar to those reported in previous adjuvant HERA (24), PHARE (25), and BEATRICE (19) studies. These data confirm that high pCR rates are associated with a significant and favorable impact on outcome. These results are in keeping with those of the NOAH trial (10), a randomized phase III trial evaluating neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer, recently updated (26), and with the findings of a retrospective review of IBC treated at the MD Anderson Cancer Center between 1989 and 2011 (9).
The results of BEVERLY-2 are encouraging as IBC is a rare yet aggressive form of breast cancer, and has poor prognosis (27). Chemotherapy-induced pCR rates were historically low in that setting, ranging from 20% to 30% (9, 28, 29). Over the past decade, clinical trials have demonstrated incremental improvements in outcome for patients with IBC. In 1999, the PEGASE 02 trial demonstrated a pCR of 32% in patients with IBC (30). Further progress was made when Buzdar and colleagues reported that treatment with trastuzumab resulted in improved pCR results for HER2-positive breast cancer (31), while Dawood and colleagues reported a 62.5% pCR rate in a retrospective study on 16 HER2-positive IBC patients treated with neoadjuvant trastuzumab and chemotherapy (32). In a retrospective analysis on 260 patients with newly diagnosed HER2-positive IBC, patients treated before the trastuzumab era were more likely to relapse than those treated after 2006 (33): 3-year OS rates were 63% for those treated before the trastuzumab era compared to 46.7% and OS rate of 77.5% for those treated after 2006. However, the number of survival events (death) in the patients who were still disease free immediately prior to surgery (n = 51). Factors identified as significantly associated with DFS in univariate analysis were included in the multivariate analysis. Abbreviations: ns, not significant; SBR, Scarff-Bloom-Richardson grading system.

Table 1. Cox regression analysis of the relationship between prognostic markers and DFS

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<thead>
<tr>
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<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
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<tr>
<td>Lymph node involvement, cN1/cN2 vs. cN0</td>
<td>0.66 (0.23–1.91)</td>
<td>0.45</td>
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<tr>
<td>Tumor size, ≥50 mm vs. &lt;50 mm</td>
<td>2.05 (0.56–7.47)</td>
<td>0.27</td>
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<tr>
<td>Lymphovascular invasion, presence vs. absence</td>
<td>2.95 (1.00–8.81)</td>
<td>0.05</td>
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<tr>
<td>Hormone receptor status, positive vs. negative</td>
<td>0.40 (0.11–1.42)</td>
<td>0.16</td>
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<tr>
<td>SBR grade, 3 vs. 1–2</td>
<td>4.33 (1.20–15.58)</td>
<td>0.02</td>
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<tr>
<td>pCR response, TA/NA or TA/NB vs. no response</td>
<td>0.32 (0.11–0.90)</td>
<td>0.03</td>
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<tr>
<td>Baseline CTCs, ≥1/7.5 mL vs. &lt;1/7.5 mL</td>
<td>3.69 (1.34–10.21)</td>
<td>0.01</td>
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NOTE: For each single factor, the analysis was performed on the subpopulation of patients for whom the factor was available. For pCR, the analysis was performed on the patient population with no CTC detected at baseline (81%). This independent prognostic impact was observed, no matter if CTC at baseline was considered as a dichotomous variable [0 vs. ≥1] or as a continuous variable (not shown). CTC detection at other time-points during the study had no statistical impact on DFS, yet the limited number of patients assessed combined with the low CTC detection rate during treatment certainly yield to a low statistical power. A number of other neoadjuvant trials have investigated the association between CTC positivity (measured by the same technique), and changes during treatment, with pCR rates and, eventually, with patient survival. In the REMAGUS 02 trial, CTCs were found in 23% of neoadjuvant chemotherapy samples and in 27% of all patients. The presence of CTC did not correlate with pCR but independently predicted early distant relapse (35). In the recent 70-month follow-up of the REMAGUS 02 study, detection of ≥1 CTC/7.5 mL at baseline was significantly associated with reduced distant metastasis-free survival and OS (36). In the GEPARQUINTO trial, Riethdorf and colleagues reported a similar CTC detection rate, and also no correlation with pCR (37). The GEPARQUINTO trial, which evaluated the addition of neoadjuvant bevacizumab, reported similar findings as in the BEVERLY-2 trial: neither the CTC count or decrease nor the observed increase in CEC during treatment correlated with pCR in that trial (38). To date, the value of CTC count on survival have not been reported for the GEPARQUATTRO and GEPARQUINTO trials. The BEVERLY-2 data therefore confirm in a population of IBC patients the findings of the REMAGUS02 survival analysis.

