Palbociclib for the Treatment of Estrogen Receptor–Positive, HER2-Negative Metastatic Breast Cancer

Aki Morikawa and N. Lynn Henry

Abstract

Palbociclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 that acts by reducing phosphorylation of the tumor suppressor gene retinoblastoma. When added to the aromatase inhibitor letrozole in a randomized phase II trial for first-line therapy of estrogen receptor–positive, HER2-negative metastatic breast cancer, palbociclib significantly increased progression-free survival compared with letrozole alone [palbociclib + letrozole: 20.2 months; 95% confidence interval (CI), 13.8–27.5; letrozole: 10.2 months; 95% CI, 5.7–12.6; HR, 0.49; 95% CI, 0.32–0.75; P = 0.0004]. On the basis of these results, the drug was recently granted accelerated approval by the FDA, and confirmatory studies are ongoing. Because this drug has a rational target in an oncologic pathway, concurrent biomarker development is of interest. In breast cancer, the most useful predictive biomarkers identified thus far are estrogen receptor and HER2 receptor status, although additional studies are ongoing. In this article, we review the development of palbociclib and its use in treatment of hormone receptor–positive metastatic breast cancer in the context of other FDA-approved agents in this setting. Clin Cancer Res; 21(16); 3591–6. ©2015 AACR.

Introduction

Targeted therapy for hormone receptor–positive breast cancer has been used clinically for more than a century, primarily in the form of blocking estrogen signaling through estrogen receptor (ER) modulation or lowering circulating estrogen levels. Adjuvant endocrine therapy has improved survival rates in early-stage ERþ breast cancer. However, for those who develop metastatic disease, the vast majority will experience progression of their cancer despite treatment with this targeted therapy and will ultimately succumb to the disease. Therefore, new targeted agents have been sought that are directly antineoplastic or that enhance the efficacy of existing therapies.

One class of targeted agents that has recently been demonstrated to have benefit for treatment of ERþ breast cancer is the cyclin-dependent kinase (CDK) 4/6 inhibitors. Cell-cycle dysregulation is one of the hallmarks of cancer, and alterations in the G1→S checkpoint pathway are frequently reported in breast cancer (1, 2). One of the most studied tumor suppressors that play a role in G1→S cell-cycle dysregulation is retinoblastoma (RB) protein. Loss of retinoblastoma function leads to oncogenic cellular proliferation. CDK4/6 is one of the key regulators of retinoblastoma and G1→S transition (Fig. 1). CDK4/6 partners with cyclin D1 to promote phosphorylation of retinoblastoma, which releases transcriptional factor E2F and subsequently leads to increased transcription of genes involved in S-phase progression (3–6). The mechanisms by which CDK4/6 dysregulation may affect cellular proliferation in breast cancer often involve enhancers (cyclin D1 overexpression or amplification) and inhibitors (loss of p16 or p27) of the CDK4/6–cyclin D1 complex (2, 4). Moreover, as cyclin D1 is a transcriptional target of ER, CDK4/6 is a rational target for drug development for ERþ breast cancer.

Alteration of the CDK4/6–cyclin D1 complex is thought to be mutually exclusive with retinoblastoma loss (2, 3, 7). Retinoblastoma loss is reported to occur in about 20% to 35% of breast cancer and has been associated with ERþ disease (2, 8). Among the ERþ breast cancers, the luminal B subtype has been more strongly associated with the retinoblastoma loss gene signature compared with the luminal A subtype (9), with cyclin D1 amplification in 29% and 58% and CDK4 gain in 14% and 25% of luminal A and B, respectively (2).

