



Original Research

# Development of peripheral neuropathy and its association with survival during treatment with *nab*-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: A subset analysis from a randomised phase III trial (MPACT)



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## KEYWORDS

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**Abstract Background:** In a phase III trial in patients with metastatic pancreatic cancer (MPC), *nab*-paclitaxel plus gemcitabine (*nab*-P/Gem) demonstrated greater efficacy but higher rates of peripheral neuropathy (PN) versus Gem. This exploratory analysis aimed to characterise the frequency, duration, and severity of PN with *nab*-P/Gem in the MPACT study.

**Patients and methods:** Patients with previously untreated MPC received *nab*-P/Gem or Gem. PN was evaluated using a broad-spectrum group of Standardised Medical Dictionary for

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Regulatory Activities Queries (SMQ) and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. A case report form was completed by physicians on day 1 of each cycle (also graded by NCI CTCAE version 3.0).

**Results:** In the *nab-P/Gem* arm, 227/421 patients (54%) experienced any-grade PN and 70 (17%) experienced grade III PN. No grade IV PN was reported. Most early-onset PN events were grade I, and treatment-related grade III PN occurred in 7% of patients who received up to three cycles of *nab-P*. Of those who developed grade III PN with *nab-P/Gem* treatment, 30 (43%) improved to grade  $\leq$ I (median time to improvement = 29 days) and 31 (44%) resumed therapy. Development of PN was associated with efficacy; median overall survival in patients with grade III versus 0 PN was 14.9 versus 5.9 months (hazard ratio, 0.33;  $P < .0001$ ).

**Conclusions:** *nab-P/Gem* was associated with grade III PN in a small percentage of patients. PN development was associated with longer treatment duration and improved survival. Grade III PN was reversible to grade  $\leq$ I in many patients (median  $\approx$  1 month) NCT00844649.

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## 1. Introduction

Advanced pancreatic cancer (PC) is associated with poor survival, with a 5-year survival rate of  $\approx$  2% in the United States [1]. Until recently, patients with advanced PC had limited treatment options. *nab-Paclitaxel* plus gemcitabine (*nab-P/Gem*) is a new treatment option that was approved based on the results of the phase III MPACT trial, in which *nab-P/Gem* demonstrated superiority over Gem [2]. The median overall survival (OS) for *nab-P/Gem* versus Gem was 8.5 versus 6.7 months (hazard ratio [HR], 0.72;  $P < .001$ ), the median progression-free survival (PFS) was 5.5 versus 3.7 months (HR, 0.69;  $P < .001$ ), and the overall response rate (ORR) by independent review was 23% versus 7% ( $P < .001$ ). In an updated report, the final OS for *nab-P/Gem* versus Gem was 8.7 versus 6.6 months (HR, 0.72;  $P < .001$ ) [3].

Peripheral neuropathy (PN) can be dose limiting and can persist indefinitely in some cases [4–6]. However, proper management of PN can potentially extend treatment. *nab-P* was developed to overcome the formulation limitations attributed to the solvent Kolliphor EL (formerly called Cremophor EL) and improve the safety profile and therapeutic index of solvent-based paclitaxel (sb-P) [7]. In phase II/III trials of various tumour types, *nab-P* regimens demonstrated improved efficacy and tolerability compared with solvent-based taxanes [8–10]. Compared with sb-P/carboplatin (C), *nab-P/C* was associated with significantly lower rates of grade  $\geq$ III PN in a phase III trial of patients with advanced non-small cell lung cancer (NSCLC) [10].

MPACT was the largest trial to date to evaluate a taxane combination in a large population of patients with advanced PC [2]. As expected, the combination arm was associated with a higher incidence of grade III/IV adverse events (AEs), including PN. Understanding and managing PN is an integral part of providing optimal therapy for patients with cancer; thus, the frequency,

duration, and severity of PN associated with *nab-P/Gem* therapy were investigated in this exploratory analysis of the MPACT trial.

