NOVEL IMMUNOTHERAPIES AND REGIONAL CHEMOTHERAPY IN UVEAL MELANOMA

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NATIONAL INSTITUTE OF ONCOLOGY
BUDAPEST, HUNGARY

SITC 2019
Gaylord National Hotel & Convention Center Nov. 6-10
NATIONAL HARBOR, MARYLAND

DISCLOSURE

I have NO conflict of interest in relation to this presentation.

UVEAL MELANOMA (UM)

- UM is a **rare cancer** with **dismal prognosis**, arising from the melanocytes of the uveal tract[1-4]
  - Choroid (85-90%)
  - Ciliary body (5-8%)
  - Iris (3-5%)

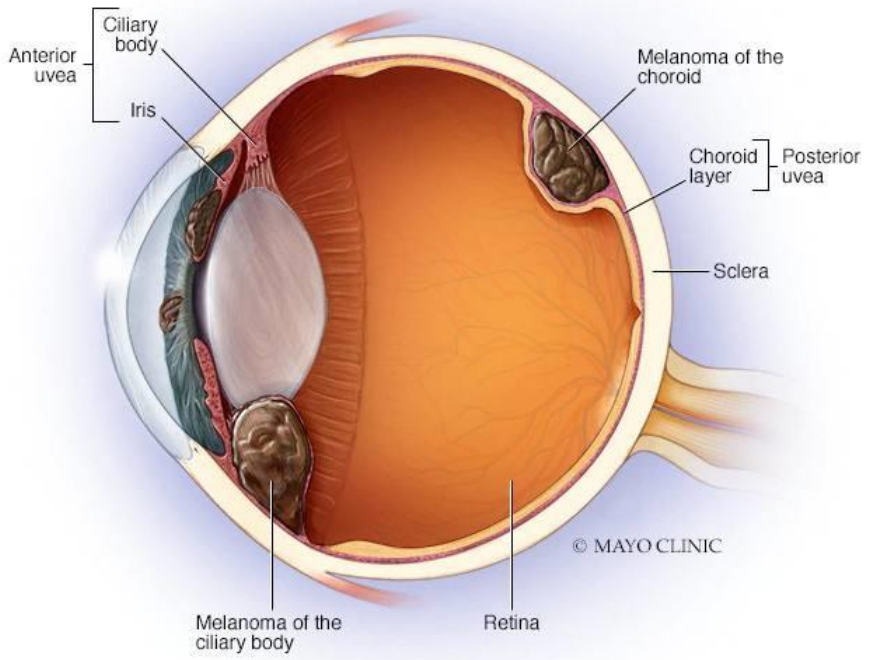
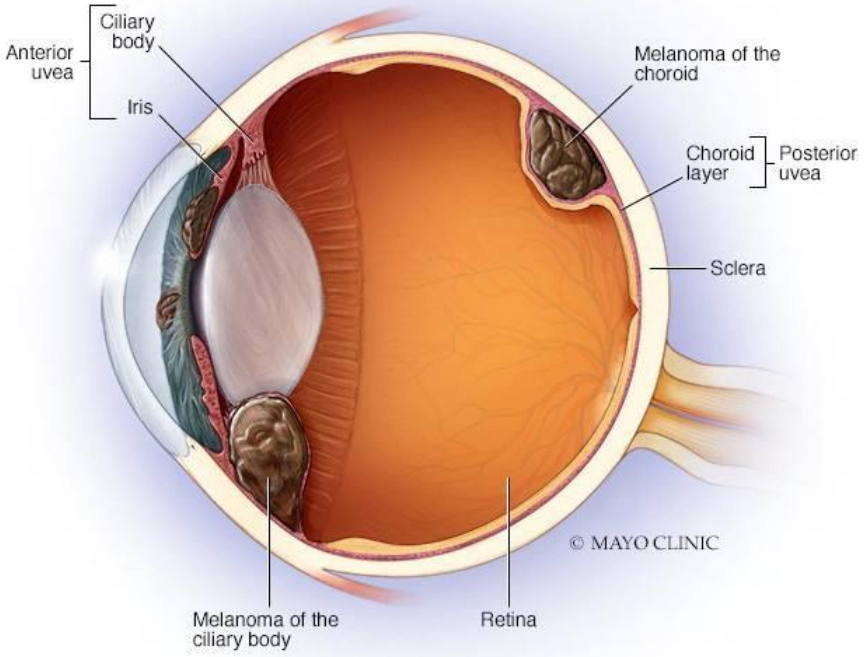


Figure adopted from Mayo Clinic.
Available at: https://newsnetwork.mayoclinic.org/discussion/what-is-ocular-melanoma/

1.Virgili G, et al. Incidence of uveal melanoma in Europe. *Ophthalmology* 2007;114(12):2309-15.
2.Krantz BA, et al. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol* 2017;11:279–289.
3.Carvajal RD, et al. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol* 2017;101(1):38–44.
4.Pandiani C, et al. Focus on cutaneous and uveal melanoma specificities. *Genes Dev* 2017;31:724–743.
5.Scott JF, Gerstenblith MR, editors. Noncutaneous Melanoma [Internet]. Brisbane (AU): Codon Publications; 2018 Mar. Available from: https://www.ncbi.nlm.nih.gov/books/NBK506988/doi: 10.15586/codon.noncutaneousmelanoma.2018
6.Mahendraraj K, et al. Trends in incidence, survival, and management of uveal melanoma: a population-based study of 7,516 patients from the Surveillance, Epidemiology, and End Results database (1973-2012). *Clin Ophthalmol* 2016;10:2113-2119.

