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New diagnostic approaches in skin cancer

This session provided an overview of new developments in diagnostic skin imaging. Of course, as the speakers pointed out, there is no need to have all these machines in a department or practice, unless you are exclusively doing research or monitoring high-risk patients. The technical feats achieved and the rate of improvement are nevertheless cause for optimism.
We are sorry we are unable to share the superb images with you, as images often speak for themselves!

Advanced 2D and 3D total body scanning for detection of melanoma
Josep Malvehy

For the past 10 years or so, some patients with atypical naevi syndromes or multiple lesions have had the opportunity to be monitored by digital dermoscopy.
The aim is to reduce the “number of lesions to be removed to avoid melanoma”. The sensitivity of the total-body photography and sequential digital dermoscopy monitoring technique is remarkable over the course of the examinations as it logically increases from less than 25% when taking the initial photos to almost 100% with subsequent monitoring.
Standardised automated solutions for 2D, 3D and/or high-resolution polarised-light total-body photography are now emerging on the market. Acquisition time is reduced.
Some stand-alone scanners that acquire a total-body image within 10 minutes also incorporate dermoscopic photos of the lesions.

Deep learning and noninvasive imaging to quantify keratinocyte atypia in a cancerisation field
Veronique del Marmol

The delineation of cancerisation fields requires the recognition of keratinocyte dysplasia/nuclear atypia (irregular, enlarged, hyperchromatic nuclei) and architectural changes (thinning of the stratum corneum), ideally using a non-invasive method that avoids the low sample sizes of traditional biopsies. Manual examination suffers from poor inter-operator reproducibility.
Confocal microscopy has already been used. LC-OCT can now also acquire images and score atypia in skin fields in vivo. As in many situations today, artificial intelligence (AI) can drastically reduce the

time factor and improve reproducibility. It has better discriminatory power and obtains better area under the curve (AUC) scores than clinicians.

Magnifying Dermoscopy (X400- x600): how far are we from histology?
Elisa Cinotti

High-magnification dermoscopy currently enables cellular details such as pigment for example to be visualised, similarly to what can be seen on confocal images. This technique can identify pigmented cells (blue-violet polymorphic melanophages, polygonal keratinocytes, dendritic melanocytes), the architecture of the dermal-epidermal junction, and vascularisation. The technique is limited in the event of hyperkeratotic or blue lesions (because they are deep!) and is always highly operator-dependent.
Some systems also enable a fluorescence light source to be added, offering surprising images of endogenous fluorescence on account of the quasi-cytological analytical quality! The future may also lie in labelled antibodies such as cetuximab 800 cW.

Non-invasive imaging and lentigo maligna surgery: where are we?
Javiera Pérez

With both LC-OCT and confocal microscopy, the virtual margin identified by the operator can be reconstructed by overlapping images, and virtual Mohs surgery can be performed to reduce the excision margins when operating on Dubreuilh's melanoma. In terms of semiology: the presence of large atypical melanocytic nuclei, pagetoid spread, and effacement of the basement membrane should cause melanoma to be suspected. Folliculotropism can also be assessed.
The speaker also mentioned the immunoMohs technique which consists of using, in addition to extemporaneous staining with **haematoxylin** and eosin, sections with rapid immunohistochemistry analysis for SOX 10, with an incubation time reduced to around 10 minutes, which enhances detection performance.

New Imaging Techniques

Overview of non-invasive skin imaging techniques: There are currently several competing methods, each of which has its own shortcomings and advantages.

Minor prerequisite:
In confocal microscopy/reflectance confocal microscopy (RCM), a composite image is studied point by point from the direct reflection of the emitted light signal. These techniques have a good definition (ability to distinguish between grey levels).

In optical coherence tomography (OCT) and line-field confocal optical coherence tomography (LC-OCT), the interference of the signal between the object and a reference mirror is analysed (either point by point with OCT or line by line with LC-OCT). There is a good resolution (ability to distinguish between two different points/pixels).
Penetration depth is limited to the papillary dermis; the resolution is 3-10 µm.

