New targets in Oncology

Sandra Donnini
Six Essential Alterations in Cell Physiology in Malignancy—Hallmarks of Cancer—2000

Hanahan & Weinberg, Cell, 2000
Emerging Hallmarks and Enabling Characteristics

Four additional hallmarks of cancer are involved in the pathogenesis of some and perhaps all cancers.

- the capability to modify, or reprogram, cellular metabolism in order to most effectively support neoplastic proliferation;
- evasion of immunological destruction, in particular by T and B lymphocytes, macrophages, and natural killer cells;
- genomic instability that drive tumor progression;
- Inflammation by innate immune cells designed to fight infections and heal wounds can instead result in their inadvertent support of multiple hallmark capabilities, thereby manifesting the now widely appreciated tumor-promoting consequences of inflammatory responses.
Ten Essential Alterations in Cell Physiology in Malignancy—Hallmarks of Cancer—2011

Emerging Hallmarks
- Deregulating cellular energetics
- Avoiding immune destruction

Enabling Characteristics
- Genome instability and mutation
- Tumor-promoting inflammation

Hanahan, D. & Weinberg, RA, Cell, 2011
Therapeutic Targeting of the Hallmarks of Cancer

- Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer.

- Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks, which also hold promise as cancer therapeutics.
Targeting of Hallmarks of Cancer

- EGFR inhibitors
  - Sustaining proliferative signaling
- Cyclin-dependent kinase inhibitors
  - Evading growth suppressors
- Immune activating anti-CTLA4 mAb
- Avoiding immune destruction
- Telomerase Inhibitors
- Enabling replicative immortality
- Selective anti-inflammatory drugs
- Tumor-promoting inflammation
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met
- Resisting cell death
- Deregulating cellular energetics
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
- Oncogene addiction?

Hanahan, D. & Weunberg, RA, Cell, 2011
**Targets importantly involved in carcinogenesis/function of tumor cells and their inhibitors**

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumor</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity/resistance</th>
<th>Disease setting</th>
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<tbody>
<tr>
<td>EGFR</td>
<td>Head and neck</td>
<td>Cetuximab</td>
<td></td>
<td>Advanced head and neck cancer</td>
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<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Gefitinib</td>
<td>Mutation of EGFR</td>
<td>Metastatic NSCLC</td>
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<td>Erlotinib</td>
<td>Mutation of EGFR</td>
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<td></td>
<td>Cetuximab</td>
<td>Skin toxicity? Degree of expression of EGFR by IHC</td>
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<td>EGFR</td>
<td>Colorectal</td>
<td>Cetuximab</td>
<td>K-Ras mutation</td>
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<td>Panitumumab</td>
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<td>C-Kit</td>
<td>GIST</td>
<td>Imatinib</td>
<td>C-Kit mutation</td>
<td>Adjuvant in high-risk patients, advanced disease</td>
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<tr>
<td>VEGF</td>
<td>NSCLC, colorectal, renal, breast</td>
<td>Bevacizumab</td>
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<td>VEGF-R</td>
<td>Renal</td>
<td>Bevacizumab</td>
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<td>mTOR</td>
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<td>Everolimus</td>
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<td>Temsirolimus</td>
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<td>VEGF-R</td>
<td>Hepatocarcinoma</td>
<td>Sorafenib</td>
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<td>VEGF-R</td>
<td>Neuroendocrine (pancreas)</td>
<td>Sunitinib, everolimus</td>
<td>--</td>
<td>Advanced disease</td>
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<td>mTOR</td>
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<td>HER2/neu</td>
<td>Breast, gastric</td>
<td>Trastuzumab, lapatinib, neratinib, pertuzumab, TDM1</td>
<td>HER2/neu amplification</td>
<td>Adjuvant (trastuzumab in breast cancer and advanced disease</td>
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<tr>
<td>EML4-ALK</td>
<td>NSCLC</td>
<td>Crizotinib</td>
<td>EML4-ALK translocation</td>
<td>Advanced NSCLC</td>
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<td>RANKL</td>
<td>Bone metastases, giant cell tumors</td>
<td>Denosumab</td>
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<td>Hedgehog</td>
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<td>Vismodegib</td>
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<td>B-Raf</td>
<td>Melanoma</td>
<td>Vemurafenib, GSK2118436</td>
<td>B-Raf mutation</td>
<td>Advanced disease</td>
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<td>PARP</td>
<td>Breast, ovary</td>
<td>Olaparib</td>
<td>BRCA mutation</td>
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<td>CTLA-4</td>
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<td>Ipilimumab</td>
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<td>Advanced disease</td>
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Farmaci a bersaglio molecolare nella terapia del cancro al polmone

Phase I
- Lapatinib
- Matuzumab
- Panitumumab
- Cetuximab
- HKI-272
- Imatinib
- PF-3512676
- Tipifarnib
- CP-751871