UVEAL MELANOMA (UM)

- Incidence: 8,000 new cases worldwide/year[4]
- It is the **most common intraocular malignancy** in adults, representing 3% of all melanomas[5,6]
- It has a peak incidence of age 55[1-3]
- Etiology:
  - UM is more common in certain patient demographics, including Caucasian males[2]
  - Predisposing factors: light skin and eye color, BAP1 mutation[2]



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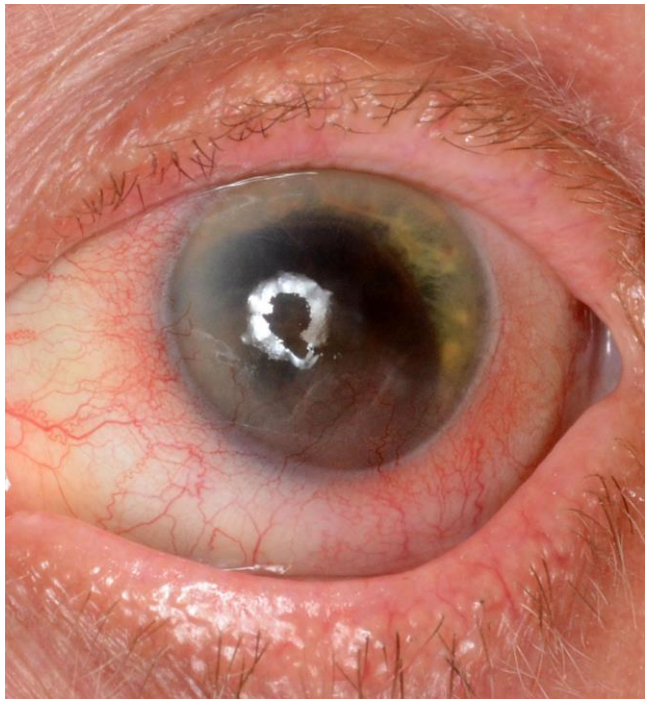
UVEAL MELANOMA METASTASIS

- UM has a **low mutational burden** versus cutaneous melanoma (CM), characterized by point mutations in the G-protein α-subunit coded for by the **GNAQ and GNA11 genes**[1,2]
- The eye has **no ocular lymphatic drainage**, UM **spreads hematogenously**[3,9]
- The mechanisms for development of metastases in the liver are still highly speculative[9]
- It is assumed that multiple factors contribute to the development of metastases[9]:

  slow hepatic blood circulation, interaction between chemo-attractans and their receptor, growth factors and angioneogenesis factors rich inthe liver, chromosomal and gentic abnormalities, the expression of adhesion molecules in the sinusoid, immunomodulatory microenvironment[9]

Image sourced from the arcvhive of the National Institute of Oncology, Budapest



1. Krantz BA, et al. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol* 2017;11:279–289.
2. Field MG, et al. PRAME as an Independent Biomarker for Metastasis in Uveal Melanoma. *Clin Cancer Res* 2016;22(5):1234–1242.
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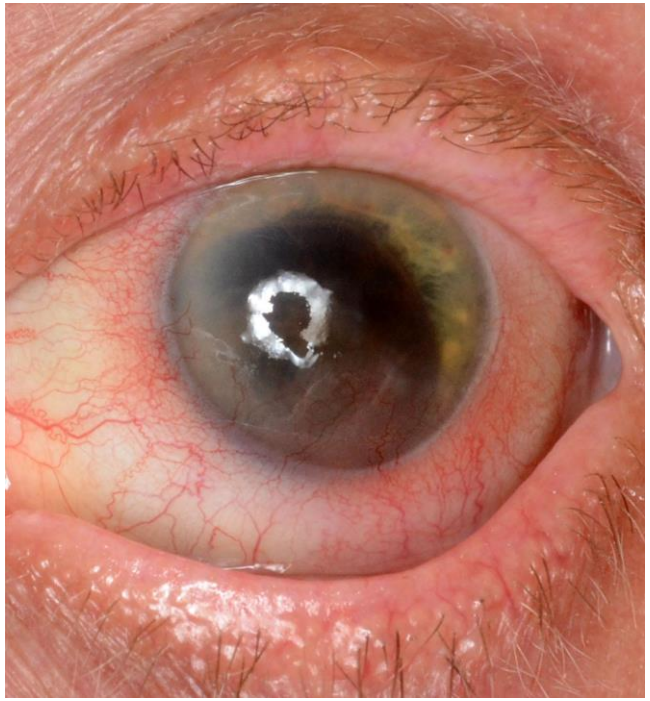
6. Algazi AP, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer* 2016;122(21):3344–3353.
7. Khoja L, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study, *Annal Onc* 2019;30(8):1370–1380.
8. Nathan P, et al. United Kingdom Uveal Melanoma Guideline Development Working Group. Uveal Melanoma UK National Guidelines. *Eur J Cancer* 2015;51(16):2404-12.
9. Terai M et al. Immunological aspect of the liver and metastatic uveal melanoma. *J Cancer Metastasis Treat* 2017;3:231-43.

