Considerations for Immuno-Oncology in Elderly Patients: A New Age in Therapy for Multiple Tumor Types

Chair: Enriqueta Felip (Spain)
Saturday, 25 October 2014
Lisbon, Portugal

Welcome and Introduction
Immuno-Oncology As an Approach to Multiple Tumor Types
Enriqueta Felip (Spain)

Housekeeping:
• Please turn off mobile phones or turn to vibrate
• Q&A session: Please hold questions until end
• Use question cards available in the booklet and hand to the hostesses or use the roving microphones
• Fill in evaluation forms and hand to the hostesses at end of the session

Update on immuno-oncology
A new age in therapy for multiple tumor types

Welcome and introduction: agenda
• Immuno-oncology as an approach in multiple tumor types. E. Felip
• PD1 inhibitors in advanced NSCLC. E. Felip
• PD1 inhibitors in advanced melanoma. A. Raimundo
• Q&A and Close. A. Raimundo & E. Felip

Outline
• How cancer cells evade immune destruction
• Rationale for checkpoint inhibition
• Differences among checkpoint targets (CTLA-4, PD1, PD-L1)
• Rationale for targeting PD1 in melanoma and lung cancer

Immuno-oncology as an approach in multiple tumor types
Enriqueta Felip, Head of Thoracic Cancer Unit, Vall d’Hebron University Hospital, Barcelona

SIOG 2014, 23-15 October 2014 Lisbon, Portugal
How cancer cells evade immune destruction

- The immune system recognizes and eliminates cancer cells from the body
- Evading immune control, a hallmark of cancer (Hanahan & Weinberg Cell 11)
- Anti-tumor immunity has innate and adaptive components working together
  - The innate system acts as 1st line of defense via:
    - Physical barriers
    - Effector cells (macrophages, NK cells, innate lymphoid cell, dendritic cells, mast cells, neutrophils, and eosinophils, among others)
    - Mechanisms of pattern recognition (toll-like receptors)
    - Humoral mechanisms (complement proteins and cytokines)

  - The adaptive response is via
    - B and T cells regulated by multiple co-stimulatory and co-inhibitory pathways

How cancer cells evade immune destruction

- However tumors may use a variety of mechanisms to evade the immune system such as:
  - An ineffective presentation of cancer cell antigens
  - Recruitment of immunosuppressive cell types
  - Inhibition of attack by immune cells e.g. disruption of T cell-activating and checkpoint pathways

Rationale for checkpoint inhibition

- T cell activity is regulated through a complex balance of activating and inhibitory ('checkpoint') signals
- Tumors can deregulate checkpoint and activating pathways, and consequently alter the immune response
- Targeting checkpoint and activating pathways with a view to restoring optimal immune response; promising approach to cancer therapy
- Efforts to restore antitumor immunity have focused on antibody interventions targeting:
  - CTLA-4 on T lymphocytes
  - PD1 on T lymphocytes and its principal ligand PDL1 on tumor cells

Differences among checkpoint targets (CTLA-4, PD1, PD-L1)

- Once a T cell becomes active, it expresses CTLA-4 on its cell surface, which then competes with CD28 for their mutually shared ligands, B7-1 or B7-2 on the APC
  - Cancer cells can stimulate abnormal expression of CTLA-4 in T cells, and these CTLA-4 aberrant T cells exhibit anergic phenotype
- First anti-CTLA-4 agent in clinical development, ipilimumab, a fully humanized immunoglobulin that antagonizes CTLA-4 and prevents ligand binding

Differences among checkpoint targets (CTLA-4, PD1, PD-L1)

- PD1, a surface receptor member expressed in activated T cells
  - PD1 engages two known ligands: PD-L1 and PD-L2
    - PD-L1:
      - Expression seen on a wide variety of solid tumors
      - Expression up-regulated by cytokines
    - PD-L2:
      - Expressed on dendritic cells, macrophages, and various tumors
- Anti-PDL1 Abs also block B7.1
- Anti-PD1 Abs also block PD-L2
PD1/PD-L1

• Limits T cell activity and plays a role in the tumor immune escape
• PD-L1 expression prevalent in human tumors and associated with prognosis
• PD1/PD-L1 inhibitors, promising results

