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Society for Immunotherapy of Cancer

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Immunotherapy – Long-therm survival in metastatic melanoma

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Presenter Disclosure Information

Czirbesz Kata

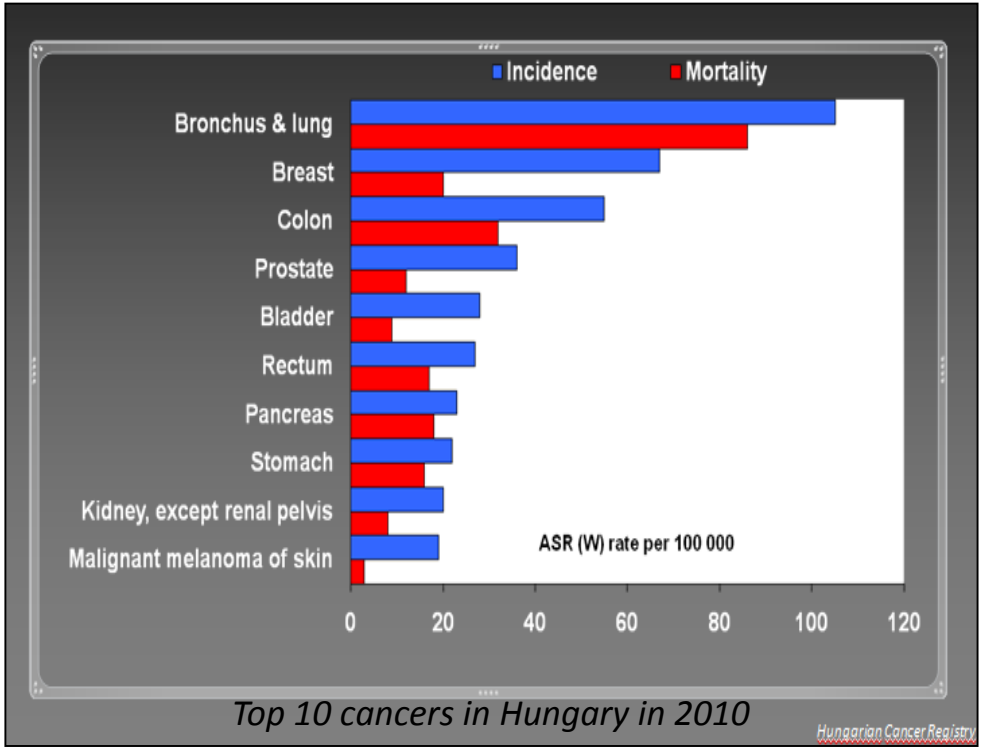
The following relationships exist related to this presentation:

No Relationships to Disclose

There will not be discussion about the use of products for non- FDA approved indications in this presentation.

Melanoma incidence

- The melanoma incidence has been increasing over the past four decades
- **Hungary**
  - In 2016 the melanoma incidence is higher than in 2010, approximately 27 new cases per 100,000[1]
- **USA**
  - In the United States almost the same, approximately 23 new cases were diagnosed in 2016[2]
  - It is now the 5.-6. most common cancer among men and women in USA
- **Australia**
  - Particularly high among Caucasian population in Australia (42.4 per 100,000)[2]



Top 10 cancers in Hungary in 2010

[1]*Hungarian Cancer Registry*
[2]*American Cancer Society 2016*

National Institute of Oncology – Dermato-oncology Department

- **Complex oncotherapy of skin tumors**
  - Targeted therapy
  - Immunotherapy
  - Chemoterapy
  - Clinical studies

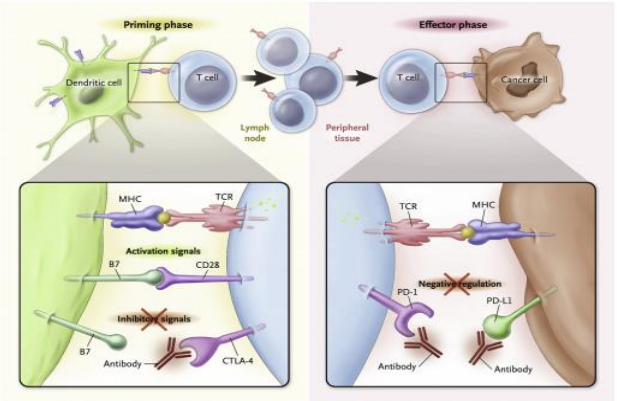
- **Structure**
  - Outpatient's department
    - 20.000 visits/year
    - 400 new melanoma cases
  - Inpatient's department
    - 20 beds