In vivo RCM
Giovanni Pellacani

What can be seen with RCM? Major and minor criteria for diagnosing melanoma: pagetoid spread, cellular and architectural atypia, and nests.
Whereas in dermoscopy, the number of lesions to be removed in order to not miss a melanoma is eight to 30, this drops to three to five in confocal microscopy.
Confocal microscopy, which has the same sensitivity (98%) and better specificity (48%), provides additional cytological information: small lesions, facial lesions (by showing folliculotropism), mucosal lesions, atypical naevi, and achromic lesions.
It eliminates the need for excision. Technical improvements in acquisition speed now allow a mosaic image to be acquired within 1 minute and a difficult naevus to be examined within a maximum of 3 minutes.
The level of evidence is high, as confirmed by a randomised study showing that it reduces unnecessary surgery by 30% (JAMA Dermatology, Effect of Reflectance Confocal Microscopy for Suspect Lesions on Diagnostic Accuracy in Melanoma, Pellacani et al 2022).
The technique saves around €15,000 per year per 100,000 inhabitants.
The technique is safe, resulting in 2% false negatives (compared with 4% for videodermoscopy with digital monitoring), which are also found to have a Breslow thickness below 0.5 mm.

Ex vivo RCM
Javiera Pérez

With ex vivo microscopy, reflectance and fluorescence can be analysed on the same image, as well as coloured images since 2018, as in HES staining. Two lasers are used: a reflectance laser, as with in vivo RCM, but with a different wavelength, which stains the high-reflectance structures in pink on the image, and a fluorescence laser which stains the DNA and therefore the nucleus in blue.
For BCCs, the sensitivity is 88% and the specificity 99% (the diagnostic traps are the sebaceous tissue and the follicles). The pitfalls lie in the technical issues of sample preparation: flattening the specimen, acquiring the whole lesion, etc.
For example, the technique enables ultra-rapid Mohs surgery to be performed: seven resectioning + reconstruction steps in just 1.5 hours!
It allows infiltrates to be seen. Even mitoses are visible!
The technique has also proven to have good sensitivity and specificity in squamous cell carcinoma.
The next step will be the integration of AI into the diagnosis.
The learning curve is three months if you have histological skills.

D-OCT
Sandra Schuh

Dynamic OCT detects moving particles such as blood cells within immobile structures, to a depth of 0.5 mm.
The five semiological criteria in dynamic OCT are as follows:
- depth (150, 300 or 500 µm),
- distribution (regular, irregular or clustered) and direction (directionless, radial (melanoma) or flowing (scars))
- distribution pattern (mottled, interlaced, branched: tree-like or bulging)
- density and diameter of the vessels (small, medium, large)
- shape (dot, cluster, corkscrew, line, curve, serpentine)

The technique is dependent on the position (sloping?) and vasodilation (e.g. rosacea, flushing, Raynaud).
The fields of application include the evaluation of ulcers, wounds, psoriasis, rosacea, and scleroderma.

In melanoma, variations in density and shape correlated with the Breslow thickness are found and are potentially discriminating with neoadjuvant treatment.
Linear images, with low density and small diameter, tend to seen with naevi, unlike with melanoma (clustered, corkscrew, serpentine).
In BCCs, the branched vessels familiar in dermoscopy are found.
In practice, dynamic OCT can identify Bowen's disease in a patient with psoriasis or detect early infiltration of squamous cell carcinomas versus keratoses.