## 2. Patients and methods

This subgroup analysis of the phase III MPACT trial was not pre-specified in the study protocol. The study design and patient characteristics have been described previously [2]; key parameters are described below. The independent ethics committee at each participating institution approved the study. All patients provided written informed consent before the initiation of the study.

### 2.1. Patients

This study enrolled adult patients with a Karnofsky performance status (KPS)  $\geq$ 70 and histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients were required to have adequate hepatic, haematologic, and renal function (including bilirubin level  $\leq$  the upper limit of normal, absolute neutrophil count  $\geq$   $1.5 \times 10^9/L$ , and haemoglobin level  $\geq$ 9 g/dl) and baseline PN grade  $\leq$ I.

### 2.2. Study design and treatment

Patients were randomised (1:1) to receive a 30–40-minute intravenous infusion of *nab-P* 125 mg/m<sup>2</sup>, followed by Gem 1000 mg/m<sup>2</sup> on days 1, 8, 15, 29, 36, and 43, or Gem alone 1000 mg/m<sup>2</sup> weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, patients received treatment on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity.

### 2.3. Safety assessments

Investigators monitored treatment-related AEs and serious AEs; weekly central laboratory data; and rates

of dose reductions, dose interruptions, and premature discontinuations. Patients who received  $\geq 1$  dose of study drug (treated population) were evaluated by physicians for safety using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0 [11], and AEs were coded to correspond with the preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0. PN was graded according to NCI CTCAE (Table A.1). PN was coded using Standardised MedDRA Queries (SMQ; broad scope); preferred terms included neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and other less commonly observed PN AEs. SMQ were not generated for treatment-emergent PN that resulted in dose reduction. PN was also evaluated by physicians using case report forms.

#### 2.4. Statistical methods

For incidence of PN by cycle, if a patient had multiple events of PN during a cycle, the worst grade among those events was counted. If a patient had PN events in  $>1$  cycle, the patient was counted in each of the corresponding cycles by worst grade reported in the respective cycle. Because patients discontinued from the study over time, the number of patients who received  $\geq 1$  dose of treatment in a specific treatment cycle was used as the denominator in the calculation of the percentage of patients with PN for that cycle. For total incidence of PN by grade, each patient was represented by the worst grade reported over the entire treatment period; in other words, each patient was counted only once even if the patient reported  $>1$  event in multiple cycles. The association of any grade of PN (none, I, II, or III) and OS was analysed with a Cox regression model by treating grade of PN as a continuous variable. A Cox regression model including PN (grade III versus grades none/I) as a time-varying covariate and other prognostic factors was used to determine the association of OS and high-grade PN.

#### 2.5. Dose modifications due to PN

Per protocol, *nab*-P treatment was withheld in patients who experienced grade  $\geq$ III PN, while Gem treatment could be continued. Once grade  $\geq$ III PN improved to grade  $\leq$ I, *nab*-P treatment could be resumed at a lower dose level in subsequent treatment cycles.

### 3. Results

#### 3.1. Patients

Overall, 431 patients were randomised to the *nab*-P/Gem arm, with 421 evaluable for safety. By SMQ

evaluation, rates of all-grade and grade III PN for *nab*-P/Gem were 54% and 17%, respectively (Table 1). Approximately 1% of patients had  $\geq 1$  serious AE of PN with *nab*-P/Gem. No grade IV PN was observed. Rates of grade III physician-assessed PN (Table A.2) were similar to those per the SMQ evaluation. In the subgroup of patients who received *nab*-P/Gem and developed grade III PN ( $n = 70$ , assessed by MedDRA), most baseline characteristics were similar to those of the intent-to-treat (ITT) population [2] as well as those in patients not developing PN (no grade). A few exceptions should be noted between patients who developed grade III PN and those who did not develop PN. A higher proportion of patients with grade III PN versus those without PN were from North America (66% versus 53%) and had a KPS of 90–100 at baseline (66% versus 51%). Furthermore, although median baseline carbohydrate antigen 19-9 was lower in patients who developed grade III PN (1583 U/ml) than in those who did not (2820 U/ml), we noted that the median number of metastatic sites, a measure of tumour burden, was similar between the groups (two each). No excess of comorbidities was observed within these subgroups versus the ITT population [2], including diabetes and renal impairment.

