BIODERMA
CONGRESS **REPORTS**

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Reports written by Dr. Oriol Yélamos (Dermatologist, Spain)

OLD AND NEW BIOMARKERS IN MELANOMA

Speaker: Prof. Caroline Robert (Paris, France)
Reports written by Dr. Oriol Yélamos

We have different types of biomarkers: prognostic biomarkers, predictive biomarkers (they predict treatment response), and both prognostic and predictive biomarkers.
What you want on a biomarker is very high sensitivity and specificity with an area under the curve close to 1.
Staging (CT scans, LDH values, B-RAF status, comorbidities...) is *per se* a way to stratify our patients.
We are going to take a look at different biomarkers.

LDH (lactate dehyDr. ogenase): an old biomarker

Patients with high LDH still benefit from new therapies (immunotherapy, targeted therapies), but they have a worse outcome compared with patients with normal LDH. Why is that? We believe that high LDH means high tumor burden, but also it is related with the tumor microenvironment, metabolism and a more acid environment, which negatively impacts on oncogenic pathways.
There are 5 different isoforms of LDH, which have critical roles in metabolism. What happens is that when we ask for LDH determination on a routine blood test we are not really measuring LDH, but a reaction led by the LDH enzyme. So, Dr. Robert's group studied the different isoforms of LDH and showed that LDH1 is good, LDH4 is bad. They have shown then that **it is good to look not only if LDH is high or normal, but to assess the LDH1/LDH4 ratio**.

PD-L1 (programmed death-ligand 1)

PD-L1 is expressed in tumor cells, and induced by IFN-γ (interferon-gamma). The problem is that PD-L1 is not homogenously expressed in the tumor, and also can be expressed by cells around the tumor. Intuitively, treatment response would be better if PD-L1 expression was high; there is, however, no clear statistical association, although there's a trend.
There's a new test: PD-1/PD-L1 proximity ligation assay, which seems a promising test to predict treatment response. However, it's still not widely available and very expensive.

TMB (tumor mutation burden)

The rationale is the following: more mutations, more neoantigens and therefore better treatment response. The problem is that although there's a trend towards more response in high-TMB tumors, not all studies show this. Hence, **the importance is not the number of mutations, but how many clonal mutations are found.**

Multi-omics classifiers for immune checkpoint inhibitors (ICI) in melanoma, transcriptomic signatures

The combination of multiple molecular techniques is **the future but can't be used routinely now because of high cost.**

Liquid biopsy

Multiple studies analyze circulating tumor DNA (ctDNA). ctDNA is rarely found on the blood tests of early melanomas but is commonly found (90%) is advanced melanoma, and this is why it **can be potentially used to detect aggressive melanomas**. The problems are related to the detection technique, since nowadays **we don't know the threshold of ctDNA that is clinically relevant**. Hence, liquid biopsy nowadays is **only done for research purposes since there are no standard methods. However, this is definitely one of the most promising techniques.**

T-cell traficking cells

Some endothelial cells may be good treatment biomarkers for ICI.

Gut microbiome

Anti-PD-1 (anti programmed-cell death 1 antibodies) response is also associated with some gut germs. There will be a whole session on this topic.

Clinical early response

Patients who respond early to ICI they do very well. So, this can be a very good marker.

SPITZOID TUMORS

Speaker: Dr. Aimilios Lallas (Greece)
Report written by Dr. Oriol Yélamos

The history of spitzoid tumors has been peculiar since their initial diagnosis in the 1940's by Dr. Sophie Spitz. Initially, they were described as childhood melanomas, even though only 9% died when at that time 90% of adult melanoma patients died. Now, we know that most of these lesions are simply peculiar nevi called Spitz nevi (SN). We also know that 80% of spitz nevi (SN) disappear over time.
SN have typically 3 dermoscopic patterns: starburst pattern, dotted vessels, negative network. Also, typically they are symmetrical. However, SN can be asymmetrical and can have melanoma-specific structures. To make it more complicated, **some spitzoid melanomas look perfectly normal and symmetrical**. Also, some lesions when excised cannot be easily diagnosed as benign or malignant and are called atypical spitz tumors (AST). Luckily, 99% of patients with AST survive.
Therefore, **what is crucial is age**; **under 12 years old these lesions are typically SN, whereas 13% of spitzoid lesions over the age of 12 are melanomas**. So, a good approach with spitzoid lesions would be:

- If patient is 12 or older – excise them;
- If patient is under 12, follow lesions that are symmetrical and have a starburst pattern.

