MED15 in prostate cancer:

A potential prognostic and predictive marker as well as a therapeutic target

BioVaria
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Institute of Pathology
University Hospital Bonn
Bonn, Germany
Disclosure

A priority patent application was filed at the European Patent Office in August 2013.
### Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>28%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>37,600</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27,880</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>854,790</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>29,720</td>
<td>10%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,260</td>
<td>28%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>26,300</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>19,480</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>14,890</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,660</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,220</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,820</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,590</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,780</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>306,920</td>
<td>100%</td>
</tr>
</tbody>
</table>
Prostate cancer progression trends & treatment options

**Local therapy:**
- radical prostatectomy
- radiotherapy

**Androgen deprivation therapy**
- chemical castration (e.g. LHRH analogs)
- surgical castration (orchiectomy)
- anti-androgens (e.g. Flutamide)
- androgen synthesis inhibitors (e.g. Abiraterone)

**Chemotherapy** (e.g. Docetaxel)

**Immunotherapy** (e.g. Sipuleucel-T)

Survival time

- Localized
- Locally advanced
- Regional metastasis
- Castration-resistant
Local therapy:
- radical prostatectomy
- radiotherapy

Androgen deprivation therapy
- chemical castration (e.g. LHRH analogs)
- surgical castration (orchietomy)
- anti-androgens (e.g. Flutamide)
- androgen synthesis inhibitors (e.g. Abiraterone)

Chemotherapy (e.g. Docetaxel)
Immunotherapy (e.g. Sipuleucel-T)

Prostate cancer progression trends & treatment options

Unfortunately, most tumors become castration resistant (mean survival 16-18 months)
Alternative AR-bypass pathways

Androgen deprivation therapy
  Altered components
  
  Increased PI3K signaling
  
  Recurrence after androgen deprivation therapy
  Castration-resistant growth

Zhang et al., Trends Biochem Sci. (2013)
Alternative AR-bypass pathways

Androgen deprivation therapy
Altered components

Increased PI3K signaling

Recurrence after androgen deprivation therapy
Castration-resistant growth

Oncogenic mutations
Loss of TGFβ-receptor or SMADs

Loss of tumorsuppressive ability
Switch to oncogenic signaling

Invasion, metastasis

Zhang et al., Trends Biochem Sci. (2013)
Alternative AR-bypass pathways

Androgen deprivation therapy
Altered components
- Increased PI3K signaling
- Recurrence after androgen deprivation therapy
- Castration-resistant growth

Oncogenic mutations
- Loss of TGFβ-receptor or SMADs
- Loss of tumorsuppressive ability
- Switch to oncogenic signaling
- Invasion, metastasis

PI3K – TGFβ crosstalk

Zhang et al., Trends Biochem Sci. (2013)
Inhibitors for PI3K and TGFβ signaling

PI3K and PI3K/mTOR inhibitors

Inhibitor for:
- EGFR
- HER2
- MET
- VEGFR

<table>
<thead>
<tr>
<th>BKM120</th>
<th>XL147</th>
<th>GDC0941</th>
<th>GSK1059615</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perifosine</td>
<td>MK2206</td>
<td>VQD-002</td>
<td>XL418</td>
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<tr>
<td>Rapamycin</td>
<td>CCI-779</td>
<td>RAD001</td>
<td>AP23573</td>
</tr>
</tbody>
</table>

TGFβ inhibitors

| SB-431542 | SB-505124 | SB-525334 | LY2109761 | LY2157299 | LY580276 | GW788388 |

Zhang et al., Trends Biochem Sci. (2013)
Inhibitors for PI3K and TGFβ signaling

**PI3K and PI3K/mTOR inhibitors**

Lack of specificity (inhibits many downstream targets)

High toxicity

**TGFβ inhibitors**

Lack of specificity (tumor supressing vs tumor promoting signaling)

Zhang et al., Trends Biochem Sci. (2013)
Inhibitors for PI3K and TGFβ signaling

**PI3K and PI3K/mTOR inhibitors**

- Lack of specificity (inhibits many downstream targets)
- High toxicity

**TGFβ inhibitors**

- Lack of specificity (tumor supressing vs tumor promoting signaling)

---

**Predictive markers for these inhibitors**

**More specific targets to inhibit**

Zhang et al., Trends Biochem Sci. (2013)
Challenges

Prognostic markers

PI3K & PI3K/mTOR inhibitors

Predictive markers
More specific therapeutic targets

TGFβ inhibitors
Mediator Complex: An integrative hub for signaling pathways

**MED15 overexpression in prostate cancer**

**MED15 nuclear overexpression** (Immunoreactive Score > 3)

<table>
<thead>
<tr>
<th>Condition</th>
<th>MED15 Expression (Immunoreactive Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0% (0/40)</td>
</tr>
<tr>
<td>PCa\textsuperscript{N0}</td>
<td>3% (3/110)</td>
</tr>
<tr>
<td>PCa\textsuperscript{VAL}</td>
<td>4% (12/290)</td>
</tr>
<tr>
<td>PCa\textsuperscript{N1}</td>
<td>15% (14/92)</td>
</tr>
<tr>
<td>CRPC\textsuperscript{LOC}</td>
<td>70% (62/89)</td>
</tr>
<tr>
<td>CRPC\textsuperscript{MET}</td>
<td>76% (53/70)</td>
</tr>
</tbody>
</table>