#### 3.2. Development of PN

Most PN events associated with *nab*-P/Gem treatment occurred within the first three cycles and were grade I. Most grade III PN developed after cycle 3; the rate of grade III PN doubled after cycle 4 and peaked at cycle 7 (Fig. 1). Seventy patients developed grade III PN during treatment. The rate of grade III PN ranged from 2–4% within each of the first three cycles; the cumulative incidence of grade III PN in patients treated for  $<3$  cycles was 7%. The median time to improvement from grade III PN to grade  $\leq$ I was 29 d. Of the 30 patients (43%) who improved to grade  $\leq$ I, 23 (77%) did so within 28 d (Table 2).

Table 1  
Peripheral neuropathy (per SMQ) in the treated population.

Peripheral neuropathy events, n (%) <sup>a</sup>	<i>nab</i> -P/Gem (n = 421)
Patients with grade $\geq$ I peripheral neuropathy AE	227 (54)
Worst grade of peripheral neuropathy	
Grade I	96 (23)
Grade II	61 (15)
Grade III	70 (17)
Patients with $\geq 1$ SAE of peripheral neuropathy	3 (1)

AE, adverse event; Gem, gemcitabine; MedDRA, Medical Dictionary for Regulatory Activities; *nab*-P, *nab*-paclitaxel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SMQ, Standardised MedDRA Queries.

<sup>a</sup> Based on MedDRA SMQ (broad range) graded by NCI CTCAE.

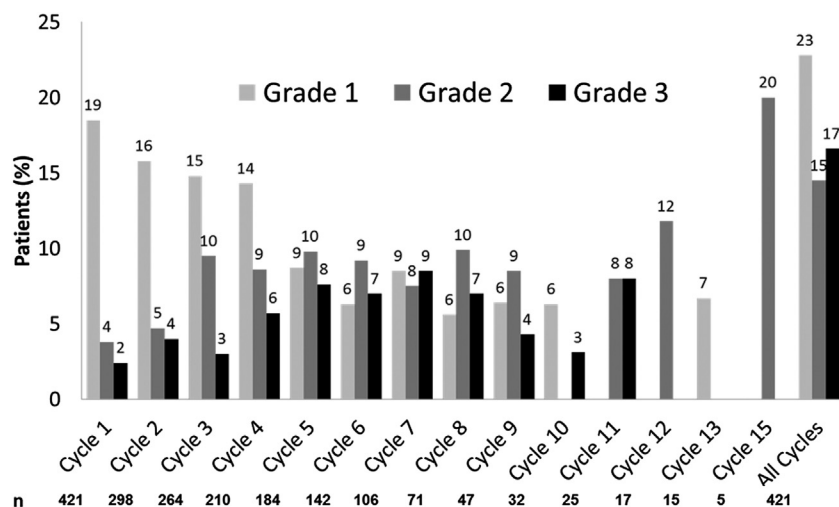


Fig. 1. Incidence of treatment-emergent peripheral neuropathy (per Standardised Medical Dictionary for Regulatory Activities Queries) in the nab-paclitaxel/gemcitabine arm by cycle and grade. The data represent the worst grade of an adverse event experienced by a patient, and a patient may have been counted in >1 cycle.

### 3.3. Treatment exposure

Patients with higher grades of PN generally had greater treatment exposure. Patients in the nab-P/Gem arm who developed grade III PN received a median of six cycles, while those who developed grades none to II PN received a median of three cycles (Table 3). Patients receiving nab-P/Gem who developed grade 3 PN had a longer median duration of treatment than those with grades none to II PN (195 versus 113 d). A higher median number of nab-P doses were administered in patients who developed grade III PN versus those who developed grades none to II PN (18 versus 11). Patients with grade III PN had a higher median cumulative dose of nab-P than those with grade none to II PN (1987.5 mg/m<sup>2</sup> versus 1275.0 mg/m<sup>2</sup>); average nab-P dose intensity was similar between these two cohorts (data not shown).