UVEAL MELANOMA METASTASIS

- Despite succesful treatment of the primary melanoma, metastatic relapse occurs in 50% of patients[4,5]
- The **liver is the primary site in 90%** of cases, unlike CM, wheres metastases commonly appear in the lymphatic system[3]
- Patients with liver metastases have a **median survival time of 2-8 months** and 1 year survival rate of ~10-40% [4, 6,7]
- Most patients with metastatic disease die from parenchymal liver failure[8]

Image sourced from the arcvhive of the National Institute of Oncology, Budapest



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CURRENT MANAGEMENT OF METASTATIC UVEAL MELANOMA

NCCN GUIDELINES VERSION 1.2019
UVEAL MELANOMA — TREATMENT OF THE METASTATIC DISEASE

National Comprehensive Cancer Network®

The NCCN believes that the best management of any patient with cancer is in a **clinical trial**.

All recommendations are **based upon lower-evidence** (category 2A).

NCCN Clinical Practice Guidelines in Oncology: Uveal melanoma Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf

THERAPEUTIC OPTIONS

OF METASTATIC UVEAL MELANOMA

1. LIVER-DIRECTED THERAPY
2. SYSTEMIC CHEMOTHERAPY
3. IMMUNE CHECKPOINT INHIBITORS
4. TARGETED THERAPY
5. OTHER AGENTS

1. LIVER-DIRECTED THERAPY IN METASTATIC UM

- Tumour resection[2,3]
- Selective internal radiation therapy (SIRT)[4]
- Radioferquency ablation (RFTA)[4]
- Hepatic perfusion (IHP: isolated h.p., PHP: percutaneous h.p.)[2]
- Intra-arterial chemotherapy and/or chemoembolisation[2]

Median progression-free survival: 5.2 months[1]

Median overall survival: 14.6 months[1]

1. Khoja L, et al. Meta-Analysis in Metastatic Uveal Melanoma to Determine Progression-Free and Overall Survival Benchmarks: an International Rare Cancers Initiative (IRCI) Ocular Melanoma study. *Ann Oncol* 2019;30(8):1370-80.
2. Agarwala SS, et al. Metastatic melanoma to the liver: a contemporary and comprehensive review of surgical, systemic, and regional therapeutic options. *Cancer* 2014 Mar 15;120(6):781-9.
3. Gomez, D. Et al. The Liverpool uveal melanoma liver metastases pathway: Outcome following liver resection. J. *Surg Oncol* 2014;109:542–547
4. Sundram FX, et al. Selective internal radiation therapy for liver tumours. *Clin Med (Lond)* 2017 Oct;17(5):449-453.

2. SYSTEMIC CHEMOTHERAPY IN METASTATIC UM

- Numerous cytotoxic agents and combinations
- Response rates range from 0% to 15%
- No agent has been shown to prolong survival

Median progression-free survival: 2.6 months[1]

Median overall survival: 9.2 months[1]

1. Khoja L, et al. Meta-Analysis in Metastatic Uveal Melanoma to Determine Progression-Free and Overall Survival Benchmarks: an International Rare Cancers Initiative (IRCI) Ocular Melanoma study. *Ann Oncol* 2019;30(8):1370-80.

3. IMMUNE CHECKPOINT BLOCKADE METASTATIC IN UM

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4
PD-1: programmed cell death-1

- Therapeutic agents:
  - Monotherapy: CTLA-4 inhibitors; PD-1 inhibitors
  - Combined checkpoint inhibition: CTLA-4 inhibitors + PD-1 inhibitors

- Much less response to checkpoint inhibitors compared with CM
- Low mutational tumor burden / low immunogenicity

Median progression-free survival: 2.8 months[1]

Median overall survival: 8.9 months[1]

1. Khoja L, et al. Meta-Analysis in Metastatic Uveal Melanoma to Determine Progression-Free and Overall Survival Benchmarks: an International Rare Cancers Initiative (IRCI) Ocular Melanoma study. *Ann Oncol* 2019;30(8):1370-80.

