How to improve the adjuvant treatment of colon cancer?

Aimery de Gramont
Franco-British Institute
Levallois-Perret
Disclosure

- Sanofi
- Roche
How to improve the adjuvant treatment of colon cancer?

Our achievements
What is ongoing?
Biomarkers
Improving our therapies
Improving our clinical research
How to improve the adjuvant treatment of colon cancer?

Our achievements
## Chemotherapy agents in adjuvant colon

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Results</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV5FU</td>
<td>Stage II MSS Stage III</td>
<td>Moertel - IMPACT - QUASAR - NSABP C03/C04</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Stage III</td>
<td>X-ACT</td>
</tr>
<tr>
<td>Oxaliplatin + FP</td>
<td>High-risk Stage II - Stage III</td>
<td>MOSAIC - NSABP C07 - XELOXA</td>
</tr>
<tr>
<td>UFT</td>
<td>Non-inferiority</td>
<td>NSABP C06</td>
</tr>
<tr>
<td>Irinotecan+FP</td>
<td>Failed</td>
<td>PETACC3 - CALGB 89803 - ACCORD 02</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td>Failed</td>
<td>PETACC 1</td>
</tr>
<tr>
<td>S1</td>
<td>Failed</td>
<td>JCOG 0910</td>
</tr>
<tr>
<td>TAS 102</td>
<td>Not tested</td>
<td></td>
</tr>
</tbody>
</table>

**Fluoropyrimidines +/- oxaliplatin**
# Tageted therapies in adjuvant colon

<table>
<thead>
<tr>
<th>Targeted therapy</th>
<th>Results</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Failed</td>
<td>NSABP C08 - AVANT</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Failed</td>
<td>N0147 - PETACC 8</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>On going</td>
<td>NSABP C13</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Not tested</td>
<td></td>
</tr>
</tbody>
</table>

Other failures:
- Interferon alpha
- Edrecolomab
Oxaliplatin in stage III C

Stage III N2
15% absolute benefit

Ándré T et al, JCO 2015
3-Yr DFS in Stage III: Results over time
3-Yr DFS in Stage III: Results over time

Survival %

- LV/5FU
- FP
- Oxaliplatin

Time:
- Feb-82
- Aug-87
- Jan-93
- Jul-98
- Jan-04
- Oct-06
## Stage Migration

Recent trials vs. MOSAIC in Stage III

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV5FU2</td>
<td>81.3%</td>
<td>84.3%</td>
<td>86.0%*</td>
<td>87.9%</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td></td>
<td>XELOX</td>
<td>mFOLFOX6</td>
<td>90.0%</td>
</tr>
</tbody>
</table>

| 3yr OS | 81.3% | 84.3% | 86.0%* | 87.9% | 90.0% |

* from curves

### FOLFOX4 MOSAIC vs. FOLFOX4 AVANT

<table>
<thead>
<tr>
<th></th>
<th>3-yr DFS</th>
<th>5-yr OS</th>
<th>3-yr DFS &lt;4LN</th>
<th>3-yr DFS ≥4LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC</td>
<td>73%</td>
<td>76%</td>
<td>72%</td>
<td>56%</td>
</tr>
<tr>
<td>AVANT</td>
<td>77%</td>
<td>85%</td>
<td>85%</td>
<td>66%</td>
</tr>
</tbody>
</table>

+4%     +9%     +13%    +10%
**Elderly - ACCENT**

<table>
<thead>
<tr>
<th>ACCENT analysis</th>
<th>Hazard ratio (95% CIs)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 years, n=3877</td>
<td>0.77 (0.68,0.86)</td>
</tr>
<tr>
<td>≥70 years, n=703</td>
<td>1.04 (0.80,1.35)</td>
</tr>
</tbody>
</table>

*Values <1 favor oxaliplatin-based therapy vs. 5-FU/LV.
†Data for oxaliplatin-based regimens.

