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Cross-border cooperation to foster the resilience of clinical management in cancer patients by establishing best practices in personalized molecular-based diagnostics, treatment, and long-term care

RORS00040

Understanding Melanoma Biology to Guide Targeted and Immune Therapies

Authors: Assist. Prof. Dr. Șerban Daniela, Assoc. Prof. Dr. Florina Bojin, Prof. Dr. Păunescu Virgil

Spitalul Clinic Județean de Urgență „Pius Brînzeu" Timișoara

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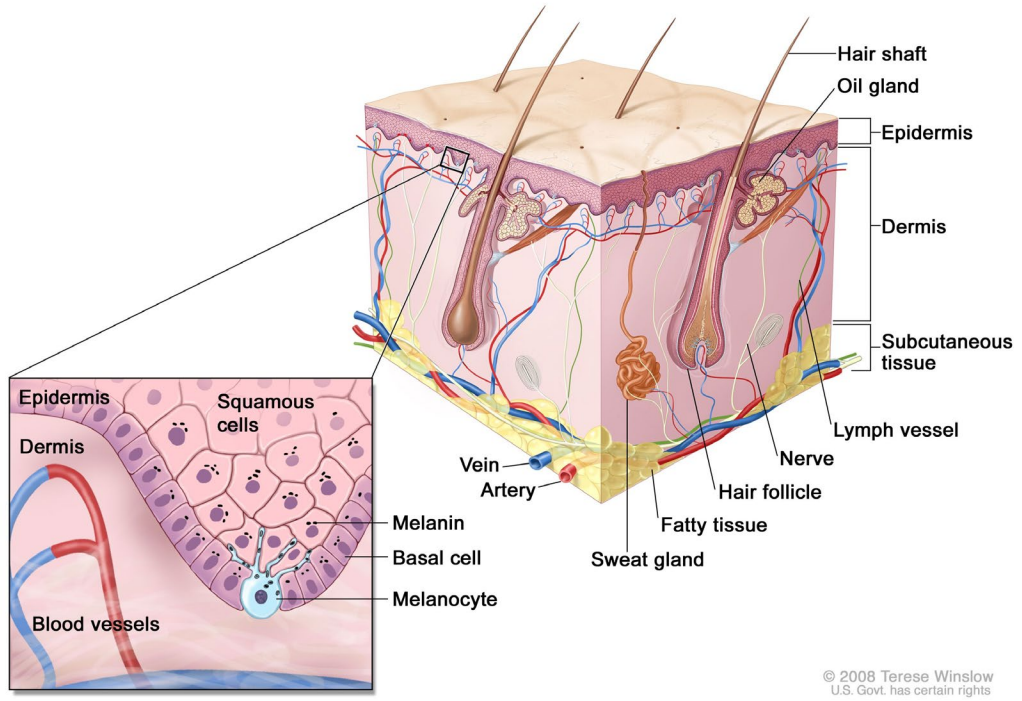
Melanoma

It is a malignant tumor arising from melanocytes and can develop wherever these cells are present

The cutaneous form is the most common, but melanoma may also occur in the eyes, mucous membranes, and the central nervous system

Most melanomas are highly pigmented, although amelanotic variants exist

Systemic melanoma is characterized by early lymphatic and hematogenous metastasis



Shain AH, Bastian BC. From melanocytes to melano- mas. *Nat Rev Cancer.* 2016;16(6):345-358 Garbe, Claus, et al. "European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022." *European Journal of Cancer* 170 (2022): 236-255.

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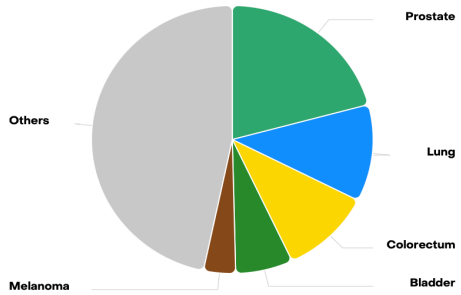
Epidemiology

Top 5 most frequent cancers**

Males

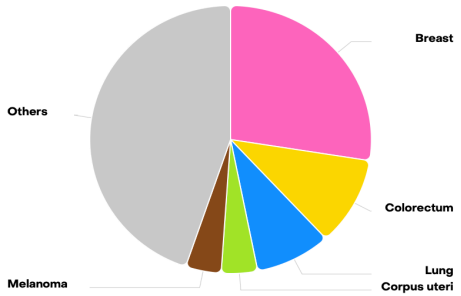


Total: 761 463

Rank	Cancer site	Number of cases	Percent
1st	Prostate	158 422	20.8%
2nd	Lung	88 993	11.7%
3rd	Colorectum	80 267	10.5%
4th	Bladder	50 133	6.6%
5th	Melanoma	28 062	3.7%
-	Others	355 586	46.7%

Number of new cases in 2022, males, all ages

Females



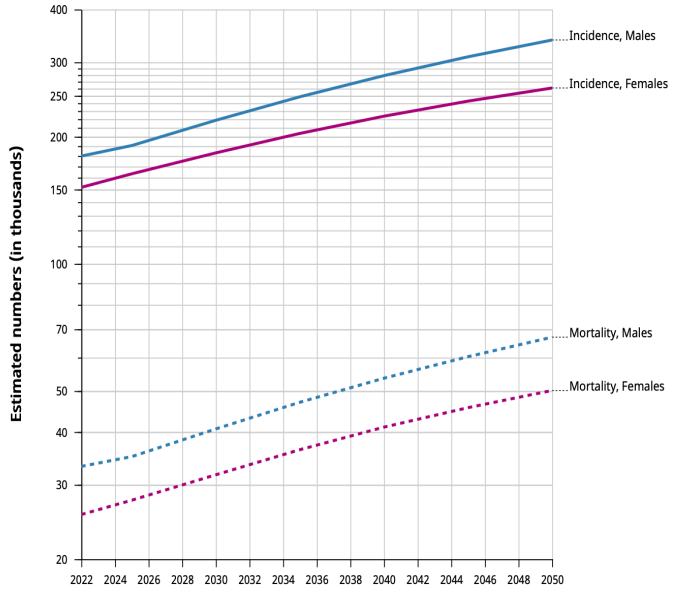
Total: 654 364

Rank	Cancer site	Number of cases	Percent
1st	Breast	180 113	27.5%
2nd	Colorectum	69 870	10.7%
3rd	Lung	56 948	8.7%
4th	Corpus uteri	27 257	4.2%
5th	Melanoma	26 833	4.1%
-	Others	293 343	44.8%

