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ORIGINAL RESEARCH

Curative immune checkpoint inhibitors therapy in patients with mismatch repair-deficient locally advanced rectal cancer: a real-world observational study

F. Tosi[1], L. Salvatore[2,3], E. Tamburini[4], S. Artale[5], S. Lonardi[6], S. Marchetti[7], A. Pastorino[8], F. Pietrantonio[9], A. Puccini[10], F. L. Rojas-Llimpe[11], B. Vincenzi[12], S. Mariano[1], F. Negri[13], K. Bencardino[1], C. Pinto[14], C. Aschele[7†] & S. Siena[1,15*†]

[1]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan; [2]Oncologia Medica, Università Cattolica del Sacro Cuore, Rome; [3]Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; [4]Department of Oncology and Palliative Care, Cardinale Panico Tricase City Hospital, Tricase; [5]Oncology Unit, Vimercate Hospital, ASST della Brianza, Vimercate; [6]Medical Oncology 3 Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [7]Department of Oncology, Ospedale Sant'Andrea, Azienda Sociosanitaria Ligure 5, La Spezia; [8]IRCCS Ospedale Policlinico San Martino, Medical Oncology Unit 1, Genoa; [9]Department of Medical Oncology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; [10]Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Rozzano, Milan; [11]Medical Oncology Unit, Department of Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [12]Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Roma; [13]Gastroenterology and Endoscopy Unit, Azienda Ospedaliero-Universitaria di Parma, Parma; [14]Oncology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia; [15]Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy

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Background: Sustained clinical complete remissions were reported in all of 23 mismatch repair deficient/microsatellite instable (dMMR/MSI) locally advanced rectal cancer (LARC) patients treated with dostarlimab alone in a recent phase II study. These results led to off-label use of dostarlimab or other immune checkpoint inhibitors (ICIs) in dMMR/MSI-LARC even before regulatory approval. The present study [STAR(t)-IT-REDUCE] describes the outcome of dMMR/MSI-LARC patients treated with ICI in Italy.

Materials and methods: Investigator-initiated, observational, retrospective-cohort, multicentric study of ICI treatment in dMMR/MSI-LARC. Patients were eligible if treated with $\geq$1 ICI dose from July 2022 to December 2023 (date of approval of dostarlimab for this indication in Italy).

Results: Seventeen dMMR/MSI-LARC patients (13 of 17 treatment-naïve) were eligible. Fourteen patients completed 6 months of treatment, two discontinued after four doses and one after five doses because of immune-related pneumonia, social constraints, or non-oncological bowel obstruction, respectively. Overall, 16 of 17 assessable patients [94.1%; 95% confidence interval (CI) 69.24% to 99.69%, 'ITT analysis'] achieved complete clinical response (cCR). Ten of 11 treatment-naïve patients completing 6 months of treatment had cCR (90.9%; 95% CI 57.12% to 99.52%, 'per-protocol analysis'). One patient with near-CR underwent rectal surgery and minimal residual intramucosal tumor was found. With a median follow-up of 9.5 months, no local relapse occurred. One patient developed unconfirmed lung metastases. Two grade 3 and no grade 4 adverse events were reported.

Conclusion: The present STAR(t)-IT-REDUCE study documents the immunoablative and curative activity of ICI monotherapy in dMMR/MSI-LARC. Toxicity and compliance issues inherent to real-world practice are limited and do not affect achievement of initial complete tumor response but may limit response duration.

Key words: locally advanced rectal cancer, dMMR/MSI rectal cancer, immunotherapy, immune checkpoint inhibitor, dostarlimab, clinical complete response

INTRODUCTION

Locally advanced rectal cancer (LARC) is typically managed with multimodal therapy involving the use of total neo-adjuvant therapy (TNT), in which chemotherapy follows or is followed by chemoradiotherapy and then surgery.[1-3] This approach results in tumor downstaging, complete clinical response (cCR), and pathological complete response (pCR) rates of 25%-30%.[4,5] In patients undergoing surgery, resection of rectum is life-altering and often warrants

*Correspondence to: Prof. Salvatore Siena, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Università degli Studi di Milano, Piazza Ospedale Maggiore, 3, 20162 Milan, Italy. Tel: +39-02-6444-2291
E-mail: salvatore.siena@unimi.it (S. Siena).