4. TARGETED THERAPY IN METASTATIC UM

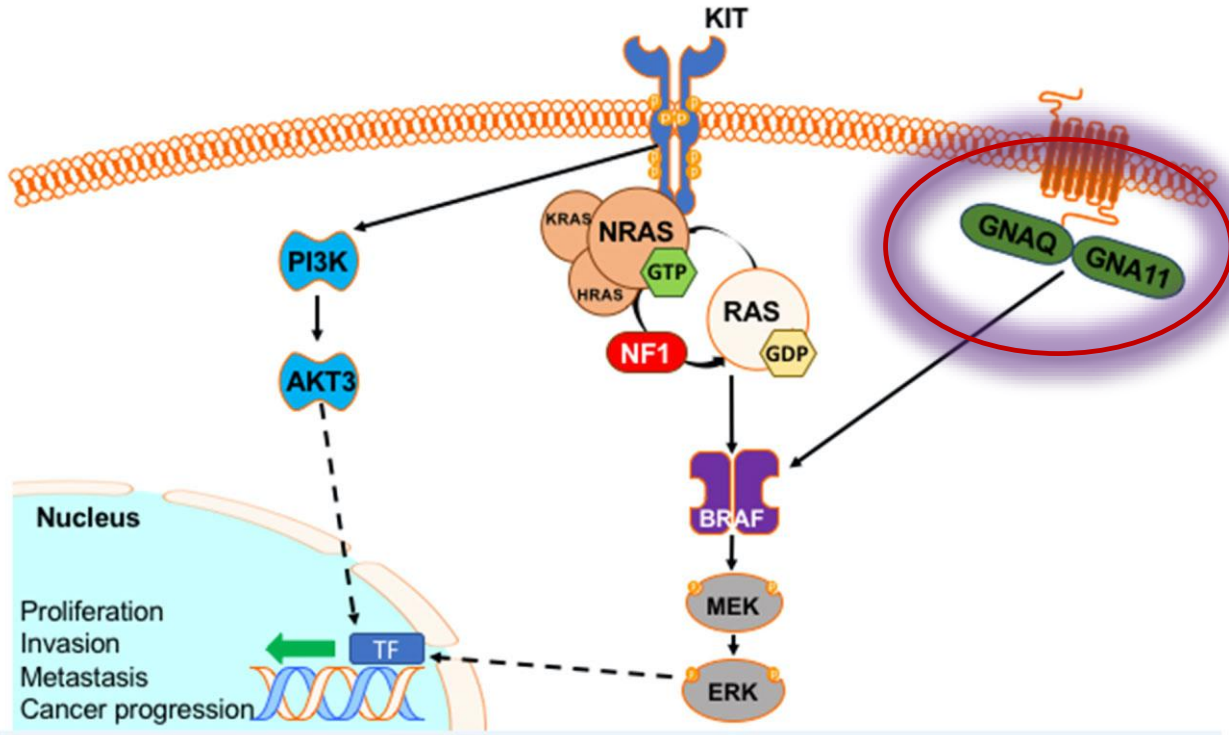

Figure adopted from: Shaughnessy et al. Clinical and therapeutic implications of melanoma genomics. *J Transl Genet Genom* 2018;2:14.

Kinase inhibitors:

- **Trametinib** (MEK inhibitor)
- Selumetinib (MEK inhibitor)
- Sorafenib (multikinase inhibitor)
- Sunitinib (multikinase inhibitor)

Median progression-free survival: 2.8 months[1]

Median overall survival: 9.1 months[1]

1. Khoja L, et al. Meta-Analysis in Metastatic Uveal Melanoma to Determine Progression-Free and Overall Survival Benchmarks: an International Rare Cancers Initiative (IRCI) Ocular Melanoma study. *Ann Oncol* 2019;30(8):1370-80.

5. OTHER AGENTS AGAINST METASTATIC UM (NOT EVIDENCE-BASED DRUGS)

- Glembatumumab vedotin (CDX-011): an antibody-drug conjugate - Phase II study[1]

  Median progression-free survival: **3.2 months**

  Median overall survival: 11.8 months

- Adoptive TIL transfer – Phase II study[2]
- Tebentafusp (IMCgp100): T cell redirection - II study[3]

  Median progression-free survival: **5.6 months**

  Median overall survival: not reaches at 19.1 months

1. Sapna Patel, et al. NCI 9855: A Phase 2 Study of CDX-011 (Glembatumumab vedotin) for metastatic Uveal Melanoma. Presented at SMR 2017. Available at : https://www.celldex.com/docs/2017%20LBA%20SMR%209855_Patel%20FINAL.PDF
2. Chandran SS, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. Lancet Oncol 2017 Jun;18(6):792-802.
3. Damato BE, et al. Tebentafusp: T Cell Redirection for the Treatment of Metastatic Uveal Melanoma. Cancers (Basel) 2019;11(7). pii: E971.

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National Institute of Oncology, Department of

RESULTS ACHIEVED BY INTRA-ARTERIAL CHEMOTHERAPY IN 50 OCULAR MELANOMA PATIENTS WITH METASTASES LOCALISED IN THE LIVER. SINGLE INSTITUTE RETROSPECTIVE STUDY.