LC-OCT
Mariano Suppa

Line-field confocal optical coherence tomography (LC-OCT) aims to overcome the technical shortcomings of OCT (deep image lacking resolution) and confocal microscopy (precise but shallow image), while maintaining a high resolution and good penetration. It allows us to see down to the dermis (penetration thickness of 2 to 3 mm, with a resolution of 6 microns). We now obtain both horizontal and vertical images in real time (with an associated dermoscopic camera enabling us to find our way around), allowing for 3D reconstruction.
The applications are as follows: recognition of cellular atypia, keratinocyte maturation, collagen fibre organisation and vessel morphology.
Up to now, the technique has proven useful for non-melanocytic lesions, especially BCC lesions (3% to 12% more accurate than dermoscopy, depending on the study): the signs are the shiny ring of collagen, the mille-feuille appearance of the nodules, and clefts. The technique can distinguish between subtypes in correlation with histology (superficial versus invasive with specificity of 96% and sensitivity of 77%).
It can distinguish between BCCs and dermal naevi (wave-like, undulating or regular appearance), sebaceous hyperplasia (granular or lobular appearance), actinic keratoses and squamous cell carcinomas. It can also be used for monitoring after non-invasive treatment.
In the event of keratinocytic lesions, the extent of keratinocytic atypia (keratosis versus Bowen's disease) and the integrity of the basal layer (in situ versus invasive) can be assessed.
The data still need to be consolidated for melanocytic lesions.
Due to recent contributions of AI, we can expect it may be used to quickly screen for atypia, particularly in the case of field cancerisation, identify infiltrating lobules, and review preoperative excision margins.
The next version includes a handpiece allowing for a dermoscopic overview of the lesion with automatic recognition of the beam's position within it during the examination.

New technologies: what is in the pipeline of innovation?
Pascale Guitera

Reflectance confocal microscopy (RCM) can be used to visualise vascularisation and leukocyte trafficking in a tumour and its microenvironment. Dr Sahu from Sloan Kettering is working to distinguish between "hot", vascularised tumours that are likely to respond to treatment because they are immunoactive, and cold, non-responding tumours.
In confocal microscopy, ENT specialists already use topical biomarkers, which allow malignant cells to be identified by fluorescence. This system is available in vivo, but for the time being it is not applicable to dermatology. However, ex vivo, the technique is used in research for basal cell carcinoma (PARP-1 biomarker).

Next, I chose to present the symposium on new diagnostic approaches and the satellite symposium of the DAMAE laboratory because the topics and speakers were complementary, so I would thus avoid redundancy.

LC-OCT, the new imaging frontier in skin cancer?

The first presentation was redundant with the previous ones:
Diagnostic performance of LC-OCT for BCC: new data from prospective and meta analytic studies. Patient management
Mariano Suppa

The role of LC-OCT in BCC margin delineation – the one-stop-shop approach
Julia Welzel

Currently, the non-invasive techniques that can be used to reduce the number of steps in Mohs surgery for BCC are not applicable in daily practice; this includes both OCT, where the resolution is not high enough and the technique is too time-consuming, and RCM. Therefore, the naked eye, dermoscopy and an additional margin of 2 mm can be used as much as possible, and then the specimen can be examined ex vivo with confocal microscopy, with varying degrees of fluorescence, before a conventional histological confirmation.
With LC-OCT, we can either use an ex vivo machine, which reconstructs a mosaic of the specimen by reflectance imaging (with a resolution comparable to that of RCM), or carry out a scan with an in vivo machine, locating the margins, ideally with the help of AI, and use integrated dermoscopy to locate the lesion.
The technique does not, of course, provide information on the deep margin (limit of the technique: maximum 400 µm), unless this is examined ex vivo after excision.

LC-OCT of melanocytic lesions – practical steps for routine diagnosis of equivocal melanocytic lesions
Javiera Perez-Anker

The data presented are currently being published (article under review). They are therefore preliminary.
The essential criteria for the diagnosis of malignant melanocytic lesions with LC-OCT could be: the presence of multiple pagetoid cells (more than 10, round or dendritic), cytological atypia and irregular epidermal architecture (these first criteria being the two found as significant after multivariate logistic regression), loss of continuity/effacement of the dermal-epidermal junction, and clefting (a term currently used to describe the dissociation, detachment or loss of cohesiveness of melanocytes within malignant epidermal nests, different from clefting or retraction spaces in BCCs). Other significant criteria are also found, including irregular honeycombed epidermal areas, a heterogeneous 3D cross-sectional distribution of the epidermal ridges and dermal papillae, and bridging of the ridges by adjoining nests.
By correlating dermoscopy and LC-OCT images (vertical and horizontal), it is observed that the dots and globules often correspond to ridge bridging, invasion of the ridges by abnormal nests, or shadowing of deeper dermal nests.
To properly explore a melanocytic lesion, the idea is to first perform a vertical scan of the entire lesion, then acquire 3D images of the regions of interest, with contrast enhancement to highlight any cytological atypia.