†Co-senior authors.

permanent colostomy. Owing to sequelae of surgery and the high frequency of pCR, interest in non-operative management is increasing. The use of cCR that is achieved with TNT as a surrogate for pCR provides survival benefit in patients, with a non-operative option, similar to surgical resection.[6,7] Approximately 2.5%-10% of rectal adenocarcinomas are mismatch repair deficient/microsatellite instable (dMMR/MSI),[8] and these tumors respond poorly to standard chemotherapy regimens, including neoadjuvant chemotherapy in LARC.[9,10]

In this scenario, revolutionary positiveness has been raised by the first phase II trial that investigated the activity of the programmed cell death protein 1 (PD-1) inhibitor dostarlimab in patients with dMMR/MSI-LARC.[11,12] Twelve patients received dostarlimab every 3 weeks and completed nine planned cycles over 6 months. With a prolonged follow-up of 12 months, all 12 consecutive patients achieved cCR (100%), and no patient required surgery, radiotherapy, or chemotherapy.[11] These data were reinforced by a subsequent report involving a larger cohort of patients.[12]

Such unprecedented results prompted clinicians to offer off-label immunotherapy with ICI instead of chemoradiotherapy and surgery to dMMR/MSI-LARC patients even before registration studies had begun and while waiting for a longer follow-up of the pivotal phase II trial and confirmatory studies to avoid the morbidities of chemoradiotherapy and surgery. We designed the present study to evaluate clinical outcome of patients with dMMR/MSI-LARC who had received neoadjuvant ICI in the real-world setting in Italy.

MATERIALS AND METHODS

Data source

This was an investigator-initiated, observational retrospective-cohort multicenter study [STAR(t)-IT-REDUCE] promoted by Grande Ospedale Metropolitano Niguarda, Università degli Studi di Milano, Milan, Italy, by the STAR Network Alliance for Rectal Cancer, by Collegio Primari Oncologi Medici Oaspedalieri (CIPOMO), and by Collegio Oncologi Medici Universitari (COMU). All oncology centers in Italy were e-mailed to report patients eligible for the STAR(t)-IT-REDUCE study by replying to a survey from the promoters.

Study design and population

Inclusion criteria were: (i) patients with histological diagnosis of dMMR/MSI-LARC adenocarcinoma; (ii) dMMR/MSI status assessed locally by immunohistochemistry, next-generation sequencing, or PCR; (iii) no distant metastases by contrast-enhanced chest—abdomen—pelvis computed tomography scan; (iv) treatment with $\geq$1 dose of dostarlimab or other ICI. Exclusion criteria were: (i) recurrent rectal cancer; and (ii) prior immunotherapy or surgery for rectal cancer. Observation was from July 2022 to December 2023.

Among eligible patients, those with prior pelvic radiotherapy, chemotherapy, or chemoradiotherapy were included but not assessed for primary endpoint. The STAR(t)-IT-REDUCE study was approved by ethical committees, and patients signed informed consent to therapeutic procedures. Clinicopathological and molecular characteristics and survival data were retrieved in an anonymized manner and collected through a dedicated ReDCap database by an e-mailed survey.

Outcome measurements

Primary endpoints were assessment of cCR rate and duration of response (DOR) in patients treated with ICI as the only treatment modality for their LARC and completing 6 months of therapy ('per-protocol population'). Secondary endpoints were cCR and DOR, in the population of patients treated with ICI with or without previous chemotherapy, chemoradiotherapy, or radiotherapy and completing 6 months of anti-PD-1 blockade ('exploratory analyses population'). ITT analyses (cCR rate, DOR, safety, and tolerability) were carried out on the whole population of eligible patients. Tumor response was determined on the basis of magnetic resonance imaging (MRI) of the rectum and/or endoscopic evaluation and/or digital rectal examination, as per practice of the participating oncological center. In particular, near-clinical complete response (ncCR) and cCR were defined as detailed in the Memorial Sloan Kettering Regression Schema.[13] In particular, cCR was the absence of residual disease on digital and endoscopic rectal examination, as well as the absence of residual disease on rectal MRI, with no restricted diffusion on T2-weighted imaging; ncCR was neither cCR nor incomplete response.[13]

Statistical analysis

The STAR(t)-IT-REDUCE study is designed with a descriptive aim, without a hypothesis-driven fixed sample size. The sample size is expected to be 17 patients. With this sample size and assuming a true proportion of patients reaching a cCR of 100%, the width of the 95% confidence interval (CI), calculated using the Exact Clopper—Pearson formula, would be around 11.5%. The proportion of patients reaching cCR after treatment with the 95% CI was calculated. Among responders, DOR was estimated using the Kaplan—Meier method. Analyses were carried out using the R software version 4.4.1.