Phase II
- Vatalanib
- Avastin
- Talabostat
- Bortezomib
- Tarceva Gefitinib
- PF-3512676

Phase III
- AZD2171
- Sunitinib
- Vandetanib
- Motesanib
- Celecoxib
- AS1404
- Vatalanib
- Avastin
- Sunitinib
- VEGF TRAP
- Motesanib
- Celecoxib
- AS1404

Approved
- Gefitinib (Tarceva)
- AZD2171
- Bortezomib
- Vandetanib
- Motesanib
- Sunitinib
- Celecoxib
- AS1404
- VEGF TRAP

Other molecules in "target therapy"
- Matuzumab
- Panitumumab
- Cetuximab
- HKI-272
- Imatinib
- PF-3512676
- Tipifarnib
- CP-751871

Inhibitors
- EGFR/HER
- Angiogenesis

Other molecules in "target therapy"
- HKI-272
TKIs vs placebo phase III studies in unselected pretreated NSCLC patients

BR 21: erlotinib vs placebo

ISEL: gefinitib vs placebo


EGFR mutations

A

<table>
<thead>
<tr>
<th></th>
<th>EGFR protein</th>
<th>EGFR gene</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patients 3 and 4</th>
<th>Patients 5 and 6</th>
<th>Patient 7</th>
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<td>TTTGGGCTGGCCAAACTGCTGGGT</td>
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Exon 19

Exon 21

B

C

A phase III study (002) by North East Japan Gefitinib Study Group.


Prima della selezione e dopo la selezione
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial

Rafael Rosell, Enric Carcereny, Radj Gervais, Alain Vergnenegre, Bartomeu Massuti, Enrique Fujita, Ramon Palma, Ramon Garcia-Gomez, Cinta Pailhères, Jose Miguel Sanchez, Rut Porta, Manuel Cobo, Pilar Garrida, Flavia Longa, Teresa Moran, Amelia Insua, Filippo De Marinis, Romain Corne, Isabel Bover, Alfonso Illa, Eric Danis, Javier de Castro, Michel Millez, Noemi Reguart, Giuseppe Altavilla, Ulrich Zimniker, Mariano Procopio, Miguel Angel Moreno, Josefa Terrasa, Jose Munoz-Langa, Javier Valdivis, Dolores Isla, Manuel Domene, Olivier Molinier, Julien Mariere, Nathalie Boire, Rosario Garcia-Campela, Gilles Robinet, Delphs Rodrigue-Abrav, Guillerma Lopez-Vizcaina, Vittorio Gabbia, Lioba Ferrara-Delgado, Pierre Bornallon, Reyes Bernabe, Alessandra Bezzar, Angel Artal, Enrico Cortesi, Christian Raffa, Maria Sanchez-Ronco, Ana Dradowskyj, Cristina Queralta, Itziar de Aguirre, Jose Luis Ramirez, Jose Javier Sanchez, Miguel Angel Molina, Miguel Taron, Luis Paz-Ares, on behalf of the Spanish Lung Cancer Group in collaboration with the Groupe Francais de Pneumo-Cancerologie and the Associazione Italiana Oncologia Toracica.

- Chemo naïve
- Stage III B/IV NSCLC
- EGFR exon 19 deletion or exon 21 L858R mutation
- ECOG PS 0–2 (n=174)

Erlotinib 150mg/day

86

PD

Stratification
- Mutation type
- ECOG PS (0 vs 1 vs 2)

Platinum-based doublet chemotherapy q3wks x 4 cycles*

87

PD

Primary endpoint
- Progression-free survival (PFS)
  - interim analysis planned at 88 events

Secondary endpoints
- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- EGFR mutation analysis in serum
- Quality of life

**EURTAC: results**

![Graph showing PFS probability over time for Erlotinib and Chemotherapy](image)

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>Chemotherapy</th>
<th>( P )</th>
<th>( HR )</th>
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</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>58%</td>
<td>15%</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Progression Free Survival (months)</td>
<td>9.7</td>
<td>5.2</td>
<td>&lt;0.0001</td>
<td>0.37</td>
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<tr>
<td>1 year PFS</td>
<td>40%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival (months)</td>
<td>19.3</td>
<td>19.5</td>
<td>1.04</td>
<td></td>
</tr>
</tbody>
</table>

Oncogenic drivers in NSCLC and target therapy
Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer

Manabu Soda, Young Lim Choi, Munehiro Enomoto, Shuji Takada, Yoshihiro Yamashita, Shunpei Ishikawa, Shin-ichiro Fujiwara, Hideki Watanabe, Kentaro Kurashina, Hisashi Hatanaka, Masashi Bando, Shoji Ohno, Yuichi Ishikawa, Hiroyuki Aburatani, Toshiro Niki, Yasunori Sohara, Yukihiro Sugiyama & Hiroyuki Mano

