Advanced in Pharmacotherapy in Solid Tumors

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Cancer cells

Tumor Blood Vessels
The Epidermal Growth Factor Pathway

Growth Factor Receptors

Extracellular Domain

Intracellular Domain

EGFR

Adaptor Proteins/Signaling Enzymes

Signaling Cascades

PKC  MAPK

Myc  Fos  Jun

M  G1  M  G2  S

Survival

Proliferation of Tumor Cells

Angiogenesis

EGFR Targeted Approaches

**MAbs to HER receptors**

1. Anti HER2 MAbs: Trastuzumab
2. Anti HER1 MAbs: Cetuximab (C225)

EGFR Targeted Approaches

1. HER1-TK inhibitors
   - Erlotinib, Gefitinib
2. Dual HER1&HER2 TKIs
   - Lapatinib
EGFR expression in NSCLC

Ligand (EGF, TGF-α)

Extracellular domain

Cell membrane

Intracellular domain

Tyrosine kinase

SOS

Ras

Raf-1

Grb2

Other enzyme or adaptor

MAPK

Gene activation, Cell cycle progression

G1

S

M

DNA damage and repair

G2

Growth Arrest or Apoptosis

Angiogenesis Effects
Blood vessel recruitment, invasion, metastases

Growth Effects
Proliferation, differentiation

Radiation or selected chemotherapy agents

Cell Motility and Metastasis
Cell adhesion, invasiveness

Study design

Patients
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

Gefitinib (250 mg / day)

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly#

Endpoints
Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor
Study conduct

- 87 centres in 9 countries in Asia
  - China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand
- 1217 patients randomised
- Randomisation period: March 2006 to October 2007
- Data cut-off: 14 April 2008
  - 950 PFS events observed in ITT population (78% maturity)
- Mean time on treatment
  - gefitinib, 6.4 months
  - carboplatin / paclitaxel, 3.4 months (median number of cycles#: 6)
- Final survival data (944 events) expected mid-2010

#limited to a maximum of 6 cycles
PFS, progression-free survival; ITT, intent-to-treat
Progression-free survival in EGFR mutation positive and negative patients

**EGFR mutation positive**

Gefitinib (n=132)  
Carboplatin / paclitaxel (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)  
p<0.0001

No. events gefitinib, 97 (73.5%)  
No. events C / P, 111 (86.0%)

**EGFR mutation negative**

Gefitinib (n=91)  
Carboplatin / paclitaxel (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)  
p<0.0001

No. events gefitinib, 88 (96.7%)  
No. events C / P, 70 (82.4%)

At risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gefitinib</th>
<th>C / P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>3 months</td>
<td>108</td>
<td>103</td>
</tr>
<tr>
<td>6 months</td>
<td>71</td>
<td>37</td>
</tr>
<tr>
<td>9 months</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>12 months</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>15 months</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>18 months</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gefitinib</th>
<th>C / P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>3 months</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>6 months</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>9 months</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>12 months</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>15 months</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>18 months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>21 months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment by subgroup interaction test, p<0.0001

ITT population  
Cox analysis with covariates
Signal transduction pathways

Cytotoxic Chemotherapy
Study Design*

Randomization Factors

- Stage
- PS
- Gender
- Histo vs cyto dx
- Brain mets hx

Cisplatin 75 mg/m², day 1 plus Pemetrexed 500 mg/m², day 1

Each cycle repeated q3weeks up to 6 cycles

Cisplatin 75 mg/m² day 1 plus Gemcitabine 1250 mg/m² day 1 & 8

Vitamin B12, folate, and dexamethasone given in both arms

### Results

<table>
<thead>
<tr>
<th></th>
<th>Pem/Cis ITT</th>
<th>Gem/Cis ITT</th>
<th>Pem/Cis Adeno</th>
<th>Gem/Cis Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td></td>
<td></td>
<td>31.9</td>
<td>24.5</td>
</tr>
<tr>
<td>P 0.024</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>4.8</td>
<td>5.1 (ns)</td>
<td>5.3</td>
<td>4.7 (ns)</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>10.3</td>
<td>10.3 (ns)</td>
<td>11.8</td>
<td>10.4 (0.81)</td>
</tr>
</tbody>
</table>
Pemetrexed: MOA