NATIONAL INSTITUTE OF ONCOLOGY BUDAPEST, HUNGARY

mour in adults, and it represents
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inger method. The brachial or
ra-arterial chemotherapy to
astases which are difficult to

RESULTS: The data processed included 28 men (56%) and 22 women (44%). The average age of patients was 61 years (between the ages of 28-81). The average time elapsed until the development of metastases was 40.66 months (SD: 45.12), and the median was 20 months. The median progression-free survival was 7 months, and the median overall survival was 11 months.

CONCLUSION: The intra-arterial chemotherapy used only in hepatic metastases resulted in a median PFS of 7 month, which is considered favourable even when compared to the outcomes of new therapies in melanoma.

	50
	28
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	61
	28-81
months)	
	40,66
	20
	7
	11

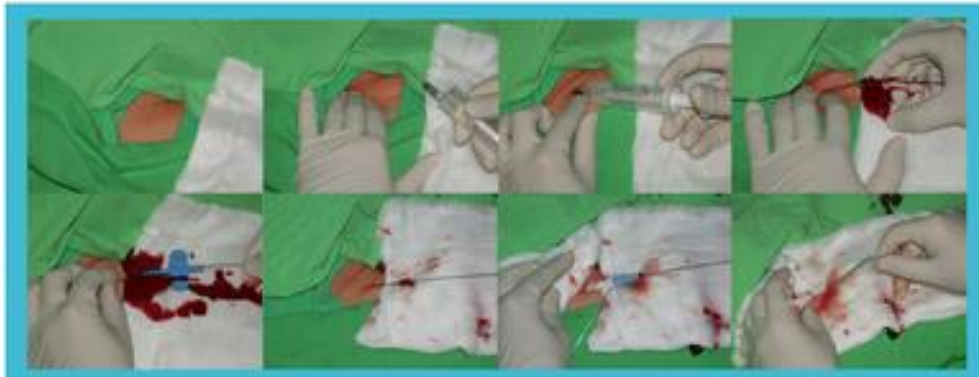
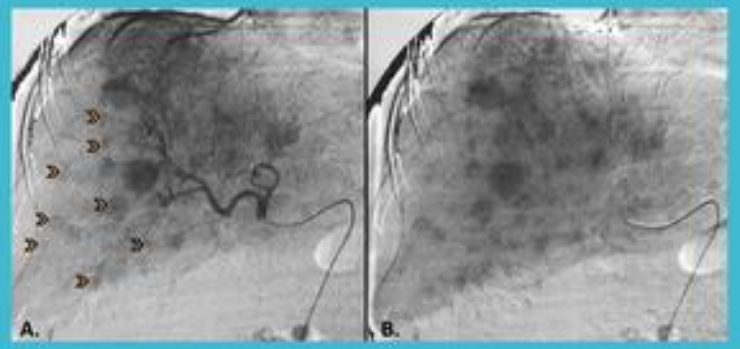
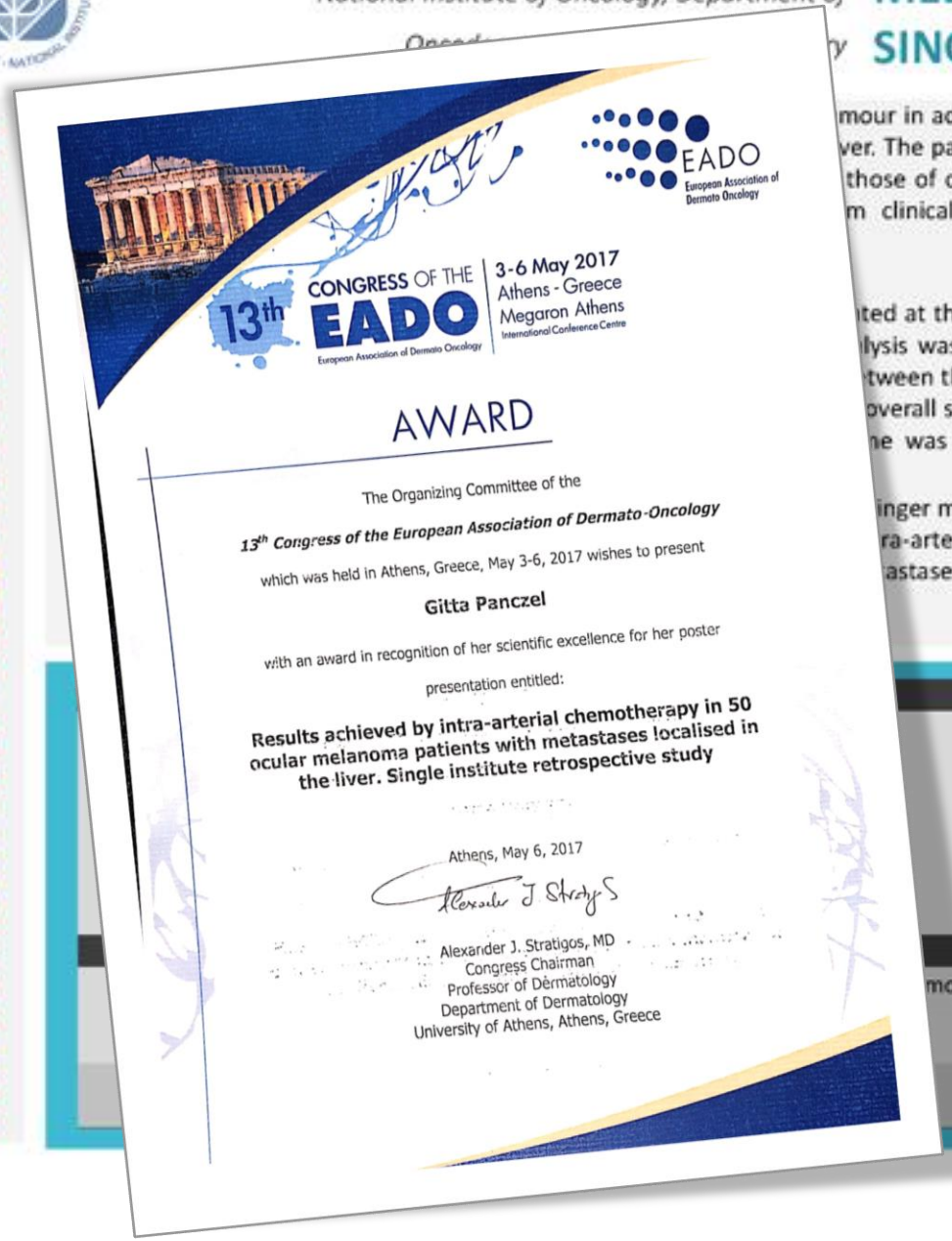