Chen D, Clin Cancer Res 2012

Rationale for targeting PD1 in melanoma and lung cancer

• Anti-PD1 strategies target immune system rather than tumor
• Activity in different tumor types including melanoma, NSCLC, renal cancer, bladder carcinoma and head & neck
• May well have greater activity in tumors with a large number of mutations, among them melanomas and lung tumors
• Manageable toxicity profile
• Potential impact on long-term survival
• Targeting PD1 means new hope for melanoma and NSCLC

PD1 Inhibitors in Advanced NSCLC

• Case Study in Metastatic NSCLC

Enriqueta Felip (Spain)

PD1 inhibitors in advanced NSCLC

Outline

• Overview of efficacy and safety of PD1 inhibitors in advanced NSCLC
• Discussion of sequencing of PD1 inhibition with CT (concurrent vs phased)
• PD-L1 expression as a potential predictive biomarker for PD1 therapy
• Case study: 77-yr-old man diagnosed with stage IV NSCLC treated with anti-PD1 compound in a clinical trial

Overview of efficacy and safety of PD1 inhibitors in advanced NSCLC
First signs of activity in NSCLC with immunotherapy

Anti–PD1 antibody

Anti–PDL1 antibody

Brahmer NEJM 2012, Topalian NEJM 2012

Efficacy by PD1 inhibitors in advanced NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>N (NSCLC)</th>
<th>Efficacy RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>Nivolumab (BMS-936558)</td>
<td>129</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (MK-3475)</td>
<td>217</td>
<td>20%</td>
</tr>
</tbody>
</table>

Brahmer ASCO 16; Gettinger ASCO 14; Garon ASCO 14; Brahmer NEJM 12

Tolerability profile of PD1 targeted therapies

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>N (NSCLC)</th>
<th>All AEs</th>
<th>Gr 3-4 AEs</th>
<th>Pneumonitis Gr 3-5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>Nivolumab</td>
<td>129</td>
<td>41</td>
<td>5</td>
<td>3 (4 pts, 3 pts)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>217</td>
<td>64</td>
<td>10</td>
<td>1 (4 pts)</td>
</tr>
</tbody>
</table>

Brahmer ASCO 14; Gettinger ASCO 14; Garon ASCO 14; Brahmer NEJM 12

MOST COMMON AES: FATIGUE, LOSS APETITE, DIARRHOEA, RASH, ARTHRAGLIA

Nivolumab in p with advanced NSCLC:

OS and clinical activity by subgroup analysis (n=129)

NSCLC responders by histology

ORR 17% (24% in 3mg/kg)

OS by nivolumab dose in NSCLC

OS by histology in NSCLC

1st-line nivolumab monotherapy (3mg/kg q 2 wks):
Safety, efficacy, and correlation with PD-L1 status (n=20)

1st-line nivolumab and ipilimumab in advanced NSCLC (NCT01454102)

• Study design:
  • Key patient inclusion criteria
    • Stage IIIB/IV NSCLC
    • Non-SCC, SCC
    • CT naïve (n=49)
  • First-line x 4 cycles
    • Nivolumab 1 mg/kg Q2W
    • Ipilimumab 3 mg/kg Q2W

  Primary endpoint: safety and tolerability; secondary endpoints: ORR and PFS at 24 weeks
  • Key results:
    • Grade 3/4 treatment-related AEs in 49% (24/49 pts)
    • In SCC, higher RR in the higher nivolumab dose group (33% vs 11%)
Safety and response with nivolumab/erlotinib in patients with advanced mutant EGFR (NCT01454102)

Key patient inclusion criteria:
- Stage IIIB/IV NSCLC
- Non-squamous
- EGFR+ 
- CT naïve (n=21)

nivolumab 3 mg/kg q2w + erlotinib 150 mg/day

Key results:
- 21 patients (20 prior treatment with erlotinib)
- Grade 3 AEs occurred in 24% of patients (no grade 4 reported)
- ORR 19%/45% SD
- PFS 29.4 weeks (4.6-81.7), OS NR (10.7-86.9)

Rizvi, poster, abstr 8022

1st-line nivolumab in combination with platinum-based doublet CT in advanced NSCLC (NCT01454102)

Study design

Key patient inclusion criteria:
- Stage IIIB/IV NSCLC
- Non-SCC, SCC
- CT naïve (n=56)

SCC
- Nivolumab 10 mg/kg q2w + Carboplatin 600 mg/m2
- Pemetrexed 500 mg/m2

Non-SCC
- Nivolumab 10 mg/kg q2w + Docetaxel 75 mg/m2
- Paclitaxel 200 mg/m2
- Carboplatin AUC 6