WHAT'S NEW IN ADVANCED NON-MELANOMA SKIN CANCER (NMSC)?

Speaker: Prof. Axel Hauschild (Kiel, Germany)
Report written by Dr. Oriol Yélamos

The incidence of NMSC is increasing, and obviously also this of advanced NMSC. Importantly, NMSC is not only SCC (squamous cell carcinomas) and BCC (basal cell carcinomas), but it also includes sarcomas, among others.

Advanced SCC

Before newer treatments were available – such as immunotherapy – survival was less than 3 years in advanced SCC. Fortunately, now we have **effective treatments, such as *cemiplimab* and *pembrolizumab*, with**

response rates around 30-50% in advanced tumors.
Also, there is now data in the neoadjuvant setting, showing promising results, especially if complete pathological response is achieved. We may thus not need to do further adjuvant immunotherapy in these patients with advanced SCC (similarly to what has been shown in melanoma).
Therefore, we need data and biomarkers to know which patients may benefit from adjuvant treatment after neoadjuvant treatment (this approach is called perioperative treatment -> neoadjuvant + surgery + adjuvant). **For the moment, however, data is limited, and these treatment regimens are not approved**.
There's also some data with combined treatment with *ipilimumab + nivolumab vs. nivolumab* in a very short course before surgery. Another study combined *avelumab* with *cemiplimab* prior to surgery. More data is needed to Dr. aw conclusions.
Intralesional treatments are also used in both SCC and BCC: intralesional *cemiplimab*, intralesional daromun, intralesional RP1 (an oncolytic modified herpes simplex virus (HSV-1))... Data is still preliminary but promising.

Advanced BCC

Now we are using the new EADO classification for advanced BCC (Peris K *et al*. Eur J Cancer 2019). The two classic treatments are *vismodegib* and *sonidegib*. In second line, *cemiplimab* is used in case of progression to sonic hedgehog inhibitors (SHI), or in cases of intolerance or contraindication to SHI.
A pilot study using *sonidegib* + *cemiplimab* seems promising, but no data is available yet.

Angiosarcoma

In very advanced angiosarcomas an option could be to use *ipilimumab + nivolumab*. Indeed, there's a study using this combination in Kaposi sarcoma showing a 78% response rate.

Merkel cell carcinoma (MCC)

Avelumab is the only Dr. ug approved in MCC with 40% response rate (not that great, but better than what was previously available). So, **there's room for improved treatment as well as for treatment combination**.

MEDICAL MESSAGES FOR PHOTOPROTECTION

Speakers: Dr. Bataille, Dr. Brochez, Dr. Puig, and Dr. Wunderlich
Report written by Dr. Oriol Yélamos

Dr. Bataille (Lille, France) highlighted the advances of the Euromelanoma campaigns, and emphasized the need to use intuitive messages but not aggressive messages against UV overexposure and skin cancer.
Dr. Lieve Brochez (Creil, France) has described the EADO recommendations regarding UV exposure The guidelines start by highlighting that **there's no safe sunbathing and no safe sunbed use**. In fact, the use of SPF is also linked to high UV exposure, as it gives a false feeling of protection, and intentional sun exposure induces a risk behavior which increases sun exposure. The 3rd recommendation is to **use UV protection measures when UV index is 3 and above**. This can be achieved by avoiding sun exposure, using clothing, hat with wide brim, sunglasses, and sunscreen with SPF 30-50.
Dr. Susana Puig (Barcelona, Spain) discussed messages for recreational and Prof. essional sun exposure. **There's an association between the number of skin cancers and the number of vacations days spent in the sun**. It is also important to highlight that photoprotection is not only using sunscreen but also clothing, glasses... Also, it is important that photoprotection is important to prevent skin cancer but also to prevent photoaging and to prevent hyperpigmentation. Hence, even darker skin people need to protect from the sun to avoid photoaging and hyperpigmentation. Something else that is very relevant is education also at work. **If workers are provided with sun protective tools and are told how to use them (i.e. how to apply sunscreen) their photoprotective behaviors improve.**
Dr. Katarina Wunderlich (Paris, France) talked about photoprotection habits in Europe. 10% of Europeans use sunbeds, with a gradient north-south (more sunbed used in northern countries). Also, most countries in Europe use sunscreen when exposed for more than 1 hour, except Spain, Ukraine, Moldova...). Also, **Euromelanoma**

campaigns to give information about sun protection, organizes yearly screening campaigns and promotes healthy lifestyles regarding sun exposure.