• EML4-ALK frequency: ≈ 4% NSCLC

• Adenocarcinoma (acinar subtype)
In 2011 the FDA approved crizotinib as the first licensed ALK inhibitor for ALK-positive (ALK+) NSCLC.
the generation of oncogenic ALK-EML4 fusion gene and its encoded protein leads to constitutive activation of the ALK kinase domain

constitutive ALK signaling induces transformation via canonical signaling networks.
PERSONALIZED THERAPY: EMLA4-ALK NSCLC
Clinical Activity of Crizotinib in Patients with ALK-positive NSCLC

- Objective response rate (ORR): 57% (95% CI: 46, 68%)
  - 63% including 5 as yet unconfirmed PRs
  - 57% (8/14) for patients with performance status 2 or 3

<table>
<thead>
<tr>
<th>No. prior regimens*</th>
<th>ORR % (n/N)</th>
</tr>
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<tr>
<td>0</td>
<td>80 (4/5)</td>
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<tr>
<td>1</td>
<td>52 (14/27)</td>
</tr>
<tr>
<td>2</td>
<td>67 (10/15)</td>
</tr>
<tr>
<td>≥3</td>
<td>56 (19/34)</td>
</tr>
</tbody>
</table>

- Unknown for 1 patient

- Response duration: 1 to 15 months
- DCR† (CR/PR/SD at 8 weeks): 87% (95% CI: 77, 93%)

Overall Survival of ALK-Positive NSCLC Patients Treated with Crizotinib (N=82)

Median OS: Not reached (NR)
1-yr OS: 74%; 2-yr OS: 54%
61% of patients in follow-up for OS with median follow-up of 18 mos

From first crizotinib dose

Crizotinib: pathway from compound identification to approval
**Study Design**

**Key entry criteria**
- ALK+ by central FISH testing
- Stage IIIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

**Endpoints**
- **Primary**
  - PFS (RECIST 1.1, independent radiology review)
- **Secondary**
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

**Randomize**

- Crizotinib 250 mg BID PO, 21-day cycle (n=159)
- Pemetrexed 500 mg/m² or Docetaxel 75 mg/m² IV, day 1, 21-day cycle (n=159)

**Crossover to Crizotinib on Profile 1005**

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*Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)*

**PROFILE 1007: NCT00932893**

Shaw A.T. et al LBA1_PR, ESMO 2012
Primary Endpoint: PFS by Independent Radiologic Review (ITT Population)

- Events, n (%): Crizotinib (n=173) 100 (68) vs Chemotherapy (n=174) 127 (73)
- Median, mo: Crizotinib 7.7 vs Chemotherapy 3.0
- HR (95% CI): Crizotinib 0.49 (0.37 to 0.64) vs Chemotherapy 0.65 (0.27 to 1.64)
- ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.001

Interim Analysis of OS

- Events, n (%): Crizotinib (n=173) 49 (28) vs Chemotherapy (n=174) 47 (27)
- Median, mo: Crizotinib 20.3 vs Chemotherapy 22.5
- HR (95% CI): Crizotinib 1.02 (0.68 to 1.54) vs Chemotherapy 0.539

Shaw A.T. et Al LBA1_PR, ESMO 2012
• **Imatinib**—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl
New drugs in CML

- DASATINIB
- NILOTINIB
- BOSUTINIB
- POMATINIB
DRUGS TARGETING MYELOMA CLONE IN THE BONE MARROW MICROENVIRONMENT

A. Apoptosis
   Growth arrest

B. Inhibition of Adhesion
   Adhesion molecule

C. Inhibition of cytokines
   IL-6
   IGF-1
   VEGF
   SDF-1α

D. bFGF
   VEGF
   Angiogenesis
   Drug resistance

Hideshima T, Blood 2004 (modificata)
Dipeptidyl boronic acid; Bortezomib; PS341
A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma

Paul G. Richardson, M.D., Bart Barlogie, M.D., Ph.D., James Berenson, M.D.,
Seema Singhal, M.D., Sundar Jagannath, M.D., David Irwin, M.D.,
S. Vincent Rajkumar, M.D., Gordan Srkalovic, M.D., Melissa Alsina, M.D.,
Raymond Alexanian, M.D., David Siegel, M.D., Robert Z. Orlowski, M.D.,
David Kuter, M.D., Ph.D., Steven A. Limentani, M.D.,
Stephanie Lee, M.D., Teru Hideshima, M.D., Ph.D.,
Dixie-Lee Esseltine, M.D., Michael Kauffman, M.D., Ph.D., Julian Adams, Ph.D.,
David P. Schenkein, M.D., and Kenneth C. Anderson, M.D.
Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