Pharmacology and Preclinical Development

Palbociclib (PD-0332991) is a selective inhibitor of CDK 4/6 (Pfizer; ref. 10). It is orally administered with a mean bioavailability of 46%. On the basis of pharmacokinetic studies, it is recommended that the drug be administered with food for more consistent absorption and exposure. Its peak concentration is consistent absorption and exposure. Its peak concentration is between 6 and 12 hours, its mean plasma half-life is 29 hours, and it reaches steady state within 8 days (11). The drug undergoes hepatic metabolism with involvement of CYP3A and SULT2A1 enzymes. Thus, the concomitant use of strong CYP3A modulators (inhibitors and inducers) is not recommended (11). In addition, palbociclib has been reported to have CYP3A inhibitory effect in vivo. Therefore, dose adjustment and monitoring are recommended if palbociclib is prescribed concomitantly with drugs that undergo CYP3A metabolism.
During its development, this compound was selected for its CDK4/6 specificity and showed equivalent potency for CDK4 and CDK6 (10). In addition, as predicted it induced G₁ arrest in retinoblastoma-positive but not retinoblastoma-negative cell lines and xenografts (10, 12, 13). The activity of the drug was associated with reduced retinoblastoma phosphorylation and decreases in the Ki67 proliferation marker. Subsequently, a panel of 47 breast cancer cell lines was treated with palbociclib, and gene expression profiles were evaluated for associations with drug response (12). The drug showed cytostatic growth inhibition of luminal ER⁺ as well as HER2⁺ cell lines. In the gene expression analyses, higher levels of RB1 and cyclin D1 and lower levels of p16 were associated with sensitivity to the drug. Retinoblastoma phosphorylation was significantly decreased in sensitive but not in resistant cell lines, suggesting that retinoblastoma phosphorylation is a potential pharmacodynamic marker for drug activity (12).

ER can directly upregulate the cyclin D1 promoter, and endocrine therapy can induce downregulation of cyclin D (9, 14). Synergy between palbociclib and endocrine therapy was therefore examined and was demonstrated in preclinical models (12). The addition of palbociclib to either letrozole or fulvestrant increased inhibition of retinoblastoma phosphorylation, reduced expression of E2F, FOXM1, and downstream target genes, and decreased cellular proliferation arrest (15). In addition, the combination of palbociclib and letrozole showed greater tumor inhibition due to cellular senescence rather than apoptosis in a xenograft model. In endocrine-resistant cell line models, palbociclib is also able to elicit a response and induce cellular senescence (9, 12). Therefore, combining a CDK4/6 inhibitor and endocrine therapy for dual targeting of the CDK4/6-cyclin D complex or to address endocrine resistance is theoretically rational.

Clinical Development

Two separate phase I trials of palbociclib monotherapy using different dose schedules have been reported. In a phase I study evaluating a 2-weeks-on/1-week-off (2/1) schedule, 33 patients with retinoblastoma-positive solid tumors and non-Hodgkin lymphoma were enrolled and treated with doses ranging from 100 to 225 mg (16). The most common toxicity was cytopenia. One partial response (PR) was observed in a patient with testicular cancer, and stable disease (SD) was noted in 29%. On the basis of the results, the recommended phase II dose (RP2D) was 200 mg (16).

In the other trial, doses ranging from 25 to 150 mg orally daily in a 3-weeks-on/1-week-off (3/1) schedule were evaluated in 41 patients with retinoblastoma-positive solid tumors and non–Hodgkin lymphoma, including 5 (12%) patients with breast cancer (17). Twelve percent of patients experienced dose-limiting neutropenia. Thirty-five percent of patients had SD, including 1 patient with breast cancer. The RP2D was 125 mg daily. Both trials demonstrated that the drug was generally well-tolerated and the most common adverse events were cytopenias and fatigue. Although 1 PR was noted in patients receiving drug on the 2/1 schedule, more patients experienced durable SD when treated on the 3/1 schedule (3/1: 16% with ≥10 cycles vs. 2/1: 10% with ≥10 cycles; refs. 16, 17).
A subsequent phase II clinical trial of 37 patients with retinoblastoma-positive breast cancer was conducted using the 125-mg dose on the 3/1 schedule (18). In this trial, 7% of patients had a PR and 50% had SD. The overall clinical benefit (PR + SD ≥ 6 cycles) was 21% among 33 ER+ patients. In this heavily pretreated group (76% with ≥2 lines of therapy), median progression-free survival (PFS) was 3.8 months for patients with ER+/HER2- disease and 5.1 months for ER-HER2+ disease. A correlative biomarker analysis examined retinoblastoma expression/localization, Ki67, p16 loss, and CCND1 amplification. Only ER+ status was associated with response. At present, on the basis of the preclinical data and the phase II trial results, ER+ or HER2+ status appears to be the best predictive biomarker for palbociclib in patients with retinoblastoma-positive breast cancer.