Controversies surrounding non-melanocytic tumours

DTT Classifications: Is it a progress?
Ketty Peris and Peter Mohr

Objectively evaluating and grading basal cell carcinoma can still be a daily challenge. The TNM classification is not suited to basal cell carcinoma because lymph node and metastatic forms are exceptional, and the prognosis remains local-regional.
The term locally advanced basal cell carcinoma (LaBCC) is widely used to refer to heterogeneous situations of invasive BCC, deemed inoperable or requiring mutilating surgery, as well as historical and/or neglected forms.
To break down therapeutically challenging BCC situations, these have been divided into five clusters:
IIa Common BCCs whose management is complicated by the tumour (poorly delimited, difficult area, recurrence) or the patient (co-morbidities, general condition, compliance with treatment): the expected surgical results are good provided that a therapeutic alliance is established
IIb Multiple or numerous complex, sporadic BCCs or Gorlin syndrome
IIIa Locally extensive or invasive BCCs in a non-functional, non-critical area: treatment is feasible without loss of function
IIIb Locally advanced BCCs in a critical functional area: curative surgical treatment is possible at the cost of a functional or aesthetic sacrifice
IIIc Extensive historical or invasive extracutaneous BCCs: a surgical solution is not feasible
These clusters are the result of a mathematical analysis, not a comparison of conflicting points of view. The data are from real life and enable relevant categories to be identified for practical application.
This breakdown has no prognostic value. It is from a multidisciplinary consensus document; it allows for the creation of homogeneous groups of patients and subsequently facilitates the evaluation of therapies.
Fortunately, these situations represent a minority of cases (less than 10%); they often have to be managed in multidisciplinary meetings.
The current shortage of medical professionals demonstrates the importance of identifying which cases require a multidisciplinary specialist approach.

Should we stop immunotherapy after achieving a complete response?
Paolo Bossi and Ines Pires da Silva

When should immunotherapy be stopped for non-melanocytic tumours?

To form an opinion, the experts analysed various data from the literature.
- Using progression-free survival results in lung cancer (NSCLC):
o Patients with a complete (and/or metabolic) response who stop immunotherapy after at least 18 months of treatment have a progression-free survival rate of 80% at 12 months
o Patients who stop due to toxicity have poorer PFS
o This is also true for patients who stop after less than 12 months of treatment
- In melanoma, whether patients have a complete response, partial response or simple stability with conventional imaging, it is the metabolic response that determines subsequent progression
- The long-term data of patients treated with cemiplimab should also be considered: the median time to complete response is 11 months, and the complete response rate continues to increase after one to two years of treatment
- After immunotherapy is stopped due to a complete response, when patients progress again and resume immunotherapy, responses are again achieved in most cases (SD 17%, PR 33% or CR 33%).
Of course, we should also keep in mind that some patients will relapse when treatment is stopped, as seen in the following:

Merkel cell carcinoma: around ¼ of patients with a complete response relapse upon discontinuation, whether after avelumab in the JAVELIN Merkel 200 study (among the 10 complete responses (CR plus six months of treatment followed by discontinuation), two relapsed on discontinuation), after pembrolizumab in KEYNOTE 017 (four of the 15 patients), or in international retrospective studies (where the response rate after rechallenge with anti-PD-1 therapy varied from 63% (Weppler et al) to 33% (Wo et al)).
Squamous cell carcinoma: a very small percentage of complete responders to cemiplimab relapse after stopping treatment, which has often lasted more than two years: from 2% (Hober et al) to 5% (Mo et al, with no response for these two patients on resuming treatment).
To summarise, in these two indications, the rate of progression after stopping immunotherapy is 1 to 5% in squamous cell carcinoma and 20 to 27% in Merkel cell carcinoma, and the duration of treatment required after obtaining a complete response seems to be around two years. Lastly, the ORR after rechallenge with anti-PD-(L)1 therapy ranges from 33 to 63% in Merkel cell carcinoma.

