ESMO VIRTUAL SUMMIT RUSSIA

An ESMO Meeting

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Welcome
CURRENT TREATMENT STANDARDS AND PRACTICE CHANGING TRIALS IN ADVANCED GASTROESOPHAGEAL CANCER

Dr Elizabeth Smyth
Cambridge, UK
Honoraria and/or travel
Astellas, AstraZeneca, BMS, Celgene, Five Prime Therapeutics, Gritstone Oncology, Merck, Servier, Zymeworks
TALK OUTLINE

1L standards and changes
2L standards
3L changing practice
HER2 targeted therapy update
Immunotherapy: the good, the bad, the indeterminate
On the horizon
Chemotherapy improves survival and quality of life for patients with advanced gastroesophageal cancer

Inoperable or metastatic gastric cancer

- Palliative chemotherapy
- Best supportive care if unfit for treatment

HER2-negative:
- Platinum+ fluoropyrimidine-based doublet or triplet regimen

HER2-positive:
- Trastuzumab + CF/CX
- Consider clinical trials of novel agents

Oxaliplatin = cisplatin in efficacy but oxaliplatin is safer and may be superior in older patients

Capecitabine = infusional 5FU in efficacy with more hand foot, less line related thrombus/infection

The 1L standard of care is a platinum and fluoropyrimidine doublet or (rarely) triplet

Median overall survival for patients with advanced gastroesophageal cancer is <1 year

ESMO GASTRIC CANCER GUIDELINES

Murad et al, Cancer. 1993
Pyrhönen et al, Br J Cancer. 1995
Cunningham et al, NEJM 2008
Al Batran et al, JCO 2016.
NEW DEVELOPMENTS IN 1L GC

- Results for doublet vs triplet (JCOG1013)
- Treatment of older/frail patients (GO2)
1L CHEMOTHERAPY FOR ADVANCED GASTRO-ESOPHAGEAL CANCER
Doublet vs triplet chemotherapy previous evidence

TAX 325 Trial Toxicity

<table>
<thead>
<tr>
<th>Toxicity ≥ grade 3</th>
<th>DCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia ≥ grade 3</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Death on treatment</td>
<td>3.6%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

In DCF arm complicated neutropenia with G-CSF was 12%

Radiological response rate DCF 37% vs 25% CF (p=0.01)

Addition of docetaxel to CF ↑ myelosupression and infection

1L TREATMENT GASTRO-ESOPHAGEAL CANCER

Doublet vs triplet chemotherapy. New evidence

JCOG1013 trial results support no benefit for addition of taxane to cisplatin/S1 chemotherapy

Treatment naïve advanced gastric cancer

- Docetaxel/cisplatin /S1 (n=370)
- Cisplatin/S1 (n=371)

Primary endpoint OS

Addition of docetaxel to cisplatin/S1 did not improve ORR, PFS or OS

1L TREATMENT GASTRO-ESOPHAGEAL CANCER
Doublet vs triplet chemotherapy. New evidence

JCOG1013 trial results support no benefit for addition of taxane to cisplatin/S1 chemotherapy

Take home message

**Triplet chemotherapy should not be the standard for most patients with advanced gastroesophageal cancer**

Addition of docetaxel to cisplatin/S1 did not improve ORR, PFS or OS

Gastro-esophageal cancer is a disease of old age. The median age of patients in clinical trials is younger (early 60s). How do we modify chemotherapy for older patients?

GO2 was a phase III open label, non-inferiority, randomised trial.

 Patients were not suitable for 3 drug chemotherapy.

 Treatment was CapOx at 100%, 80% or 60% dose.

 CapOx = oxaliplatin 130mg/m² q21d plus capecitabine 625mg/m² bd x 21 d.
1L TREATMENT GASTRO-ESOPHAGEAL CANCER

What has changed? GO2 trial results

The primary endpoint of non-inferiority for PFS was confirmed

Overall survival was comparable

Level A (100%)  7.5 months
Level B (80%)   6.7 months
Level C (60%)   7.6 months

Hall et al, ASCO 2019
1L TREATMENT GASTRO-ESOPHAGEAL CANCER
GO2 trial results: toxicity and quality of life

High grade toxicity was consistently lower in patients treated with reduced dose chemotherapy

Quality of life improved for patients treated on lower dose chemotherapy arms (B&C)

Hall et al, ASCO 2019
1L TREATMENT GASTRO-ESOPHAGEAL CANCER

GO2 trial results: toxicity and quality of life

Take home message

Elderly/frail patients can be treated with ↓ dose chemotherapy without compromising survival.