- Antifolate group; - TS, - GARFT (glycinamide ribonucleotide transformylase)
- Active agent = pentaglutamate of PMX
- Factors determine the activity of antifolate
  - Level of folic acid: Inc folate Dec activity, Dec level of folic Inc activity
Squamous histology

Clinical
Male, smoker
Central, cavitation

Molecular
Ras and EGFR mutation rare
High TS and EGFR overexpression common
### Smoker adeno histology

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Male, smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral, pleural disease</td>
<td>High ras mutation, EGFR over expression, low EGFR mutation, low TS</td>
</tr>
</tbody>
</table>

### Non smoker - adeno histology

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Female, non smoker, asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral, multifocal, ground glass appearance</td>
<td>Frequent EGFR mutation, EGFR over expression, Ras mutation rare, low TS</td>
</tr>
</tbody>
</table>

Pemetrexed work best in **low TS** environment
Prescription

• Standard dose either SA or combination = 500 mg / m²

• Premedication before pemetrexed 7 days before first dose

• 1. Vitamin B₁₂ : 1000 µg : 1 wk before, then q 9 wks

• 2. Folic acid : 350 - 1000 mcg at least 5 doses in 7 days prior PMX, during and 21 days after
Recommendation regarding folic supplement

- **400 mcg of folate per day** should be the best dose (induce near maximal decrease in homocysteine)

- Equivalent to dose in multivitamin tablet

- Excess folate should be avoided in order not to reduce drug efficacy

- **No evidence of excess vit B12** has any negative impact on PMX activity
Why B12 & folic before PMX

1. PMX toxicity correlate with increase intracellular level of homocysteine (homocysteine level is a sensitive indicator of B12 & folic deficiency; 400 mcg of folic induce near maximal decrease in homocysteine level)

2. Added folic acid markedly dec toxicity of PMX and allow more cycles

3. Greater therapeutic window
Evidence based management decision for 1st line NSCLC good ECOG

- **EGFR mutation +**
  - EGFR TKIs

- **EGFR unknown**
  - Squamous CA
    - Traditional 3rd gen doublet CT (non-pemetrexed)
  - Non-squamous
    - Bev + doublet CT
    - Or
    - Pem doublet CT
    - Or
    - Traditional CT
From pathology to molecular biology

Histological Types of Lung Cancer
Relative Incidence

- 10% EGFR mutation
- 3% FGFR4
- 3% EML4-ALK translocation
- 3% MET amplification
- 2% HER2 alteration
- 20% K-RAS mutation
- IGF-1R activation
- HER4...

- 40% Adenocarcinoma
- 15% Small cell carcinoma
- 15% Squamous cell carcinoma
- 15% Large cell carcinoma
- 10% NSCLC
- 5% SCLC
Prospective Identification of ALK$^+$ NSCLC Patients

Break-Apart FISH Assay for ALK Fusion Genes

Potential ALK Fusion Partners:

- EML4
- KIF5B
- TFG

Shaw et al., JCO, 2009
Tumor Responses to crizotinib, NSCLC with ALK fusion

As 2nd, 3rd and 4th line of treatment
Retrospective Analysis of Crizotinib vs Comparable Controls in ALK+ NSCLC

- Median OS not yet reached in ALK+ crizotinib-treated patients from phase I study (N = 82): 1-yr OS: 74%; 2-yr OS: 54%
- OS significantly prolonged in ALK+ crizotinib-treated pts vs ALK+ crizotinib-naive controls (clinically and geographically comparable historic controls)
  - ALK-positive status did not confer favorable prognosis

<table>
<thead>
<tr>
<th>OS Outcome</th>
<th>ALK+/Crizotinib (n = 30)</th>
<th>ALK+/Control (n = 23)</th>
<th>WT/Control (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>1-yr OS, %</td>
<td>70</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>2-yr OS, %</td>
<td>55</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>HR vs ALK/control</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR vs WT/control</td>
<td>0.49</td>
<td>1.42</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.02</td>
<td>.18</td>
<td></td>
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</tbody>
</table>

Tumor Blood Vessels
VEGF: Central mediator of angiogenesis

**Epigenetic**
- Hypoxia, pH
- Growth factors
- Hormones

**Genetic**
- Tumor suppressor gene
  - (p53, PTEN, VHL)
- Oncogenes
  - (ras, src, EGFR, erbB-2)
Strategies for Blocking VEGFR and EGFR