Nivolumab 10 mg/kg q2w until PD or unacceptable toxicity

Any histology
- Nivolumab 5 mg/kg q3w until PD or unacceptable toxicity

Key results:
- No DLTs were seen during the first 6 weeks of treatment
- ORR 33-47% and similar between treatment arms
- 1-year OS 50–87%
- Grade 3–4 treatment-related AEs 45%

Antonia et al. ASCO 2014, poster, abstr 8113

KEYNOTE 001 MK-3475 (pembrolizumab) (NCT01295827) treated/untreated NSCLC patients. Phase I

KEYNOTE 001: phase I study of pembrolizumab in pre-treated NSCLC patients

Primary endpoints:
- ORR
- AEs
- Response rate (primary RECIST, secondary iRECIST)
- Biomarker expression

Best overall response n = 159 n= 35 n = 177 n = 40
ORR, % 23 9 19 12
Disease control rate, % 42 31 51 53
Disease control duration, weeks, median 31 NR NR NR
Median, weeks 11 10 16 16

Grade 3–4 pneumonitis in 2 patients in each dosing arm
Grade 3–4 immune-related AEs in 2 patients in each dosing arm with:
- Fatigue, arthralgia and neck pain

Most common treatment-related AE: fatigue 20%
10% had ≥1 grade 3–5 treatment-related AEs
Incidence of fatigue, arthralgia and nausea, <1% each
Grade 3–4 pneumonitis in 2 patients in each dosing arm
Grade 3–4 immune-related AEs in 2 patients in each dosing arm with:
- Fatigue, arthralgia and neck pain

Garon poster, abstr 8020; Rizvi oral, abstract 8007

Discussion of sequencing of PD1 inhibition with CT (concurrent vs phased)

1st line ipilimumab plus carboplatin/paclitaxel in advanced NSCLC patients

CA184-041: phase 2 study results, no prior therapy, stage IIIB/IV NSCLC, ECOG PS ≤1, all histologies

1st line ipilimumab + concurrent CT
1st line ipilimumab + phased CT

Lynch JCO 12
Reck Ann Oncol 13

Phased ipilimumab improved irPFS vs control [HR 0.64, p=0.03]
- No improvement in PFS [HR 0.93, p=0.37] or OS [HR 0.75, p=0.13]
- Median irPFS: 6.4 mo for phased, 5.7 mo for concurrent, 5.3 mo for control arm
- Median OS: 12.9 mo for phased, 9.1 mo for concurrent, 9.9 mo for control arm
- Grade 3/4 AEs 17% for phased, 21% for concurrent, 9% for control

Ongoing randomized phase III study in ED SCLC platin/etoposide +/- ipilimumab

PD-L1 expression as a potential predictive biomarker for PD1 therapy

Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

Responders by histology
- Key results
  - Overall ORR 30% (2 CR, 1 SCC, 1 non-SCC)
  - Response at first assessment (11 weeks) in 39% (5/6 pts)
  - PD-L1 expression status correlate with response (50% in PD-L1+; 0 PD-L1-)
  - PFS rate at 24 weeks was 60%, 1-year OS 75%
  - Grade 3–4 treatment-related AEs 20%

Responders by PDL-1

Safety and clinical activity of MK-3475 as initial therapy in p with advanced NSCLC and PDL1 expressing tumors
- MK-3475 showed ORR of 26% by independent central review and 47% by investigator assessment (table)

<table>
<thead>
<tr>
<th></th>
<th>RECIST v1.1 per investigator per central review</th>
<th>Immune-related responses effects per investigation assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI), %</td>
<td>26 (14, 42)</td>
<td>47 (22, 62)</td>
</tr>
<tr>
<td>Median irPFS (95% CI), weeks</td>
<td>12.5 (11.3, 14.6)</td>
<td>12.5 (11.3, 14.6)</td>
</tr>
<tr>
<td>Response ongoing, n/N (%)</td>
<td>12/11 (100)</td>
<td>12/11 (100)</td>
</tr>
<tr>
<td>Responders remaining on treatment, n/N (%)</td>
<td>7/11 (64)</td>
<td>7/11 (64)</td>
</tr>
</tbody>
</table>

