L’oncologie aujourd’hui et demain

traitements ciblés ou personnalisés ?
Cancer = cell autonomous disease
Conventional chemotherapy targeting dividing cells

But normal cells also divide ➔ severe side effects
The role of the tumor microenvironment

Hodgkin’s lymphoma

Pancreatic cancer

Courtesy Dr T Mckee and M Genevay
The tumor micro-environment

The intracellular signaling pathways
Signal transduction via Tyrosine or serine/threonine kinases
Outside: mAbs

Inside: Tyrosine or serine threonine kinase inhibitors

NEJ Med 2007;357:39
Tyrosine and serine/threonine kinase inhibitors
Trastuzumab (Herceptin®): Breast cancer

**HER2 Amplification**

~ 20 %
Trastuzumab: major impact in both the metastatic and adjuvant settings

Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

NEJ Med 2005
Rituximab: major impact for most lymphomas
Diffuse large B cell lymphoma (DLBCL)

Aggressive CT

Chemo-immunotherapy


JCO 2005; 23: 4117
Could we do better? ➔ the antibody-drug-conjugates

- mAb: Trastuzumab
- Stable binding with a linker: thioether
- Cytotoxic drug: emtansine

T-DM1: traztuzumab-emtansine

Juntila et al. Br Cancer Res 2011
T-DM1: How does it work?

Emtansine release
Inhibition of microtubule polymerization
Lysosome
Internalization

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group
EMILIA: randomized phase III

- HER2-positive LABC or MBC (N=980)
  - Prior taxane and trastuzumab
  - Progression on metastatic treatment or within 6 months of adjuvant treatment

- T-DM1
  - 3.6 mg/kg q3w IV

- Capecitabine
  - 1000 mg/m² PO bid, days 1–14, q3w
  - + Lapatinib
  - 1250 mg/day PO qd

- Primary endpoints: PFS by independent review, OS, and safety
- Key secondary endpoints: PFS by investigator, ORR, DOR

Figure 2. Second Interim Analysis of Overall Survival.

Shown are Kaplan–Meier estimates of overall survival in the intention-to-treat population, stratified according to world region, number of prior chemotherapy regimens (0 or 1 vs. >1), and site of disease involvement (visceral vs. nonvisceral). The second interim analysis was conducted on the basis of 331 deaths and met the predefined O’Brien–Fleming stopping boundary. The data-cutoff date was July 31, 2012. Median follow-up was 18.6 months (range, 0 to 41) in the lapatinib–capecitabine group and 19.1 months (range, 0 to 40) in the T-DM1 group.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lapatinib plus Capecitabine (N=488)</th>
<th>T-DM1 (N=490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events of Any Grade</td>
<td>Grade 3 or 4 Events</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Any event</td>
<td>477 (97.7)</td>
<td>278 (57.0)</td>
</tr>
<tr>
<td>Specific events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>389 (79.7)</td>
<td>101 (20.7)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysesthesia</td>
<td>283 (58.0)</td>
<td>80 (16.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>143 (29.3)</td>
<td>22 (4.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42 (8.6)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>42 (8.6)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>136 (27.9)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>218 (44.7)</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>93 (19.1)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>39 (8.0)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>43 (8.8)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>46 (9.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (2.5)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

**LESS TOXICITY**
Brentixumab: another antibody-drug-conjugate targeting CD30

Brentuximab vedotin (SGN-35) ADC
- monomethyl auristatin E (MMAE), potent antimicrotubule agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex traffics to lysosome
MMAE is released
MMAE disrupts microtubule network
G2/M cell cycle arrest
Apoptosis

Phase 2 pivotal study of brentuximab in patients with rel/ref HL post ASCT

Best clinical response per IRF
- Complete remission
- Partial remission
- Stable disease
- Progressive disease

Tumor size (% change from baseline)

Individual patients (n=98)