Number of new cases in 2022, females, all ages

Estimated numbers from 2022 to 2050, Males and Females, age [0-85+]
Melanoma of skin

GLOBAL CANCER OBSERVATORY



Cancer Tomorrow | IARC - https://gco.iarc.who.int/tomorrow
Data version : Globocan 2022 (version 1.1)

International Agency for Research on Cancer
World Health Organization

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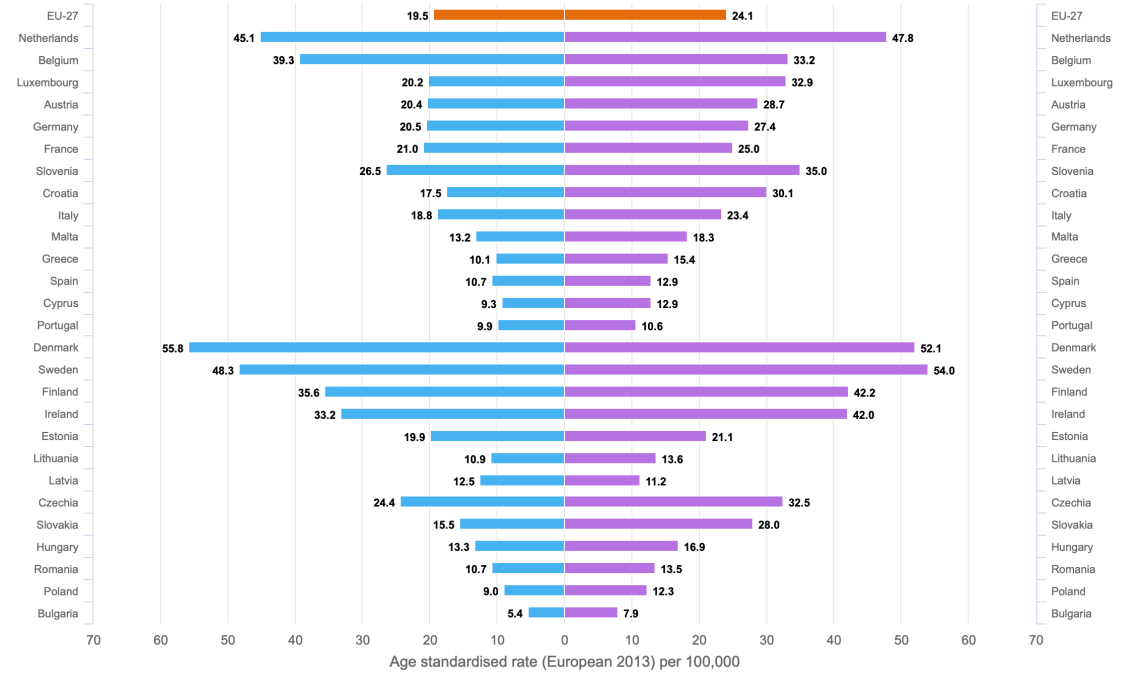
Incidence

Estimated incidence by country - Comparison by sex

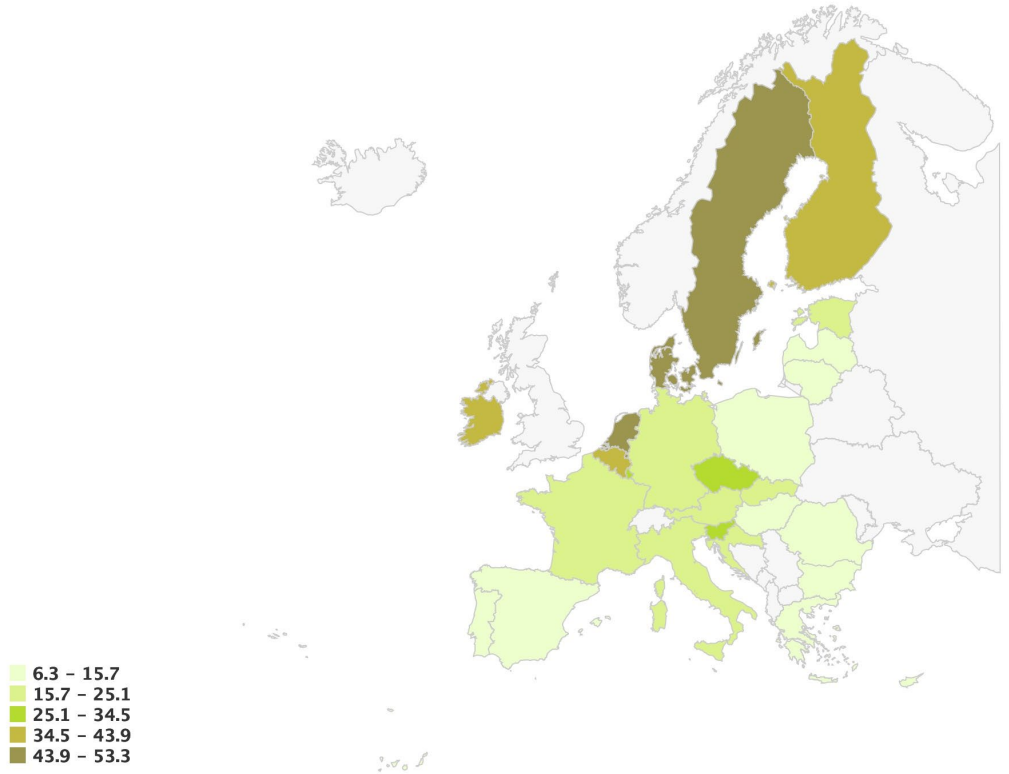
EU27, Both sexes, Melanoma skin, All ages, 2022