MANAGEMENT OF ACTINIC KERATOSES (AK) AND FIELD CANCERIZATION

Speakers: Prof. Fargnoli, Prof. Kandolf, Prof. Mosterd, and Dr. Kellener-Smeets
Report written by Dr. Oriol Yélamos

Actinic keratosis and field cancerization: definition and diagnosis

Prof. Maria Concetta Fargnoli (L'Aquila, Italy)
AK prevalence is 14% worldwide. AK can regress spontaneously (15-53% cases), or can progress into invasive SCC (0.1-16% cases). **AK can be classified clinical according to the Olsen classification (I to III, depending on the degree of thickness).** The concept of field cancerization is not standardized but refers to the photodamage around an area of AK. **Some features help suspect invasive SCC: Olsen grade III, dermoscopic presence of dotted, glomerular or polymorphous vessels**.

Factors that influence treatment decision

Prof. Lidija Kandolf (Belgrade, Serbia)
The main problem when treating AKs is the fact that we don't know if a flat grade I AK may progress into an invasive SCC. Since treatment, we have to discuss treatments with patients, since the treatment Since treatment goal is to prevent its progression into SCC, we have to discuss it with patients. **Weinstock *et al*. performed a study giving preventative topical *5-fluorouracil* (5-FU) with a reduction of SCC. However, this effect disappeared after 4 years, so retreatments are necessary**.
Treatment is based on the number of lesions, compliance, short course *vs.* long course, home-based treatment or office-based treatment, age and comorbidities, immunosuppression. There are also some special locations, such as the lower lip or ears, which present a high risk of SCC, and eventually may require surgery.

Non-surgical treatment options for actinic keratosis

Prof. Klara Mosterd (Maastricht, The Netherlands)
Cryotherapy is low cost and easy to perform, but it's use-dependent and is worse compared to *5-FU* or *imiquimod*. Laser treatments (CO2 or erbium ablative treatments) can work well but are expensive. Later she discussed field treatments:

- *5-FU* is the most cost-effective treatment, but has significant irritation side effects;
- *imiquimod* is a good Dr. ug if there's also BCC but be careful in transplant patients;
- *resiquimod* is a new Dr. ug but without conclusive results;
- diclofenac 3% has very good tolerability but poor efficacy;
- *tirbanibulin* is the newest Dr. ug, and has the advantage of 5 days of application;
- photodynamic therapy (PDT) is an office-based treatment which improves adherence, although it can be painful.

Treatment for AK will most likely be repeated. It is thus important to deal with side effects, which may affect future compliance.

Tailored treatment for AK patients

Dr. Nicole Kellener-Smeets (Maastricht, The Netherlands)
She discussed the latest EADV guidelines on AK management (Kaldolf *et al. JEADV 2024*):

- For single lesions, self-monitoring is an option, or they can be treated with a destructive treatment (cryotherapy, curettage) or *5-FU*.
- For multiple lesions, the most cost-effective is *5-FU*; tirbanibulin is an alternative for people who don't want local skin reactions. Also, PDT helps improve compliance.

In high risk patients (immune suppression, lots of photodamage), it's a good idea to discuss preventative measures such as oral retinoids or nicotinamide, as well as performing retreatments.

NEW THERAPIES: ANTIBODY DRUG CONJUGATES (ADC)

Speakers: Dr. Neri, Dr. Eigentler, Dr. Samimi, and Dr. de Masson
Report written by Dr. Oriol Yélamos

Principles of ADC/bispecifc antibodies

Dr. Dario Neri (Zurich, Switzerland)

Antibody Dr. ug conjugates (ADC) use Dr. ugs attached to antibodies to target tumor cells. So, it's an antibody that has a molecule/Dr. ug attached to it to exert a given function. These molecules/Dr. ugs can be anticancer Dr. ugs (chemotherapeutical agents), interleukins, cytokines... depending on the intended goal (destroy a cell, recruit lymphocytes…). It is intuitive to think that if we use molecules that target precisely the tumor, the efficacy will increase and decrease toxicity.

For melanoma, there's a promising ADC using IL2 + TNF, which is called *daromun*. ***Daromun* is used intralesionally in stage III melanoma patients with positive results** (pending to be presented at ASCO 2024). This same ADC has been used in BCC (basal cell carcinoma) and results will be published soon.

The reason why *daromun* (ADC with IL2 + TNF) is used intralesionally – instead of injecting IL2 or TNF directly – is to ensure that the molecules stay within the tumor. In other words, the presence of an antibody allows it to attach to the tumor and remain there, whereas if you inject the molecules directly, they will quickly disappear.