Finally, it was determined that by combining pCR and CTC positivity, it was possible to define specific patient subgroups at treatment certainly yield to a low statistical power. A number of other neoadjuvant trials have investigated the association between CTC positivity (measured by the same technique), and changes during treatment, with pCR rates and, eventually, with patient survival. In the REMAGUS 02 trial, CTCs were found in 23% of neoadjuvant chemotherapy samples and in 27% of all patients. The presence of CTC did not correlate with pCR but independently predicted early distant relapse (35). In the recent 70-month follow-up of the REMAGUS 02 study, detection of ≥1 CTC/7.5 mL at baseline was significantly associated with reduced distant metastasis-free survival and OS (36). In the GEPARQUINTO trial, Riethdorf and colleagues reported a similar CTC detection rate, and also no correlation with pCR (37). The GEPARQUINTO trial, which evaluated the addition of neoadjuvant bevacizumab, reported similar findings as in the BEVERLY-2 trial: neither the CTC count or decrease nor the observed increase in CEC during treatment correlated with pCR in that trial (38). To date, the value of CTC count on survival have not been reported for the GEPARQUATTRO and GEPARQUINTO trials. The BEVERLY-2 data therefore confirm in a population of IBC patients the findings of the REMAGUS02 survival analysis.

Finally, it was determined that by combining pCR and CTC positivity, it was possible to define specific patient subgroups at...
very low (no CTC detected at baseline and pCR), intermediate, and high (CTC detected at baseline and no pCR) risk of early relapse. The isolation of a subgroup with excellent survival despite the inflammatory features of breast cancer is particularly interesting from a clinical standpoint, and has not been reported so far. Furthermore, these findings from a homogeneous population of HER2-positive patients with IBC demonstrate that the response to therapy of the primary tumor, although being an important prognostic factor, cannot fully revert the worse prognosis associated with the presence of a disseminating/micrometastatic disease process at diagnosis, as assessed by the CTC detection. These findings, obtained after a follow-up of 3 years, will have to be further validated by the preplanned analysis at 5 years. Importantly, other metastasis-related biomarkers have been proposed (39), such as circulating tumor DNA, but are still under investigation, with a currently limited level of evidence (40). In summary, despite HER2-positive IBC being an aggressive form of locally advanced breast cancer, the high pCR rate and improved DFS suggests that our treatment regimen, including bevacizumab and trastuzumab, is effective in this type of breast cancer.

**Disclosure of Potential Conflicts of Interest**

J.-Y. Pierga reports receiving a commercial research grant from and is a consultant/ advisory board member for Roche. M. Campone reports receiving speakers’ bureau honoraria from and is a consultant/ advisory board member for Roche. J. Gligorov reports receiving speakers’ bureau honoraria from and is a consultant/ advisory board member for Roche Genentech. H. Roché reports receiving speakers’ bureau honoraria from Roche. T. Bachelot reports receiving speakers’ bureau honoraria from Novartis and is a consultant/ advisory board member for Novartis and Roche. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**

Conception and design: J.-Y. Pierga, H. Roché, P. Viens

Development of methodology: J.-Y. Pierga, P. Viens

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.-Y. Pierga, T. Petit, C. Lévy, J.-M. Ferrero, M. Campone, J. Gligorov, F. Lerebours, H. Roché, T. Bachelot, J. Bonneterre, F.-C. Bidard, P. Viens

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.-Y. Pierga, J. Gligorov, E. Charafe-Jauffret, J. Bonneterre, J. Hernandez, F.-C. Bidard, P. Viens

Writing, review, and/or revision of the manuscript: J.-Y. Pierga, J.-M. Ferrero, M. Campone, J. Gligorov, H. Roché, T. Bachelot, J. Bonneterre, J. Hernandez, F.-C. Bidard, P. Viens

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.-Y. Pierga, J. Gligorov, J. Hernandez

**References**


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