Sex
Female
Male

Estimated incidence by country

EU27, Both sexes, Melanoma skin, All ages, 2022



Age standardised rate (European 2013) per 100,000

Joint Research Centre- ECIS - European Cancer Information System

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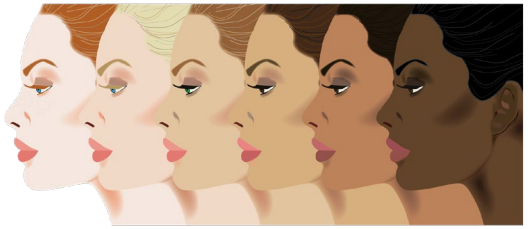
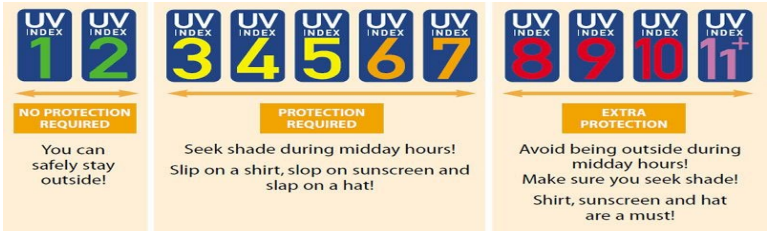
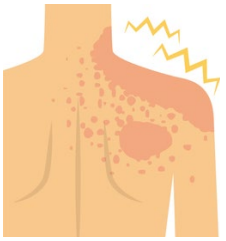
Risk factors

- Exposure to UV radiation (natural and artificial)
- Sunburns
- Skin phototype
- High number of nevi (>50) and dysplastic nevi
- Family history (CDKN2A, CDK4 mutations) and personal history of melanoma
- Age







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Clinical aspects

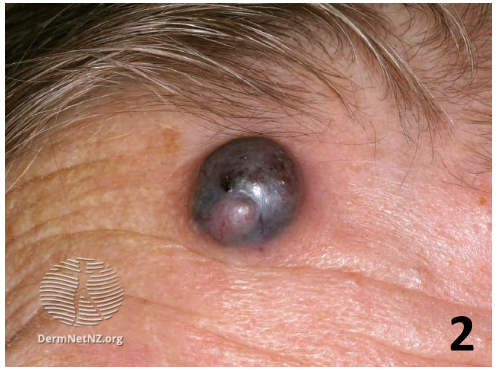
A. Cutaneous melanoma

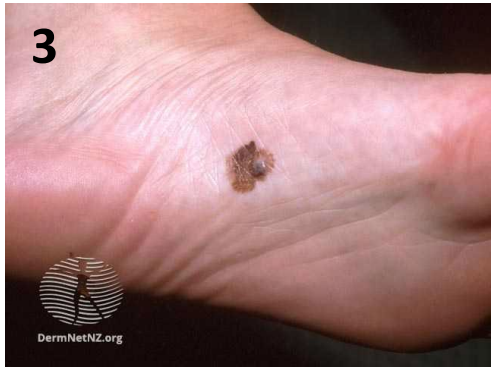
Types:

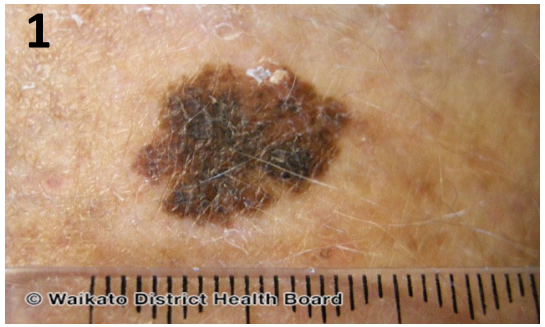
1. **Superficial spreading** melanoma: the most common type; initially grows horizontally, followed by vertical invasion
2. **Nodular** melanoma: exhibits only vertical growth, becomes rapidly invasive, and frequently ulcerates
3. **Acral lentiginous** melanoma: located on the palms, soles, and nail bed
4. **Lentigo maligna melanoma**: remains in situ for a prolonged period, later progressing to vertical growth

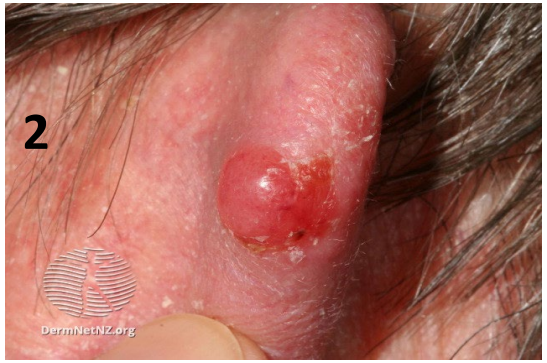
B. Mucosal melanoma

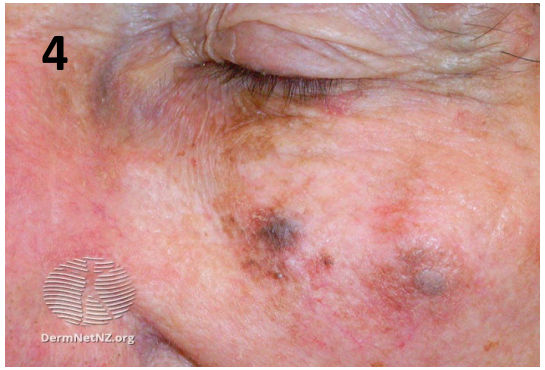
C. Leptomeningeal melanoma











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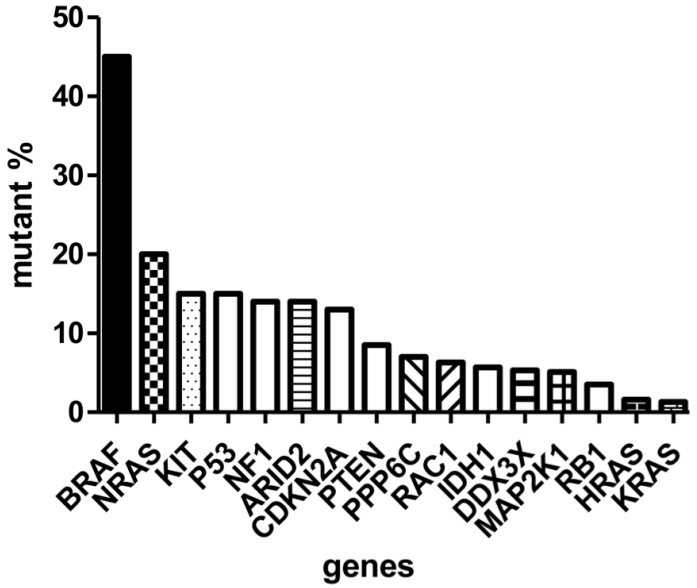
Molecular Biology of Melanoma