- **Antibody to VEGF-A**
  - Blocks ligand binding
  - Blocks receptor activation and signaling

- **Antibody to VEGFR-2**
  - Blocks ligand binding
  - Blocks receptor activation and signaling

- **TKI to VEGFR-2**
  - Blocks receptor kinase activation and signaling
Proposed MoA of Bevacizumab: A dynamic effect throughout treatment

**EARLY EFFECTS**

1. Regression
   - Decreases tumour size

2. Normalization
   - Improves delivery of CTx

**CONTINUED EFFECTS**

3. Inhibition
   - Suppresses new vessel growth
   - Suppresses regrowth via vessel ‘scaffolds’
How Does Bev Enhance Chemo Efficacy? Applying a Brake During the Break

- Clinical implications of antiangiogenic therapies

2 pivotal trials address the benefit of Bevacizumab in mCRC

**Phase III trial of IFL ± bevacizumab in mCRC (AVF2107g): PFS**

- **Bevacizumab + IFL** (n=402)
- **Placebo + IFL** (n=411)

HR=0.54, p<0.001

**Phase III trial of XELOX/FOLFOX ± bevacizumab (N016966): PFS**

- **Bevacizumab + FOLFOX4/XELOX** (n=69)
- **Placebo + FOLFOX4/XELOX** (n=701)

HR=0.83 (ITT), p=0.0023

Hurwitz, et al. NEJM 2004
Saltz, et al. JCC
2 pivotal trials address the benefit of Bevacizumab in mCRC

**Phase III trial of IFL ± bevacizumab in mCRC (AVF2107g) : OS**

- **Bevacizumab + IFL (n=402)**
- **Placebo + IFL (n=41)**

**HR=0.66**
**p<0.001**

_Hurwitz, et al. NEJM 2001_

**Phase III trial of XELOX/FOLFOX ± bevacizumab (NO16966) : OS**

- **Bevacizumab + XELOX/FOLFOX4 (n=699)**
- **Placebo + XELOX/FOLFOX4 (n=701)**

**HR=0.89 (ITT)**
**p=0.0769**

_Saltz, et al. JCO 2003_
Strategies for Blocking VEGFR and EGFR

- Antibody to VEGF-A
  - Blocks ligand binding
  - Blocks receptor activation and signaling

- Antibody to VEGFR-2
  - Blocks ligand binding
  - Blocks receptor activation and signaling

- TKI to VEGFR-2
  - Blocks receptor kinase activation and signaling
Expanded Treatment options for mRCC
Era of Targeted Therapy

### RCC: Molecular Pathogenesis

<table>
<thead>
<tr>
<th>Tumour Type Histology</th>
<th>Clear Cell</th>
<th>Papillary (type I)</th>
<th>Chromophobe</th>
<th>Oncocytic</th>
<th>Collecting Duct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, % of all RCCs</td>
<td>75–85</td>
<td>12–14</td>
<td>4–6</td>
<td>2–4</td>
<td>1</td>
</tr>
<tr>
<td>Genetic Mutation</td>
<td>VHL</td>
<td>c-MET</td>
<td>FH</td>
<td>BHD</td>
<td>BHD</td>
</tr>
</tbody>
</table>

- **Sporadic RCC:** loss of VHL = 97%
- **Inherited RCC:** loss of VHL = 100%
VHL Protein Regulates Genes Involved in Angiogenesis in RCC

A

- pVHL
- Ubiquitin attachment
- HIF
- HIF\(\alpha\) degradation
- Proteasome

B

- pVHL
- HIF
- Constitutively expressed HIF\(\alpha\) translocates into the nucleus
- Induction of hypoxia-inducible genes, e.g., VEGF, PDGF, TGF\(\beta\)
Consequences of VHL gene mutation

VHL complex disrupted

- Multiprotein complex
- VHL protein
- Mutant α-domain
- β-domain

HIF1-α, HIF2-α accumulation

- CXCR4
- VEGF
- PDGF
- TGF-α

Organ-specific metastasis
Angiogenesis
Endothelial stabilisation
Autocrine growth stimulation