**Elderly patients do not benefit of oxaliplatin**

McCleary et al. ASCO 2009 (poster 4010), JCO 2014
Role of Gender in Elderly Patients

DFS (recurrence & death of other causes)

MOSAIC: elderly women did better than elderly men
<table>
<thead>
<tr>
<th>KRAS wt</th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Hazard Ratio 95% CI (adjusted*)</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1025</td>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55 (1.32, 1.82)</td>
</tr>
<tr>
<td></td>
<td>Cet</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48, 2.32)</td>
</tr>
<tr>
<td></td>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05, 1.65)</td>
</tr>
</tbody>
</table>

**19.3 MONTHS IS A BIG DIFFERENCE!!**
Left and Right Colon

Weiss JM et al. JCO 2011

SEER database
HR 1.259 (1,026 to 1,545)  
P = 0.0236

Stage III  
Left > Right
Left and Right Colon

Stage II
Right > Left

HR 0.633 (0.462 to 0.8633)
P = 0.0075

Overall Survival

Survival probability (%)

Time
0 2 4 6 8 10 12 14

Number at risk
Group: 1 Left 493
Group: 2 Right 317

AND(Study="MOSAIC", Stage=2)

465 432 384 216 151 20 0
305 289 265 144 106 28 0

MOSAIC
Left and Right Colon

Survival after relapse

LV5FU2

FOLFOX4

MOSAIC

André A et al. JCO 2015
How to improve the adjuvant treatment of colon cancer?

What is ongoing?
Clinical trials June 2016

- "adjuvant colon cancer" N=250
  - Ongoing studies N=99
    - Adjuvant colon, unpublished Updated or ongoing N=43
      - Therapy N=17
        - IDEA/IDEA like n=3
        - Aspirin n=5
        - Regorafenib n=2
        - Liver/peritoneal n=3
        - Maintenance n=1
        - FOLFIRI vs FOLFOX n=1
        - Elderly N=1
        - Traditional medicine n=1
      - Immunology N=5
        - CIKC n=3
        - GM-CSF n=1
        - Vaccine n=1
      - Support N=3
        - Neurotoxicity n=2
        - Behavioral n=1
      - Pathology N=1
        - LN detection n=1
      - Biomarkers N=6
        - microRNA n=3
        - Immunoscore n=1
        - Coloprint n=1
        - Free DNA/CTC n=1
      - Physical activity N=3
        - IDEA/IDEA like n=3
        - Aspirin n=5
        - Regorafenib n=2
        - Liver/peritoneal n=3
        - Maintenance n=1
        - FOLFIRI vs FOLFOX n=1
        - Elderly N=1
        - Traditional medicine n=1

15  4  4  3  2  2
IDEA – Meta-Analysis

mFOLFOX6/XELOX
12/8 cycles

mFOLFOX6/XELOX
6/4 cycles

stage II-III

Non inferiority trial (HR<1.12)

N= 2436

N= 12626

N= 4081

GERCOR IDEA

N= 2020

SCOT

TOSCA

CALGB/SWOG 80702

N= 1364

HORG

N= 656

ACHIEVE

N= 1313
What’s Involved?

If you decide to participate in this study you will be in one of two treatment groups.

Group 1:
Physical Activity Program and General Health Education Materials
You will take part in a three-year individualized physical activity program to increase the amount of physical activity you do in your free time. The program will include a combination of counseling and education sessions about your physical activities and supervised physical activity sessions at a fitness centre. Both types of sessions will be led by a qualified exercise specialist that is linked with the cancer centre that you attend. You will also be provided with handouts about diet and physical activity.

Group 2:
General Health Education Materials
You will be provided with handouts containing recommendations for diet and physical activity.

All participants will undergo fitness testing at different time points.

Challenger Trial

This phase III clinical trial is currently recruiting participants, both adult men and women.

Initiated 2008
Feasibility reported at ASCO 2016
Inclusions > 400
Target 962 (HR 0.75)

Sponsored by:
NCIC Clinical Trials Group
NCIC Groupe des essais cliniques
Cancer Clinical Trials Division
Cancer Research Institute
Queen’s University
10 Stuart Street
Kingston ON Canada K7L 3N6

Talk to your doctor if you are interested in participating in the CHALLENGE study.

