Low Risk of Malignancy in Maraviroc-treated patients in the Maraviroc Clinical Development program is preserved in older age groups

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Background

- AIDS-defining malignancy risk is decreased with ART
- Non-AIDS malignancies appear to be increasing in incidence\(^1\)\(^-\)\(^4\)
- Age is a risk factor for development of malignancies\(^2\)
- During maraviroc (MVC) development malignancy incidence was prospectively collected
  - New class, potential for immunomodulation
  - Cluster of malignancies in vicriviroc studies\(^5\)


Presented at the 1st Int. workshop on HIV & Aging, 4 – 5 Oct. 2010, Baltimore, USA
Objectives

- To assess the incidence of and risk factors for malignancies among more than 1400 MVC-treated patients included in the phase 2b/3 studies of the MVC development program
- To assess the effect of age on the observed incidence of malignancies
Methods

• In the MVC phase 2b/3 studies malignancies were reported prospectively

• This is an analysis of treatment-emergent malignancies among patients treated with MVC or placebo/active control during MOTIVATE 1 and 2,1,2 MERIT3 and study A40010294.


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## MVC Phase 2b/3 Study Design

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<thead>
<tr>
<th><strong>MOTIVATE 1 &amp; 2 (N = 1049)</strong></th>
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<tr>
<td><strong>Patients</strong></td>
<td>Treatment-experienced (TE)</td>
</tr>
<tr>
<td><strong>Tropism and entry viral load</strong></td>
<td>R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL</td>
</tr>
<tr>
<td><strong>Randomized treatment arms</strong></td>
<td>OBT plus</td>
</tr>
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</tr>
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<td></td>
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<td><strong>Open-label treatment</strong></td>
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\(^a\)Patients receiving protease inhibitors (except tipranavir) and/or delavirdine received 150 mg MVC, all others received 300 mg.

3TC, lamivudine; AZT, zidovudine; CBV, combivir; EFV, efavirenz; OBT, optimized background therapy; PBO, placebo
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<td>Treatment-naïve (TN)</td>
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### Tropism and entry viral load
- **R5 HIV-1**
- **HIV-1 RNA ≥ 5000 copies/mL**
- **R5 HIV-1**
- **HIV-1 RNA ≥ 2000 copies/mL**

### Randomized treatment arms

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<td>AZT/3TC (CBV) plus</td>
</tr>
<tr>
<td>MVC 150 mg&lt;sup&gt;a&lt;/sup&gt; twice daily (n = 426)</td>
<td>MVC 300 mg once daily (n = 174)</td>
<td></td>
</tr>
<tr>
<td>PBO (n = 209)</td>
<td>MVC 300 mg twice daily (n = 360)</td>
<td></td>
</tr>
<tr>
<td>EFV 600 mg twice daily (n = 361)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Nominal duration of blinded treatment
- **48 weeks**
- **96 weeks<sup>b</sup>**

### Open-label treatment
- **Open-label MVC twice-daily for eligible patients**
- **Open-label continuation of therapy within treatment groups<sup>b</sup>**

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<sup>3TC</sup>, lamivudine; <sup>AZT</sup>, zidovudine; <sup>CBV</sup>, combivir; <sup>EFV</sup>, efavirenz; <sup>OBT</sup>, optimized background therapy; <sup>PBO</sup>, placebo

<sup>a</sup>Patients receiving protease inhibitors (except tipranavir) and/or delavirdine received 150 mg MVC, all others received 300 mg.

<sup>b</sup>The MVC once-daily arm was discontinued at 16 weeks following the results of an interim analysis. Patients in this arm were subsequently eligible to receive open-label MVC 300 mg twice-daily.

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<th>A4001029 (N = 186)</th>
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<td>Treatment-naïve (TN)</td>
<td>Treatment-experienced (TE)</td>
</tr>
<tr>
<td><strong>Tropism and entry viral load</strong></td>
<td>R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL</td>
<td>R5 HIV-1 HIV-1 RNA ≥ 2000 copies/mL</td>
<td>Non-R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL</td>
</tr>
<tr>
<td><strong>Randomized treatment arms</strong></td>
<td>OBT plus • MVC 150 mg(^a) once daily (n = 414) • MVC 150 mg(^a) twice daily (n = 426) • PBO (n = 209)</td>
<td>AZT/3TC (CBV) plus • MVC 300 mg once daily (n = 174) • MVC 300 mg twice daily (n = 360) • EFV 600 mg twice daily (n = 361)</td>
<td>OBT plus • MVC 150 mg(^a) once daily (n = 63) • MVC 150 mg(^a) twice daily (n = 62) • PBO (n = 61)</td>
</tr>
<tr>
<td><strong>Nominal duration of blinded treatment</strong></td>
<td>48 weeks</td>
<td>96 weeks(^b)</td>
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<td>Open-label MVC twice-daily for eligible patients</td>
<td>Open-label continuation of therapy within treatment groups(^b)</td>
<td>Open-label MVC for eligible patients in MVC arms</td>
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\(^a\)Patients receiving protease inhibitors (except tipranavir) and/or delavirdine received 150 mg MVC, all others received 300 mg.