Overall Survival

OS at 3 years: 63%

Courtesy Dr Tom McKee
Outside: mAbs

Inside: Tyrosine or serine threonine kinase inhibitors
Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approved indication</th>
<th>Target(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>NSCLC</td>
<td>EGFR</td>
</tr>
<tr>
<td>Axitinib</td>
<td>RCC</td>
<td>VEGFR</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>CML</td>
<td>Bcr-abl</td>
</tr>
<tr>
<td>Cabozantanib</td>
<td>MTC</td>
<td>RET, VEGFR, MET, TRKB, TIE2</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Colon, NSCLC, HNC</td>
<td>EGFR</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>NSCLC</td>
<td>EML4–ALK, ROS1, MET</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Melanoma</td>
<td>BRAF V600E</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>CML</td>
<td>Bcr-abl, SRC, cKIT, PDGFR</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>NSCLC</td>
<td>EGFR</td>
</tr>
<tr>
<td>Everolimus</td>
<td>RCC, breast, pNET</td>
<td>mTOR, TSC1, TSC2</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>MCL</td>
<td>BTK</td>
</tr>
<tr>
<td>Imatinib</td>
<td>CML, GIST</td>
<td>Bcr-abl, cKIT</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Breast</td>
<td>EGFR</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>CML</td>
<td>Bcr-abl</td>
</tr>
<tr>
<td>Pansitumumab</td>
<td>Colon</td>
<td>EGFR</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>RCC, STS</td>
<td>VEGFR, PDGFR, FGFR, KIT</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Breast</td>
<td>HER2</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Colon</td>
<td>VEGFR, TIE2, PDGFR, RET, cKIT</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Myelofibrosis</td>
<td>JAK1, JAK2</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>RCC, HCC, DTC</td>
<td>BRAF, KIT, FLT-3, RET, VEGFR, PDGFR</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>RCC, GIST, pNET</td>
<td>PDGFR, VEGFR, KIT, FLT-3, RET</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>RCC</td>
<td>mTOR</td>
</tr>
<tr>
<td>Trametinib</td>
<td>Melanoma</td>
<td>MEK1, MEK2</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Breast, gastric</td>
<td>HER2</td>
</tr>
<tr>
<td>Trastuzumab emtansine</td>
<td>Breast cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>MTC</td>
<td>RET, EGFR, VEGFR, TIE2</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Melanoma</td>
<td>BRAF V600E</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>BCC</td>
<td>SMO</td>
</tr>
</tbody>
</table>

Non exhaustive List of TKI

Nature Rev Clin Oncol 2014 i
Metastatic melanoma in 2010

median survival
6 months
For melanoma? 

Mutated BRAF is present in many cancers:
- >50% melanomas
- ~10% colorectal
- ~8% all solid tumors

Adapted from JID 2010; 130: 28 and NEJMed 2005; 353: 2135
WT and V600E BRAF signaling:

**Normal cell**
- RTK
- RAS
- WT BRAF
- MEK
- ERK
- Cell survival & proliferation

**Melanoma cell**
- RTK
- RAS
- BRAF V600E
- MEK
- ERK
- Cell survival & proliferation

Vemurafenib
Selective anti-tumor effect: BRAF V600E

Tsai J et al. PNAS 2008 105 3041
Role of Vemurafenib: Phase I-III Waterfall Plots

Phase I (2\textsuperscript{nd} line +)

Phase II (2\textsuperscript{nd} line +)

Phase III (1\textsuperscript{st} line)

Anti-tumor effects are - rapid - in all metastatic sites

NEJMed 2010; 363: 809
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., 
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., 
Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., 
Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., 
Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., 
Antoni Ribas, M.D., Steven J. O’Day, M.D., Jeffrey A. Sosman, M.D., 
John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., 
Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., 
Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., 
and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*
**BRIM-3: PFS**

Progression-free Survival

Hazard ratio, 0.26; 95% CI, 0.20 to 0.33; P<0.001

**mPFS: 5.3 months**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacarbazine (N=274)</td>
<td>274</td>
<td>213</td>
<td>85</td>
<td>48</td>
<td>28</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vemurafenib (N=275)</td>
<td>275</td>
<td>268</td>
<td>211</td>
<td>122</td>
<td>105</td>
<td>50</td>
<td>35</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Chapman & al, NEJM, 2011**
Acquired resistance to BRAF inhibition