Paul G. Richardson, M.D., Pieter Sonneveld, M.D., Michael W. Schuster, M.D., David Irwin, M.D., Edward A. Stadtmauer, M.D., Thierry Facon, M.D., Jean-Luc Harousseau, M.D., Dina Ben-Yehuda, M.D., Sagar Lonial, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Jesus F. San-Miguel, M.D., Joan Bladé, M.D., Mario Boccadoro, M.D., Jamie Cavenagh, M.D., William S. Dalton, M.D., Anthony L. Boral, M.D., Ph.D., Dixie L. Esseltine, M.D., Jane B. Porter, M.S., David Schenkein, M.D., and Kenneth C. Anderson, M.D., for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators*
Bortezomib-Mechanism of Action

<table>
<thead>
<tr>
<th>Best Confirmed Response</th>
<th>Bortezomib (N=315)</th>
<th>Dexamethasone (N=312)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete or partial response</td>
<td>121 (38)</td>
<td>56 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response, immunofixation-negative</td>
<td>20 (6)</td>
<td>2 (1)</td>
<td>&lt;0.001</td>
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<tr>
<td>Partial response</td>
<td>101 (32)</td>
<td>54 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nearly complete response, immunofixation-positive‡</td>
<td>21 (7)</td>
<td>3 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor response</td>
<td>25 (8)</td>
<td>52 (17)</td>
<td>ND</td>
</tr>
<tr>
<td>No change</td>
<td>137 (43)</td>
<td>149 (48)</td>
<td>ND</td>
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<tr>
<td>Progressive disease</td>
<td>22 (7)</td>
<td>41 (13)</td>
<td>ND</td>
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<tr>
<td>Could not be evaluated</td>
<td>10 (3)</td>
<td>14 (4)</td>
<td>ND</td>
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</tbody>
</table>

* All patients who received at least one dose of a study drug and who had measurable disease at baseline were evaluated for a response. Of the 669 patients enrolled, only 627 could be evaluated, since 6 did not receive a study drug and 36 did not have measurable disease (as defined by a serum M protein level that could be measured quantitatively, a urinary M protein level that could be measured quantitatively, or a measurable soft-tissue plasmacytoma).

† P values were calculated with the Cochran–Mantel–Haenszel chi-square test, with adjustment for stratified randomization. ND denotes not determined.

‡ All criteria for a complete response were met except that immunofixation remained positive.
New Actors in lymphoma non hodgkin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>n. Pts</th>
<th>ORR %</th>
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<tr>
<td>Alisertib</td>
<td>Aurora A Kinase inhibitor</td>
<td>15 DLBCL 13 MCL</td>
<td>20</td>
<td>Friedberg, ASH 2011</td>
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<tr>
<td>Pixantrone</td>
<td>AZA-anthracenedione</td>
<td>70 DLBCL</td>
<td>37</td>
<td>Pettengell, ASH 2010</td>
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<td>Everolimus</td>
<td>mTOR inhibitor</td>
<td>47 DLBCL 19 MCL</td>
<td>30</td>
<td>Witzig, Leukemia 2011</td>
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<td>SAR3419</td>
<td>Anti-CD19 DC</td>
<td>16 DLBCL</td>
<td>33</td>
<td>Coiffier, ASCO 2011</td>
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<td>Fostimatinib</td>
<td>SyK inhibitor</td>
<td>23 DLBCL</td>
<td>22</td>
<td>Friedberg, Blood 2010</td>
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<tr>
<td>PCI-32765</td>
<td>BTK inhibitor</td>
<td>8 ABCDLBCL 39 MCL</td>
<td>25 67</td>
<td>Staudt, ASH 2011 Wang, ASH 2011</td>
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<tr>
<td>CAL-101 (GS-1101)</td>
<td>PI3K inhibitor</td>
<td>38 MCL</td>
<td>42</td>
<td>Kahl, Lugano 2011</td>
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</tbody>
</table>
Bruton’s Tyrosine Kinase (BTK)

- Important component of the B-cell signaling pathway
  - Required for B cell receptor (BCR) signaling
  - Overexpressed in B-cell malignancies.
  - Interference leads to cell apoptosis
- PCI-32765 (Pharmacyclicks) is an oral BTK inhibitor that is in phase I for NHL
  - Small molecule; binds irreversibly to cys-481 of BTK
- B-cell specific (does not affect T cells)
CAL-101 - Inhibits PI3K p110δ

- CAL-101 (Calistoga Pharmaceuticals) is selective for p110δ (rather than α, β, or γ)
- IC50 for p110δ = 2.5 nM
- P110δ is expressed in over 90% of lymphoma cell lines and in many primary lymphoma samples
  - Results in constitutive Akt phosphorylation
- CAL-101 reduces p-Akt levels; blocked downstream effectors such as p-S6, and GSK-3β

Lanutti B et al Blood. 2011;117(2):591-4
Brentuximab vedotin antibody-drug conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody

Brentuximab Vedotin
Mechanism of Action

ADC binds to CD30
ADC-CD30 complex is internalized and traffics to lysosome
MMAE is released
MMAE disrupts microtubule network