In addition to palbociclib monotherapy, palbociclib in combination with endocrine therapy has also been studied. Postmenopausal women with ER+/HER2- metastatic breast cancer (MBC) were treated on a phase I trial using a starting dose of 125-mg palbociclib given on the 3/1 schedule in combination with 2.5 mg daily of the aromatase inhibitor letrozole (19). No additional toxicity concerns were raised with the addition of an aromatase inhibitor.

A randomized phase II trial of letrozole with or without palbociclib as first-line treatment (PALOMA-1/TRIO-18) was conducted in 165 postmenopausal women with ER+/HER2- MBC (20). Investigator-assessed PFS was the primary endpoint, and median follow-up was about 28 months. Initially, there were 2 independent cohorts, patients with ER+/HER2- tumors (cohort 1) and patients who also had CCND1 amplification and/or loss of p16 (cohort 2). Unplanned interim analysis revealed that cohort selection based on the CCND1 or p16 biomarkers would not improve outcome compared with using ER+ and HER2- alone, so enrollment into cohort 2 was stopped. Pooled analysis of the 2 cohorts revealed that the median PFS with the combination was 20.2 months [95% confidence interval (CI), 13.8–27.5] and with letrozole alone was 10.2 months (95% CI, 5.7–12.6), with an HR of 0.49 (95% CI, 0.32–0.75, \( P < 0.001 \)). The overall response rates were 43% (95% CI, 32–54) versus 33% (95% CI, 23–45) in favor of the combination treatment (\( P = 0.13 \)). Median overall survival (OS) was 37.5 months (95% CI, 28.4 to not estimable) for the combination group and 33.3 months (95% CI, 26.4 to not estimable) for the letrozole group, with an HR of 0.81 (95% CI, 0.49–1.35, \( P = 0.42 \)).

On the basis of the result of this randomized phase II trial, palbociclib received the breakthrough therapy designation in April 2013 and accelerated approval by the FDA in February 2015. The approval is contingent upon results of confirmatory studies, which are fully accrued and results are pending. The recommended starting dose is 125 mg orally daily for 21 days followed by 7 days off in 28-day cycles in combination with letrozole 2.5 mg orally daily continuously.

There were some notable findings from this trial. Overall, the patients treated on the letrozole alone arm had a PFS of 10.2 months, which is similar to that previously reported in multiple clinical trials of first-line endocrine therapy (Table 1). However, it is interesting that in cohort 1, which included unselected patients with ER+/HER2- disease, the letrozole arm had a lower-than-expected median PFS compared with historical data (Table 1). It is uncertain whether this represents a true difference in the patients accrued to this trial relative to prior trials or if it is an artifact due to the small sample size of this subset of patients. In a subanalysis, the degree of benefit seen from the addition of palbociclib to letrozole was less in the biomarker-enriched cohort than in cohort 1. This suggests that p16 loss and CCND1 amplification may not be predictive for response to CDK4/6 inhibition but may be prognostic.

Findings from the confirmatory trial PALOMA-2, a double-blind, 2:1 randomized phase III trial of palbociclib plus letrozole versus placebo plus letrozole for the first-line treatment of postmenopausal patients with ER+/HER2- advanced breast cancer is expected to be reported later this year. In the second-line setting, palbociclib plus fulvestrant was recently demonstrated to result in an improvement in PFS compared with placebo plus fulvestrant in the PALOMA-3 phase III trial, which was stopped early for efficacy (21). The median PFS was 9.2 months (95% CI, 7.5 to not estimable) for the palbociclib-containing regimen and 3.8 months (95% CI, 3.5–5.5) for the fulvestrant plus placebo arm (HR, 0.42; 95% CI, 0.32–0.56, \( P < 0.001 \)). At the time of reporting, OS data were not mature, and double blinding has been continued in the follow-up period.

In addition, palbociclib and other CDK4/6 inhibitors are being further studied as a single agent or in combination with other drugs in different clinical settings for breast cancer (Table 2), as well as for additional solid tumors and hematologic malignancies. For example, on the basis of evidence that this class of drugs is able to penetrate the blood–brain barrier and has activity in HER2+ disease, clinical trials for patients with brain metastases and with HER2+ disease have been initiated, including trials of abemaciclib (NCT02308020) and of palbociclib plus TDM-1 (NCT01976169).