CXCR4 = chemokine receptor 4
HIF-α = hypoxia-inducible factor-alpha

Reproduced from J Urol, 170, Linehan WM, et al, 2163–72, copyright (2003), with permission from the American Urological Association
## Summary of efficacy data from phase III trials in mRCC

<table>
<thead>
<tr>
<th>Investigational Drug</th>
<th>Control</th>
<th>Stage Px</th>
<th>ORR (%)</th>
<th>PFS (mons)</th>
<th>OS (mons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>INF</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>31* vs 6</td>
<td>11* vs 5.1</td>
<td>26.4 vs 21.8</td>
</tr>
<tr>
<td>Bev + IFN</td>
<td>Plac + INF</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>31* vs 13</td>
<td>10.2* vs 5.4</td>
<td>23.3 vs 21.3</td>
</tr>
<tr>
<td>Bev + IFN</td>
<td>INF</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>26* vs 13</td>
<td>8.5* vs 5.2</td>
<td>18.3 vs 17.4</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Tem + INF</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line (P)</td>
<td>8.6 vs 8.1 NS</td>
<td>5.5* vs 4.7</td>
<td>10.9 vs 8.4*</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Plac</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>30* vs 3</td>
<td>9.2* vs 4.2</td>
<td>21.1* vs 18.7</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Plac</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>10* vs 2</td>
<td>5.5* vs 2.8</td>
<td>17.8 vs 15.2</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Plac</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>5 vs 0 (NS)</td>
<td>4.9* vs 1.9</td>
<td>14.8 vs 14.4</td>
</tr>
</tbody>
</table>
Cancer target is not just only the cells or blood vessels! In the 2011 era ...
Host Immune System play role in cancer control
## 2010 Was a Very Good Year for CRPC: OS Benefit in Recent CRPC Trials

<table>
<thead>
<tr>
<th>Trial/Agent Approved</th>
<th>Disease State</th>
<th>Comparator</th>
<th>HR</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>IMPACT [1] (Sipuleucel-T vaccine)</td>
<td>Chemo-naive CRPC</td>
<td>Placebo</td>
<td>0.775</td>
<td>.032</td>
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<tr>
<td>TROPIC [3] (Cabazitaxel)</td>
<td>Post-docetaxel CRPC</td>
<td>Mitoxantrone Prednisone</td>
<td>0.70</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>COU-AA-301 [4] (Abiraterone acetate)</td>
<td>Post-docetaxel CRPC</td>
<td>Placebo Prednisone</td>
<td>0.646</td>
<td>&lt; .0001</td>
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</table>

Cabazitaxel selection

• Discovery objectives for compound selection:
  – Same potency as docetaxel against sensitive tumour models
  – More potent than docetaxel against tumour models resistant to chemotherapy including docetaxel
  – Activity on tubulin polymerisation
  – In vitro activity against tumour cell lines sensitive to docetaxel
    • In vitro against P388 or KB leukemia
  – In vitro activity against docetaxel-resistant tumour cell lines
    • In vitro against P388/VCR or KB/Velbe
  – In vivo activity against docetaxel-sensitive followed by docetaxel-resistant tumour models
    • In vivo against B16 melanoma
    • In vivo against B16/TXT melanoma
      – Tumour model developed in house with in vivo induced resistance to docetaxel

Cabazitaxel was selected out of 450 molecules for further clinical development, based on encouraging activity in cancer preclinical models sensitive and resistant to docetaxel
Cabazitaxel selection

• Discovery objectives for compound selection:
  – Same potency as docetaxel against sensitive tumour models
  – More potent than docetaxel against tumour models resistant to chemotherapy including docetaxel

• **Screening procedure (~450 derivatives)**
  – Activity on tubulin polymerisation
  – In vitro activity against tumour cell lines sensitive to docetaxel
    • In vitro against P388 or KB leukemia
  – In vitro activity against docetaxel-resistant tumour cell lines
    • In vitro against P388/VCR or KB/Velbe
  – In vivo activity against docetaxel-sensitive followed by docetaxel-resistant tumour models
    • In vivo against B16 melanoma
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Cabazitaxel was selected out of 450 molecules for further clinical development, based on encouraging activity in cancer preclinical models sensitive and resistant to docetaxel.
Cabazitaxel mechanism of action