- Treatment-related AEs (any grade) occurring in >5% of patients were: fatigue (22%), pruritus (13%), hypothyroidism (9%), dermatitis aciform (7%), diarrhoea (7%), dyspnoea (7%) and rash (7%)

Antitumor activity of pembrolizumab in a pooled analysis of advanced NSCLC p
- Robust antitumour activity was observed in both treatment-naïve and previously treated advanced NSCLC observed for all doses and schedules assessed

<table>
<thead>
<tr>
<th></th>
<th>Treatment naive</th>
<th>Previously treated</th>
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<tbody>
<tr>
<td>ORR (95% CI), %</td>
<td>26 (14, 42)</td>
<td>26 (14, 42)</td>
</tr>
<tr>
<td>Median irPFS (95% CI), weeks</td>
<td>26 (14, 42)</td>
<td>26 (14, 42)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>26 (14, 42)</td>
<td>26 (14, 42)</td>
</tr>
</tbody>
</table>

Rizvi J Clin Oncol 2014; 32 (suppl 5; abstr 8007)
Strong PD-L1 tumour expression correlated with improved response, PFS and OS.
Pembrolizumab effective in patients with treatment-naïve or previously treated, in particular, patients with strong PD-L1 tumour expression may benefit from this treatment.

Antitumor activity of pembrolizumab and correlation with PD-L1 expression in a pooled analysis of advanced NSCLC patients.

PFS (RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Strong</th>
<th>Weak</th>
<th>Negative</th>
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<tbody>
<tr>
<td>OS</td>
<td>44</td>
<td>53</td>
<td>49</td>
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<td></td>
<td>28</td>
<td>43</td>
<td>30</td>
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<td>12</td>
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<td></td>
<td>1</td>
<td>6</td>
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</table>

Overall survival, %

<table>
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<tr>
<th></th>
<th>Strong</th>
<th>Weak</th>
<th>Negative</th>
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<tbody>
<tr>
<td></td>
<td>44</td>
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<td>6</td>
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Pembrolizumab: ongoing studies in NSCLC

- **KEYNOTE-024**
  - Phase 3 study comparing pembrolizumab monotherapy with platinum-based doublet CT in treatment-naïve patients with PD-L1-positive metastatic NSCLC.

- **KEYNOTE-010**
  - Phase 2/3 study comparing two doses of pembrolizumab with docetaxel in previously-treated NSCLC patients.

PD-L1 positivity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Assay</th>
<th>Analysis</th>
<th>Definition of positivity</th>
</tr>
</thead>
</table>
| Pembrolizumab | Dako automated IHC assay (22C3 mouse Ab) | Tumour biopsy within 60 days prior to first dose of pembrolizumab | Tumour dependent:  
  - Melanoma > 1%  
  - NSCLC PD-L1 (+): Strong (≥50%) and weak staining (1–49%) PD-L1 (-): no staining |
| Nivolumab  | Dako automated IHC assay (28-8 rabbit Ab) | Archival FFPE | 2% and 5% cut-off |

Challenges with PD-L1 assessment

- Tumor heterogeneity
- Small tumor sample
- Fresh tumor vs archival samples
- PD-L1 expression may change over time
- Different IHC mAB, different cut-off for PD-L1 positivity

Immune-checkpoint inhibitors: clinical questions to answer

- Optimal dose and treatment sequence?
- Best predictive marker for response: PD-L1, smoking history, mutations?
- Optimal cut-off for PD-L1 positivity and the best IHC mAB?
- Best surrogate of efficacy (RECIST vs irRC)?
- Activity in the CNS?
- Any role in molecularly-driven tumours?

Case study
Clinical case

• A 77-yr-old man
• Smoker, 50 packs/year
• November 2013: history of 2-month dry cough, no other symptoms
• Chest-X-ray: mass in right hilus
• Physical examination: normal, ECOG PS 1
• CT-thorax: 8 cm mass in upper right lobe, bilateral mediastinal lymph nodes, contralateral lung metastases
• Blood tests: normal except LDH 467

Clinical case

• Bronchoscopy: tumor in anterior branch of right upper lobe
• Histology: squamous cell-cell carcinoma
• PET-CT: primary tumor, bilateral mediastinal nodes, right supraclavicular lymph node, contralateral lung metastases
• Brain MRI: no brain metastases
• No EGFR mutation or ALK rearrangement
• P was enrolled in the KEYNOTE 001 MK3475 study cohort F1
  — Central determination of PD-L1, positive