Another interesting therapeutic approach is the use of intralesional ADC plus other treatments such as immune checkpoint inhibitors (ICI), or targeted therapies. This increases the efficacy of ICI.

Dr. Neri also described the concept of bispecific antibodies, which are antibodies where one arm binds to the tumor cells while the other arm recruits immune cells, typically T-cells, although some other antibodies recruit NK cells.

ADC in melanoma and squamous cell carcinoma (SCC)

Dr. Thomas Eigentler (Berlin, Germany)

Glembatumumab vedotin is a new ADC for melanoma that targets glycoprotein NMB (GPNMB), a membrane protein target. It works best in BRAF-mutated patients. If a skin rash appears, it is considered a favorable prognostic sign. It has been tested in two phase II trials in advanced metastatic cutaneous melanoma, as well as in metastatic uveal melanoma. Additionally, there's another phase II trial combining it with ICI. Other tumor membrane protein targets include PMEL17 (premelanosome protein). *Camidanlumab tesirine* targets PMEL17, in a preclinical trial.

Receptor targets being studied include HER3(Human Epidermal growth factor Receptor 3), AXL-107 (a receptor tyrosine kinase), and ETBR (Endothelin B Receptor). Targets against the tumor stroma are very promising, and actually there are several trials studying an ADC with IL2+TNF (*daromun*) in melanoma and BCC (basal cell carcinoma).

For SCC (squamous cell carcinoma) there are several ADC available for the head and neck SCC but none is specifically designed for skin SCC. Promising antigens include, among others, CD44v6 (the ADC is *bivatuzumab*) and tissue factor or TF (ADC is *tisotumab vedotin*). However, some have significant toxicity.

To summarize, the ADC concept is clever but finding the right target is essential, since most targets are not specific, and toxicities are common.

ADC in Merkel cell carcinoma (MCC)

Dr. Mahtab Samimi (Tours, France)

Why is there a need for ADC in MCC? Because around 50% of MCC are resistant to antiPD-1/PD-L1 Dr. ugs.

Lorvotuzumab mertansine is a first-generation anti-CD56 antibody for MCC. It was also investigated in other carcinomas with promising preclinical results, but clinical trials led to disappointing outcomes, particularly in lung carcinomas, with significant toxicity. The company Imunogen, which was developing the Dr. ug, withDr. ew its development.

However, Dr. Samimi's group in Tours continued research with anti-CD56 Dr. ugs in MCC, showing promising results in cell lines and *in vivo* studies. Nonetheless, a major concern is the potential toxicity, since CD56 is

expressed in healthy NK (natural killer) cells. To mitigate this, they used a novel glycosylated ADC, and further research is ongoing.
Potentially, particles of the Merkel cell polyomavirus could be used as targets in MCC, but this is work in progress.

ADC in cutaneous lymphomas

Dr. Adèle de Masson (Paris, France)
Currently, only one ADC is approved for cutaneous lymphoma: *brentuximab vedotin* (BV). It is an anti-CD30 ADC coupled with the microtubule-disrupting agent MMAE (monomethyl auristatin E), which induces apoptosis by acting as a spindle poison. Approximately two-thirds of patients develop peripheral neuropathy, which in most cases is reversible. The overall response rate (ORR) is around 50% in patients with mycosis fungoides (MF), which is relatively high for this disease. Progression-free survival (PFS) is around 17 months in MF patients, so BV is now included in the treatment guidelines for MF and can serve as a bridge to bone marrow transplant in cases of extensive blood involvement.
BV has also been used in Sézary synDr. ome (SS), and there's evidence that it is effective, although SS patients were not included in the pivotal studies of BV. Like erythrodermic MF, BV can serve as a bridge to bone marrow transplant.
There are some experimental ADC in cutaneous lymphomas: anti-TRBC1, anti-CD25, anti-ICOS, anti-CD38.