Reduced dose regimens have ↓ toxicity and ↑ QoL

High grade toxicity was consistently lower in patients treated with reduced dose chemotherapy.

Quality of life improved for patients treated on lower dose chemotherapy arms (B&C).

Hall et al, ASCO 2019
SECOND LINE STANDARDS FOR ADVANCED GASTRO-ESOPHAGEAL CANCER
2\textsuperscript{ND} LINE CHEMOTHERAPY FOR ADVANCED GC

**COUGAR-02**

- Previously treated advanced gastric cancer
  - Docetaxel (n=84)
  - BSC (n=84)

**Korean trial**

- Previously treated advanced gastric cancer
  - Docetaxel or irinotecan (n=133)
  - BSC (n=69)

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**Median OS**

- 5.2m docetaxel vs 3.6m BSC
- Median gain in OS is ~6 weeks

**ORR**

- 7-15\% for 2L chemo regardless of regimen

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**WG4007 trial**

- Paclitaxel equivalent to irinotecan

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*Ford et al, Lancet Oncol. 2014
Kang et al, J Clin Oncol. 2012
Hironaka et al, J Clin Oncol. 2013.*
2ND LINE CHEMOTHERAPY FOR ADVANCED GC

Benefit is greatest in ECOG 0 patients with sustained response to 1st line therapy

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Events/patients</th>
<th>Docetaxel events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22/24 (91.7%)</td>
<td>-6.0 81</td>
<td>0.48 (0.24-0.95)</td>
</tr>
<tr>
<td>1</td>
<td>45/46 (97.8%)</td>
<td>-5.0 22.7</td>
<td>0.80 (0.53-1.21)</td>
</tr>
<tr>
<td>2</td>
<td>13/14 (92.9%)</td>
<td>-1.2 5.9</td>
<td>0.81 (0.35-1.82)</td>
</tr>
<tr>
<td>Stratified</td>
<td>80/84 (95.2%)</td>
<td>-12.2 36.7</td>
<td>0.72 (0.52-0.99)</td>
</tr>
</tbody>
</table>

Progression

- During treatment: 36/36 (100%) vs 34/35 (97.1%) -3.1 16.9 0.83 (0.52-1.34)
- Within 3 months: 26/27 (96.3%) vs 21/22 (95.5%) -2.6 10.7 0.79 (0.43-1.43)
- 3-6 months: 18/21 (85.7%) vs 26/25 (100%) -9.6 8.7 0.33 (0.17-0.65)
- Stratified: 80/84 (95.2%) vs 81/84 (95.4%) -15.3 36.4 0.66 (0.47-0.91)

Heterogeneity between groups χ²=5.3, p=0.07

Unstratified: 80/84 (95.2%) vs 81/84 (95.4%) -15.3 37.6 0.67 (0.48-0.92)

(p=0.01)

2L TREATMENT GASTRO-ESOPHAGEAL CANCER:
ANTI-VEGFR2: RAMUCIRUMAB

Ramucirumab improves OS compared to placebo

REGARD
2nd line advanced GC/GEJ post platinum/5FU chemotherapy

Ramucirumab
N=238
Placebo
N=117

Median OS 5.2m vs 3.8m ram vs placebo

Ramucirumab + paclitaxel is superior to paclitaxel alone

RAINFOW Trial
2nd line advanced GC/GEJ post platinum/5FU chemotherapy

Paclitaxel plus ramucirumab
N=330
Paclitaxel plus placebo
N=335

Median OS 9.6m vs 7.4m ORR 28% vs 14,

Low ORR (4%), survival similar with 2L chemo

Fuchs et al, Lancet. 2014
Wilke et al, Lancet Oncol. 2014
2L TREATMENT ADVANCED GC

Comparison best supportive care (BSC), chemo, ramucirumab and combination

**Take home message**
- Ramucirumab + paclitaxel > paclitaxel alone
- Benefit to chemo compared to BSC
- Patient selection is important
3RD LINE STANDARDS FOR ADVANCED GASTRO-ESOPHAGEAL CANCER