Clinical case

• in summary, a 77-yr-old man diagnosed with stage IVa squamous cell carcinomas included in the MK3475 study cohort F1, with a central determination of PD-L1 positivity
  — December 31, 2013 he started pembrolizumab (10 mg/kg every 3 wks)
  — After 9 wks of treatment a CT-scan revealed PR
  — October 21, 2014, still on treatment, maintaining PR
  — Toxicity: G1 pruritus

Long PR > 10 months, no toxicity, good general health

Clinical case

• Pembrolizumab: our experience in clinical trials in NSCLC
  — Two trials at my Institution
    — Phase I
    — Randomized phase II/III trial vs docetaxel
  — 19 NSCLC p treated to date with pembrolizumab
    — The first p started treatment on October 9, 2013 (ongoing PR)
    — 9 p still on treatment
    — Well tolerated agent
  — No age restriction in the trials
    — 5 p ≥70 yrs old (70, 72, 77, 78, 84)
  — 2 PR (one ongoing, 77 yrs old starting treatment on December 31, 2013)
  — 2 SD
  — 1 PD
  — Well tolerated agent in these p

PD1 inhibitors in advanced NSCLC

• Immune checkpoints are implicated in the downregulation of antitumor immunity
• Responses in all histologic types, regardless of driver alterations
• Toxicity profiles differ from that of CT; generally much better tolerated
• Identification of biomarkers for PD1 inhibitors is complex; PD-L1 the most analyzed but some PD-L1 negative p also benefit
• PD1 inhibitors, promising results in NSCLC, potential impact on long-term survival
Thanks!!!

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PD1 Inhibitors in Advanced Melanoma
Ana Raimundo (Portugal)

Immunotherapy history
- 19th century W. B. Colley observed tumor regressions following the injection of a bacterial fragments into malignant lesions
- Spontaneous regression of MM described since 19th. century:
  - ≈ 15% in primary melanoma
  - < 1/400 patients with metastatic melanoma • 5-year survival ≈ 49%
  - Extensive lymphocytic infiltration / overexpression helper T cells / inflammatory cytokines

Considerations for Immuno-Oncology in Elderly Patients:
A new age in therapy for multiple tumor types
PD1 inhibitors in advanced melanoma

Ana Raimundo
Medical Oncology Department
Instituto Português de Oncologia - Porto
Melanoma – How to increase T-response?

- Melanoma is an immunogenic cancer

  BUT

- The ability of the I.S. to eradicate melanoma is affected by intrinsic negative regulatory mechanisms

- Melanoma is potentially treatable using immunologically-based therapies

- Infiltrating T-cells fail to be sufficiently activated to result in tumor control

- Therapy to enhance the T-cell response against melanoma

MDX010-20

Screening

Induction

2:1 Reinduction (eligible patients)

<table>
<thead>
<tr>
<th>previously treated, HLA-A*0201+ patients with advanced melanoma (n = 676)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ipilimumab + gp100 (n = 402)</td>
</tr>
<tr>
<td>ipilimumab alone (n = 137)</td>
</tr>
<tr>
<td>gp100 alone (n = 136)</td>
</tr>
</tbody>
</table>

Follow-up

Induction: ipilimumab at 3 mg/kg, with or without gp100, q3w for 4 treatments.
Reinduction: Patients with SD for 3 months’ duration from Wk 12, or a confirmed CR or PR, could receive additional therapy with their assigned treatment regimen upon PD.

Failure of anti-CTLA-4 antibody therapy

- Melanoma treatment remains a challenge with few effective treatment options

- PD-1 is an inhibitory receptor expressed by activated T-cells that downmodulates effector functions and limits the T-cell proliferation, cytokine release, cytotoxicity generation and immune memory

- Many tumors, including melanoma, suppress cytotoxic T-cell activity by expressing PD-1 ligand (PD-L1) on cell surface; PD-L2 may also play a role in helping tumor cells evade the immune response

- Pembrolizumab (MK-3475) is a highly selective, humanized, monoclonal antibody IgG4-kappa, against PD-1 receptor

Pembrolizumab (MK-3475) in Advanced Melanoma: Phase Ib Trial

- Melanoma expansion cohort of phase I KEYNOTE-001 study
  - Advanced, unresectable disease with ECOG PS 0-1
  - Ipiplusumab-treated patients must have PD with resolution of related AEs