RESULTS

Patient, therapy, and tumor characteristics

Twelve institutions in Italy reported treatment of 17 eligible patients, from July 2022 to December 2023, as detailed in Table 1 and Figure 1. Tumor stage was predominantly clinical stage III, almost totality (94%) medium and low rectal tumors. Ten patients received dostarlimab 500 mg i.v. q21 days, six received pembrolizumab 200 mg i.v. q21 days, and one nivolumab (3 mg/kg) i.v. q14 plus ipilimumab (1 mg/kg) q21. Fourteen of 17 patients completed 6 months of treatment. The remaining three patients received at least one dose of ICI: one (ID-03-002) received four doses and discontinued for no compliance due to social constraints,

Table 1. Characteristics of patients, rectal cancers, and therapy with ICI

Total patients	*N* = 17 (100%)
Median age in years (range)	56 (23-77)
Gender	
Men	10 (59%)
Women	7 (41%)
ECOG performance status at diagnosis	
0	11 (65%)
1	5 (29%)
2	0 (0%)
3	1 (6%)
Race	
White	17 (100%)
Tumor stage	
T1 or T2	3 (18%)
T3	8 (47%)
T4	6 (35%)
Median distance of tumor from anal verge in cm (range)	5 (0-15)
Nodal status	
Positive	12 (71%)
Negative	4 (23%)
Not known	1 (6%)
Involvement of mesorectal fascia	
Positive	8 (47%)
Negative	9 (53%)
Comorbidities	8 (50%)
Cardiovascular	3
Cerebrovascular	1
Pulmonary disorder	2
Metabolic disorders	5
Cystic fibrosis	1
Infammatory bowel disease	1
Previous non-oncological abdominal surgery	1
Type of ICI received	
Dostarlimab	10 (59%)
Pembrolizumab	6 (35%)
Nivolumab + ipilimumab	1 (6%)
Systemic/locoregional treatment before ICI	
Prior chemotherapy	2 (12%)
Prior radiotherapy	1 (6%)
Prior chemoradiotherapy	1 (6%)

ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor.

one (ID-02-002) received five doses and discontinued because of non-oncological intestinal occlusion, and one (ID-09-001) received four doses and discontinued for pneumonitis. Four patients received systemic (chemotherapy) or local (radiotherapy) treatment before ICI. In particular, two patients (ID-07-001 and ID 01-001) received chemotherapy with oxaliplatin and 5-fluorouracil, respectively, three cycles and one cycle with evidence of tumor shrinkage; one patient received 'short-course' pelvic radiotherapy (ID-09-001) and one concomitant 'long-course' chemoradiotherapy (ID-12-001), both with stable disease. To evaluate the response at ICI treatments, ecoendoscopy was carried out in all 17 patients, and 16 patients underwent pelvic MRI. Three patients underwent rectal surgery after ICI treatment.

Germline analysis identified pathogenic genomic alterations in 9 of 17 patients, confirming Lynch syndrome (Table 2).

Efficacy and safety

As shown in Figure 1, 10 of 11 patients receiving an ICI as the sole treatment for their LARC and completing the protocol-defined 6-month treatment period achieved a cCR (90.9%; 95% CI 57.1% to 99.5%, planned 'primary analysis'). One of eleven had an nCR and underwent surgery displaying only minimal foci of intramucosal residual disease at pathological assessment.

On ITT analysis, 16 of 17 patients had a cCR and 1 an nCR [corresponding to ypT in-situ (ypTis) at surgery], with a cCR rate of 90.9% (95% CI 57.12% to 99.52%, 'per-protocol analysis').

Thirteen out of 14 patients completing 6 months of ICI treatment with or without previous chemotherapy and/or radiotherapy reached a cCR of 92.9% (95% CI 66.1% to 99.8%, 'planned secondary analysis').

Three patients underwent rectal surgery after 6 months of ICI treatment. Two in cCR (ID-04-001 and ID-03-001) showed a pCR while one with an ncCR (ID-11-001) had minimal intramucosal residual disease (ypTis).

Three out of 17 patients discontinued ICI treatment. In one patient (ID-02-002), dostarlimab was discontinued after cycle 5 due to non-oncological intestinal occlusion. This patient did not receive further oncological therapy and 5 months later had unconfirmed lung relapse. In one patient (ID-09-001) pembrolizumab was discontinued after four cycles due to grade 3 pneumonitis, and no tumor relapse has occurred. In the last patient (ID-03-002), dostarlimab was discontinued after four doses due to social constraints and a cCR was reached after 6 months.

During the median follow-up of 9.5 months (95% CI 7.54-11.6 months), only one patient (ID-02-002) experienced unconfirmed distant recurrence (lung lesions). No local regrowth or relapse occurred. All the 17 patients are alive.

The median DOR of the entire population was not reached.