- The high frequency of mutations in key genes involved in pathogenesis has led to the development of a molecular classification, which provides the foundation for targeted therapies tailored to the tumor's genetic profile:
  - **BRAF-mutant**
  - **RAS-mutant**
  - **NF1-mutant**
  - **Triple wild-type**

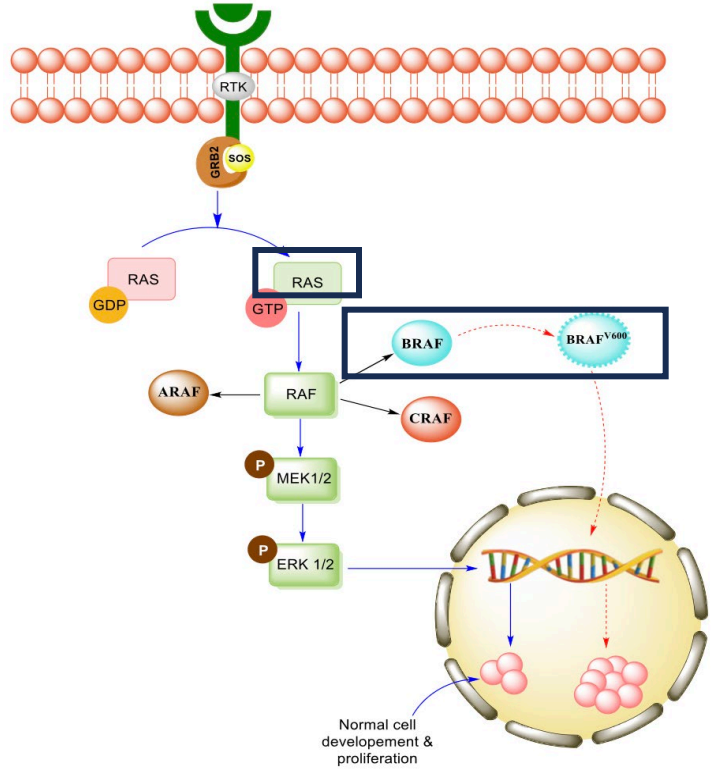


Mutation spectrum of driver genes (oncogenes and suppressor genes) of skin melanoma based on TCGA (The Cancer Genome Atlas)

Tímár, J.; Ladányi, A. Molecular Pathology of Skin Melanoma: Epidemiology, Differential Diagnostics, Prognosis and Therapy Prediction. Int. J. Mol.Sci. 2022, 23, 5384. https://doi.org/10.3390/ijms23105384

Molecular Biology of Melanoma

Mutation	Key Biological Effect
BRAF (most often V600E) 40–60% of cases	Abnormal activation of the MAPK pathway → **increased cell proliferation**; alters tumor microenvironment by attracting immunosuppressive cells (Tregs, TAMs, MDSCs)
NRAS (often Q61 mutations) 15–25% of cases	Constant activation of MAPK and PI3K/AKT pathways → **uncontrolled tumor growth**
NF1 (loss-of-function) 10–15% of cases	Loss of neurofibromin → RAS pathway remains active, **promoting proliferation and survival**



Rebecca Adams, Jack E M Coumbe, Ben G T Coumbe, Jennifer Thomas, Zena,Willsmore, Marija Dimitrievska, Monica Yasuzawa-Parker, Maximilian Hoyle, Suhaylah Ingar,Jenny L C Geh, Alastair D MacKenzie Ross, Ciaran Healy, Sophie Papa, Katie E Lacy & Sophia NKaragiannis (2022) BRAF inhibitors and their immunological effects in malignant melanoma,Expert Review of Clinical Immunology, 18:4, 347-362, DOI: 10.1080/1744666X.2022.2044796. NRAS mutant melanoma: Towards better therapies, Randic, Tijana et al. Cancer Treatment Reviews, Volume 99, 102238. Teixido, C.; Castillo, P.; Martinez-Vila, C.; Arance, A.; Alos, L. Molecular Markers and Targets in Melanoma. Cells 2021, 10, 2320. https://doi.org/10.3390/cells10092320

Triple wild-type melanoma

- Triple wild-type melanomas are those without BRAF, NRAS, or NF1 mutations.
- They often develop in areas with low or absent UV exposure.

Table 1. The classification of melanomas (modified from 2018 World Health Organization Classification).