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Methods

- Analysis included blinded and open-label treatment periods for all studies
  - Except placebo arm of the MOTIVATE studies (open-label period excluded)

- Malignancies were assessed separately for each study
  - Treatment comparisons within each study summarized by rate ratios and corresponding 95% CI

- Physicians reviewed all malignancies to discard non-malignant tumors
Methods

• Malignancies were categorized in two non-mutually exclusive ways
  – AIDS-defining versus non-AIDS-defining
  – Infection-related versus non-infection-related*
• Risk factors for malignancies were assessed for the pooled population from the 3 studies using univariate and stepwise multivariate Cox proportional hazard regression models
• The incidences of malignancies were stratified by age
  – Age <30 years, 30-50 years, and over 50 years

### Treatment Exposure by Age and Study

<table>
<thead>
<tr>
<th>Number (PY)</th>
<th>MOTIVATE 1 &amp; 2 (TE)</th>
<th>MERIT (TN)</th>
<th>A4001029</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MVC + OBT</td>
<td>PBO + OBT</td>
<td>MVC + CBV</td>
<td>EFV + CBV</td>
</tr>
<tr>
<td>Overall</td>
<td>840 (1437)</td>
<td>209 (160)</td>
<td>534 (1127)</td>
<td>361 (768)</td>
</tr>
<tr>
<td>&lt;30 yrs</td>
<td>9 (8.6)</td>
<td>2 (0.6)</td>
<td>114 (211)</td>
<td>82 (172.5)</td>
</tr>
<tr>
<td>30-50 yrs</td>
<td>608 (1014)</td>
<td>156 (119)</td>
<td>367 (795)</td>
<td>244 (520)</td>
</tr>
<tr>
<td>&gt;50 yrs</td>
<td>223 (415)</td>
<td>51 (40.1)</td>
<td>53 (121)</td>
<td>35 (75)</td>
</tr>
</tbody>
</table>

CBV, Combivir; EFV, efavirenz; MVC, Maraviroc; OBT, optimized background therapy; PY, person years of exposure; TE, treatment experienced; TN, treatment naive.

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Overall Results

• Exposure-adjusted incidences of malignancies across the 3 studies were generally lower in the combined MVC arms than in the comparator arms.

• These differences were associated with a significantly lower overall risk of malignancy and significantly lower risks of AIDS-defining and infection-related malignancies among patients receiving MVC than among patients receiving placebo in MOTIVATE.
Exposure-adjusted Incidence of Malignancies Was Generally Numerically Lower on MVC Compared to EFV or PBO

<table>
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<tr>
<th>Study</th>
<th>MVC + OBT (N = PY)</th>
<th>PBO + OBT (N = PY)</th>
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<td>125, 134</td>
<td>61, 36</td>
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*Potentially related to infection with HPV, EBV, HBV, HCV, HHV-8, or HTLV-1.

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MOTIVATE Studies: Significantly Lower Exposure-adjusted Risks of Overall, AIDS-Defining and Infection-Related Malignancies in TE Patients Receiving MVC Compared With PBO

Overall 0.46 (0.22–0.95)

AIDS-defining 0.18 (0.06–0.54)

Non-AIDS-defining 0.84 (0.30–2.40)

Infection-related* 0.28 (0.12–0.63)

Non-infection-related 2.36 (0.32–17.55)

MVC, Maraviroc; PBO, placebo; TE, treatment experienced.

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Risk Factors

- In a multivariate analysis* of pooled data from all 3 studies a reduced risk of malignancy was associated with:
  - **CD4⁺ cell increase on treatment (per 25 cells/mm³)**
    - HR **0.908 (95% CI 0.861-0.957)**
  - Achieving HIV-1 RNA levels < 50 copies/mL
    - HR **0.262 (95% CI 0.142-0.482)**
- An increased risk of malignancy was associated with:
  - Older age (per additional year)
    - HR **1.085 (95% CI 1.055-1.116)**
  - MSM transmission
    - HR **1.874 (95% CI 1.014-3.465)**
- These risk factors were independent of treatment arm

HR, hazard ratio; CI, confidence interval; MSM, men who have sex with men.
*Stepwise Cox proportional hazard model. Variables included in the model were baseline covariates of age, gender, CD4+ count and HIV-1 RNA level, mode of infection, hepatitis B or C co-infection, prior treatment status (TE vs TN), past history of malignancy, and treatment arm; time-dependent covariates were change from baseline in CD4+ count and HIV-1 RNA level.

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Age Stratified Results

- Malignancies were infrequent in patients <30 years of age
- Malignancies were most frequent in patients over 50 years of age, however
  - The incidence was numerically lower in the MVC arm than in the comparator arm across studies and across malignancy categories
  - The difference between the MVC arm and the comparator arm was more pronounced in this age group than in patients aged 30 to 50 years
Higher Exposure-adjusted Incidence of Malignancies in Over 50’s but Reduced Incidence With MVC vs. Comparator Across Patient Types

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Conclusions (1)

In this retrospective analysis of more than 1400 patients:

- MVC-treated patients had a low incidence of malignancies, regardless of virus tropism or degree of antiretroviral treatment experience
- Malignancies were more frequent in patients over 50 years of age
- Overall, the exposure-adjusted incidence of malignancies was generally numerically lower in the MVC group compared to PBO or EFV
  - This reduced incidence was most apparent in patients over 50 years of age
Conclusions (2)

- In a multivariate analyses, age and MSM transmission were independently associated with an increased risk of malignancy, independent of treatment arm.
- Increase in CD4$^+$ count and undetectable viral load were associated with a reduced risk of malignancy, independent of treatment arm.
Thanks for your attention

I would like to acknowledge and thank the study participants in the maraviroc development program.

The many investigators and study teams.