PRACTICE CHANGING TRIALS
USE OF LATER LINES OF TREATMENT IN ADVANCED GC
REAL-LIFE DATA

Previously there was no Level 1 evidence to support treatment after 2L in advanced gastro-eophageal cancer

Outside Asia, a very similar proportion of patients are treated with 2L and 3L treatment

Hess et al. Gastric Cancer
Cafferkey et al. ESMO 2017
Fanotto et al. Oncologist 2017
**PRACTICE CHANGING TRIALS IN 3L GC**

**TAGS – Trifluridine tipiracil vs placebo in chemorefractory GC**

**Patients with mGC (including GEJ cancer)**
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 years in Japan)
**Target sample size: 500**

**FTD/TPI (TAS-102) + BSC**
- (n=337)
- 35 mg/m² BID orally on days 1–5 and 8–12 of each 28-day cycle

**Placebo + BSC**
- (n=170)
- BID orally on days 1–5 and 8–12 of each 28-day cycle

**End points**
- **Primary:**
  - OS
- **Key secondary:**
  - PFS, safety
- **Other secondary:**
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

**R 2:1**

- Treatment until progression, intolerable toxicity or patient withdrawal
- Multicentre, randomised, double-blind, placebo-controlled, phase 3 study
- Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)

Shitara et al, Lancet Oncol 2019
Overall survival is significantly improved with trifluridine-tipiracil compared to placebo: 2.1 month gain
PFS is short but also statistically significantly improved.
ORR is 4%
**PRACTICE CHANGING TRIALS IN 3L GC**

**ATTRACTION-02: Nivolumab vs BSC in chemorefractory GC**

**Key eligibility criteria:**
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Refractory to/intolerant of ≥2 standard therapy regimens
- ECOG PS of 0 or 1

**Randomization:**
- 2:1

**Nivolumab 3 mg/kg IV Q2W**
- **Stratification:**
  - Country (Japan vs South Korea vs Taiwan)
  - ECOG PS (0 vs 1)
  - Number of organs with metastases (<2 vs ≥2)

**Placebo**

**Primary endpoint:**
- OS

**Secondary endpoints:**
- Efficacy (PFS, BOR, ORR, TTR, DOR, DCR)
- Safety

**Exploratory endpoint:**
- Efficacy by tumor PD-L1 expression

**ATTRACTION-2 patient characteristics**

- **ECOG PS (%)**
  - 0 vs 1: 29 vs 71

- **Site of disease (%)**
  - Gastric vs other: 82 vs 18

- **Prior regimens (%)**
  - 2 vs 3 vs ≥4: 20 vs 40 vs 40

**ATTRACTION-02 was a phase III, placebo controlled, randomised trial conducted primarily in Asian countries**

PRACTICE CHANGING TRIALS IN 3L GC

ATTRACTION-2: Nivolumab vs BSC in chemorefractory GC

Recall response rates are 12%.

Responses in PD-L1–positive and –negative patients

38% reduction in risk of death in nivolumab treated patients. PD-L1 had no effect on outcome.

PRACTICE CHANGING TRIALS IN 3L GC

ATTRACTION-2: Nivolumab vs BSC in chemorefractory GC

**ATTRACTION-2**

First trial to show that immune checkpoint blockade could ↑ survival in advanced gastro-esophageal cancer

CAVEAT: Asian patients only included

BUT: very similar ORR and OS results in non-randomised KEYNOTE-059 trial

38% reduction in risk of death in nivolumab treated patients

PD-L1 had no effect on outcome

RECIST response rates are 12%

Responses in PD-L1–positive and –negative patients

Patients with RECIST PR to nivolumab have a median OS of > 2 years

Stable disease on nivolumab have improvement in 1 year survival and trend towards median OS improvement

How best to select patients for chemotherapy vs immune checkpoint blockade?

Retrospective data suggest worse outcomes for anti-PD-1 in high burden of disease, liver mets, poor PS

KEYNOTE-059 (pembrolizumab) data support PD-L1 CPS as weakly predictive biomarker
HER2 TARGETING IN ADVANCED GASTRO-ESOPHAGEAL CANCER
Trastuzumab plus chemotherapy is the standard of care for HER2 positive patients. Patients with tumours which are IHC3+ or IHC2+ FISH positive are eligible.