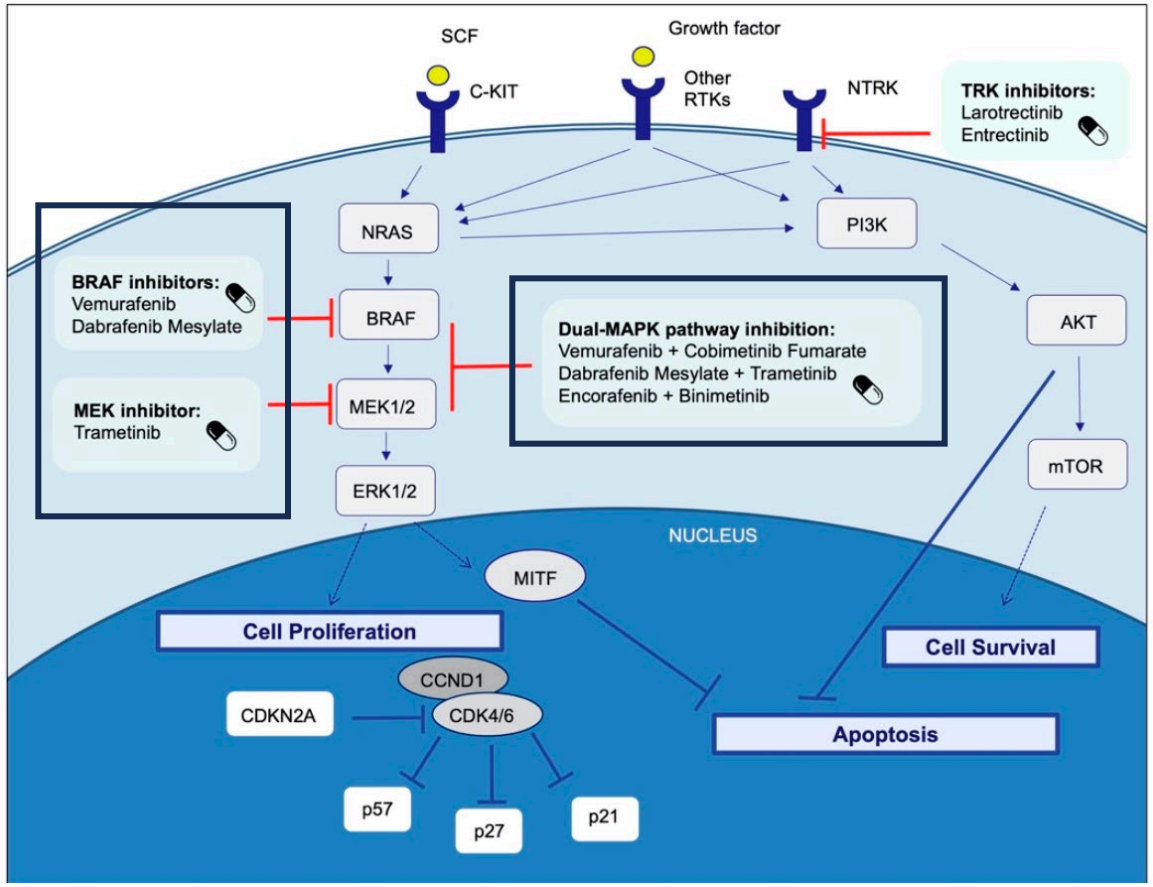
UV Exposure	Categories	Melanoma Subtype	Key Molecular Genes	
Low UV/CSD	I	Superficial spreading melanoma	*BRAF*V600 mut *CDKN2A* mut *NRAS* mut	*TERT* mut *PTEN* mut *TP53* mut
High UV/CSD	II	Lentigo maligna melanoma	*NRAS* mut *BRAFnon-V600E* mut *KIT* mut *TERT* mut	*CDKN2A* mut *PTEN* mut *TP53* mut
	III	Desmoplastic melanoma	*NF1* mut *NFKBIE* mut	*NRAS* mut *PIK3CA* mut
Low or no UV/CSD	IV	Spitz melanoma	*ALK* rearr *NTRK1* rearr *NRTK3* rearr	*CDKN2A* mut *HRAS* mut
	V	Acral melanoma	*KIT* mut *NRAS or BRAF* mut *ALK* rearr *NRTK3* rearr	*CDKN2A* mut *CCND1* amp *TERT* mut
	VI	Mucosal melanoma	*KIT* mut *NRAS or BRAF* mut *CDKN2A* mut *SF3B1* mut	*CCND1* amp *CDK4* mut *MDM2* amp
	VII	Melanoma in congenital nevus	*NRAS* mut	*BRAFV600E* mut
	VIII	Melanoma in blue nevus	*GNA11* mut *GNAQ* mut *CYSLTR2* mut	*BAP1* mut *EIFAX* mut *SF3B1* mut
	IX	Uveal melanoma	*GNA11* mut *GNAQ* mut *CYSLTR2* mut *PLCB4* mut	*BAP1* mut *EIFAX* mut *SF3B1* mut

Abbreviations: amp, amplification; CSD, cumulative sun damage; mut, mutation; rearr, rearrangement.

Teixido, C.; Castillo, P.; Martinez-Vila, C.; Arance, A.; Alos, L. Molecular Markers and Targets in Melanoma. Cells 2021, 10, 2320. https://doi.org/10.3390/cells10092320

Targeted Therapy

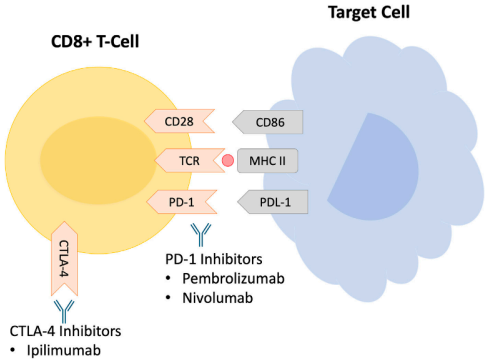
- Understanding the molecular mechanisms has led to the development of **targeted therapies** and **immunotherapies** for advanced melanoma (stages III - IV).
- Selective BRAF-V600 inhibitors:
  - **vemurafenib, dabrafenib, encorafenib -** show strong antitumor activity but have limited durability due to rapid resistance and paradoxical MAPK activation.
- MEK inhibitors:
  - **trametinib, cobimetinib, binimetinib -** are combined with BRAF inhibitors in BRAF-V600 - mutant melanoma and used as monotherapy in NRAS-mutant disease.



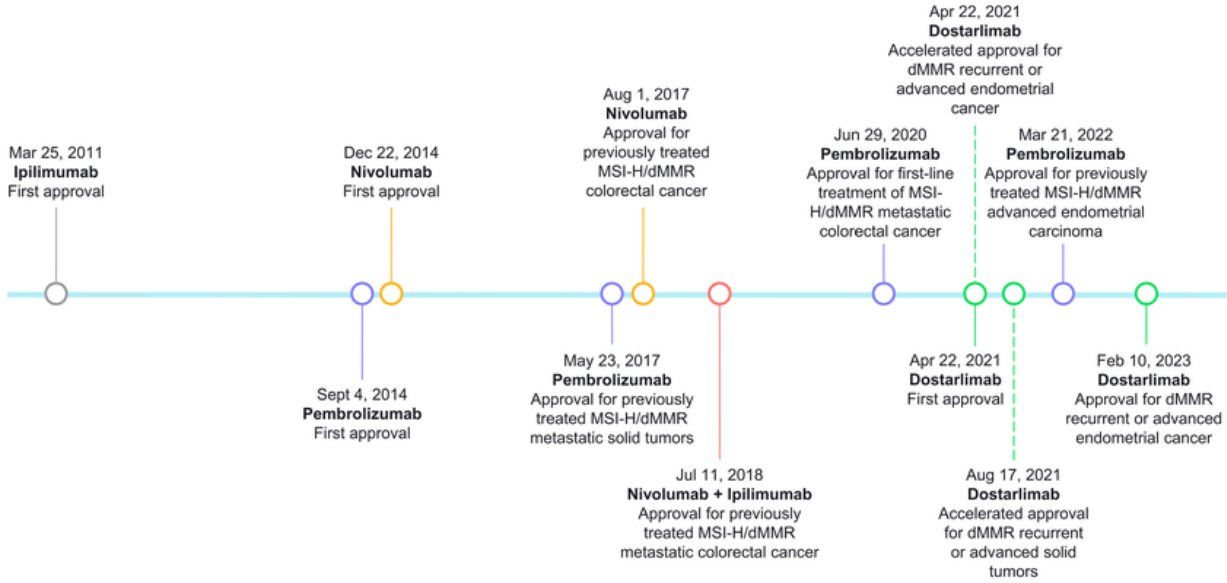
Teixido, C.; Castillo, P.; Martinez-Vila, C.; Arance, A.; Alos, L. Molecular Markers and Targets in Melanoma. Cells 2021, 10, 2320. https://doi.org/10.3390/cells10092320