Should every patient with basal cell and squamous cell carcinoma be treated?
Richard Scolyer and Iris Zalaudek

Can we refrain from treating certain patients with squamous cell and basal cell carcinoma? Of course, this concerns elderly patients, whom we all hesitate to over-treat at some point. This controversy does not provide a clear-cut answer to these complex situations.
The authors emphasise that delaying or refraining from treatment in the elderly may seem appealing for many patients and doctors, but it often means taking the risk of costly or incurable situations later on, which may be detrimental to quality of life.
The idea is to treat the patient in a way that is in line with the oncogeriatric assessment, using the right approach at the right time, sometimes favouring non-surgical solutions.

Adjuvant therapy in melanoma

Adjuvant therapy in melanoma: a long story started 25 years ago
Alexander Eggermont

Immunotherapy has approximately the same effects in adjuvant and metastatic situations, with anti-PD-1 and anti-CTLA-4 combination therapy coming in at the top of the list, followed by anti-PD-1 therapy alone, and then anti-BRAF/anti-MEK combination therapies.
In adjuvant situations, the respective HRs RFS (recurrence-free survival) versus a placebo are 0.75 for ipilimumab, 0.57 for pembrolizumab (+-0.5) and 0.47 (+-0.5) for dabrafenib/trametinib; versus ipilimumab, the HR is 0.65 (+-0.5) for nivolumab (also including resected Stage 4).
EORTC 18071, high-dose ipilimumab vs a placebo: impact found to be the same at 10 years on recurrence-free survival, overall survival and distant metastasis-free survival, HR ≈ 0.75.
Anti-BRAF/anti-MEK combination therapy showing efficacy at five years in terms of recurrence-free survival and distant metastasis-free survival.
Checkmate 238, nivolumab compared with ipilimumab 10 mg/kg (standard of care in the US): HR RFS 0.71 (0.6-0.86) at two years.
For these latter adjuvant studies, in the absence of a cross-over study, it becomes very difficult to obtain overall survival results, as the compared treatments are used in subsequent lines of therapy, which distorts the assessment.
With Keynote 054, pembrolizumab versus a placebo: this time, we have the cross-over study to answer the following question: are there benefits of adjuvant treatment, or can we only treat at recurrence?

HR DMFS at 3.5 years of 0.6, and recurrence-free survival at three years of 63.7% with pembrolizumab vs 44.1% for the placebo with an HR of 0.56.
The HRs RFS remain homogeneous in the Stage III subgroups (A, B and C, AJCC 7) and significant regardless of the PD-L1 status and BRAF status, with a greater benefit in BRAF-mutated patients (25% absolute benefit vs 15.3% in BRAF wild-type disease, to be compared with the 20% obtained with dabrafenib/trametinib in COMBI-AD).
Five-year analysis of EORTC 1325, pembrolizumab vs a placebo as adjuvant therapy: same efficacy impact on both RFS and DMFS and also after cross-over in those who had relapsed with the placebo. The overall survival results are expected in 2026.
Experiencing immune-induced adverse events during anti-PD-1 adjuvant treatment significantly leads to progression-free survival that is around 40% longer than when no side effects occur – should they be considered as a biomarker correlated with efficacy?
The combination of ipilimumab and nivolumab has also been evaluated as adjuvant therapy in two studies.
IMMUNED study, adjuvant therapy in resected Stage 4, nivolumab 1 ipilimumab 3 vs nivolumab 3 mg vs a placebo, showing superiority of the ipilimumab/nivolumab combination over the anti-PD-1 treatment alone.
Checkmate 915, adjuvant therapy with nivolumab 240 every two weeks/ipilimumab 1 mg/kg every six weeks (i.e. a dose of ipilimumab six times lower than ipilimumab 3 mg/kg every three weeks) vs nivolumab 480 every four weeks in Stage IIB2C to IV: this negative study, probably due to the very low dose in Keynote 716 – a double-blind study of pembrolizumab vs a placebo in IIb-c – showed significant efficacy of pembrolizumab in terms of both recurrence-free survival and distant recurrence-free survival with an HR of 0.6.
Checkmate 76k IIb IIc also showed significantly better recurrence-free survival with nivolumab than with the placebo with an HR of 0.42, which will lead to probable authorisation this summer.
For the future: The challenge will be to identify Stage I/IIA patients with micrometastatic disease, beyond the current AJCC classification, who are at higher risk of relapse and who will benefit from adjuvant immunotherapy at any stage, without the need for a sentinel node biopsy.
Thanks to the clinicopathologic and gene expression profile (CP-GEP), three risk levels for recurrence-free survival, specific overall survival and distant recurrence-free survival have been identified: patients with a low risk of recurrence (negative sentinel node, low-risk CP-GEP), high-risk patients (positive sentinel node, high-risk CP-GEP) and an intermediate category, grouping a positive sentinel node + low-risk GEP and a negative sentinel node + high-risk CP-GEP.
Nivomela: it is testing the relevance of adjuvant therapy in high-risk Stage II patients, conditional on the result of the Melagenix test (simple observation for low-risk patients, nivolumab 480 every four weeks for 12 months or observation for high-risk patients, then follow-up for at least five years); the results are expected for early next year.
With neoadjuvant therapy, by stimulating many more Lt clones through the existing tumour, we are moving towards more treatment, shorter treatment cycles and less surgery.