G2/M cell cycle arrest
Apoptosis
Phase 2, Multicenter, Open-Label Study of Brentuximab Vedotin in Relapsed/Refractory sALCL

- Relapsed or refractory systemic ALCL
- Age ≥12 years
- Measurable disease ≥1.5 cm FDG-avid
- ECOG 0–1

Brentuximab vedotin (ADCETRIS™) 1.8 mg/kg IV every 21 days
- Administered outpatient over 30 min
- Max 16 cycles for SD or better
- Restage* at Cycles 2, 4, 7, 10, 13, 16

* Revised Response Criteria for Malignant Lymphoma (Cheson 2007); postbaseline PET scans obtained in Cycles 4 and 7 only

Every 12 weeks
## Demographics and Baseline Characteristics

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<th>Characteristic</th>
<th>Value</th>
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<tr>
<td><strong>N</strong></td>
<td>58</td>
</tr>
<tr>
<td><strong>Age (Median (range))</strong></td>
<td>52 yr (14–76)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>33 M / 25 F</td>
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<tr>
<td><strong>ECOG status</strong></td>
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<td>0</td>
<td>33%</td>
</tr>
<tr>
<td>1</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td><strong>ALCL confirmed by central pathology</strong></td>
<td>97%</td>
</tr>
<tr>
<td><strong>ALK-negative</strong></td>
<td>72%</td>
</tr>
<tr>
<td><strong>Refractory to frontline therapy</strong></td>
<td>62%</td>
</tr>
<tr>
<td><strong>Refractory to most recent treatment</strong></td>
<td>50%</td>
</tr>
<tr>
<td><strong>No response to any prior treatment</strong></td>
<td>22%</td>
</tr>
<tr>
<td><strong>Prior chemotherapy regimens</strong></td>
<td>2 (1–6)</td>
</tr>
<tr>
<td><strong>Prior radiation</strong></td>
<td>45%</td>
</tr>
<tr>
<td><strong>Prior autologous stem cell transplant (SCT)</strong></td>
<td>26%</td>
</tr>
</tbody>
</table>
# Key Response Results

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>N=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate (95% CI)</td>
<td>86% (75, 94)</td>
</tr>
<tr>
<td>Complete remission (CR) rate (95% CI)</td>
<td>59% (45, 71)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Duration</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (95% CI)</td>
<td>13.2 (5.7, NE)</td>
</tr>
<tr>
<td>Response in patients with CR (95% CI)</td>
<td>Not reached (13, NE)</td>
</tr>
</tbody>
</table>

NE=not estimable
Brentuximab vedotin: pivotal Phase II study in Hodgkin lymphoma

- 102 patients with relapsed or refractory HL post-ASCT

### Treatment (n=102)

- Relapsed or refractory CD30+ HL
- Age ≥12 years
- Measurable disease ≥1.5 cm
- ECOG 0–1
- Prior ASCT

- Brentuximab vedotin 1.8 mg/kg IV every 21 days
- Administered outpatient over 30 min
- Max 16 cycles for SD or better
- Restage at Cycles 2, 4, 7, 10, 13, 16
- Every 12 weeks

Revised Response Criteria for Malignant Lymphoma (Cheson, 2007) ALCL, anaplastic large-cell lymphoma; ASCT, autologous stem cell transplant; SD, stable disease; ECOG, Eastern cooperative oncology group

1. Chen R et al. Presented at American Society of Hematology annual meeting, Orlando, FL, USA; 4–7 December 2010: Oral presentation Abstract #283
Brentuximab vedotin: pivotal Phase II study in Hodgkin lymphoma – patient characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>31 yr (15–77)</td>
</tr>
<tr>
<td>Gender</td>
<td>48 M/54 F</td>
</tr>
<tr>
<td>Prior chemotherapy regimens</td>
<td>3.5 (1–13)</td>
</tr>
<tr>
<td>Refractory to frontline therapy*</td>
<td>71%</td>
</tr>
<tr>
<td>Refractory to most recent treatment*</td>
<td>42%</td>
</tr>
<tr>
<td>Prior radiation*</td>
<td>66%</td>
</tr>
<tr>
<td>Prior ASCT*</td>
<td>100%</td>
</tr>
<tr>
<td>Time from ASCT to first post transplant relapse</td>
<td>6.7 mo</td>
</tr>
</tbody>
</table>

*% of patients

ASCT, autologous stem-cell transplantation
Brentuximab vedotin: pivotal Phase II study in Hodgkin lymphoma – response (n=102) ¹

<table>
<thead>
<tr>
<th>Objective response rate (95% CI*)</th>
<th>75% (65, 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>34% (25, 44)</td>
</tr>
<tr>
<td>Median duration of OR (95% CI)</td>
<td>6.7 mo (3.6,14.8)</td>
</tr>
<tr>
<td>Median duration of response in patients with CR</td>
<td>20.5 mo (10.8, −)</td>
</tr>
</tbody>
</table>