Immunotherapy

- Over the past two decades, immunotherapy has transformed the treatment of advanced melanoma, offering patients real chances for long-term survival.
- The main classes of immune checkpoint inhibitors used are:
  - **Anti-CTLA-4**: ipilimumab
  - **Anti-PD-1:** pembrolizumab, nivolumab
  - **Anti-PD-L1**: atezolizumab



Sarem Rashid, Michael Shaughnessy, Hensin Tsao,Melanoma classification and management in the era of molecular medicine,Dermatologic Clinics,Volume 41, Issue 1,2023,Pages 49-63,ISSN 0733-8635,ISBN 9780323972840,https://doi.org/10.1016/j.det.2022.07.017.



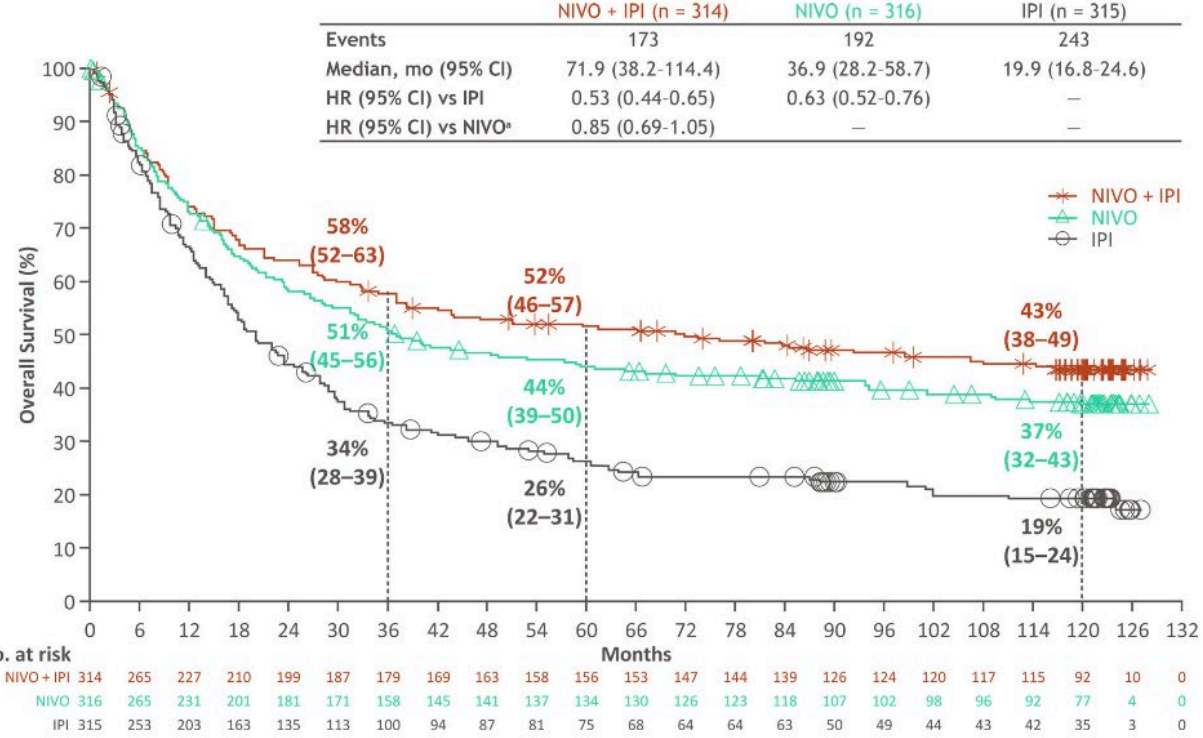
Kavun, Alexandra & Veselovsky, Egor & Lebedeva, Alexandra & Belova, Ekaterina & Kuznetsova, Olesya & Yakushina, Valentina & Grigoreva, Tatiana & Mileyko, Vladislav & Fedyanin, Mikhail & Ivanov, Maxim. (2023). Microsatellite Instability: A Review of Molecular Epidemiology and Implications for Immune Checkpoint Inhibitor Therapy. Cancers. 15. 10.3390/cancers15082288.

Immunotherapy

Published in final edited form as:
N Engl J Med. 2025 January 02; 392(1): 11–22. doi:10.1056/NEJMoa2407417.

Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma

- In the CheckMate 067 phase III clinical trial, median overall survival was:
  - 71.9 months with nivolumab + ipilimumab
  - 36.9 months with nivolumab alone
  - 19.9 months with ipilimumab alone
- Ten-year survival rates were:
  - 43% for nivolumab + ipilimumab
  - 37% for nivolumab
  - 19% for ipilimumab



- Patients with no disease progression at 3 years had a **>95% probability of being alive at 10 years**.
- Progression-free survival (PFS) at 3 years appears to be a strong predictor of long-term survival.