The NCIC Clinical Trials Group (NCIC CTG) is a cancer clinical trials cooperative group that conducts phase I-III trials testing anti-cancer and supportive therapies across Canada and internationally. It is one of the national programmes and networks of the Canadian Cancer Society Research Institute, and is supported by the Canadian Cancer Society. The NCIC CTG’s Central Office is located at Queen’s University in Kingston, Ontario, Canada.
Aspirin in mutant PIK3CA

A. Colorectal Cancer-Specific Mortality, Mutant PIK3CA

- No aspirin use
- Aspirin use
- P<0.001 by log-rank test

B. Colorectal Cancer-Specific Mortality, Wild-Type PIK3CA

- Aspirin use
- No aspirin use
- P=0.76 by log-rank test

C. Overall Mortality, Mutant PIK3CA

- No aspirin use
- Aspirin use
- P=0.01 by log-rank test

D. Overall Mortality, Wild-Type PIK3CA

- Aspirin use
- No aspirin use
- P=0.96 by log-rank test
Aspirin in PIK3CA-mutation Selected
Patients after Resection of Colorectal Cancer

Eligible patient

Aspirin 200mg
1 tablet daily
3 years

Placebo
1 tablet daily
3 years
Neoadjuvant chemotherapy

Inadequate Rx staging (post surgery CT group):
50% of Rx T4 were pT3
44% of Rx N+ were pN0

Time from rando to chemotherapy
13 days neoadjuvant group
61 days adjuvant group

Lancet Oncol 2012

http://www.birmingham.ac.uk/Documents/college-mds/trials/bctu/foxtrot/FOxTROTProtocolv60090712.pdf
Neoadjuvant chemotherapy PePiTA2

PET response

N=225
BDGO

A Hendliz et al, BMC cancer 2013

H0
50% PET responders after C1
60% stage III
3-yr DFS 55% non responders vs 83% responders
How to improve the adjuvant treatment of colon cancer?

**Biomarkers**

Main goals are to define who should be treated in stage II and who should not be treated (oxaliplatin) in stage III.
MSI in Colorectal Cancer

Sporadic CRC patients have a significantly worse OS compared with familial cases, while no difference was observed in DFS.

Zaanan A et al, ASCO 2015

Boland CR, Goel A. Gastroenterology 2010
DFS in MSI patients, pooled data

Stage II (N=102)

Stage III (N=63)

FP alone should not be given

Small benefit of FP alone

Sargent, JCO 2009
Oxaliplatin is active in Stage III MSI

Fluoropyrimidinide
Stage III (N=63)

FOLFOX4
Stage III (N=47)

5 yr DFS
Untreated 62%
Treated 67%

Sargent, JCO 2009
André, JCO 2015
KRAS/BRAF and MS status

Figure 3. Effect of KRAS and BRAF Status on Disease-Free Survival (DFS) in Patients With Microsatellite-Stable and Microsatellite-Unstable Tumors

A. KRAS status in patients with microsatellite-stable tumors

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. at risk</th>
<th>KRAS wild type</th>
<th>KRAS mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1042</td>
<td>558</td>
<td>484</td>
</tr>
<tr>
<td>1</td>
<td>952</td>
<td>478</td>
<td>474</td>
</tr>
<tr>
<td>2</td>
<td>706</td>
<td>400</td>
<td>306</td>
</tr>
<tr>
<td>3</td>
<td>498</td>
<td>336</td>
<td>162</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>126</td>
<td>74</td>
</tr>
</tbody>
</table>

Univariate HR, 1.47 (95% CI, 1.21-1.77); P < .001
Multivariate HR, 1.64 (95% CI, 1.29-2.08); P < .001

B. BRAF status in patients with microsatellite-stable tumors

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. at risk</th>
<th>BRAF wild type</th>
<th>BRAF mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1382</td>
<td>94</td>
<td>1239</td>
</tr>
<tr>
<td>1</td>
<td>1239</td>
<td>78</td>
<td>1260</td>
</tr>
<tr>
<td>2</td>
<td>961</td>
<td>52</td>
<td>809</td>
</tr>
<tr>
<td>3</td>
<td>726</td>
<td>35</td>
<td>691</td>
</tr>
<tr>
<td>4</td>
<td>273</td>
<td>12</td>
<td>261</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Univariate HR, 1.41 (95% CI, 0.97-2.04); P = .07
Multivariate HR, 1.74 (95% CI, 1.14-2.69); P = .01

C. KRAS status in patients with microsatellite-unstable tumors

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. at risk</th>
<th>KRAS wild type</th>
<th>KRAS mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>146</td>
<td>30</td>
<td>116</td>
</tr>
<tr>
<td>1</td>
<td>123</td>
<td>27</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