THE ENTIRE INTEGUMENT AS A DIAGNOSTIC TARGET

Speakers: Dr. Gaudy-Marqueste, Dr. Monnier, Dr. Lyopiris, and Dr. Malvehy
Report written by Dr. Oriol Yélamos

2D and 3D total body photography for high risk melanoma patients: state of the art in clinical practice

Dr. Caroline Gaudy-Marqueste (Marseille, France) & Dr. Jilliana Monnier (Marseille, France)
2D total body photography (TBP) has been used for decades, but there are no established standards regarding the number of pictures needed, both macro and microscopic, and these systems are often time-consuming and operator dependent. However, a new commercially available 3D TBP device, Vectra 360, adDr. esses these issues by acquiring images quickly and in an unsupervised manner. It utilizes 96 cameras with cross-polarized light to obtain dermoscopy-like images and can reconstruct them into a 3D avatar.
Furthermore, the system can automatically identify new lesions, and with the integration of artificial intelligence (AI) algorithms, it can detect changes. However, there are limitations related to the presence of hairs, tattoos, wrinkles, and special locations such as the scalp and genital area. The main limitation is the cost of the device, as well as its size, requiring a large room for installation. There are other 2D devices which also use AI in order to obtain images in a more standard fashion, and identify new or changing lesions.
However, there are currently no prospective data regarding the performance of these technologies (whether they are better than previous TBP machines), if they are cost-efficient or not (these newer machines are substantially more expensive), and how they will impact the clinic workflow of patients with high risk for melanoma.

AI for the detection of skin cancer in dermoscopy and TBP (Total Body Photography) and dermoscopy: fiction or reality?

Dr. Konstantinos Liopyris (Athens, Greece)
AI is utilized by various TBP machines for tasks such as facial recognition, automatic image acquisition, and change identification. Additionally, some machines integrate explainable AI (xAI), which not only detects changes but also provides explanations for their relevance. However, these AI systems often experience failures and require further training.
In response to these challenges, hackathons and AI challenges among IT experts are increasingly focusing on TBP images. For example, the next ISIC challenge, a yearly competition on AI algorithms, will specifically concentrate on clinical images obtained from TBP.

Deep imaging for biomarker discovery in skin cancer

Dr. Joseph Malvehy (Barcelona, Spain)

There are now attempts to use AI and TBP to identify phenotypes that may be linked to genetic mutations which may increase the risk of melanoma. For example, we know that patients harboring a mutation in MITF (Microphtalmia-associated Transcription Factor) have nevi with discrete reticulation; if it could be identified automatically *via* images obtained with TBP, this would be great to identify high risk patients without needing necessarily to perform genetic testing. Nevertheless, research in this field is very preliminary.

Newer TBP machines also capture total body dermoscopy images, which expedite the examination process. Examples of such machines include Deviskan or Squaremind, which automatically obtain dermoscopic images. While these machines are ready for the market, they are not yet widely available.

Another way of phenotyping patients is quantifying sun damage using AI, and some work has been done using the Vectra 360 devices.

Finally, there's a collaborative project in Europe called iTOBOS (Intelligent Total Body Scanner for Early Detection of Melanoma) which integrates not only imaging data but also clinical and genetic data.

CELLULAR THERAPIES, VACCINES, CHEMICAL DR. UGS: WHAT IS THE FUTURE?

Speaker: Prof. John Haanen (Amsterdam, The Netherlands)

Report written by Dr. Oriol Yélamos

There's a need to develop new Dr. ugs for patients with PD-1-refractory melanoma. We'll discuss some of the potential treatments which can be used in this setting.

- **Tumor-infiltrating lymphocytes (TILs) therapy** is coming back again after being forgotten for several years. What is done with TILs is that we extract lymphocytes from the patient's metastases, we expand the lymphocyte population, add IL-2, and reinfuse the TILs into the patient. This process takes about 2 weeks and has and overall response rate (ORR) of 41% with TILs in monotherapy.

There is a commercially available TIL called Lifileucel.

There are new trials using TILs and combining them with anti-PD-1 Dr. ugs, IL-7...

- Another approach involves removing a metastasis, extracting tumor peptides, exposing them to denDr. itic cells, and later exposing lymphocytes, which are then reinfused into the patient. However, this approach may take 2-4 months.
- **Bispecific antibodies and T-cell engagers** work by creating an antibody that uses one arm to attach to the tumor and the other arm to stimulate a T-cell response. *Tebentafusp* is a bispecific antibody used in uveal melanoma with good results, recently approved for use.

There are multiple bispecific antibodies targeting PD-1, LAG-3 (Lymphocyte Activation Gene-3), and other checkpoints. The question remains whether these bispecific antibodies are more efficacious than single antibodies that are not bispecific. More data regarding their efficacy and safety is needed.