### Toxicity

In the phase II monotherapy trial, cytopenias were the most frequently observed adverse events: grade 3 or 4 leukopenia 51%, neutropenia 54%, lymphopenia 30%, thrombocytopenia 19%, and anemia 35%. Dose modification occurred in 51% of patients who were on 125-mg oral dose, primarily because of neutropenia or thrombocytopenia. Of the nonhematologic toxicities, fatigue was the most common adverse event (14% grade 2; ref. 18).

The addition of an aromatase inhibitor to palbociclib did not reveal any unexpected toxicities. The most common adverse events from the phase II PALOMA-1/TRIO-18 trial were neutropenia (48% grade 3, 6% grade 4), leukopenia (19% grade 3), fatigue (36% grade 2, 4% grade 3/4; ref. 20). Notably, despite the increased incidence of neutropenia, no neutropenic fever was reported. Other nonhematologic side effects reported more commonly in the combination arm included nausea, vomiting, arthralgia, alopecia, and diarrhea, although only alopecia was statistically significant. In the combination group, dose delay was required in 45%, and dose reduction was required in 40%. Because of the hematologic toxicity, blood count monitoring is recommended, and dose holds or reduction may be warranted.

On the basis of cross-trial comparison of phase I data of the other CDK4/6 inhibitors currently being evaluated in breast cancer [LEE001 and abemaciclib [LY2835219]], neutropenia was more frequently reported in palbociclib (all grade 66%–70% in palbociclib vs. 40% in LEE001 and 16% in abemaciclib), whereas diarrhea was the most common adverse event reported for abemaciclib (16, 17, 22).