Univariate HR, 0.65 (95% CI, 0.25-1.65); P = .36
Multivariate HR, 0.94 (95% CI, 0.32-2.75); P = .91

D. BRAF status in patients with microsatellite-unstable tumors

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. at risk</th>
<th>BRAF wild type</th>
<th>BRAF mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>113</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Univariate HR, 0.54 (95% CI, 0.25-1.17); P = .12
Multivariate HR, 0.23 (95% CI, 0.06-0.92); P = .04

Taieb J et al, JAMA Oncol 2016
Oxaliplatin is active in BRAF mut

RFS Stage III

André, JCO 2015
The Recurrence Score is a standardized, quantitative, reverse transcriptase polymerase chain reaction (RT-PCR) assay that measures the expression of 12 genes (seven recurrence and five reference genes) in fixed, paraffin-embedded (FPE) primary colon tumor tissue. The recurrence genes integrate the activity of two key biologic pathways, cell cycle control and stromal response.

Gray RG et al, J Clin Oncol 2011. 29:4611-4619
ColoPrint is a 18 gene expression signature identified from fresh frozen tissue to improve prognosis prediction of stage II and III colorectal cancer. 60% of patients are classified as low risk and 40% as high risk.

GUCY2C mRNA was quantified by RT-PCR, Previstage®
Immunoscore

Presence of T cells in and around the tumor is a powerful prognosis parameter, Immunoscore combines an immuno-histochemistry (IHC) assay to quantify CD3 & CD8 positive cells in 2 zones, core tumor and invasive margin and an automated quantification using digital pathology.

Low-IM identified a subgroup of patients with high-risk stage II CC.

Caudal-type homeobox transcription factor 2 (CDX2) is a gene with expression in colon cancer that was negatively linked to the activated leukocyte-cell adhesion molecule (ALCAM/CD166) which is a marker of immature colon epithelial cells.

7% of stage II CC are CDX2-Negative

The consensus molecular subtypes of CRC

CMS1 – MSI – Immune 14%
- Microsatellite instability
- CIMP high
- Hypermutation, *BRAF* mutations
- Immune activation

CMS2 – Canonical 37%
- High chromosomal instability
- Microsatellite stable
- CIMP negative
- WNT and MYC activation

CMS3 – Metabolic 13%
- Heterogeneous chromosomal/microsatellite status
- *KRAS* mutations
- Metabolic reprogramming

CMS4 – Mesenchymal 23%
- High chromosomal instability
- TGFβ activation
- Invasion, matrix remodeling
- Angiogenesis

The consensus molecular subtypes of CRC

NSABP C-07: CMS4 have the worst prognosis

Son N et al. JAMA Oncol 2016
CMS is not predictive of the benefit of oxaliplatin
How to improve the adjuvant treatment of colon cancer?

Improving our therapies
The consensus molecular subtypes of CRC

Scientific Approach

- **CMS1 - MSI – Immune 14%**
  - Microsatellite instability
  - CIMP high
  - Hypermutation, *BRAF* mutations
  - Immune activation

- **CMS3 – Metabolic 13%**
  - Heterogeneous chromosomal/microsatellite status
  - *KRAS* mutations
  - Metabolic reprogramming

- **CMS2 – Canonical 37%**
  - High chromosomal instability
  - Microsatellite stable
  - CIMP negative
  - WNT and MYC activation

- **CMS4–Mesenchymal 23%**
  - High chromosomal instability
  - TGFβ activation
  - Invasion, matrix remodeling
  - Angiogenesis

- **PD1 blockade**
  - Immune checkpoint inhibitors
  - Immune regulators
  - BRAF-driven strategies

- **combination of**
  - pan-RAF / MEK inhibitors
  - with metabolic enzyme inhibitors

- **Revisiting anti-EGFR**
  - combination with drugs targeting oncogene
  - amplifications/overexpression

- **combination of immune-stimulatory drugs and inhibitors of immune suppression**

Tabernero 2016
Immunotherapy

Immune checkpoint inhibitor

Le DT et al, NEJM 2015

http://fr.slideshare.net/PaulDRennert/the-immune-checkpoint-landscape-in-2015-combination-therapy
**Chemoimmunotherapy**

5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity.

**Oxaliplatin** immunogenic effects include modulation of STAT signaling; induction of an immunogenic cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1); and enhancement of the effector immune response through modulation of PDL1 and mannose-6-phosphate receptor expression.