### 3.4. Dose modifications due to PN in patients receiving nab-P/Gem

Per protocol, most patients developing grade III PN had ≥1 nab-P dose modification (dose delay [80%] and/or

Table 2  
Improvement in grade III peripheral neuropathy over time in the nab-P/Gem arm.

Grade III peripheral neuropathy	nab-P/Gem (n = 70)
Improvement to grade ≤I	
Patients, n (%)	30 (43)
Time to improvement	
≤ 14 d	9 (30)
>14 to 28 d	14 (46.7)
>28 to 42 d	5 (16.7)
>42 d	2 (6.6)

Gem, gemcitabine; nab-P, nab-paclitaxel.

reduction [41%]), most of which occurred at or before cycle 6 (Table 4). Most patients required only one dose modification. Of the 31 patients who developed grade III PN and were able to resume treatment after a dose delay, 21 (68%) received a total of ≥6 cycles of therapy, and only 4 (13%) discontinued treatment due to PN. Of the 70 patients who developed grade III PN, 40 did not improve to grade ≤I; most of these patients received no further treatment with nab-P.

### 3.5. Efficacy outcomes in patients who developed PN after treatment with nab-P/Gem

Patients who developed PN (grades I–III) had significantly better outcomes versus those who did not (Table 3). Among patients with grade III PN versus no PN, the ORR was 43% versus 8% (relative risk reduction, 5.54; 95% confidence interval [CI], 3.18–9.67;  $P < .0001$ ), the median PFS was 9.1 versus 3.5 months (HR, 0.27; 95% CI, 0.18–0.41;  $P < .0001$ ), and the median OS was 14.9 versus 5.9 months (HR, 0.33; 95% CI, 0.23–0.48;  $P < .0001$ ). Each increasing grade of PN was associated with a longer median OS than the grade before it (Fig. 2). The 1-year OS rate for patients who developed grade III PN versus no PN was 61% versus 17%, and the 2-year OS was 24% versus 3%. Even in patients who had >4 cycles of therapy, those who developed grade III PN versus no PN had an improved survival (median OS, 15.7 versus 11.4 months; Table A.3); these patients received a similar median number of nab-P doses (Table A.4).

The development of PN during treatment with nab-P/Gem (from grades none to III) was associated with longer survival; every grade increase was associated with a 35% reduction in risk of death (HR, 0.65; 95% CI, 0.58–0.72;  $P < .0001$ ). In multivariate analysis, after



Table 3  
Efficacy outcomes in patients by grade of peripheral neuropathy developed in the *nab*-paclitaxel/gemcitabine arm.

Outcome	Grade of peripheral neuropathy developed				No grade versus III	
	0 (n = 194)	1 (n = 96)	2 (n = 61)	3 (n = 70)	HR/RRR	P for HR/RRR
OS, median (95% CI), months	5.9 (4.67–6.90)	9.0 (8.34–12.32)	12.6 (9.59–15.74)	14.9 (11.86–19.15)	0.33 (0.23–0.48)	<.0001
PFS, median (95% CI), months	3.5 (3.06–3.78)	5.6 (4.47–6.18)	9.3 (7.23–12.62)	9.1 (7.52–11.50)	0.27 (0.18–0.41)	<.0001
ORR (95% CI), %	8 (4.4–12.4)	29 (20.3–39.3)	43 (30.0–55.9)	43 (31.1–55.3)	5.54 (3.18–9.67)	<.0001
Number of cycles administered, median (min, max)	1 (1, 13)	4 (1, 17)	6 (1, 23)	6 (1, 22)	–	–

CI, confidence interval; HR, hazard ratio; max, maximum; min, minimum; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRR, relative risk reduction.

adjusting for all other prognostic factors found in previous reports (baseline KPS, presence of liver metastases, age, and region) [12], PN (grade III versus grades none/I) as a time-varying covariate remained associated with survival for all patients (HR, 0.55; 95% CI, 0.39–0.79;  $P = .0007$ ; Table A.5).