Neoadjuvant treatment performs better than adjuvant therapy: Phase 2 SWOG S1801 trial with a plateau trend from 24 months (adjuvant pembrolizumab 18 x 200 vs pembrolizumab 3 + 15 x 200 every three weeks, HR 0.58 at 36 months): three doses before surgery reduces the occurrence of subsequent carcinological events by an additional 40% or so.

The pooled analysis of neoadjuvant therapy in Stage III showed superiority of PD-1 or PD-1 CTLA-4 immunotherapy vs dabrafenib/trametinib since only after immunotherapy were there almost no subsequent carcinological events, with a three-year follow-up period for patients with even a partial histological response.
The PRADO study recommended simple monitoring with no additional dissection or adjuvant immunotherapy for the 60% of IIIB/C patients with a complete or near-complete histological response

after two neoadjuvant infusions of ipilimumab 1 mg/kg + nivolumab 3 mg/kg. Currently, the initial data at three years show only two recurrences among the first 99 patients.
Studying the interferon signature after neoadjuvant therapy helps identify good responders, for whom less toxic monotherapy can be used, while more toxic but more effective dual immunotherapies can be reserved for poor responders.

Today, can we cure patients with adjuvant therapies or just prolong DFS?
Axel Hauschild

In oncology, cure is still synonymous with incongruity.
To express the notion of cure: it is more appropriate to refer to long-term recurrence-free survival than to long-term overall survival. In 2020, Ugurel et al. analysed survival data from significant randomised studies with checkpoint inhibitors and targeted therapies, and found a 17% difference between recurrence-free survival and overall survival, which therefore includes those patients who have relapsed, have been treated with a new line of therapy, and are still alive.

So who are these patients who do not relapse?
30% of Stage IV patients (in Checkmate 067) have not relapsed after seven years. For Stages II/III, it can be concluded from the five-year RFS and DMFS analyses of COMBI AD, CM 238 and KN-054 that the risk of recurrence is reduced by 40 to 50% with treatment.
Some studies are able to propose an estimated recovery rate, based on recurrence-free survival figures (and not overall survival figures, which are impacted by all treatments potentially received after the treatment studied): in COMBI-AD, it was 17%, with recurrence-free survival reaching a plateau after three years.
A pitfall when analysing the results of adjuvant treatment studies lies in the post-protocol treatments proposed in cases of recurrence.
It is necessary to determine whether the proposed treatment may have contributed to the difference in overall survival: by analysing progression-free survival over time, after recurrence, and for each treatment.

Another therapeutic threshold has recently been reached.
For melanoma, the number of patients to be treated to avoid an oncological event is finally being published!
If we have treatment with an HR of 0.5, we must treat eight Stage IIb patients and six Stage IIc patients to avoid one death by melanoma over a period of 10 years. These figures (also available for an HR of 0.75) have been calculated from COMBI-AD, which is the only study for which a direct comparison is available.
It is therefore necessary to explain to patients when proposing adjuvant treatment that we are currently over-treating certain patients unnecessarily, continue undertaking research to improve genetic profiling, and identify predictive markers of the occurrence of irreversible side effects; in the interests of transparency, it may also be necessary to calculate the number of patients needed to harm (NNH).