Week 15

JCO 2011, N Wagle
Secondary skin tumors

Acanthopapilloma

Kerato-acanthoma

SCC
a single solution for two problems? ➔ Dual inhibition

Normal cell

- RTK
- RAS
- WT BRAF
- MEK
- ERK
- Cell survival & proliferation

Melanoma cell

- RTK
- RAS
- BRAF V600E
- MEK
- ERK
- Cell survival & proliferation

Resistances:
- BRAF splice variant
- NRAS, MEK mutations
- COT...

Adapted from O Michielin
Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D.,

RTK → RAS → BRAF V600E → MEK → ERK → Cell survival & proliferation

Vemurafenib

Cobimetinib

Melanoma cell

NEJmed 2014 In press
Overall Survival (%)

- Vemurafenib + cobimetinib (N=247)
- Vemurafenib + placebo (N=248)

Hazard ratio, 0.65 (95% CI, 0.42–1.00)  
P = 0.046

Patients Who Died  
Vemurafenib + cobimetinib  
Vemurafenib + placebo  

Median Survival  
NR

No. at Risk  
Vemurafenib + cobimetinib  
Vemurafenib + placebo  

<table>
<thead>
<tr>
<th>Months</th>
<th>243</th>
<th>229</th>
<th>182</th>
<th>112</th>
<th>62</th>
<th>20</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>245</td>
<td>227</td>
<td>166</td>
<td>101</td>
<td>53</td>
<td>21</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
# Summary of Selected AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vemurafenib + Placebo (n=239)</th>
<th>Vemurafenib + Cobimetinib (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Serous retinopathy*</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased ejection fraction</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td>8 (3)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

No cases of retinal vein occlusion were reported.

*Includes specific terms chorioretinopathy and retinal detachment.

Cobimetinib is not yet registered in Switzerland

Data Cutoff: May 9, 2014
BRAF inhibiteur
Interdit
MEKi

imatinib

BRAF inhibiteur
Immunotherapy

Immune checkpoints blockade
Tumor immunity

- Incidence of cancers is increased
  - Souris Rag-/- et STAT-1 -/-
  - Constitutive Immunodeficiencies
  - HIV
  - Immunosuppressive treatments
    - transplantation

Cancer 2005; 104: 1962
T lymphocytes are killer cells
Lymphocytes T ➜ spontaneous regression

Regressive Melanoma
T cells invade tumors
Intratumoral T cells: Good prognosis factor

Colon Cancer
Activated Lymphocytes

Survival (%) vs Months

High density of CD45RO+
P < 0.001

Low density of CD45RO+

PAGES F, N ENGL J MED 2005; 353: 2654
Tumor immunity: how does it work?

Tumor

Cancer cells

APCs/DCs

Draining lymph node

MHC + tumor peptide

TCR

CD80 CD86

CD28

T cell
cancer is like a fortress

1. Cell-cell contact inhibition (FasL, PDL1)
2. Soluble mediators (TGF-β, IL-10, PGE2, ...)
3. Cell mediators (Tregs, MDSCs, ...)
4. Rampart (IDO, ...)
Tumor immune control: A delicate balance?

T cell response immunotherapies

Escape
Improving T cell activation and function?

Could we re-inforce?

1) T cell activation

2) T cell killing function

Tumor
- Cancer cells
- APCs/DCs

Draining lymph node
- T cell
- MHC + tumor peptide
- CD80, CD86, CD28
The role of immune checkpoints

**Activation**
- Dendritic Cell
- CD38
- B7
- CTLA-4
- 48-72h

**Inhibition**
- Dendritic Cell
- CTLA-4
- Ipilimumab

Courtesy O Michielin
Metastatic melanoma in 2010

median survival 6 months
Randomized phase III study: 020 trial

676 HLA A2+ patients with stage III or IV non operable melanoma, 2nd line

(1) Ipilimumab 3mg/kg q3w + vaccination gp100

(2) Ipilimumab 3mg/kg q3w + placebo

(3) Placebo + vaccination gp100

Methodology:
Primary endpoint: Overall survival (OS)
Secondary endpoint: PFS, response rate