#### 4. Discussion

This exploratory analysis of the MPACT trial revealed that, although the incidence of all-grade PN was relatively high in patients receiving *nab*-P/Gem, no grade IV PN was reported, with most events being grades  $\leq$ II.

Table 4  
*nab*-P dose modifications due to grade III peripheral neuropathy and retreatment.

Patients with $\geq 1$ <i>nab</i> -P dose modification due to grade III peripheral neuropathy <sup>a</sup>	<i>nab</i> -P/Gem (n = 70)
Total dose delays, n (%)	
Cycle 1	6 (8.6)
Cycle 2	9 (12.9)
Cycle 3	7 (10.0)
Cycle 4	12 (17.1)
Cycle 5	13 (18.6)
Cycle 6	8 (11.4)
>6 cycles	13 (18.6)
Total dose reductions, n (%)	
Cycle 1	4 (5.7)
Cycle 2	9 (12.9)
Cycle 3	4 (5.7)
Cycle 4	4 (5.7)
Cycle 5	6 (8.6)
Cycle 6	2 (2.9)
>6 cycles	5 (7.1)
Patients retreated after developing grade III peripheral neuropathy, n (%)	31 (44.2)
Number of cycles administered, n (%)	
1	2 (6.5)
2	1 (3.2)
3	3 (9.7)
4	3 (9.7)
5	1 (3.2)
6	5 (16.1)
>6	16 (51.6)

Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

<sup>a</sup> Patients were counted multiple times if they had dose modifications in different cycles.

This is consistent with previous studies of weekly *nab*-P regimens in advanced PC and advanced NSCLC [10,13,14]. Despite the development of grade III PN with *nab*-P/Gem, PN was manageable with dose reductions or delays in nearly half of those affected, considering most patients who resumed treatment received  $\geq 6$  cycles of therapy total and the duration of treatment in patients developing grade III PN was 6.4 months. Of patients resuming treatment, only 13% discontinued *nab*-P therapy due to PN; thus, resumption of therapy appeared to be safe in these patients.

The course of grade III PN related to *nab*-P therapy in this study was cumulative in nature. The median time to onset of grade III PN was 140 d [2], and grade III PN peaked at cycle 7. This is important to note because patients who experienced grade III PN received a median of six cycles of *nab*-P/Gem; the median number of cycles delivered in this arm was three in the ITT population and three in those not developing PN [15]. Therefore, development of grade III PN did not impact administration of *nab*-P/Gem.

Patients receiving *nab*-P/Gem and developing PN had a significantly better ORR, median OS, and median PFS than patients not developing PN. Interestingly, the efficacy outcomes in patients developing grade III PN were numerically better than those observed in the ITT population (no formal statistical analyses were performed) [2]. Baseline characteristics in patients developing PN were similar to those in the ITT population and in patients who did not develop PN [2]. Therefore, differences in patient characteristics likely did not play a role in the differences observed in efficacy outcomes in these patient subsets. PN maintained an association with survival after multivariable analysis of other known prognostic factors. The most likely explanation is a biologic one related to chemoresponsiveness: patients with tumours that are intrinsically chemoresponsive have resultant higher response rates and, thus, an increased chance of prolonged treatment and ultimately of developing grade III PN. However, even in those with longer treatment duration, patients developing PN gained a survival advantage. Ongoing study of biomarkers may reveal novel insights into predictive factors for prolonged benefit. Single nucleotide polymorphisms