*CI, Confidence interval; IRF, Independent review facility

¹.Chen R et al. Presented at American Society of Clinical Oncology annual meeting, Chicago, USA; 4–6 June 2011: Oral presentation Abstract #8031
# Pivotal Phase II in Hodgkin lymphoma: treatment-emergent adverse events (AE)

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades (% of pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral sensory neuropathy (^{1,2})</td>
<td>47</td>
</tr>
<tr>
<td>Fatigue (^{1,2})</td>
<td>46</td>
</tr>
<tr>
<td>Nausea (^{1})</td>
<td>42</td>
</tr>
<tr>
<td>Upper respiratory tract infection (^{1,2})</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhoea (^{1,2})</td>
<td>36</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29</td>
</tr>
<tr>
<td>Neutropaenia (^{1})</td>
<td>22</td>
</tr>
<tr>
<td>Vomiting (^{1,2})</td>
<td>22</td>
</tr>
<tr>
<td>Cough (^{1,2})</td>
<td>21</td>
</tr>
</tbody>
</table>

Pivotal Phase II in Hodgkin lymphoma: Grade 3/4 adverse events (AE)

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropaenia</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>8%*</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopaenia</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

- Total patients with any ≥Grade 3 event = 55%
- No deaths occurred within 30 days of last dose


*Update from ASCO 2011 2–peripheral sensory neuropathy 9%
Nuove strategie per il melanoma metastatico
Principali capisaldi terapeutici nel melanoma metastatico.

European Medicines Agency recommends approval of first-in-class treatment for metastatic or unresectable melanoma. Available on www.ema.europa.eu
Agents

- **Vaccines** (MAGE-3, NY-ESO-1, TG40, Allovecin)
- **Cytokines** (IFN-α, Thymosin α-1)
- **Immunomodulating antibodies** (anti-CTLA-4, anti-D137, anti-PD1, anti-PD-L1)
- **Imunoconiugates** (F16IL2, L19IL2)
- **Targeted therapies** (vemurafenib, dabrafenib, nilotinib, masatinib, axitinib, mek inhibitors)
- **Cytotoxics/anti-angiogenetics/anti-apoptotics** (nab-paclitaxel, eribuline, oblimersen, E7080)
New therapeutic options available for metastatic melanoma — *in 2012* —

- Ipilimumab
- Vemurafenib
New therapeutic options available for metastatic melanoma — in 2012 —

• Ipilimumab

• Vemurafenib
Balance Between Tumour and Host’s Immune System

- Premalignant lesion
- Cancer transformation
- Tumor growth
- Immune surveillance
- Immune selection
- Immune exhaustion

- Elimination
- Equilibrium
- Escape

Tumor cell activity Immune system
Evaluation of Clinical Responses:
Differences in the mechanism of action of tumour vaccines vs ‘direct’ anti-tumoural drugs (chemotherapy, oncogene-inhibitors...)

Chemotherapy/Target therapy

Immunotherapy

Immune system activation

Tumor cell destruction
Chemotherapy/Targeted Agents and Immuno-therapy Differ in Action and Outcome

![Graph comparing chemotherapy and targeted therapies to immunotherapy over time](image-url)
What is an immunostimulatory mAb?

+ Receptor agonist

- Receptor antagonist

CD137
CD40
OX40
GITR
CD27

CTLA-4
PD1
B7-H1
BTLA
TGF-β
IL-10
Anti CTLA-4 Monoclonal Antibody

IL-2

T-cell

TCR

Antigen

CD28

B7

MHC

APC

IL-2

TCR

CD28

CTLA-4

Anti-CTLA-4 mAb
Study 024: Overall Survival

Estimated Survival Rate

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>2 Year</th>
<th>3 Year</th>
<th>4 Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab + DTIC</strong>&lt;br&gt;n=250</td>
<td>47.3</td>
<td>28.5</td>
<td>20.8</td>
<td>19</td>
</tr>
<tr>
<td><strong>Placebo + DTIC</strong>&lt;br&gt;n=252</td>
<td>36.3</td>
<td>17.9</td>
<td>12.2</td>
<td>9.6</td>
</tr>
</tbody>
</table>

*M.Maio, ESMO Meeting 2012
### Overall survival rates with ipilimumab at 10 mg/kg

**Survival rate, % (95% CI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year *</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 184-008</td>
<td>47.2</td>
<td>32.8</td>
<td>23.3</td>
<td>19.7</td>
<td>18.2</td>
</tr>
<tr>
<td>CA 184-022</td>
<td>48.6</td>
<td>30.4</td>
<td>25.4</td>
<td>21.5</td>
<td>21.5</td>
</tr>
<tr>
<td>CA 184-007</td>
<td>55.9</td>
<td>41.1</td>
<td>38.7</td>
<td>36.2</td>
<td>36.2</td>
</tr>
</tbody>
</table>