- IPI Naive
  - 10 mg/kg q2w (n = 41)
  - 10 mg/kg q3w (n = 24)
  - 2 mg/kg q3w (n = 22)

- IPI Treated
  - 10 mg/kg q2w (n = 16)
  - 10 mg/kg q3w (n = 32)

- IPI Refractory
  - 10 vs 2 mg/kg q3w (n = 173)
  - IPI naïve 10 vs 2 mg/kg q3w (n = 103)

- Nonrandomized cohorts (n = 135)

- Randomized cohorts (n = 276)

Total: 411 patients
Pembrolizumab (MK-3475) in Advanced Melanoma: Phase Ib Trial

- 411 patients with advanced melanoma enrolled in multiple cohorts (7) from KEYNOTE-001
- Melanoma expansion cohorts of KEYNOTE-001
  - 135 ipilimumab-treated (IPI-T) and IPI-naïve (IPI-N) patients received pembrolizumab 2mg/kg Q3W, 10mg/kg Q3W and 10mg/kg Q2W
  - 9% CR and 40% ORR (RECIST v1.1, central review)
  - mPFS > 7 months / m OS NR
  - Responses were durable
  - m FU 11 months, 81% of responders still receiving the study treatment
  - Manageable AE profile


**KEYNOTE-001 Inclusion Criteria for All Cohorts**

- Advanced, unresectable melanoma
- Measurable disease
- ECOG 0-1
- No active autoimmune disease
- No active or untreated CNS metastases
- Previously treated CNS metastases stable for ≥2 months
- No protocol-mandated baseline brain MRI in patients without known brain metastases

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IPI-Naive n = 190</th>
<th>IPI-Treated n = 221</th>
<th>Total N = 411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>61 (25–94)</td>
<td>61 (18-88)</td>
<td>61 (18–94)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>116 (61)</td>
<td>131 (59)</td>
<td>247 (60)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>151 (79)</td>
<td>150 (68)</td>
<td>301 (73)</td>
</tr>
<tr>
<td>1</td>
<td>39 (21)</td>
<td>71 (32)</td>
<td>110 (27)</td>
</tr>
<tr>
<td>BRAF status, n (%)</td>
<td>55 (29)</td>
<td>42 (19)</td>
<td>97 (24)</td>
</tr>
<tr>
<td>Wild type, n (%)</td>
<td>131 (69)</td>
<td>179 (81)</td>
<td>310 (75)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>4 (2)</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>History of brain metastases, n (%)</td>
<td>11 (6)</td>
<td>22 (10)</td>
<td>33 (8)</td>
</tr>
<tr>
<td>Tumor size baseline, mm</td>
<td>75 (15-404)</td>
<td>121 (10-895)</td>
<td>98 (10-895)</td>
</tr>
</tbody>
</table>

**Exposure to treatment and Treatment-Related AEs by prior Ipilimumab**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IPI-Naive n = 190</th>
<th>IPI-Treated n = 221</th>
<th>Total N = 411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on therapy, weeks, Mean (range)</td>
<td>34 (0.1–97)</td>
<td>28 (0.1–90)</td>
<td>30 (0.1–97)</td>
</tr>
<tr>
<td>Number of doses, Median (range)</td>
<td>11 (1-47)</td>
<td>9 (1-46)</td>
<td>10 (1-47)</td>
</tr>
<tr>
<td>Grade 3-5 treatment-related AEs, N (%)</td>
<td>26 (14%)</td>
<td>25 (11%)</td>
<td>51 (12%)</td>
</tr>
<tr>
<td>Serious treatment-related AEs, N (%)</td>
<td>20 (11)</td>
<td>12 (5)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, N (%)</td>
<td>7 (4)</td>
<td>10 (5)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Treatment-related death, N (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Treatment-related AEs with incidence > 5%**

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

**Similar safety profiles in IPI-N and IPI-T patients**
Immune-mediated AEs

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>32 (8)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>13 (3)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Colitis</td>
<td>3 (1&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

* Other immune-mediated AEs reported in <1% of patients: nephritis, hypophysitis, uveitis

Management of irARs with Ipilimumab generally depends upon their severity and persistence