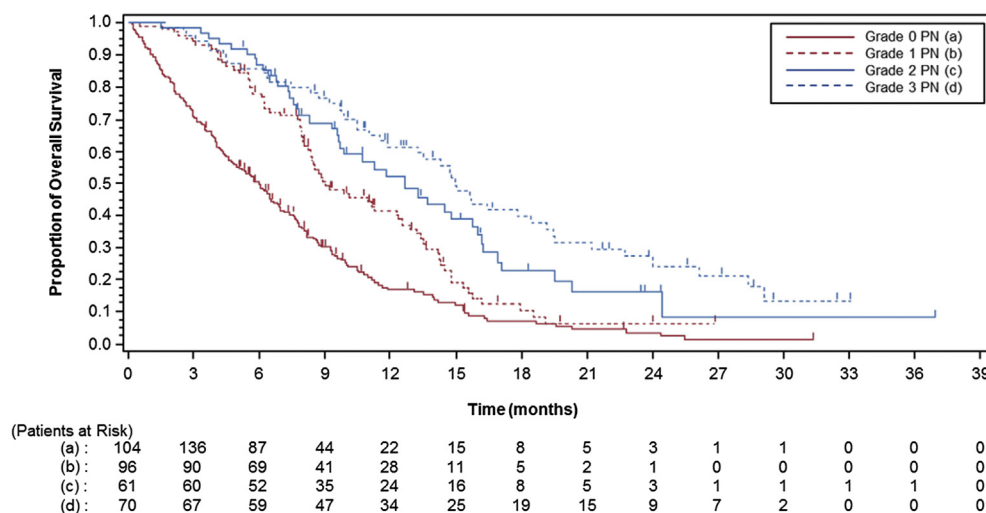


Fig. 2. Kaplan-Meier curve for overall survival by grade of peripheral neuropathy in the *nab*-paclitaxel/gemcitabine arm.

have been associated with the development of taxane-related neuropathy, and these may be the subject of future work [16].

Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) have also demonstrated significant clinical benefit over single-agent Gem [17]. Results from a recent meta-analysis of randomised phase III trials in patients with advanced PC (N = 9989) demonstrated that FOLFIRINOX was ranked the worst of six treatments with available data (including *nab*-P/Gem) with respect to development of grade  $\geq$ III PN [18]. The neuropathy that results with FOLFIRINOX is likely due to oxaliplatin, as neurotoxicity is a common dose-limiting toxicity of this agent [19,20]. Unlike in our findings with *nab*-P, PN caused by oxaliplatin can persist for many months after discontinuation [21]. In a single-centre study of 24 patients treated with oxaliplatin, nearly 80% reported residual symptoms of PN at a median of 25 months post-therapy [22]. Although 38% of the residual symptoms were classified as grade I, 29% and 13% were classified as grades II and III, respectively. More than 40% of patients reported significant functional issues with daily tasks, like walking and fine-motor skills. A second study of 20 patients with colorectal cancer previously treated with oxaliplatin (median of 13 months after therapy) reported similar findings [23]; 60% of patients self-reported significant physical limitations due to PN. These findings support the fact that chemotherapy-related PN can affect patient quality of life during and after treatment. Therefore, choice of therapy, particularly in the adjuvant setting, will need to take into account the competing risk of long-term toxicity, such as persistent neurotoxicity, and follow appropriate management strategies, such as careful monitoring for PN development and dose modifications, when it is identified.

In conclusion, this exploratory analysis of the MPACT trial demonstrated that although *nab*-P/Gem was associated with a higher rate of PN than Gem, the majority of PN experienced was grade  $\leq$ II. No patients developed grade IV PN, and many of those who developed grade III PN saw improvement to grade  $\leq$ I within  $\approx$  1 month. These findings were consistent with those of previous studies of weekly *nab*-P regimens in patients with advanced solid tumours [9,10,14].

#### Conflict of interest statement

DG: consultant or advisory role and research funding, Celgene Corporation; DDVH: consultant or advisory role, honoraria, and research funding, Celgene Corporation; MM: consultant or advisory role and research funding, Celgene Corporation; EG: research funding, Celgene Corporation; GT: nothing to disclose; RKR: consultant or advisory role, honoraria, and research funding, Celgene Corporation; TM: consultant or advisory role and honoraria, Celgene Corporation; HL: employment or leadership position and stock ownership, Celgene Corporation; RP: employment or leadership position and stock ownership, Celgene Corporation; SF: employment or leadership position and stock ownership, Celgene Corporation; BL: employment or leadership position and stock ownership, Celgene Corporation.

#### Role of the funding source

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2015.10.017>.

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