Bang et al, Lancet. 2010
TARGETING HER2 IN GASTROESOPHAGEAL CANCER

TOGA trial

Trastuzumab plus chemotherapy is the standard of care for HER2 positive patients

Patients with tumours which are IHC3+ or IHC2+ FISH positive are eligible

Negative trials have been a challenge in HER2 positive gastro-esophageal cancer

1L – JACOB (pertuzumab + trastuzumab + chemotherapy)
2L – GATSBY (TDM1)
2L – T-ACT (trastuzumab + paclitaxel)

Bang et al, Lancet. 2010
CHALLENGES OF HER2 IN GC

Heterogeneity

<table>
<thead>
<tr>
<th>TOGA HER2 % of positive cells in IHC3 + patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cells</td>
</tr>
<tr>
<td>% patients</td>
</tr>
</tbody>
</table>

What is the best cut off?

Disease specific

Dynamic changes

AMNESIA heterogenous resistance mechanism

Van Cutsem et al, Gastric Cancer. 2015
Ock et al, Clin Cancer Res. 2015
Gomez-Martin J Clin Oncol. 2013
TARGETING HER2 IN GASTRIC CANCER
New hope on the horizon – trastuzumab deruxtecan

Payload – topo-isomerase inhibitor
Higher drug:antibody ratio than TDM1
High bystander effect (kills nearby cells)

Trial in Japanese/Korean GC patients
DESTINY-Gastric 01

Previously treated advanced HER2 GC/GEJ post platinum/5FU chemotherapy

Trastuzumab deruxtecan
N=125

Chemotherapy
N=62

*Archival tissue for study entry (IHC3+ or 2+ FISH positive)
HER2 low arms not yet reported

TARGETING HER2 IN GASTRIC CANCER
New hope on the horizon – trastuzumab deruxtecan

Results appear very promising
Randomised trials needed in non-Asian patients

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>14%</td>
<td>3.5m</td>
<td>8.4m</td>
</tr>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>51%</td>
<td>5.6m</td>
<td>12.5m</td>
</tr>
</tbody>
</table>
IMMUNOTHERAPY IN ADVANCED GASTRO-ESOPHAGEAL CANCER

The good, the bad, and the indeterminate
### IMMUNE CHECKPOINT BLOCKADE IN GC

3L results from ATTRACTION-2 and KEYNOTE-059

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS months (95% CI)</th>
<th>OS months (95% CI)</th>
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<tr>
<td>Nivolumab</td>
<td>12%</td>
<td>1.61 (1.54–2.30)</td>
<td>5.3 (4.6–6.34)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>12.6%</td>
<td>2.0 (2.0–2.1)</td>
<td>5.6 months (4.3–6.9)</td>
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Kang et al, Lancet 2017
Fuchs et al, JAMA Oncol. 2018
# IMMUNE CHECKPOINT BLOCKADE IN GC

3L results from ATTRACTION-2 and KEYNOTE-059

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS months (95% CI)</th>
<th>OS months (95% CI)</th>
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<tr>
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<td>12.6%</td>
<td>2.0 (2.0-2.1)</td>
<td>5.6 months (4.3-6.9)</td>
</tr>
<tr>
<td><strong>PD-L1 negative</strong></td>
<td>6.4%</td>
<td>2.1 (2.0-2.1)</td>
<td>4.9m (3.4-6.5)</td>
</tr>
<tr>
<td><strong>PD-L1 ≥ CPS1</strong></td>
<td>15.5%</td>
<td>2.0 (1.9-2.0)</td>
<td>5.8m (4.5-7.9)</td>
</tr>
</tbody>
</table>

Kang et al, Lancet 2017
Fuchs et al, JAMA Oncol. 2018
### IMMUNE CHECKPOINT BLOCKADE IN GC

3L results from ATTRACTION-2 and KEYNOTE-059

<table>
<thead>
<tr>
<th>ORR, PFS and OS results in PD-1 treated chemorefractory GC</th>
<th>ORR</th>
<th>PFS months (95% CI)</th>
<th>OS months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 12% 1.61 (1.54–2.30) 5.3 (4.6–6.34)</td>
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<td></td>
</tr>
<tr>
<td>Pembrolizumab PD-L1 negative 15.5% 2.1 (2.0-2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab PD-L1 ≥ CPS1 6.4% 2.0 (1.9-2.0)</td>
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</tbody>
</table>

3L trials were compared to placebo (ATTRACTION-2) or were non randomised (KEYNOTE 059)
Pembrolizumab did not improve OS compared to chemotherapy in PD-L1 CPS≥1 patients.