- Cabazitaxel is as potent as docetaxel in stabilising microtubules

<table>
<thead>
<tr>
<th></th>
<th>Cabazitaxel</th>
<th>Docetaxel</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>(LT_{50}) µmol/l</td>
<td>0.05</td>
<td>0.05</td>
<td>0.085</td>
</tr>
<tr>
<td>(dIC_{50}) µmol/l</td>
<td>0.12</td>
<td>0.12</td>
<td>0.17</td>
</tr>
</tbody>
</table>

- More potent than docetaxel against mdr-1-expressing tumour cells resistant to chemotherapeutic agents including taxanes

<table>
<thead>
<tr>
<th>Resistant cell line</th>
<th>Resistance factors*</th>
<th>(mdr-1) mRNA level**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Cabazitaxel</td>
</tr>
<tr>
<td>P388/DOX</td>
<td>50.7</td>
<td>10.0</td>
</tr>
<tr>
<td>P388/TXT</td>
<td>4.8</td>
<td>1.8</td>
</tr>
<tr>
<td>P388/VCR</td>
<td>5.8</td>
<td>1.8</td>
</tr>
<tr>
<td>HL60/TAX</td>
<td>8.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Calc18/TXT</td>
<td>23.5</td>
<td>4.3</td>
</tr>
<tr>
<td>KB V1</td>
<td>59.0</td>
<td>7.6</td>
</tr>
</tbody>
</table>

TROPIC – Study design
146 centres in 26 countries

Stratification factors
• ECOG PS (0, 1 vs 2)
• Measurable vs non-measurable disease

mHRPC patients progressing during and after treatment with a docetaxel-based regimen (N = 755)

Randomise

Cabazitaxel 25 mg/m² q3w + prednisone* for 10 courses (CBZP) (n = 378)

Mitoxantrone 12 mg/m² q3w + prednisone* for 10 courses (MP) (n = 377)

*Oral prednisone/prednisolone: 10 mg daily

Premedication
• Premedication in the cabazitaxel group: antihistamine, steroid, and H₂ antagonist administered by IV infusion at least 30 minutes prior to each dose of cabazitaxel
• Antiemetic prophylaxis was administered when necessary

Primary end point: OS

Primary end point – Overall survival
Updated ITT analysis*

![Graph showing overall survival](image)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.72</td>
<td></td>
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<tr>
<td>95% CI</td>
<td>0.61–0.84</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.0001</td>
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</tr>
</tbody>
</table>

28% reduction in risk of death

Combined median follow-up: 13.7 months
**Most frequent adverse events**

<table>
<thead>
<tr>
<th></th>
<th>MP (n = 371)</th>
<th></th>
<th>CBZP (n = 371)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Grade ≥3 (%)</td>
<td>All grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>88.4</td>
<td>39.4</td>
<td>95.7</td>
<td>57.4</td>
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<tr>
<td>Febrile neutropenia</td>
<td>1.3</td>
<td>1.3</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10.5</td>
<td>0.3</td>
<td>46.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.5</td>
<td>3</td>
<td>36.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>12.1</td>
<td>3</td>
<td>16.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.9</td>
<td>0.3</td>
<td>34.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.2</td>
<td>0</td>
<td>22.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Haematuria</td>
<td>3.8</td>
<td>0.5</td>
<td>16.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.5</td>
<td>0</td>
<td>11.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

- **Grade 3 peripheral neuropathy** was uncommon with 3 (0.8%) patients in each arm.
- **Grade 2 increased lacrimation** occurred in 1 (0.3%) patients in cabazitaxel arm.
- **Onycholysis** was rare with 2 (0.5%) patients in each arm.
April 29, 2010

Sipuleucel-T

The First Cancer Vaccine
Immunotherapy for Prostate Cancer: Mechanism(s) of Action

Activated dendritic cell

Tumor antigen

Class I MHC

TCR

Class II MHC

Activated CD8+ T cells: traffic to tumor, lyse tumor cells

CD4+ T cell

CD8 T cell

Antibodies: circulate in sera bind to tumor cells

Activated dendritic cell

Tumor antigen

Class I MHC

TCR

Class II MHC

Cytokines

Activated CD8+ T cells: traffic to tumor, lyse tumor cells

Antibodies: circulate in sera bind to tumor cells

Activated CD8+ T cells: traffic to tumor, lyse tumor cells

Antibodies: circulate in sera bind to tumor cells
Active Cellular Immunotherapy (Sipuleucel-T)