Results:
Comparison gp100 + ipi vs. gp100 alone (arm 1 vs. 3):
Median OS 10.0 vs. 6.4 m, \textit{p}=0.0004, HR 0.68 (CI 0.55 – 0.85)
Comparison ipi alone vs. gp100 alone (arm 2 vs. 3):
Median OS 10.1 vs. 6.4 m, \textit{p}=0.0026, HR 0.66 (CI 0.51 – 0.87)
Comparison of the 2 ipi arms: no significant differences

Hodi & al, NEJM, 2010
Improved Survival with Ipilimumab
(> 4.5 Years of Follow-Up)

Comparison | HR | P-value
---|---|---
Arms A vs C | 0.68 | <0.001
Arms B vs C | 0.66 | 0.003

No separation in curves for first 3 months

Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma

- 4846 patients, various ipilimumab regimens
- Plateau appears to prolong largely after year 3

Schadendorf & al, JCO, 2015
Immune side effects ➔ proof of concept

• Skin erythema

• Colitis

• Hepatitis

• hypophysitis

Immune checkpoints

Nat Rev cancer 2012, 12:252
Other checkpoint inhibitors

Cancer cells → DCs → Draining lymph node

- CTLA4
- Ipilimumab

PDL1 / PD1

Less toxic?
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,
David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D.,
Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D.,
Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D.,
Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D.,
Tracee L. McMillen, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D.,
Daniel McDonald, M.B.A., Georgia D. Kolia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D.,
and Mario Sznol, M.D.

- Nivolumab

- Advanced melanoma, NSCLC, CRPC, RCC, colorectal cancer

- N = 296 patients
Results and toxicity

• *less side effects* than anti-CTLA4

• *Objective responses* (this is new !) in
  – melanoma,
  – renal-cell cancer
  – NSCLC
Melanoma: overall survival is 48% at 2 years

Died/Treated: 64/107
Median OS, mo (95% CI): 17.3 (12.5, 36.7)

- 1 year OS 63%
- 2 year OS 48%
- 3 year OS 41%

<table>
<thead>
<tr>
<th>OS</th>
<th>Pts at risk, n</th>
<th>Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Mo</td>
<td>86</td>
<td>82 (74, 88)</td>
</tr>
<tr>
<td>1 Yr</td>
<td>63</td>
<td>63 (53, 71)</td>
</tr>
<tr>
<td>2 Yr</td>
<td>44</td>
<td>48 (38, 57)</td>
</tr>
<tr>
<td>3 Yr</td>
<td>22</td>
<td>41 (31, 51)</td>
</tr>
</tbody>
</table>

S. Hodi, ASCO 2014, CA209-003
Eligible patients with unresectable stage III or IV melanoma (N=418)

- BRAF WT
- Treatment-naïve

Stratified by:
- PD-L1 status†
- M-stage

Double-blind

Nivolumab
3 mg/kg IV Q2W
+ Placebo
IV Q3W
N=210
(206 treated)

Treat until progression* or unacceptable toxicity

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- ORR
- PD-L1 correlates

Placebo
IV Q2W
+ Dacarbazline
1000 mg/m² IV Q3W
N=208
(205 treated)

†PD-L1 positive: ≥ 5% tumor cell surface staining.

*Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.
Nivolumab, Anti-PD1
Immune checkpoint inhibitors for other cancers
Squamous cell non small cell lung carcinoma

Median Overall Survival
mo (95% CI)
Nivolumab (N=135) 9.2 (7.3–13.3)
Docetaxel (N=137) 6.0 (5.1–7.3)

1-Yr Overall Survival
% of patients (95% CI)
Nivolumab 42 (34–50)
Docetaxel 24 (17–31)

No. of Deaths
Nivolumab 86
Docetaxel 113

Hazard ratio for death, 0.59 (0.44–0.79)
P<0.001

No. at Risk
Nivolumab 135 113 86 69 52 31 15 7 0
Docetaxel 137 103 68 45 30 14 7 2 0

How to select patients?
More mutations $\rightarrow$ more neo-antigens

Finn et al. 2008 NEJM

Some level of immune tolerance
Neoantigens as a predictive biomarker for ipilimumab

1 Snyder & al. *NEJM* 2014
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Table 2. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N=10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N=18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%) ‡</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %§</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA‡</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA‡</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

A  Biochemical Response

Change in Tumor Marker Level (%)

Days

Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer

0% (no change)

B  Radiographic Response

Change from Baseline in the Sum of Longest Diameters (%)

20% increase (progressive disease)

30% decrease (partial response)
Targeted therapy
Within a cancer type (e.g., lung cancer)

Chemotherapy:
Clinical benefit 15%

Lung cancer

Mutated EGFR (15%):
• Clinical benefit 70%
  • with erlotinib

ALK Rearrangement (4%):
• Clinical benefit
  • 80% with crizotinib
  • 95% with AF802

BRAF V600E (2%):
• Clinical benefit
  • 40% with BRAFi
Targeted therapy: across cancer types

- HER2 targeting
  - Breast cancer
  - Gastric cancer, colon cancer
- BRAF inhibitors
  - Melanoma
  - Lung
  - Low grade astrocytoma
  - Hairy cell leukemia

The New England Journal of Medicine

Original Article

BRAF Mutations in Hairy-Cell Leukemia

Enrico Tiacci, M.D., Vladimir Trifonov, Ph.D., Gianluca Schiavoni, Ph.D.,

June 16, 2011
Implementing personalized cancer care?

Diagnosis bar-code

Treatment bar-code

Efficacy +++++  Toxicity +/-  ............ COST - ?
Back up slides
CAR T cells: exploiting properties of both antibodies and T cells

- killing
- homing
- memory

- strong affinity binding
- no MHC restriction
- for all patients
- MHC is allowed

Nat Rev Cancer 2013, 13. 525 MH Kershaw
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D.,
Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D.,
Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A.,
Zhao-Hui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D.,
Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D.,
David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D.,
David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

N = 30
Refractory or relapsing ALL
CR in 27 / 30 !!
Overall survival 6 months 78 %
Combined with CT, targeted therapies and RT for promoting immunogenic cell death
Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

Unresectable or Metastatic Melanoma
- Previously untreated
- 945 patients

Randomize 1:1:1

Stratify by:
- PD-L1 expression*
- BRAF status
- AJCCM stage

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Primary endpoints:
- PFS, OS

Secondary endpoints:
- ORR, PD-L1 as biomarker, safety

* Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

** Patients could have been treated beyond progression under protocol-defined circumstances.

PFS (Intent-to-Treat):
9 months FU (DB lock 17.2.15)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.4)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>314</td>
<td>316</td>
<td>315</td>
</tr>
<tr>
<td>0</td>
<td>314</td>
<td>316</td>
<td>315</td>
</tr>
<tr>
<td>3</td>
<td>219</td>
<td>177</td>
<td>137</td>
</tr>
<tr>
<td>6</td>
<td>173</td>
<td>147</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>151</td>
<td>124</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
PFS by PD-L1 Expression Level (1%)

**PD-L1 ≥1%**

- **NIVO + IPI**: mPFS 12.4 months, HR 0.44
- **NIVO**: mPFS 12.4 months, HR 0.46
- **IPI**: mPFS 3.9 months

**PD-L1 <1%**

- **NIVO + IPI**: mPFS 11.2 months, HR 0.38
- **NIVO**: mPFS 2.8 months, HR 0.67
- **IPI**: mPFS 2.8 months

*No. at Risk*

<table>
<thead>
<tr>
<th>Group</th>
<th>NIVO + IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 ≥1%</strong></td>
<td>155</td>
<td>113</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>78</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>PD-L1 &lt;1%</strong></td>
<td>171</td>
<td>115</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>83</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.