Adverse events were as follows: (i) grade 1-2—three diarrhea (ID-03-002, ID-03-001, and ID-11-001), one hyperglycemia (ID-03-002), one hypothyroidism (ID-01-004), and one hypophysitis (ID-06-001); (ii) grade 3—one diarrhea (ID-02-002) and one pneumonitis (ID-09-001); and (iii) grade 4—none.

DISCUSSION

To our knowledge, these are the first European real-world data on upfront use of ICI in the treatment of dMMR/MSI-LARC. The present STAR(t)-IT-REDUCE study documents the extremely high activity of dostarlimab and also of pembrolizumab, or nivolumab + ipilimumab in dMMR/MSI-LARC. All but 1 of the 17 patients reassessed for tumor response achieved a cCR, independent of the specific ICI received, previous treatment with radiotherapy and/or chemotherapy, and the number of ICI doses received (6 months versus early discontinuation). Notably, the only patient with nCR had only microscopic tumoral foci within rectal mucosa upon surgical resection.

These findings appear to confirm the high and elective activity of ICIs in dMMR rectal tumors and lack of primary resistance.

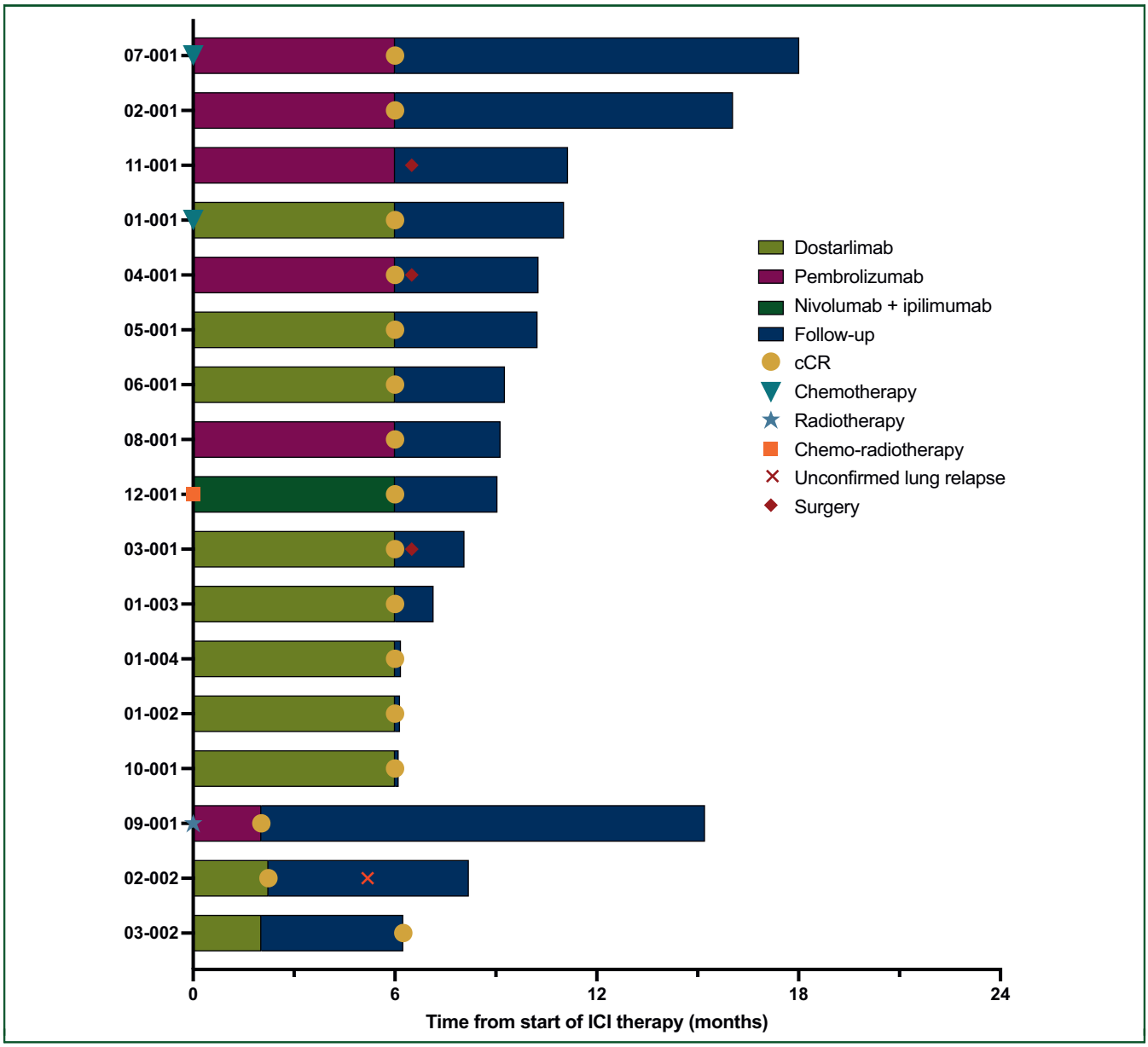

Figure 1. Swimmer plot of individual patients treated with indicated immune checkpoint inhibitor as part of total neoadjuvant therapy of dMMR/MSI locally advanced rectal adenocarcinoma.
cCR, complete clinical response; ICI, immune checkpoint inhibitor.