Blood and tissue gene expression-profiling and implications for adjuvant therapy in melanoma
Susana Puig

Predictive biomarkers are being developed to identify: responders, patients with a poor prognosis, patients with a high risk of serious side effects, and patients with a high risk of developing certain diseases.
Initially in melanoma, circulating S100 was studied, compared with tyrosinase, which is not present in the blood and is therefore presumed to come from circulating melanoma cells.

At present, we analyse free circulating nuclear or mitochondrial DNA, which has a different size depending on whether it is derived from apoptosis (160-188 bp) or from cell necrosis (>10,000 bp), and in which somatic mutations such as BRAF or NRAS can be identified.
This can be collected from circulating blood/a liquid biopsy, for early diagnosis or analysis of residual disease, choice of treatment, monitoring of treatment efficacy, emergence of a resistant predominant clone, etc.
As is already the case in other tumours (breast, lung, colon, pancreas), searching for mutations in total plasma DNA (a recently validated marker associated with tumour burden) helps predict survival in melanoma.
All mutations common in The Cancer Genome Atlas (TCGA) are potential candidates.
The BRAF mutation is widely present in many naevi, but there are very few cases of false positives (patients with circulating BRAF and without melanoma). The test has good sensitivity (detects 71% of Stage 4 patients).
In patients with congenital naevi, which frequently contain the NRAS mutation, this mutation is not usually found in the circulating blood and can therefore be used as a marker for NRAS-mutant melanoma.
The results of analyses of circulating free DNA in serum from seroma drainage, or from the intraoperative lavage of surgical cavities with sentinel node biopsies, correlate with the histological result of the sentinel node biopsy.
Different gene expression profiles have been identified: highly immunogenic profiles (high immune) associated with a better prognosis versus profiles with a poorer prognosis (high MITF): associated with pigmentation and proliferation, higher Breslow thickness, and more mitoses.
Tests are now available that analyse certain key genes in a simplified manner.
In the example presented by Dr Puig, 88 patients with a negative sentinel node were classified as high- or low-risk patients, with good predictive values (both negative and positive).
By analysing the expression profile of these 31 genes, and incorporating clinical and histological criteria (thickness, ulceration, age, mitoses), predictive estimates of sentinel node positivity can now be established, followed by DFS, DMFS and MSS, adjusted where appropriate to the sentinel node result. The data are currently retrospective. The Phase III prospective randomised Nivomela study will hopefully show whether this approach can lead to a reduction in the number of sentinel node biopsies and the selection of patients who will benefit from adjuvant therapy.
Prognostic markers that can be used less expensively in immunohistochemistry are also being discovered: AMBRA1 (a protein that regulates autophagy) and loricrin, a marker of epidermal terminal differentiation. Their joint decrease or loss in the peri-tumoural environment is associated with an increased risk of metastatic spread in non-ulcerated Stage I and II patients, independent of the Breslow thickness. This value also helps identify some melanomas with a high Breslow thickness but an apparently lower metastatic risk. It also seems that AMBRA1 can be used to predict the response to anti-PD-1 therapy.

The concept of rechallenge with adjuvant therapy
Brigitte Dréno

It is important to distinguish between retreatment (treatment at recurrence with the same molecule that was used in adjuvant therapy), rechallenge (new use at progression of a previously beneficial molecule for an earlier metastatic line) and escalation (addition of an additional molecule at progression).
It should be noted that anti-PD-1 drugs are authorised for use as adjuvant therapy for resected Stage III lymph node and Stage IV melanoma. Ipilimumab is authorised by the FDA for resected Stage III, at 10 mg for four induction doses and then every 12 weeks for a maximum period of three years.
There are few publications on post-adjuvant therapy. One found two long-lasting responses among five patients retreated with an anti-PD-1 drug after adjuvant treatment. The second studied the 12% of