### Treatment options for ER+ MBC

For ER+/HER2- MBC, palliative treatment with endocrine therapy is often preferred as the initial treatment of choice. Traditionally, serial treatment with different endocrine therapies...
<table>
<thead>
<tr>
<th>Drugs</th>
<th>N</th>
<th>Study population</th>
<th>Phase</th>
<th>ORR</th>
<th>PFS/TTP</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen (T) vs. anastrozole (A) (combined North America and TARGET)</td>
<td>1,021</td>
<td>ER(^+) or unknown receptor, postmenopausal; 60% ER(^+), 67% no prior endocrine therapy</td>
<td>III</td>
<td>T: 27.1%</td>
<td>T: 7 mo</td>
<td>T: 40.1 mo</td>
<td>Bonnetiere et al. (29), Nabholtz et al. (30)</td>
</tr>
<tr>
<td>Tamoxifen (T) vs. letrozole (L)</td>
<td>916</td>
<td>ER(^+) or unknown receptor</td>
<td>III</td>
<td>T: 21%</td>
<td>T: 6 mo</td>
<td>T: 30 mo</td>
<td>Moundsen et al. (31)</td>
</tr>
<tr>
<td>Tamoxifen (T) vs. exemestane (E) (EORTC)</td>
<td>371</td>
<td>ER(^+) or unknown receptor</td>
<td>III</td>
<td>T: 31% E: 46%</td>
<td>T: 5.8 mo</td>
<td>E: 10.7 mo</td>
<td>Pandaeus et al. (32)</td>
</tr>
<tr>
<td>Fulvestrant (F) vs. anastrozole (A) (FIRST)</td>
<td>205</td>
<td>ER(^+) postmenopausal, 75% no prior endocrine therapy</td>
<td>II</td>
<td>F: 36%</td>
<td>F: Not reached</td>
<td>F: 54.1 mo</td>
<td>Robertson et al. (33–35)</td>
</tr>
<tr>
<td>Anastrozole + fulvestrant (AF) vs. anastrozole (A) (FACT)</td>
<td>514</td>
<td>ER(^+) postmenopausal or premenopausal with ovarian suppression, 30.2–34.4% with no prior endocrine therapy; fulvestrant at 250-mg dose</td>
<td>III</td>
<td>AF: 31.8%</td>
<td>AF: 10.8 mo</td>
<td>AF: 37.8 mo</td>
<td>Bergh et al. (36)</td>
</tr>
<tr>
<td>Anastrozole + fulvestrant (AF) vs. anastrozole (A) (SWOG)</td>
<td>707</td>
<td>ER(^+) postmenopausal, 59.7% no prior adjuvant tamoxifen; fulvestrant at 250-mg dose</td>
<td>III</td>
<td>AF: 27%</td>
<td>AF: 15 mo</td>
<td>AF: 47.7 mo</td>
<td>Mehta et al. (37)</td>
</tr>
<tr>
<td>Temsirolimus + letrozole (TL) vs. letrozole (L) (HORIZON)</td>
<td>1,112</td>
<td>AI-naive ER(^+), 21% HER2(^+)</td>
<td>III</td>
<td>TL: 27%</td>
<td>TL: 9 mo</td>
<td>NS</td>
<td>Wolff et al. (38)</td>
</tr>
<tr>
<td>Fulvestrant + letrozole + bevacizumab (FLB) vs. fulvestrant + letrozole (LEA)</td>
<td>574</td>
<td>ER(^+)HER2(^-) postmenopausal, 48% no prior endocrine therapy; fulvestrant at 250-mg dose</td>
<td>II</td>
<td>FLB: 41% FL: 22%</td>
<td>FLB: 19.5 mo</td>
<td>FL: 14.4 mo</td>
<td>Martin et al. (39)</td>
</tr>
<tr>
<td>Palbociclib + letrozole vs. letrozole (PALOMA-1/TRIO-18)</td>
<td>165</td>
<td>ER(^+)HER2(^-) postmenopausal</td>
<td>II</td>
<td>Overall: P + L: 43%</td>
<td>Overall: P + L: 20.2 mo</td>
<td>Overall: P + L: 37.5 mo</td>
<td>Finn et al. (20)</td>
</tr>
<tr>
<td>Palbociclib + fulvestrant vs. placebo + fulvestrant (PALOMA-3)</td>
<td>521</td>
<td>ER(^+)HER2(^-) postmenopausal or premenopausal with ovarian suppression</td>
<td>II</td>
<td>Overall: P + F: 10.4% Placebo + F: 6.3%</td>
<td>Overall: P + F: 9.2 mo</td>
<td>Placebo + F: 3.8 mo</td>
<td>Turner et al. (21)</td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; NS, no statistically significant difference; ORR, overall response rate; OS, overall survival; TTP, time to progression.
has been used until the development of endocrine resistance and/or rapidly progressive disease, at which time patients are transitioned to chemotherapy. However, as more is learned about key pathways driving cancer growth, rationally designed drugs to target endocrine resistance pathways are being developed. These drugs have the potential to be less toxic and more tolerable than traditional cytotoxic chemotherapy and may delay the time to initiation of chemotherapy.

One such example is everolimus, which targets the PI3K/AKT/MTOR pathway. The combination of everolimus and aromatase inhibitor therapy was previously approved by the FDA for treatment of ER+ MBC resistant to aromatase inhibitor therapy (23). There are several other therapies that target different oncogenic pathways, which are also currently being evaluated in combination with endocrine therapy (Supplementary Table S1). In addition, many of the pathways thought to be involved in endocrine resistance, such as growth factor receptors associated with mitogenic signals (EGFR, IGFR, and HER2), are upstream of the CDK4/6-cyclin D1 complex. Therefore, it is plausible that CDK4/6 inhibitors can also be combined with agents that target other pathways to enhance antitumor efficacy.

Use of CDK4/6 inhibition in combination with radiation or chemotherapy may actually result in decreased response to therapy, and therefore careful evaluation will be required. In preclinical studies, administration of palbociclib in combination with radiation therapy or the DNA-damaging agent carboplatin, ameliorates hematologic toxicity (24, 25). In the radiation studies, the CDK4/6-dependent cell line was resistant to the effects of radiation when treated with a CDK4/6 inhibitor. Similarly, in studies evaluating the combination of DNA-damaging carboplatin chemotherapy and CDK4/6 inhibitors using a retinoblastoma-competent murine model of breast cancer, decreased antitumor effect was noted with the combination compared with chemotherapy alone (25, 26). Such differential effects were not observed in a retinoblastoma-incompetent murine model. In contrast, an alternating dosing schedule of palbociclib and paclitaxel has been shown to be synergistic in a preclinical model and has shown antitumor activity in a phase I trial (27).