***p < 0.001

Shaikhibrahim et al., Int J Cancer (2013)
**MED15** overexpression defines a highly lethal phenotype

**p < 0.02

**Shaikhibrahim et al., Int J Cancer (2013)**
**MED15** overexpression defines a highly lethal phenotype

**MED15** knockdown reduces proliferation of prostate cancer cells

**p < 0.02**

<table>
<thead>
<tr>
<th>MED15 Expression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>r = 0.49** ***</td>
</tr>
<tr>
<td>PHH3</td>
<td>r = 0.48** ***</td>
</tr>
</tbody>
</table>

**p < 0.02**

Shaikhibrahim et al., Int J Cancer (2013)
Androgen deprivation leads to increased MED15 expression

Matched tissues from patients before and after androgen deprivation therapy (ADT) (n=29):

Increased MED15 expression after ADT: 21/28 patients (73%)
Androgen deprivation leads to increased MED15 expression

Matched tissues from patients before and after androgen deprivation therapy (ADT) (n=29):

Increased MED15 expression after ADT: 
21/28 patients (73%)

Unmatched tissues from patients without ADT (n=112) or after ADT (n=145):

Higher mean IRS for MED15
After ADT (IRS=23.6) 
compared to untreated (IRS=20.9) 
(p < 0.05)
Androgen deprivation leads to increased MED15 expression

Matched tissues from patients before and after androgen deprivation therapy (ADT) (n=29):

- Increased MED15 expression after ADT: 21/28 patients (73%)

Unmatched tissues from patients without ADT (n=112) or after ADT (n=145):

- Higher mean IRS for MED15 after ADT (IRS=23.6) compared to untreated (IRS=20.9) (p < 0.05)
Androgen deprivation leads to increased MED15 expression

Via which pathway?
MED15 correlates with TGFβ signaling
Alternative AR-bypass pathways

MED15

TGFβ & PI3K Signaling

GF Receptor Tyrosine Kinases

PI3K

AKT

mTORC1

SMAD2/3

SMAD4

SMAD2/3
Bypass pathways lead to increased MED15 expression
MED15 correlates with TGFβ and PI3K signaling.

<table>
<thead>
<tr>
<th></th>
<th>pAKT</th>
<th>pSMAD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>236</td>
<td>227</td>
</tr>
<tr>
<td>r</td>
<td>0.341</td>
<td>0.263</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
MED15 correlates with TGFβ and PI3K signaling

* p<0.05, ** p<0.01, *** p<0.001
MED15 can be targeted by PI3K/mTOR inhibitors
Conclusion

MED15 may serve as a **prognostic** marker for prostate cancer patients.

MED15 can be **targeted** by PI3K/mTOR inhibitors.

MED15 may serve as a **predictive** marker for response to PI3K/mTOR inhibitors.

MED15 may serve as a **therapeutic target** for treatment of castration-resistant prostate cancer.
MED15 may serve as a **prognostic** marker for prostate cancer patients

MED15 can be **targeted** by PI3K/mTOR inhibitors

MED15 may serve as a **predictive** marker for response to PI3K/mTOR inhibitors

MED15 may serve as a **therapeutic target** for treatment of castration-resistant prostate cancer

Ongoing experiments & development status can be discussed upon the signing of a non-disclosure agreement in a closed session
Acknowledgement

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## Therapeutic agents in clinical oncology development for CRPC