Vincent J, et al Cancer Res 2010
Hato Clin Cancer Res 2014
Wiersma Front Oncol 2015

Munzone NRCO 2015

Metronomic chemotherapy

- Immune system
  - Immunogenic cell death
  - Enhanced APC through DC
  - Depletion of T\(_{\text{REG}}\) cells
  - MDSC modulation
  - Enhanced tumour specific T cells and \(\gamma\delta T\) cells

**Phagocytosis**

- ‘Eat-me’
- ‘Don’t eat-me’
- No phagocytosis

**Phagocyte**
## Immunomodulation

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>gpA33-CD3</td>
<td>MGD007</td>
<td>Moore AACR 2014</td>
</tr>
<tr>
<td>phosphatidyserine</td>
<td>Bavituximab</td>
<td>Huang ASCO 2015</td>
</tr>
<tr>
<td>CD137</td>
<td>Urelumab</td>
<td>Sanmamed Cancer Res 2015</td>
</tr>
<tr>
<td>MUC5AC/ADCC</td>
<td>Enzituximab</td>
<td>Beg ASCO 2015</td>
</tr>
<tr>
<td>β1,3β1,6 glucan</td>
<td>ImprimePGG</td>
<td>Qiu AAI 2016</td>
</tr>
<tr>
<td>Histone diacetylase</td>
<td>Romidepsin</td>
<td>Prince CCR 2012</td>
</tr>
<tr>
<td>MEKI</td>
<td>Cobimetinib</td>
<td>Bendell ASCO 2016</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKG2A/HLAE</td>
<td>Monalizumab</td>
<td>Seymour Ann Oncol 2015</td>
</tr>
<tr>
<td>Autologous (patient-specific) tumor cells</td>
<td>Oncovax</td>
<td>Vermorken Lancet 1999</td>
</tr>
<tr>
<td>Target</td>
<td>Drug</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Dormancy/Angiogenesis</td>
<td>Antiangiogenic agents</td>
<td>AVANT Lancet Oncol 2014 Naumov <em>Breast Cancer Res</em> 2003</td>
</tr>
<tr>
<td>Cancer stem cell</td>
<td>BBI608</td>
<td>Jonker ASCO 2014</td>
</tr>
</tbody>
</table>
How to improve the adjuvant treatment of colon cancer?

Improving our clinical research
Cost of an adjuvant trial

>100 000 000 €
Adjuvant trials

New drug
→ Registration in advanced disease
→ Good sales
→ Adjuvant trial

Rationale for adjuvant

Academic groups
Public & private fundings
New Adjuvant trial

Registration in advanced disease

New drug
## Conclusions

### Stage and new prognostic biomarker

<table>
<thead>
<tr>
<th>Predictive biomarkers</th>
<th>No predictive biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk stage II &amp; III (risk 3-10%)</strong></td>
<td></td>
</tr>
<tr>
<td>MSI BRAF mut</td>
<td>PD1/PLD1 I</td>
</tr>
<tr>
<td>PI3K mut</td>
<td>Aspirin</td>
</tr>
<tr>
<td><strong>Intermediate-risk stage II &amp; III (risk 10-25%)</strong></td>
<td></td>
</tr>
<tr>
<td>MSI</td>
<td>PD1/PLD1 I</td>
</tr>
<tr>
<td>POLE</td>
<td>PD1/PLD1 I</td>
</tr>
<tr>
<td>Her2</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>PI3K mut</td>
<td>Aspirin</td>
</tr>
<tr>
<td>BRAF mut</td>
<td>BRAFI/EGFRI/MEKI</td>
</tr>
<tr>
<td><strong>High-risk stage II &amp; III (risk &gt;25%)</strong></td>
<td></td>
</tr>
<tr>
<td>MSI</td>
<td>PD1/PLD1 I</td>
</tr>
<tr>
<td>POLE</td>
<td>CTL4 combination Immunomodulation</td>
</tr>
<tr>
<td>Her2</td>
<td>Trastuzumab/dual HER2 HER3</td>
</tr>
<tr>
<td>PI3K mut</td>
<td>Aspirin</td>
</tr>
<tr>
<td>BRAF mut</td>
<td>BRAFI/EGFRI/MEKI</td>
</tr>
</tbody>
</table>