* Lebbè C., ESMO2012
## EAP 10 mgs - Overall survival rates

<table>
<thead>
<tr>
<th>Time</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>34.8</td>
<td>23.5</td>
<td>20.9</td>
<td>20.9</td>
</tr>
<tr>
<td>SE%</td>
<td>(9.6)</td>
<td>(8.4)</td>
<td>(8.0)</td>
<td>(8.0)</td>
</tr>
</tbody>
</table>

*Di Giacomo AM, ESMO Meeting 2012*
IPILIMUMAB PATTERN OF RESPONSE

Induction Phase  IPI 10mg/Kg ev d1, Q3ws x 4

Maintenance Phase  IPI 10mg/Kg ev d1, Q12ws

Di Giacomo AM., Cancer Immunol Immunother., 2011
IPILIMUMAB PATTERN OF RESPONSE

**Baseline**

**W 12**

**W 24**

---

**Induction Phase**  
IPI 10mg/Kg ev d1, Q3ws x 4

**Maintenance Phase**  
IPI 10mg/Kg ev d1, Q12ws

Di Giacomo AM., Cancer Immunol Immunother., 2011
Histopathology of cutaneous biopsy at week 56

Haematoxylin and eosin staining depicting strong regressive changes both in flat and nodular areas of the tumor biopsy; neoplastic melanocytes were virtually absent throughout the whole lesion.

Di Giacomo AM. , Cancer Immunol Immunother., 2011
Histopathology of liver biopsy at week 102

Histological examination of a liver melanoma mts showed massive necrosis of melanocytes. On left, well-preserved fibroblasts with rare lymphocytes inside a fibrotic septum, and melanophages are recognizable (original magnification 200x)

Di Giacomo AM. and Maio M., Cancer Immunol Immunother., 2011
IPILIMUMAB PATTERN OF RESPONSE

Baseline

W 12

W 24

W 156

Induction Phase  IPI 10mg/Kg ev d1, Q3ws x 4

Maintenance Phase  IPI 10mg/Kg ev d1, Q12ws

Di Giacomo AM., Cancer Immunol Immunother., 2011
Immunotherapies Associated with Novel Immune-Related Toxicities

- Immunotherapies
  - Breaking peripheral tolerance to self
    - Tumour infiltration of lymphocytes
    - Expansion of self-reactive T cells/inflammatory T-cell infiltration
  - Anti-tumour immune response
  - Immune-related side effects
Therapeutic combinations

Chemotherapy

Surgery

Immunotherapy

Target

Radiotherapy
Fully human monoclonal antibody against PD1 (BMS-936558)

- PD1 expression is increased in patients with NSCLC\(^1\)
- PD-L1 expression is associated with poor prognosis in patients with NSCLC\(^2\)
Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes

42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.

*2 pts still under evaluation
Trials with anti-PD-1 antibody in Lung Cancer

- CA209-017: An Open-Label Randomized Phase III Trial of BMS-936558 Versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)

- CA209-057: An Open-Label Randomized Phase III Trial of BMS-936558 Versus Docetaxel in Previously Treated Advanced or Metastatic Non-squamous Cell Non-small Cell Lung Cancer (NSCLC)
Trial with anti-PD-1 antibody in Kidney Cancer

- CA209-025: A Randomized, Open-Label, Phase 3 Study of BMS-936558 vs. Everolimus in Subjects With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy
Trial with anti-PD-L1 antibody in Advanced Solid Tumors

CD-ON-MEDI4736-1108: A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors (MedImmune)
Trials with anti-PD-1 antibody in Metastatic Melanoma

- CA209-037: A Randomized open label phase 3 trial of BMS 936558 versus Investigator choise in advanced (unresectable or metastatic) melanoma patients progressing after anti-CTLA-4 therapy

- CA209-066 - A Phase 3, Randomized, Double-Blind Study of BMS-936558 vs Dacarbazine in Subjects with Previously Untreated Unresectable or Metastatic Melanoma
Immunomodulating mAb in solid tumors

- Lung cancer (NSCLC, SCLC)
- Breast cancer
- Gastroesophageal cancer
- Pancreatic cancer
- Colorectal cancer
- Melanoma
- Renal cancer
- Prostate cancer

1) Ribas A. Semin. Oncol 2010;
2) Calabrò L. Semin. Oncol 2010;
3) Wolchok JD. Clin Cancer Res 2009
4) Di Giacomo AM. Semin. Oncol 2010
New therapeutic options available for metastatic melanoma—*in 2012*—

- **Ipilimumab**
- **Vemurafenib**
The first BRAF inhibitor: Vemurafenib

40-60% of melanomas

BRAF\textsuperscript{V600E} → MEK → ERK → Cellular Proliferation

Chapman P. et al Abs LBA4 ASCO 2011
Role of Oncogenic *BRAF* in Cancer

- Mutated *BRAF* is frequently identified in cancer
- Highest incidence of *BRAF* mutation is in melanoma

Patients underwent FDG-PET at baseline and on Day 15 of the first 4 weeks of therapy. A marked decrease in tumor uptake of FDG was observed at Day 15 after Vemurafenib treatment.