Table 2. Currently ongoing studies of palbociclib in breast cancer

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Study setting</th>
<th>Study population</th>
<th>Phase</th>
<th>Clinicaltrials.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib + letrozole (PALLET)</td>
<td>Neoadjuvant</td>
<td>ER+ HER2</td>
<td>II</td>
<td>NCT02296801</td>
</tr>
<tr>
<td>Palbociclib + anastrozole</td>
<td>Neoadjuvant</td>
<td>Stage II/III ER+ HER2</td>
<td>II</td>
<td>NCT01723774</td>
</tr>
<tr>
<td>Palbociclib + fulvestrant (PALOMA-3)</td>
<td>Advanced, after endocrine failure</td>
<td>ER+ HER2</td>
<td>III</td>
<td>NCT01942315</td>
</tr>
<tr>
<td>Palbociclib + cetuximab</td>
<td>Advanced, first line, Asian</td>
<td>ER+ HER2</td>
<td>III</td>
<td>NCT02297438</td>
</tr>
<tr>
<td>Palbociclib + endocrine therapy (AI or tamoxifen)</td>
<td>Adjuvant</td>
<td>ER+ HER2</td>
<td>II</td>
<td>NCT02040857</td>
</tr>
<tr>
<td>Palbociclib + fulvestrant or tamoxifen</td>
<td>Advanced</td>
<td>ER+ breast cancer, exposed to aromatase inhibitor or PI3K inhibitor</td>
<td>II</td>
<td>NCT02384239</td>
</tr>
<tr>
<td>Palbociclib + endocrine therapy (PENELOPE-B)</td>
<td>Adjuvant in residual disease after neoadjuvant</td>
<td>ER+ HER2</td>
<td>III</td>
<td>NCT01864746</td>
</tr>
<tr>
<td>Palbociclib + PI3K inhibitor and fulvestrant</td>
<td>Advanced</td>
<td>ER any, subcohort with PI3KCA mutant</td>
<td>I</td>
<td>NCT02389842</td>
</tr>
<tr>
<td>Palbociclib + exemestane vs. letrozole</td>
<td>Advanced, refractory to nonsteroidal AI</td>
<td>ER+ HER2</td>
<td>III</td>
<td>NCT02028507</td>
</tr>
<tr>
<td>Palbociclib vs. palbociclib + letrozole</td>
<td>Advanced, first line</td>
<td>HER2+</td>
<td>I/II</td>
<td>NCT01684215</td>
</tr>
<tr>
<td>Palbociclib + TDM-1</td>
<td>Advanced, progression on prior anti-HER2 therapy</td>
<td>HER2+</td>
<td>I</td>
<td>NCT01976169</td>
</tr>
</tbody>
</table>

Abbreviation: AI, aromatase inhibitor.

Conclusions and Future Directions

The CDK4/6 inhibitor palbociclib has single-agent activity in breast cancer. In addition, palbociclib in combination with endocrine therapy has demonstrated significant PFS benefit over endocrine therapy alone. The history of palbociclib illustrates the successful identification of an oncogenic pathway in the laboratory and subsequent design and development of a drug that targets a specific molecular characteristic for use in the clinic. However, the development of this drug has also reminded us of the complexity of these pathway networks and challenges in biomarker development to predict response (28). Currently, ER status is the most reliable predictive marker for palbociclib, although fewer than half of ER+ patients in the phase II PALOMA-1 trial responded to therapy (20). It will be essential to identify additional biomarkers with demonstrated clinical use to help guide treatment decision making.

Palbociclib is a welcome and exciting addition to an existing array of endocrine and other targeted therapies for treatment of ER+ MBC. With each new therapeutic, we are making progress toward examining potential mechanisms related to endocrine resistance and translating science into the practice of precision medicine.

Disclosure of Potential Conflicts of Interest

A. Morikawa reports receiving commercial research support from Eli Lilly. N.L. Henry reports receiving commercial research funding from BioMarin Pharmaceutical, Celldex Therapeutics, and Sanofi-Aventis. No other potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A. Morikawa, N.L. Henry
Writing, review, and/or revision of the manuscript: A. Morikawa, N.L. Henry

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