Background on Melanoma

- Cutaneous melanoma is the most aggressive form of all skin cancers with high rates of mortality and morbidity
- Until 2011 metastatic melanoma had no accepted effective therapy, the treatment options as chemotherapies displayed a very low level of efficacy
  - with 5-year survival rate of 10-15%
- In recent years, improved knowledge of molecular pathway mechanism and better understanding of the role of the immune system in tumor control have led to the developement and approval of several **targeted agents** and **immunotherapies** as new treatment options for metastatic melanoma.
- The identification of antibodies directed against the immune checkpoints (that suppress T-cell activation) , **cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)** and **programmed cell death-1 (PD-1)** have demonstrated a significantly higher survival benefit and achieved significant improvements in long therm survival for metastatic melanoma patients.

Melanoma-immune checkpoint inhibitors

- **Ipilimumab** – is the first-in-class immune checkpoint inhibitor approved by FDA in 2011 for the treatment of irresectable, metastatic melanoma
  - **Anti CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) monoclonal antibody**, that cause blockade of CTLA-4 signaling, resulting in **prolonged T cell activation, proliferation and an amlification of T cell mediated immunity** leading to an enhanced antitumor immune response
  - There is now long therm survival data of 1861 patients treated with ipi across 12 clinical studies – collectively patents receiving ipi had **median overall survival (OS) of 11.4** months**, 3 year OS of 22%**[3]
  - There is a **plateau in mortality beyond 3 year time-point that has extended out to nearly 10 years of follow up**
  - **Most common Side effects are: mainly autoimmun AEs like** rash, pruritus, vitiligo, diarrhoea, colitis, hypophisitis



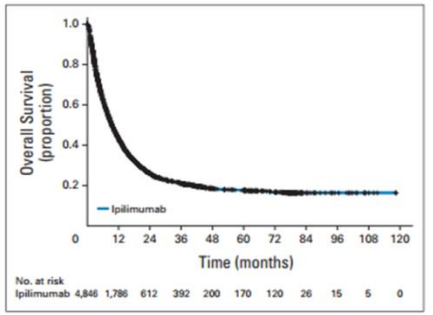


Fig 4. Pooled overall survival (OS) analysis with expanded access protocol (EAP) data. Individual patient survival data were pooled from 1,861 patients with metastatic melanoma from 12 clinical investigations of ipilimumab and 2,985 patients with metastatic melanoma from a US EAP (n = 4,846). Median OS was 9.5 months (95% CI, 9.0 to 10.0 months) with a 3-year survival rate of 21% (95% CI, 20% to 22%). Crosses indicate censored patients.

[3] Schadendorf D., Hodi F., Robert C., Wolchok J.D. Pooled analysis of long-term survival from phase II and phase III trials of ipilimumab. J. Clinical. Oncol. 2015;33:1889–1894. doi: 10.1200/JCO.2014.56.2736.

Melanoma-immune checkpoint inhibitors

- **Pembrolizumab, nivolumab** –
  - Anti Programmed cell death-1 (PD-1) monoclonal antibodies (IgG4), approved by FDA in 2015 for the treatment of irresectable, metastatic melanoma
  - Blocking the interaction between PD-1 and its ligands
  - 1 year OS 71-73%[4], 2 year OS 55-58%, 3 year 40-41%
  - mOS 16 months[5]
  - The most common AEs included fatigue, diarrhoea, endocrine disorders, rash, pruritus
- The combination of nivolumab and ipilimumab results even better response rates, but at the expense of considerable autoimmun effects
  - Gr3-4 toxicities occured in 53% of patients

[4]Robert C, Long GV et al, Nivolumab in previously untreated melanoma without BRAF mutation.

[5]Larkin J et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial.

Our results (National Istitute of Oncology Budapest, Hungary)

- **Ipilimumab**
  - In our study we evaluated the therapeutic impact of ipilimumab therapy in connection with patient selection in our metastatic melanoma patients.
  - We studied retrospectively 47 advanced melanoma patients, who received ipilimumab (3 mg/kg) between 2010 and 2015 in our Institute
    - The median follow up time was 10 month
    - **Median Progression free survival (PFS) 2.7 months, median OS 9.8 months, ORR 17%**
    - **1 year survival 40%, 2 years survival 28%**
    - We found with multivariant analises significant correlation between LDH level and OS
  - Our results are equivalent to the reported data