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Understanding Melanoma at the Genetic Level

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRAF V600E B-Raf proto-oncogene, serine/threonine kinase	**atezolizumab + cobimetinib + vemurafenib** [1] **binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **cobimetinib + vemurafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] **vemurafenib** [1, 2] BRAF inhibitor + MEK inhibitor encorafenib ipilimumab + nivolumab	**binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] cobimetinib + vemurafenib dabrafenib + MEK inhibitor encorafenib + panitumumab selumetinib vemurafenib	55
PTEN L112Q phosphatase and tensin homolog	None	**niraparib** [1] bevacizumab + olaparib	28
TP53 V274F tumor protein p53	None	None	13
SMARCB1 c.1119-41G>A SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	None	None	1

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRAF V600E B-Raf proto-oncogene, serine/threonine kinase	**atezolizumab + cobimetinib + vemurafenib** [1] **binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **cobimetinib + vemurafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] **vemurafenib** [1, 2] BRAF inhibitor + MEK inhibitor encorafenib ipilimumab + nivolumab	**binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] cobimetinib + vemurafenib dabrafenib + MEK inhibitor encorafenib + panitumumab selumetinib vemurafenib	56
CDKN2A E61, CDKN2A E69** cyclin dependent kinase inhibitor 2A	None	None	6

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
NRAS Q61R NRAS proto-oncogene, GTPase	anti-CTLA-4 + anti-PD-1 anti-PD-1 binimetinib	None	23
TP53 G245S tumor protein p53	None	None	13
KIT M541L KIT proto-oncogene, receptor tyrosine kinase	None	None	9

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

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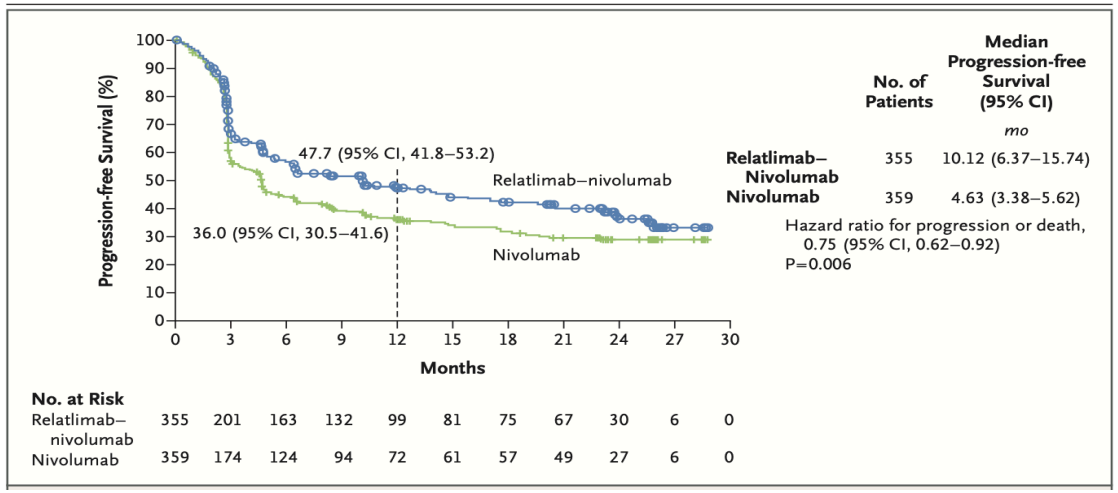
Resistance to Therapy

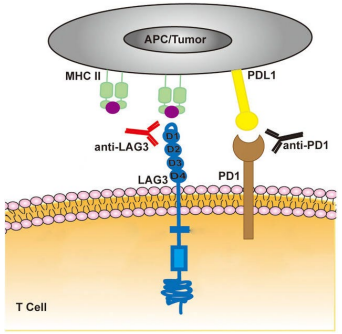
- Targeted therapies **(BRAFi/MEKi)** often lead to **acquired resistance** through MAPK pathway reactivation, mutations in NRAS/MEK, or activation of alternative pathways such as PI3K/AKT.

- The presence of **primary non-responders** to immunotherapy remains one of the most important current clinical limitations, affecting a significant proportion of patients.

- The use of combination therapies (anti-PD-1 + anti-CTLA-4, anti-PD-1 + BRAFi/MEKi) is associated with **a higher rate of immune-mediated toxicities,** grade III/IV, which limits their applicability in some cases.

Current Challenges and Future Directions





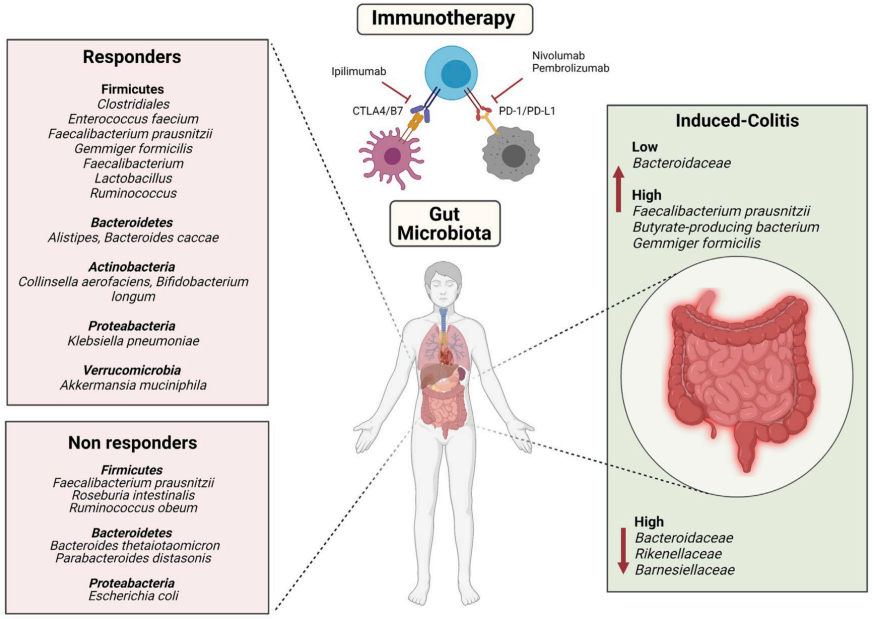
Development of New Molecules for Immunotherapy

LAG-3: expressed on T lymphocytes, it binds to MHC class II on antigen-presenting cells, leading to inhibition of T cell proliferation and activation.

- **RELATIVITY-047, phase III study – 12-month PFS:**
  - Relatlimab + Nivolumab: 47,7%
  - Nivolumab: 36,0%
- This was the first approved combination (2022) of a LAG-3 inhibitor (relatlimab) with a PD-1 inhibitor (nivolumab) for metastatic melanoma.