<table>
<thead>
<tr>
<th>Three-step approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat symptomatically</td>
</tr>
<tr>
<td>Persistent mild or moderate</td>
</tr>
<tr>
<td>Treat with oral corticosteroids (1 mg/kg daily or equivalent)</td>
</tr>
<tr>
<td>Oral steroid dose if PFSR fails to resolve or recurs</td>
</tr>
<tr>
<td>Symptoms worsen, irAE serious or life-threatening</td>
</tr>
<tr>
<td>Treat with high dose (30 mg/kg) methylprednisolone daily or equivalent; if symptoms improve, then consider a prednisone taper over at least 4 weeks</td>
</tr>
<tr>
<td>If symptoms do not respond within 5-7 days, then consider alternative irAE management/palliative care</td>
</tr>
<tr>
<td>Permanently discontinue YERVOY</td>
</tr>
</tbody>
</table>

Patient education is critical to successful management of irARs

Early diagnosis and appropriate management are essential to minimize life-threatening complications

It is critical to educate patients to:

- Immediately report any immune-related adverse reactions
- Not to attempt self-treatment of any symptoms
  - Always consult his doctor

Immune-related Response Criteria

| Complete | Disappearance of all lesions in two consecutive responses |
| Partial | ≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart |
| Stable | <50% decrease in tumor burden compared with baseline and <25% increase in tumor burden compared with nadir |
| Progressive | ≥25% increase in tumor burden compared with baseline and disease nadir in two consecutive observations at least 4 weeks apart |

New lesions Do not automatically define progression; incorporated into tumor burden

Immune-related Response Criteria: Rationale

Cancer cell
Lymphocyte
Macrophage
Immunotherapy

Clinical response per irRC criteria

Disease progression per irRC criteria

Clinical response per RECIST criteria

IrRC = immune-related response criteria; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

Confirmed ORR in subgroups — Age, Gender, BRAF, Prior IPI...

**RECIST v1.1, Central review**

Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>N</th>
<th>Alive 1-year</th>
<th>HR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
<td>135</td>
<td>54.8%</td>
<td>2.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>225</td>
<td>77.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475**

Joseph RJ, et al. ASCO 2014. Abst 3015

| LDH | Elevated | 135 | 54.8% | 2.33 | <0.001 |
|     | Normal   | 225 | 77.2% |    |         |

| M-Stage | M1c | 213 | 64.9% | 1.56 | <0.05 |
|         | Not M1c | 152 | 75.4% |    |         |

| ECOG | 0 | 261 | 79.6% | 2.23 | <0.001 |
|      | 1 | 164 | 55.0% |    |         |

Baseline tumor size

| > 90mm | 194 | 54.8% | 3.51 | <0.001 |
| ≤ 90mm | 171 | 84.3% |    |         |

**Antitumor Activity by prior Ipilimumab**


<table>
<thead>
<tr>
<th>IPI-N</th>
<th>IPI-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, Wk (95% CI)</td>
<td>24 (16-48)</td>
</tr>
<tr>
<td>24-Wk PFS, %</td>
<td>52</td>
</tr>
</tbody>
</table>

**IPI-N**

| Median PFS, Wk (95% CI) | 27 (24-54) | 56 | 58 |

**IPI-T**

**Time to and Durability of Response (RECIST v1.1)**

Progression-Free Survival (RECIST v1.1, Central Review)


**Estimate of Overall Survival**


**Conclusions**

- ORR (RECIST, v1.1, CR): 34%
  - Treatment-N patients: 44%
  - IPI-N patients: 40%
  - IPI-T patients: 28%
- Response are durable for IPI-T and IPI-N patients, and at all doses and schedules
  - Ongoing responses in 88% patients
  - Median duration of response not reached (6+ to 76+ wk)
- Median PFS: 5.5 months
- OS at 1-year: 69% (median OS not reached)
- Manageable side effects across doses and in IPI-N and IPI-T patients
- Pembrolizumab provided a favorable benefit risk profile, suggesting it is a promising treatment option for advanced melanoma
**Pembrolizumab**

- Pembrolizumab approved by FDA in September 2014 for treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs.
- Its use is approved following treatment with ipilimumab. For melanoma patients whose tumors express the gene mutation BRAF V600, Pembrolizumab is intended for use after treatment with ipilimumab and a BRAF inhibitor.
- Based on these randomized data, comparing 2 mg/kg and 10 mg/kg every three weeks, and an additional cohort of randomized data comparing 10 mg/kg every two or three weeks, the recommended dose proposed for Pembrolizumab in advanced melanoma is 2 mg/kg once every three weeks.