<table>
<thead>
<tr>
<th>Therapeutic agent</th>
<th>Clinical trial status</th>
<th>Therapeutic efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>FDA approved</td>
<td>Overall survival benefit and palliation of cancer-associated symptoms</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>FDA approved for patients after failure of docetaxel</td>
<td>Overall survival benefit and palliation of cancer-associated symptoms</td>
</tr>
<tr>
<td>Sipuleucel-T (Provenge)</td>
<td>FDA approved</td>
<td>Increase in overall survival but not progression-free survival</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>FDA approved in the pre- and post-docetaxel settings</td>
<td>Increase in overall survival (almost 4 months), radiographic progression-free survival, time to PSA progression, and palliation of cancer-associated symptoms</td>
</tr>
<tr>
<td>MDV3100 (Enzalutamide)</td>
<td>FDA approved in the post-docetaxel setting Phase III clinical trial in comparison with placebo in chemotherapy-naive patients</td>
<td>Increase of overall survival (4.8 months), radiographic progression-free survival and time to PSA progression. Results pending</td>
</tr>
<tr>
<td>BEZ235</td>
<td>Phase I/II clinical trials in combination with Abiraterone acetate (NCT01717898)</td>
<td>Results pending</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>RAD001 (Everolimus)</td>
<td>Phase II clinical trial in combination with bicalutamide (NCT00630344)</td>
<td>Failure to show increase in time to progression</td>
</tr>
<tr>
<td>Dovitinib (TK1258)</td>
<td>Phase II clinical trial in patients after failure of docetaxel-based chemotherapy (NCT01741116)</td>
<td>Results pending</td>
</tr>
</tbody>
</table>
| Cabozatinib (XL184) | Phase II clinical trial in patients with mCRPC (NCT01428219)  
Phase III clinical trial in comparison with prednisone in patients previously treated with docetaxel and abiraterone or MDV3100 (COMET-1, NCT01605227)  
Phase III clinical trial in comparison with mitoxantrone and prednisone (COMET-2, NCT01522443) | Reduction of soft tissue lesions, resolution of bone scans, increase of progression-free survival  
Results pending  
Results pending |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target(s)</th>
<th>Tumors</th>
<th>Toxicities</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib (CAL-101)</td>
<td>p110-δ</td>
<td>CLL/SLL, iNHL, MCL</td>
<td>Pyrexia, nausea, decrease appetite, fatigue</td>
<td>III</td>
</tr>
<tr>
<td>Buparlisib (BKM-120)</td>
<td>p110-α, -β, -δ, -γ</td>
<td>Breast, GBM, NSCLC</td>
<td>Rash, hyperglycemia diarrhea, anorexia</td>
<td>IB/II</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>p110-α, -β, -δ, -γ</td>
<td>Breast, NSCLC, melanoma endometrial, pancreatic</td>
<td>Nausea, diarrhea, rash vomiting, anorexia</td>
<td>IB/II</td>
</tr>
<tr>
<td>PX-866</td>
<td>p110-α, -β, -δ, -γ</td>
<td>Ovarian, prostate, GBM, NSCLC</td>
<td>Fatigue, diarrhea thromboembolism</td>
<td>II</td>
</tr>
<tr>
<td>GDC-0032</td>
<td>p110-α, -δ, -γ</td>
<td>Breast, NSCLC</td>
<td>Diarrhea, hyperglycemia fatigue, nausea, decreased appetite</td>
<td>I</td>
</tr>
<tr>
<td>BAY 80-6946</td>
<td>p110-α, -β</td>
<td>NHL, esophageal, sarcoma pancreatic</td>
<td>Alopecia, dysgeusia anemia, mucositis</td>
<td>I</td>
</tr>
<tr>
<td>IPI-145</td>
<td>p110-δ, -γ</td>
<td>CLL/SLL, iNHL, MCL</td>
<td>Cytopenias liver enzyme elevations</td>
<td>I</td>
</tr>
<tr>
<td>BEZ-235</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>Breast, GBM</td>
<td>Mucositis</td>
<td>IB/II</td>
</tr>
</tbody>
</table>
### PI3K inhibitors in clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target(s)</th>
<th>Tumors</th>
<th>Toxicities</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>BYL-719</td>
<td>p110-α</td>
<td>Breast, cervical, endometrial, ovarian, H&amp;N</td>
<td>Nausea, diarrhea hyperglycemia, vomiting</td>
<td>IB/II</td>
</tr>
<tr>
<td>BGT-226</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>Solid tumors, breast</td>
<td>Nausea, vomiting diarrhea</td>
<td>I/II</td>
</tr>
<tr>
<td>PF-04691502</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>Endometrial</td>
<td>Fatigue, nausea, vomiting decreased appetite, rash</td>
<td>II</td>
</tr>
<tr>
<td>GDC-0980</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>Prostate</td>
<td>Hyperglycemia, rash mucositis</td>
<td>IB/II</td>
</tr>
<tr>
<td>GSK-2126458</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>RCC, bladder</td>
<td>Nausea, vomiting diarrhea</td>
<td>I</td>
</tr>
<tr>
<td>PF-05212384</td>
<td>p110-α, -γ/mTOR</td>
<td>Solid tumor, CRC</td>
<td>Rash, mucositis transaminitis, hyperglycemia</td>
<td>II</td>
</tr>
<tr>
<td>XL-765</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>NSCLC, gliomas</td>
<td>Nausea, diarrhea elevated liver enzymes</td>
<td>IB/II</td>
</tr>
<tr>
<td>XL-147</td>
<td>p110-α, -β, -δ, -γ/mTOR</td>
<td>Solid tumor, GBM</td>
<td>Nausea, vomiting diarrhea</td>
<td>I/II</td>
</tr>
</tbody>
</table>

Simultaneously activated in advanced tumor progression (head & neck cancer and pancreatic cancer)
Combined inhibition of PI3K and mTOR

More effective activity than single agents in human prostate cancer cells

Enhanced growth inhibitory effect

Strongly inhibited the expression of PI3K/Akt/mTOR downstream proteins

Mazzoletti et al. *Combination of PI3K/mTOR inhibitors: antitumor activity and molecular correlates.* Cancer Res 2011