Figure 3: Percutaneous cannulation by Seldinger method.

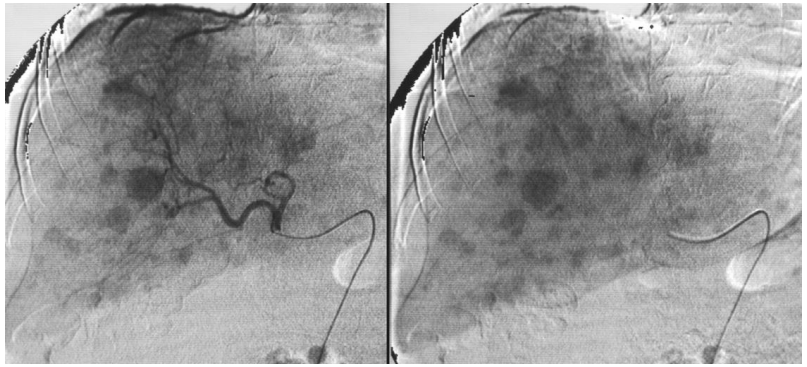
*Figure 4: Multiple liver metastases of ocular melanoma. Arteriography. **A.** Arterial phase. **B.** Parenchymal phase*



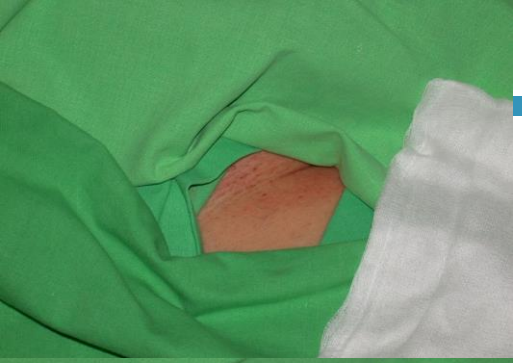
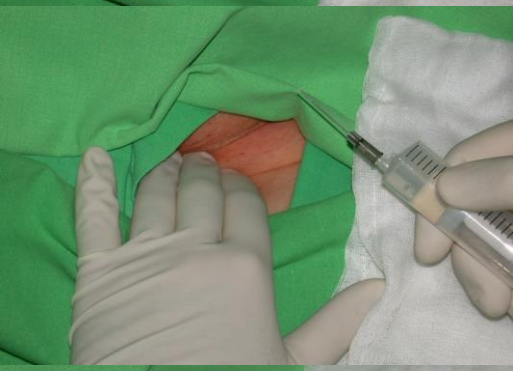
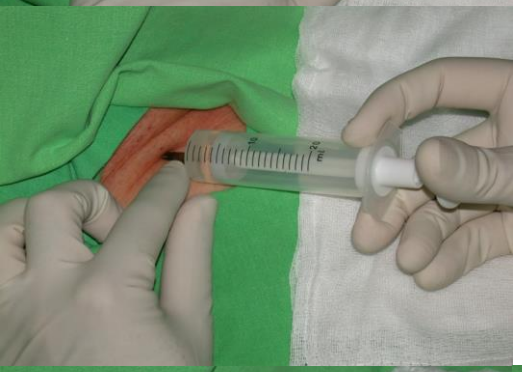


Presented at EADO 2017 Athens. Poster P022.