Two ongoing multicenter, randomized, controlled, therapeutic confirmatory trials in patients with unresectable or metastatic melanoma, either ipilimumab refractory (Trial P002) or ipilimumab naïve (Trial P006), each with co-primary endpoints of progression-free survival and overall survival.

**Proposed baseline factors to identify slow and fast progressors**

- The next challenge will be to find predictive markers that could help identify these 2 populations.
- Molecular studies performed on biopsy at baseline and progression in patients treated with BRAF inhibitors.

**Anti-CTLA-4 (ipilimumab) clinical activity irrespective of mutational status: Italian EAP (melanoma)**

<table>
<thead>
<tr>
<th>BRAF</th>
<th>Mutated, n (%)</th>
<th>Wildtype, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated</td>
<td>173 (37)</td>
<td>296 (63)</td>
</tr>
<tr>
<td>Wildtype</td>
<td>266 (38)</td>
<td>14 (17)</td>
</tr>
</tbody>
</table>

Safety profile is consistent across all groups with respect to mutation status.

**Sequencing of ipilimumab and BRAF inhibitors: Italian EAP**

- Longer mOS for patients who received ipilimumab followed by a BRAF inhibitor vs those who received the reverse sequence.

**Best sequencing algorithms for the current available agents?**

**Association anti-CTLA-4 plus anti-PD-1 IS IT THE FUTURE?**

Survival, response duration, and activity by BRAF mutation status of nivolumab and ipilimumab concurrent therapy in advanced melanoma.
**Characteristics of responses**

- All patients maintained ongoing response.
- Recurrence of disease was observed following treatment discontinuation.
- Median follow-up of 22 months and 6 months for cohorts 1 and 2, respectively.
- All patients treated with Nivo 0.3_IPI 3 who discontinued therapy were alive and in ongoing response.
- BRAF status: Wildtype 6% (3/53) Mutant 94% (50/53).

**ORR by BRAF status for concurrent cohorts**

<table>
<thead>
<tr>
<th>Nivo (mg/kg) + IPI (mg/kg)</th>
<th>Evaluate samples</th>
<th>ORR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent (32)</td>
<td>36</td>
<td>16/36(44)</td>
</tr>
<tr>
<td>Mutant</td>
<td></td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>Wildtype</td>
<td></td>
<td>24/46(52)</td>
</tr>
<tr>
<td>1 x 3.0 (4 cohort)</td>
<td>24</td>
<td>0/24</td>
</tr>
<tr>
<td>Mutant</td>
<td></td>
<td>0/24</td>
</tr>
<tr>
<td>Wildtype</td>
<td></td>
<td>0/24</td>
</tr>
<tr>
<td>Sequenced (30)</td>
<td>28</td>
<td>0/28</td>
</tr>
<tr>
<td>Mutant</td>
<td></td>
<td>1/28 (7)</td>
</tr>
<tr>
<td>Wildtype</td>
<td></td>
<td>0/28</td>
</tr>
</tbody>
</table>

**Concurrent cohorts 1–3**

<table>
<thead>
<tr>
<th>Nivo (mg/kg) + IPI (mg/kg)</th>
<th>Evaluate samples</th>
<th>ORR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent (32)</td>
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<td></td>
<td>1/28 (7)</td>
</tr>
<tr>
<td>Wildtype</td>
<td></td>
<td>0/28</td>
</tr>
</tbody>
</table>

**Most common grade 3–4 related AE**

<table>
<thead>
<tr>
<th>AE</th>
<th>Any grade, n (%)</th>
<th>Grade 3-4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent cohort (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase 1</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Lipase 2</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ALT 1</td>
<td>13 (25)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Concurrent cohort (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase 1</td>
<td>6 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Lipase 2</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ALT 1</td>
<td>12 (23)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Sequential cohort (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase 1</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lipase 2</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ALT 1</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

- 43% ORR with 17% CRs and 82% in remission for all concurrent ipilimumab/nivolumab patients.
- 62% rate of grades 3–4 irAEs at optimal doses; LFTs, lipase, amylase, rash, colitis.
- BRAF status and PD-L1 tumour staining not clearly associated with response.
- Response in sequential patients associated with ipilimumab pharmacokinetic levels prior to starting anti-PD-1 antibody.
- Concurrent 2-year OS 79% = impressive.
- Benefit justified by the toxicity seen.
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Q&A and Closing Remarks

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