N Engl J Med 2022;386:24-34. DOI: 10.1056/NEJMoa2109970

Current Challenges and Future Directions

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journal homepage: www.elsevier.com/locate/pharmthera

The gut microbiome and efficacy of cancer immunotherapy

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The Link Between the Gut Microbiome and Immunotherapy Effectiveness:

- Preliminary data suggest an important relationship between the gut microbiome and the effectiveness of immunotherapy. This has led to the design and implementation of clinical studies aimed at:
  - improving the response to cancer treatments
  - identifying new predictive or prognostic biomarkers for immunotherapy.

Current Challenges and Future Directions

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Personal Neoantigen Vaccines Induce Persistent Memory T Cell Responses and Epitope Spreading in Patients with Melanoma

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A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer

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ORIGINAL RESEARCH
OPEN ACCESS

Personalized therapy with peptide-based neoantigen vaccine (EVX-01) including a novel adjuvant, CAF®09b, in patients with metastatic melanoma

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Long Synthetic Peptide Vaccines

This is an innovative method to stimulate the anti-tumor immune response in melanoma. These vaccines use long synthetic peptides that correspond to neoantigens identified in each patient's tumor.

Advantages:

- High safety and low toxicity profile
- Potential for personalization (vaccines based on tumor-specific neoantigens)
- Possibility to combine with immunotherapy (e.g., anti-PD-1/PD-L1) for superior results

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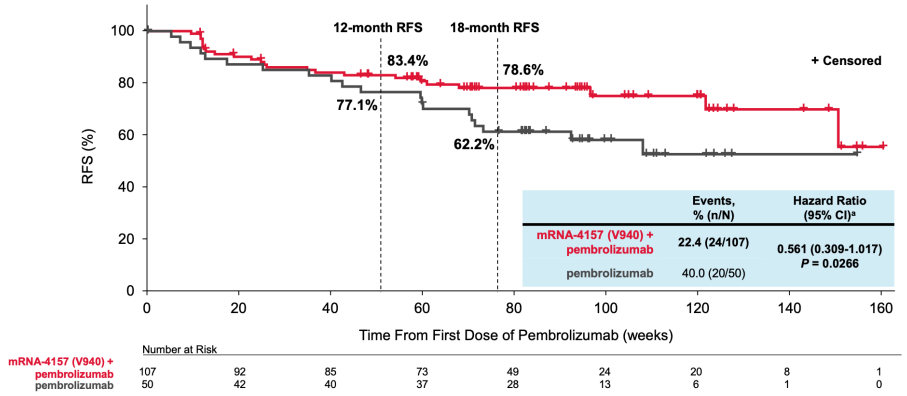
Co-funded by the European Union

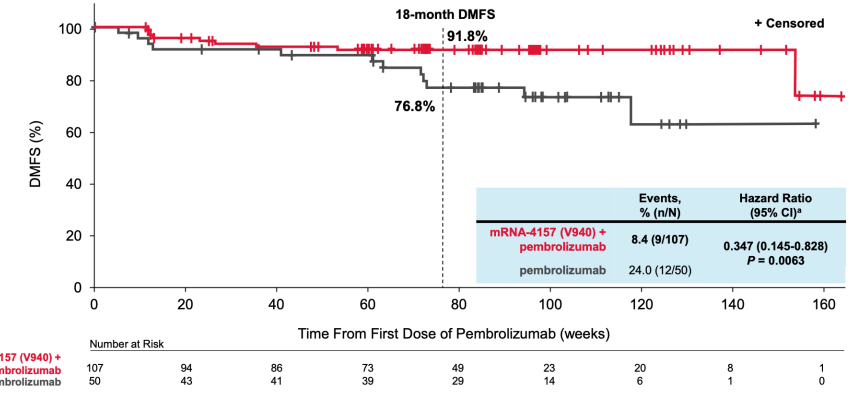
Current Challenges and Future Directions

Primary Efficacy Endpoint: RFS[1]



[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization.
1. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14-19, 2023; Orlando, FL, USA. Oral presentation CT001.

Secondary Efficacy Endpoint: DMFS



[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. At 18-months, the estimated DMFS rates were 91.8% (95% CI, 84.2-95.8) versus 76.8% (95% CI, 61.0-86.8) in the combination and monotherapy arm, respectively.

Abstract CT001: A personalized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma: Efficacy and safety results from the randomized, open-label Phase 2 mRNA-4157-P201/Keynote-942 trial FREE

Adnan Khattak; Matteo Carlino; Tarek Meniawy; George Ansstas; Theresa Medina; Matthew H. Taylor; Kevin B. Kim; Meredith McKean; Georgina V. Long; Ryan J. Sullivan; Mark Faries; Thuy Tran; Charles Cowey; Andrew Pecora; Jennifer Segar; Victoria Atkinson; Geoffrey T. Gibney; Jason Luke; Sajeve Thomas; Elizabeth Buchbinder; Peijie Hou; Lili Zhu; Tal Zaks; Michelle Brown; Praveen Aanur; Robert S. Meehan; Jeffrey S. Weber

+ Author & Article Information
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https://doi.org/10.1158/1538-7445.AM2023-CT001

Personalized Vaccines:

- **mRNA-4157-P201** is a personalized mRNA-based vaccine created for each patient, encoding up to 34 neoantigens.
- **The KEYNOTE-942 / mRNA-4157-P201** study is the first randomized trial to show a significant improvement in RFS (Recurrence-Free Survival) and DMFS (Distant Metastasis-Free Survival) using a personalized neoantigen-based therapy.
- This represents a major breakthrough in personalized oncology and paves the way for integrating mRNA vaccines into the adjuvant treatment of melanoma.

Spitalul Clinic Județean de Urgență „Pius Brînzeu" Timișoara
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Општа болница "Борђе Јовановић" Opšta bolnica "Đorđe Joanović" 1895

Conclusions

- The management of melanoma has evolved dramatically in recent years, with significant advances in surgery, targeted therapy, and immunotherapy.
- Early diagnosis, accurate staging, and appropriate surgical management remain the foundation for successful treatment.
- Sentinel lymph node biopsy is crucial for staging and guiding adjuvant therapy decisions.
- Targeted therapies and immunotherapies have greatly improved long-term survival in advanced melanoma.
- New approaches - including LAG-3 inhibitors, microbiome modulation, long peptide vaccines, and personalized mRNA vaccines - are opening new possibilities for personalized treatment.

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Thank you!
Hvala!

Spitalul Clinic Județean de Urgență „Pius Brînzeu" Timișoara

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