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS (m, 95% CI)</th>
<th>OS (m, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPS ≥1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14%</td>
<td>4·1 (3·1–4·2)</td>
<td>8·3 (7·6–9·0)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>16%</td>
<td>1·5 (1·4–2·0)</td>
<td>9·1 (6·2–10·7)</td>
</tr>
</tbody>
</table>

Early progression is common in low PD-L1 expressing patients.
Pembrolizumab did not improve OS compared to chemotherapy in PD-L1 CPS≥1 patients. Subgroups with higher PD-L1 expression and microsatellite unstable tumours had more benefit.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORR</th>
<th>PFS (m, 95% CI)</th>
<th>OS (m, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPS ≥1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14%</td>
<td>4.1 (3.1–4.2)</td>
<td>8.3 (7.6–9.0)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>16%</td>
<td>1.5 (1.4–2.0)</td>
<td>9.1 (6.2–10.7)</td>
</tr>
<tr>
<td><strong>CPS ≥10 (n=108)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>9%</td>
<td></td>
<td>8.0 (5.1–9.9)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>25%</td>
<td></td>
<td>10.4 (5.9–17.3)</td>
</tr>
<tr>
<td><strong>MSI (n=27)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>17%</td>
<td></td>
<td>8.1 (2.0–16.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>47%</td>
<td></td>
<td>Not reached (5.6–NR)</td>
</tr>
</tbody>
</table>
IMMUNE CHECKPOINT BLOCKADE IN 1L GC

KEYNOTE-062: win, lose or draw?

6 primary analyses, 4 tested in parallel. Downstream test cannot be positive if upstream negative. Very strict alpha for multiple tests.
IMMUNE CHECKPOINT BLOCKADE IN 1L GC

Non-inferiority analysis: Pembro vs chemo in PD-L1 CPS ≥ 1

Survival was comparable between arms
10.6m pembro vs 11.1m chemo

Non-inferiority margin was not crossed
Pembro is deemed non-inferior to chemo

BUT low ORR (15%) and PFS (2.0 months) in pembrolizumab treated patients
IMMUNE CHECKPOINT BLOCKADE IN 1L GC

Superiority analysis: Pembro vs chemo in PD-L1 CPS ≥ 10

Survival was longer in pembro treated patients (17.4m vs 10.6m)

BUT there was no alpha for this analysis so the result cannot be deemed significant
AND low ORR (25%) and PFS (2.9 months) in pembrolizumab treated patients
Although ORR and PFS were improved with chemo + pembro there was overall survival benefit.
KEYNOTE-062

Take home messages

1) Pembrolizumab was statistically non-inferior to chemotherapy in CPS ≥ 1 patients
   Concerns regarding low ORR and early progression

2) Pembrolizumab shows higher activity and a trend towards survival ↑ in CPS ≥ 10
   Similar concerns regarding ORR and early progression even in more sensitive patients

3) Pembrolizumab + chemotherapy is no more effective than chemotherapy alone,
   regardless of PD-L1 status.

   Clinical selection, other biomarkers (MSI, TMB) and combinations will be important in future
# LOOKING FORWARD: ONGOING TRIALS IN ADVANCED GASTRO-ESOPHAGEAL CANCER

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>HER2</th>
<th>New targets</th>
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</thead>
</table>
| **CHECKMATE 649**  
1L chemo ± nivolumab | **DESTINY series**  
trastuzumab deruxtecan | **SPOTLIGHT**  
Chemo ± claudiximab in CLN18.2 positive |
| **KEYNOTE 811**  
1L chemo + trastuzumab ± pembro | **MAHOGANY**  
Margetuximab + chemo ± immune checkpoint inhibitor | **FIGHT**  
Chemo ± bemarituzumab in FGFR2 positive |
| Anti-PD-1 + TKI (e.g nivo-rego or pembro-lenavatinib) | | |

**ESMO VIRTUAL SUMMIT RUSSIA**
CURRENT TREATMENT STANDARDS AND PRACTICE CHANGING TRIALS IN ADVANCED GASTROESOPHAGEAL CANCER

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