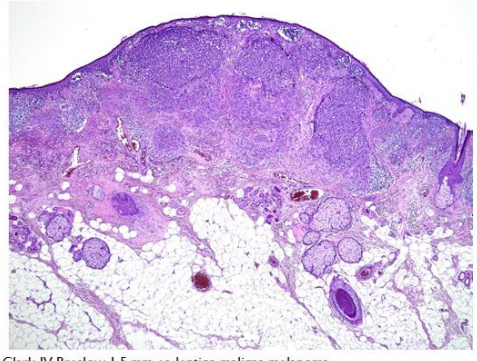
Our results (National Istitute of Oncology Budapest, Hungary)

- Anti PD-1 therapy (nivolumab, pembrolizumab)
  - In our study we evaluated the therapeutic impact of anti PD-1 therapy in connection with patient selection in our metastatic melanoma patients
  - We studied retrospectively **49 advanced melanoma patients, who received pembrolizumab and nivolumab between 2015 and 2017 in our Institute**
  - The **median follow up time** was **13.5 months**
  - **Median Progression free survival (PFS) 7.5 months, ORR 34.6% (nivolumab), ORR 43.5% (pembrolizumab)**
  - **1 year survival rate 55%**
  - We detected side effects in 35% of our patients, and found significant association between the efficiency and Grade 3-4 side effect

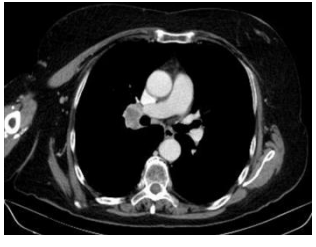
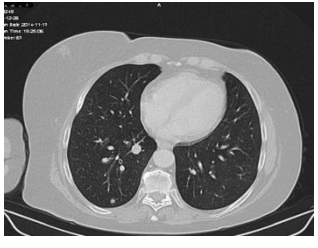
Results

- We demonstrate with our 3 long-therm survival patients the importance of patient selection in concern of the adquate therapy and long-therm survival
  - First patient
    - 29 year old male patient
      - ECOG 0 performance status
      - had been suffering since 2011 metastatic disease
      - recieved ipilimumab for 6 unresectable mediastinal lymph node metastasis in 2013 April
        - the baseline LDH level was normal
      - After 4 infusion, the computer tomography scan detected **complete response**
        - The patient had no side effects at all
        - After 4 years no metastasis was found
        - **PFS 51 months**

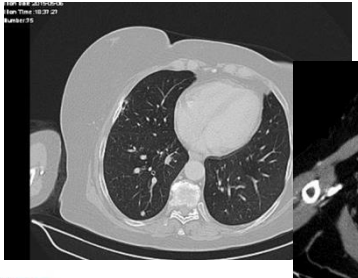
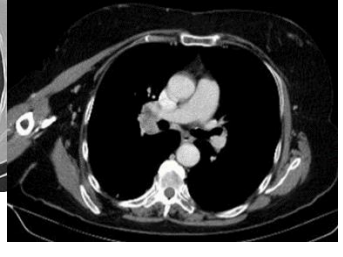
Results


Clark IV Breslow 1,5 mm-es lentigo maligna melanoma.

- Second patient
  - 65 year old, ECOG 1, female **patient metastatic disease was found after 16 years of the primary tumor excision**
  - She recieved ipilimumab for **2 solid pulmonary and mediastinal lymph node metastasis** in 2015

  - The baseline LDH level was normal
  - After 4 infusion, the computer tomography scan with immun response criteria a **stabile disease**
  - The patient **after 2 years of immunotherapy still in a stabile metastatic disease with no sign of side effects**

Results

- Third patient
  - 52 year old, ECOG 0, female patient
  - recieved ipilimumab therapy in 2015 after 3 cycle of intra-arterial chemoterapy for **cutan-subcutan metastasis**
  - The baseline LDH level was normal
  - After the terapy we found **complete response**, with no sign of side effects.

Lessons and Take Home Messages- Conclusions

- We would like to demonstrate with our 3 cases, that with good prognostic factors improved long-therm survival is acceptable with ipilimumab immunotherapy
  - low tumor mass
  - normal LDH level in baseline
  - slow progression disease

  Sign of better response
- These patients are in an adequate performance status and they don't need any active oncotherapy after the ipilimumab induction
- **Monoclonal antibodies against different immune checkpoints have been revolutionizing the treatment and demonstrate an increased overall response of metastatic melanoma and other type of metastatic cancers too**

Thank You very much for your attention !

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