Patient’s white blood cells harvested

Pt peripheral blood mononuclear cells including APCs

Short-term culture with protein “cassette”

GM-CSF

Prostatic acid phosphatase (PAP)
Active Cellular Immunotherapy (Sipuleucel-T)

Patient’s white blood cells harvested

Pt peripheral blood mononuclear cells including APCs

Short-term culture with protein “cassette”

Prostatic acid phosphatase (PAP)

GM-CSF

Shipping

Cells infused back into patient (IV)
**IMPACT: Phase III Study**

- **Patients with metastatic, asymptomatic or minimally symptomatic CRPC, no visceral metastases**
- **Placebo** q2w x 3
- **Sipuleucel-T** q2w x 3

**Primary endpoint: OS**

**Secondary endpoint: TTP**

*Prepared using cryopreserved peripheral blood lymphocytes*

**IMPACT: Baseline Characteristics**

- **Key Inclusion Criteria**
  - Metastatic and castrate resistant
  - Asymptomatic or minimally symptomatic
  - Prior chemotherapy permitted

- **Selected Patient Characteristics**
  - Median age: 71
  - Median PSA: 50 ng/mL
  - Hemoglobin: 12.8 g/dL
  - Bone-only disease: 50%
  - Bone and soft-tissue disease: 44%

IMPACT Study: OS (ITT Population)

- **P = .032 (Cox model)**
- **HR: 0.775 (95% CI: 0.614-0.979)**
- **Median survival benefit: 4.1 mos**

- **Sipuleucel-T (n = 341)**
  - Median survival: 25.8 mos

- **Placebo (n = 171)**
  - Median survival: 21.7 mos

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Evolving Modalities of Systemic Therapy

**Chemotherapy:**
- Dacarbazine

**Immunological:**
- Interferon alfa-2
- Interleukin 2

**Adjuvant HDI**

Approved 1976-1998
TILs in Vertical Growth Phase Melanoma

Brisk lymphocytic infiltrate patterns
Evolving Modalities of Systemic Therapy

Chemotherapy: Dacarbazine

Immunological:
- Interferon alfa-2
- Interleukin 2

Adjuvant HDI

Approved 1976-1998
Ipilimumab, CTLA-4 Blocking mAb, Augments T-Cell Activation

T-Cell Activation

resting T cell

TCR
CD28
HLA
B7

APC

CTLA-4

T-Cell Inactivation

T cell

TCR
CD28
HLA
B7

APC

CTLA-4

T-Cell Remains Active

T cell

TCR
CD28
HLA
B7

APC

CTLA-4

Ipilimumab

MDX-024: Ipilimumab + Dacarbazine vs Dacarbazine in Unresectable Melanoma

- **Phase III trial**

  Patients with previously untreated unresectable stage IIIc/IV melanoma

  **(N = 502)**

<table>
<thead>
<tr>
<th>Induction Therapy</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab 10 mg/kg q3w for 4 cycles + Dacarbazine 850 mg/m² q3w for 8 cycles (n = 250)</td>
<td>Ipilimumab 10 mg/kg q12w</td>
</tr>
<tr>
<td>Placebo q3w for 4 cycles + Dacarbazine 850 mg/m² Q3W for 8 cycles (n = 252)</td>
<td>Placebo Q12W</td>
</tr>
</tbody>
</table>

  **Estimated Survival (%)**

  - **Yr 1**: 47.3% for Ipilimumab + DTIC, 36.3% for Placebo + DTIC
  - **Yr 2**: 28.5% for Ipilimumab + DTIC, 17.9% for Placebo + DTIC
  - **Yr 3**: 20.8% for Ipilimumab + DTIC, 12.2% for Placebo + DTIC