- Best OR: complete or partial tumor regression in 81% (unconfirmed*) of patients in the extension phase (N=32, RECIST, version 1.0) with metastatic melanoma with the BRAG\textsuperscript{V600} mutation.¹

<table>
<thead>
<tr>
<th></th>
<th>Evaluable patients (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change from baseline (sum of lesions size)</td>
</tr>
<tr>
<td>1</td>
<td>Complete response, n=2</td>
</tr>
<tr>
<td>2</td>
<td>Partial response, n=24 (≥ 30% tumor regression) – 15 patients &gt; 50% tumor regression</td>
</tr>
<tr>
<td>3</td>
<td>Minor responses, n=6 (10–30 % tumor regression)</td>
</tr>
<tr>
<td>4</td>
<td>Median PFS &gt; 7 months</td>
</tr>
</tbody>
</table>

Progression-free survival (February 01, 2012 cut-off) censored at crossover

Hazard ratio 0.38
(95% CI: 0.32–0.46)
Log-rank p<0.001 (post-hoc)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Dacarbazine</th>
<th>Vemurafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=338</td>
<td>338</td>
<td>337</td>
</tr>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>269</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>186</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>113</td>
</tr>
<tr>
<td>18</td>
<td>22</td>
<td>77</td>
</tr>
<tr>
<td>24</td>
<td>14</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Overall survival (February 01, 2012 cut-off) censored at crossover

- Vemurafenib (n=337)
  - Median f/u 12.5 months
- Dacarbazine (n=338)
  - Median f/u 9.5 months

Hazard ratio 0.70
(95% CI: 0.57–0.87)
p<0.001 (post-hoc)

CASE STUDY 2

Treatment RO5185426

June 2010

BRAF MUTANT MELANOMA

September 2012 (33 cycles)

M. Maio, Unpublished
## Selected adverse events (% of patients)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib, n=337</th>
<th>Dacarbazine, n=287</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>↑LFTs</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>–</td>
</tr>
</tbody>
</table>

Discontinuations due to AE: 7% vemurafenib; 2% dacarbazine

8 patients reported new primary melanomas in the vemurafenib group

BRIM-7 Results: AEs attributed to either vemurafenib or GDC-0973 in all patients* (6 July 2012)

### Most common AEs attributed to either vemurafenib or GDC-0973

<table>
<thead>
<tr>
<th>AEs</th>
<th>n=70</th>
<th>Grade 3 or 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total number of patients with AEs</td>
<td>20</td>
<td>28.6</td>
<td>67</td>
</tr>
<tr>
<td>Non-acneiform rash(^a)</td>
<td>5</td>
<td>7.1</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>5.7</td>
<td>36</td>
</tr>
<tr>
<td>Photosensitivity / Sunburn</td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>1.4</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1.4</td>
<td>20</td>
</tr>
</tbody>
</table>

### Selected AEs attributed to either vemurafenib or GDC-0973

<table>
<thead>
<tr>
<th>AEs</th>
<th>n=70</th>
<th>Grade 3 or 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Creatine phosphokinase elevation</td>
<td>3</td>
<td>4.3</td>
<td>14</td>
</tr>
<tr>
<td>Liver function test elevation(^b)</td>
<td>3</td>
<td>4.3</td>
<td>14</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>Serous chorioretinopathy(^c)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma, KA</td>
<td>1</td>
<td>1.4</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\)Includes all patients reporting each of AE general terms, even for zero incidence.
\(^b\)Non-acneiform rash includes MedDRA terms rash, rash generalised, rash maculo-papular, rash macular, rash papular, rash erythematous, erythema, rash pruritic, dermatitis, skin exfoliation, dermatitis exfoliative, lividity
\(^b\)LFT elevation includes MedDRA terms alkaline phosphatase increased, bilirubin increased, hyperbilirubinaemia, AST & ALT increased, transaminases increased, and gamma-glutamyltransferase increased.
\(^c\)Serous chorioretinopathy includes MedDRA terms chorioretinal disorder, chorioretinopathy, 1 pt with blurred vision later diagnosed as serous chorioretinopathy.

Adapted from Gonzales R. et al. LBA28_PR, ESMO Congress, Vienna 2012
Clinical Protocol  MO25743

An open-label, single-arm, multicenter study to evaluate the efficacy of vemurafenib in metastatic melanoma patients with brain metastases