MATERIALS AND METHODS

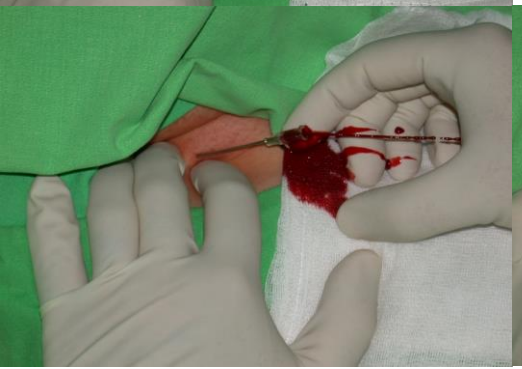
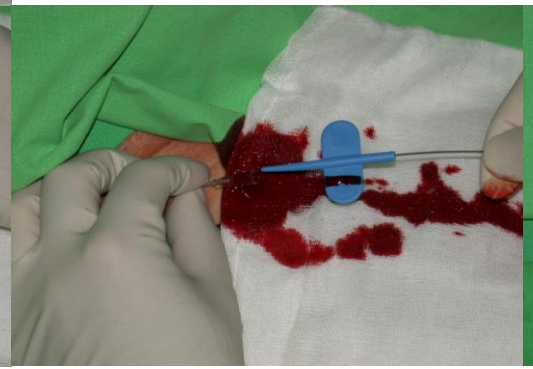
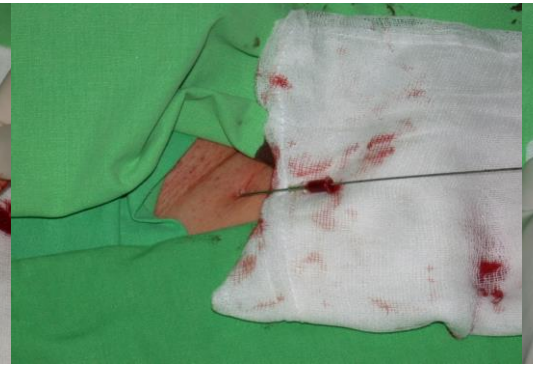
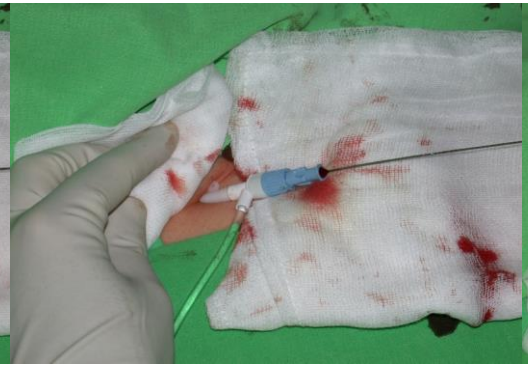
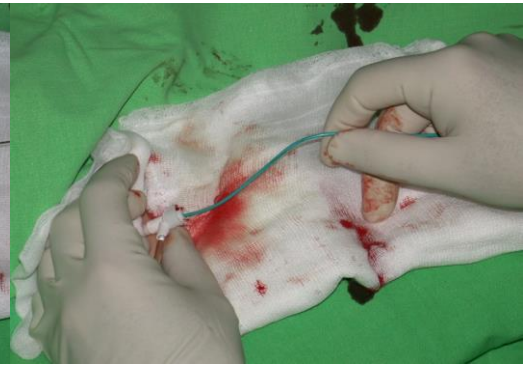


- National Institute of Oncology, Budapest, Hungary
- **50 UM patients with liver metastases**
  - 28 male (56%), 22 female (44%)
  - Average age: 61y (28-81y)
- We focused on **progression-free survival** and the **overall survival**
- The minimum follow-up time was set at 12 months, and the average follow-up time was 60.4 months (12-257 months).

- Intra-arterial administration of chemotherapeutics was performed by **Seldinger method**: The brachial or the femoral artery was cannulated percutaneously.
- We preferred **intra-arterial chemotherapy** to **chemoembolisation** in cases of multiple liver metastases or in case of metastases which are difficult to reach due to anatomical conditions.
- Used chemotherapeutic agents:

  20 mg/m^2 cisplatine, 20 mg/m^2 epirubicine

RESULTS

Median progression-free survival: 7 months

Median overall survival: 11 months

The 7 month PFS rate of the intra-arterial chemotherapy is superior than the PFS rate observed in the medical literature.

PFS: progression-free survival

SURVIVAL DATA OF 10 PATIENTS TREATED WITH ANTI-PD1 IMMUNOTHERAPY FOR METASTATIC OCULAR MELANOMA. SINGLE INSTITUTE RETROSPECTIVE STUDY.

PANCZEL G, ET AL.