  **mOS, Mos**
  - Ipilimumab + DTIC (n = 250): 11.2 yrs
  - Placebo + DTIC (n = 252): 9.1 yrs

  **P = .0009 (HR: 0.72; 95% CI: 0.59-0.87)**

## MDX-024: Median OS, PFS, and Response

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ipilimumab + Dacarbazine (n = 250)</th>
<th>Placebo + Dacarbazine (n = 252)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos*</td>
<td>11.2</td>
<td>9.1</td>
<td>0.72</td>
<td>.0009</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(0.59-0.87)</td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>2.8</td>
<td>2.6</td>
<td>0.76</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.63-0.93)</td>
<td></td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>33.2</td>
<td>30.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1.6</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>13.6</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>18.0</td>
<td>19.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>44.4</td>
<td>52.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of response, mos</td>
<td>19.3</td>
<td>8.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MDX-024: Safety

- Substantially more grade 3/4 adverse events in ipilimumab + dacarbazine arm

<table>
<thead>
<tr>
<th>Select Adverse Event, %</th>
<th>Ipilimumab + Dacarbazine (n = 247)</th>
<th>Placebo + Dacarbazine (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>33.2</td>
<td>21.9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>29.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29.6</td>
<td>2.0</td>
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<tr>
<td>Rash</td>
<td>24.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Colitis</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<td>0</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>0.8</td>
<td>0</td>
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<tr>
<td>Hyperthyroidism</td>
<td>0.4</td>
<td>0</td>
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</tbody>
</table>

Ipilimumab Pattern of Response

- Responses after appearance and subsequent disappearance of new lesions

Evolving Modalities of Systemic Therapy

Chemotherapy:
- Dacarbazaine

Immunological:
- Interferon alfa-2*
- Interleukin 2
- Anti-CTLA4

Adjuvant HDI
- Adjuvant pegIFN

Approved 1976-1998
Approved 2011
## Oncogenes in Melanoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Target</th>
<th>Prevalence, %</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1984</td>
<td>NRAS</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>BRAF</td>
<td>50</td>
<td>Sorafenib, PD0325901, selumetinib, GSK1120212, RAF-265, XL281, vemurafenib, GSK2118436</td>
</tr>
<tr>
<td>2005</td>
<td>c-kit</td>
<td>1</td>
<td>Imatinib, dasatinib, nilotinib</td>
</tr>
<tr>
<td>2008</td>
<td>GNAQ/GNA11</td>
<td>1*</td>
<td></td>
</tr>
</tbody>
</table>
Distribution of Genetic Alterations in BRAF, NRAS, and KIT by Primary Site

Change in Tumor Size with Vemurafenib in 132 $^{V600E}$BRAF-Mutant Patients

Disease stage
- M1a
- M1b
- M1c

Percent Change From Baseline in Diameter of Target Lesion

Individual Patients Treated With Vemurafenib

*7 confirmed CRs.

Phase III BRIM-3 Study Design

Screening

V600E BRAF mutation

Stratification
- Stage
- ECOG PS (0 vs 1)
- LDH level (↑ vs nl)

Randomization (N = 675)

Vemurafenib
- 960 mg PO BID (n = 337)

Dacarbazine
- 1000 mg/m² IV q3w (n = 338)

Vemurafenib vs Dacarbazine in BRAF V600E–Positive Melanoma: OS

HR: 0.37
(95% CI: 0.26-0.55; log-rank P < .0001)

Vemurafenib (n = 336)
Est 6-mo survival: 84%

Dacarbazine (n = 336)
Est 6-mo survival: 64%

Patients in follow-up, n

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>336</td>
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<td>11</td>
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<td>9</td>
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<tr>
<td>12</td>
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</tbody>
</table>

Evolving Modalities of Systemic Therapy

Chemotherapy: Dacarbazine

Immunological:
- Interferon alfa-2*
- Interleukin 2
- Anti-CTLA4
- Adjuvant HDI
- Adjuvant pegIFN

Targeted: BRAFi

Approved 1976-1998
Approved 2011
Evolution Modalities of Systemic Therapy

Chemotherapy:
- Dacarbazine

Immunological:
- Interferon alfa-2
- Interleukin 2
- Anti-CTLA4
- Anti-PD1
- Vaccines
- Adjuvant HDI
- Adjuvant pegIFN

Targeted:
- BRAFi
- MEKi
- C-Kit

Approved 1976-1998
Approved 2011
Pending Approval 2011
NO PLAN. NO BACKUP. NO CHOICE.

TOM CRUISE

MISSION: IMPOSSIBLE

GHOST PROTOCOL

IN THEATRES AND IMAX THIS DECEMBER