- **IL-2 is a molecule of great interest in melanoma**. In recent years, there was a trial studying a novel IL-2 called *bempegaldesleukin*, a pegylated IL-2 designed to activate CD8 T-lymphocytes. *Bempegaldesleukin* was investigated in combination with *nivolumab* but did not show better results than *nivolumab* alone, leading to the discontinuation of the study. However, there are numerous studies using IL-2 in other forms, such as encapsulated IL-2, IL-2 bound to CD8, IL-2 bound to the tumor microenvironment (TME), and IL-2 bound to TNF (tumor necrosis factor) in an ADC (antibody Dr. ug conjugate).
- T-VEC is a **modified oncolytic herpesvirus** and has been approved for intralesional in transit metastases in melanoma. RP-1 (vusolimogene) is another oncolytic herpesvirus with ORR of 28%.
- **mRNA vaccines** are well tolerated and have several advantages: they don't integrate into the genome, they are non-infectious, easily degradable, and inexpensive. There are numerous trials using them in melanoma, and we can expect to see exciting data in the near future with this technology.

REDUCTION OF SURGICAL INTERVENTIONS IN MELANOMA

Speaker: Dr. Alexander Eggermont (Utrecht, The Netherlands)
Report written by Dr. Oriol Yélamos

With the advent of immunotherapy, surgery will change Dr. amatically in melanoma. It already changed a lot after the MSLT-II trial (Multicenter Selective Lymphadenectomy Trial II) which showed that no benefit was obtained from complete lymph node dissection after positive sentinel lymph node biopsy (SNLB). Since then, we stopped doing complete node dissection in SLNB-positive patients.
Now also we have approval of immunotherapy for stage IIB/IIC melanomas (thick melanomas), since we know that stage IIB/IIC melanomas have a worse prognosis than stage IIIA melanomas. Therefore, it is intuitive to think that we may not perform SLNB in thick melanomas, thus reducing surgery in SLNB in about 50%.
Next developments are the advent of gene expression Prof. iling (GEP) tests performed in the primary tumor. These tests classify the patient in high risk or low risk. In patients with low risk, it may not be necessary to do anything else, whereas in high-risk patients adjuvant treatment may be need. In fact, some trials, such as the NivoMela trial (*nivolumab* + MelaGenix), classify stage II patients using the GEP from MelaGenix (a quantitative RT-PCR assay based on expression of eleven genes – 8 prognostic and 3 reference genes) into low-risk or high-risk:

- low-risk patients are simply observed,
- and high-risk patients are randomized into adjuvant therapy with *nivolumab* or observation.

The results from this trial will be very important to see whether GEPs can be used in clinical practice. Also intuitively, if GEPs work well they may end up substituting SNLB.
Additionally, the combination of clinical factors, such as age and pathological factors like Breslow index, with GEP tests appears to be the most promising approach. This integrated approach may eventually replace SLN and better identify patients at risk of relapse who may benefit from adjuvant treatment.
Regarding therapeutic complete node dissection in patients with macro metastases, surgery may also be reduced with the advent of neoadjuvant treatment. Patients with a major pathological response after neoadjuvant immunotherapy (defined as 100% necrosis or >90% necrosis) may not even need complete node dissection, as survival rates exceed 95%.
Similarly, for in-transit metastases, surgery may be reduced thanks to immunotherapy.
So, currently we are seeing how surgery is decreasing in the treatment of melanoma.

THE MICROBIOME IN IMMUNOTHERAPY

Speaker: Dr. Laurence Zitvogel (Paris, France)
Report written by Dr. Oriol Yélamos

There is numerous evidence of the importance of the gut microbiome in immunotherapy. For example, **when antibiotics are administered while taking immune checkpoint inhibitors (ICI), the efficacy of ICI decreases**. This is because antibiotics affect the diversity of bacterial and fungal microorganisms in the gut. Additionally, antibiotics downregulate the molecule Madcam-1, which is a gut immune checkpoint for cancer immune-surveillance. Thus, if serum Madcam-1 levels are low, the response to immunotherapy is worse.
In addition, in melanoma, the gut microbiota is associated with Dr. ug responses. In non-responders, stool transplantation from responders has been shown to potentially induce a response. **Fecal microbial transplantation improves response rates by 20% and circumvents resistance to PD-1 blockade in about 30% of melanoma cases.**
Why does fecal transplant work? By resetting the gut microbiome, fecal transplant restores metabolism and reprograms systemic immunity.
Additionally, fecal transplant can be used in ICI-induced colitis, with remission observed in 82-92% of cases.

Furthermore, another approach to improve ICI response is by administering probiotics such as *Clostridium butyricum*. This probiotic has been used in kidney cancer to enhance the response to ICI, suggesting its potential application in melanoma.