On the other hand, the kinetics and rapidity of tumor response may depend on unknown underlying additional biological determinants of immune response. This may affect the classification of tumor response at a pre-specified time point for a single patient. In this study three patients underwent surgery after achieving a cCR or ncCR. This probably reflects a prudential and conservative approach of the participating clinicians also due to the off-label setting. The appropriate timing for surgical exploration in patients with radiological residual disease after anti-PD-1 blockade remains to be defined. Of interest, this time may be different from that commonly used in patients with an nCR to chemo-radiotherapy.

Response duration may vary according to the number of ICI doses received, but the short follow-up of this study does not allow speculations in this regard.

This study has some limitations. Firstly, it is a retrospective study with observational methodology that can lead to possible selection bias. Secondly, the median follow-up was short due to the novelty of ICI use in LARC. Data during longitudinal follow-up (with endoscopy or MRI) were not required by the survey unless a local regrowth or distant metastases occurred.

Despite these limitations, STAR(t)-IT-REDUCE is important for the future clinical use of ICI in rectal cancer. Two of the three patients discontinuing treatment before completing the protocol-specified 6-month treatment in our study would have not been eligible for a clinical trial because of major social constraints and multiple previous surgeries related to Lynch syndrome, respectively. Real-world studies indeed reflect more closely the characteristics of the case-mix of everyday patients in clinical

Table 2. Characteristics of rectal cancers and Lynch syndrome

Total patients	*N* = 17 (100%)
Lynch syndrome	
Assessed and confirmed	9 (53%)
Suspected and under evaluation	4 (23.5%)
Assessed and not found	4 (23.5%)
Pathogenic mutational status[a]	*n* = 9
MLH1	2 (22%)
PMS2	0 (0%)
MSH2	6 (67%)
MSH6	3 (33%)
Previous cancer(s)[a]	6 (38%)
Colon cancer, with/without Lynch syndrome	5/0
Endometrial cancer, with/without Lynch syndrome	2/0
Urothelial cancer, with/without Lynch syndrome	1/0
Cervix cancer, with/without Lynch syndrome	1/0
Ampullary cancer, with/without Lynch syndrome	1/0
Prostate cancer, with/without Lynch syndrome	1/0
MMR assessment method in tumor sample[a]	
Protein expression by IHC	12 (71%)
Gene mutations by PCR	5 (29%)
Gene mutations by NGS	3 (18%)
Pathogenic mutational status[a]	*n* = 16
MLH1	7 (44%)
PMS2	4 (25%)
MSH2	7 (44%)
MSH6	7 (44%)

IHC, immunohistochemistry; MMR, mismatch repair; NGS, next-generation sequencing.
[a]More than one item can occur in the same patient.

practice. The results of STAR(t)-IT-REDUCE and those of the pivotal phase II study are thus reassuring for routine applicability of this strategy.

Interestingly, in the original MSKCC phase II study, there were no patients discontinuing treatment due to toxicity.[11,12] Therefore, maintenance of optimal toxicity profile may be crucial to guarantee the maximum immune-ablative effect of ICI therapy in dMMR/MSI-LARC.

Present data in European patients are in line with the real-world data published in an Asian retrospective study of 20 patients, with a complete response of 90% after seven cycles of sole ICI treatment.[14] Less-encouraging results came from another Asian retrospective 29-patient cohort study in which 69% complete response was achieved after a median 5 cycles of therapy with ICI differently combined with chemotherapy or other very heterogeneous treatments.[15]

Conclusions

Evidence generated in the real-world setting of the STAR(t)-IT-REDUCE study reinforces the recommendation to test MMR status in all LARCs before treatment decision and, most importantly, supports the groundbreaking clue that in dMMR/MSI-LARC, PD-1 or programmed death-ligand 1 blockade is safe and leads to impressive cCR rate even without chemotherapy, radiotherapy, and rectal surgery, thus allowing organ preservation and quality of life.

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DISCLOSURE

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