POSTER PRESENTATION AT 9TH POST-CHICHAGO MELANOMA/SKIN CANCER MEETING 2019, MUNICH, GERMANY

PATIENTS AND METHODS

- National Institute of Oncology, Budapest, Hungary
- Between 2015 and 2018
- 10 patients with metastatic UM were studied
- Patients were received systemic anti-PD1 immunotherapy
- **Response rate**, **progression-free survival** and **overall survival** were retrospectively determined
- Disease response was measured by iRECIST

PATIENTS AND METHODS

- 5 female (50%) and 5 male (50%) were enrolled
- Average age was 64y (49–79y) at the time of dissemination
- ECOG performance status: 0–1
- 6 patients had localised liver metastasis
- 4 patients had extrahepatic dissemination

PATIENTS AND METHODS

Lines of therapy:

- 1stL therapy: 2 patients
- 2ndL therapy: 6 patients
- 3rdL or higher: 2 patients

Therapeutic agents:

- Pembrolizumab: 8 patients
- Nivolumab: 2 patients

Prior therapies:

- Prior ipilimumab therapy: 1 patient
- Prior intra-arterial liver chemotherapy: 6 patients

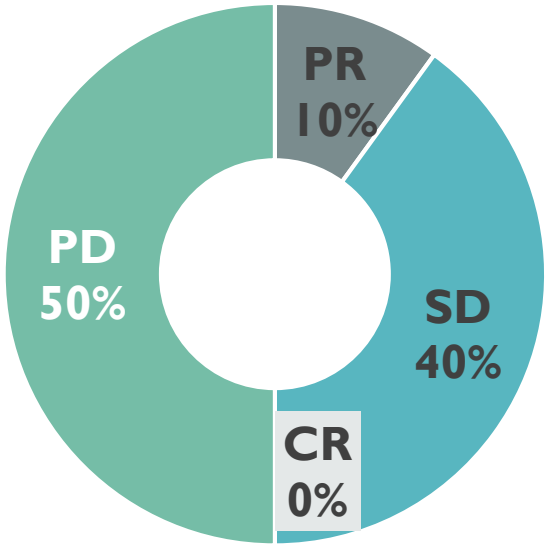
RESULTS

- Toxicities were as expected:
  - Grade 3-4 adverse events: 2 patients (20%) - laboratory deviations
  - None of the patients discontinued therapy due to toxicity

- At the time of analysis 6 patients (60%) were alive

RESULTS

Response rate



CR: complete response – 0 (0%)
PR: partial response – 1 (10%)
SD: stable disease – 4 (40%)
PD: progressive disease – 5 (50%)

Median **PFS: 5 months** (2-15 months)

Median **OS: 9 months** (3–32 months)

PFS: progression-free survival
OS: overall survival

IN SUMMARY

- Current treatment options in CM and UM are similar but vary in benefit[1-6]
- No survival benefit shown with either treatment regimen
- Neither targeted therapy nor immune checkpoint blockade could show convincing efficacy, possibly due to lack of immunogenicity/mutagenicity[6-7]
- There is no standardized approach to the management of UM
- There are ongoing clinical trials looking at novel treatment options for patients with metastatic UM

1. Ugurel S, et al. Dacarbazine in Melanoma: From a Chemotherapeutic Drug to an Immunomodulating Agent. *J Investig Dermatol* 2013;133:289-92.
2. Luke, JJ, et al. Targeted agents and immunotherapies: optimizing outcomes in melanoma. *Nat Rev Clin Oncol* 2017;14(8), 463-482.
3. Algazi AP, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer* 2016;122(21):3344–3353.
4. Rodriguez JMP, et al. Phase II multicenter, single arm, open label study of Nivolumab in combination with Ipilimumab in untreated patients with metastatic uveal melanoma. *Ann Oncol* 2018;29(8):442-466.
5. Carvajal RD, et al. Effect of Selumetinib vs Chemotherapy on Progression-Free Survival in Uveal Melanoma: A Randomized Clinical Trial. *JAMA* 2014;311(23):2397–2405.
6. Robertson AG, et al. Integrative Analysis Identifies Four Molecular and Clinical Subsets in Uveal Melanoma. *Cancer Cell* 2017;32(2):204-220.
7. Javed A, et al. PD-L1 expression in tumor metastasis is different between uveal melanoma and cutaneous melanoma. *Immunotherapy* 2017;9(16):1323-1330.

IN SUMMARY

- The intra-arterial chemotherapy is a rational option for the treatment of isolated liver metastases
- The intra-arterial chemotherapy used only in liver metastases resulted in a **median progression-free survival of 7 months** in our study, which is considered favourable even when **compared to** the outcomes of novel therapies of melanoma (**2.6-5.6 months**)[1]

1. Panczel G, Balatoni T, Szavcsur P, Liszkay G. Resuts achieved by intra-arterial chemotherapy in 50 ocular melanoma patients with metastases localised in the liver. Single institute retrospective study. Presented at EADO 2017 Athens. Poster P022.

THANK YOU FOR YOUR ATTENTION!

Budapest, Hungary