patients who progressed after anti-PD-1 adjuvant therapy: one response (13%) among the 18% treated with ipilimumab, and 13 (36%) of the 36 patients treated with anti-PD-1 + ipilimumab combination therapy. The third looked at the treatments received by 20 patients who progressed after adjuvant anti-PD-1 therapy: two patients who relapsed at five and 13 months after the end of adjuvant therapy responded for five to 10 months to retreatment with anti-PD-1 therapy; two patients treated with ipilimumab at recurrence responded, as did nine of the 10 patients treated with anti-BRAF + anti-MEK therapy. The fourth and final study investigated patients from Keynote 054 who relapsed six months or more after the end of adjuvant pembrolizumab: of these 47 patients, 43% were rechallenged with pembrolizumab. Their response and PFS rates were lower than those of treatment-naive patients, and the toxicity profiles were comparable.
The mechanisms of resistance to anti-PD-1 drugs include mutations in JAK ½ that decrease the response to interferon, alterations in antigen presentation, polarisation towards an immunosuppressive microenvironment, changes in the gut microbiota, and inflammatory metabolic pathways.
With regard to targeted therapies, only the dabrafenib + trametinib combination is approved for Stage III melanoma. For these molecules, we have information from patients from the BRIM8 and COMBI-AD studies. Of the 85 patients who relapsed, 78% did so after adjuvant therapy, with no difference being noted in median overall survival between patients who relapsed during or after adjuvant therapy. Patients were treated with the combination of ipilimumab + nivolumab, with a two-year survival rate of 92%, with an anti-PD-1 drug +- another therapy with an OS of 84%, with targeted therapies with an OS of 49%, and with ipilimumab with an OS of 45%.

These data suggest that retreatment with anti-PD-1 therapy should only be proposed for patients who relapse at least six months after the end of adjuvant immunotherapy. We will wait for the results of the rechallenge cohort planned in KN 716 (for Stages IIB/C) and for future trials testing nivolumab + relatlimab (anti-LAG3 Ig).

One solution could be therapeutic escalation with: TILs, intra-tumour treatment with oncolytic viruses or TLR9 agonists, multiple-receptor TKIs, histone deacetylase inhibitors or a faecal transplant.

What is the role of adjuvant radiotherapy in melanoma in the era of systemic therapy?
Alessandro Di Stefani

Adjuvant radiotherapy is mainly used to ensure prolonged local control of the irradiation field.
It has a role to play in cases of mucosal, naso-oral, genital and anorectal melanomas, in order to obtain local control, but has no efficacy in terms of overall survival.
For cutaneous melanomas, the aim of adjuvant radiotherapy is also to achieve local control (nearly 80% at five years), always without any improvement in overall survival; however, it is seldom proposed (it is mainly reserved for non-reoperable facial melanoma and desmoplastic forms).
The situation is similar when irradiating a lymph node area after dissection, especially in the event of capsular rupture, with the risk of lymphoedema of the limb where applicable.
We should bear in mind that if radiotherapy is considered concomitantly with BRAF inhibitor treatments, the latter must be discontinued at least three days beforehand and also after irradiation if fractionation is reduced to 1 with stereotaxis because of radiosensitisation.
In combination with immunotherapies, radiotherapy theoretically promotes a T-mediated response and potentially causes an abscopal (outside the field) effect.
The timing of irradiation also varies. It may be undertaken sequentially (neoadjuvant or adjuvant) or concomitantly (to achieve better local control).
We speak of post-escape radiotherapy when it is combined with immunotherapy after escape and recurrence, and of peri-induction radiotherapy if it is performed during the induction phase of immunotherapy.

Most of the data on combination with immunotherapy concern irradiation in metastatic situations; very few concern the irradiation of locally advanced stages, and almost no data relate to adjuvant treatment.
Only one retrospective study compared the three-year recurrence and overall survival rates of patients treated after an adenoidectomy with systemic therapy, with or without radiotherapy, and found no significant results.
Radiotherapy therefore plays a marginal role in the adjuvant treatment of melanoma, with certain indications to be discussed on a case-by-case basis at a multidisciplinary meeting.

Controversies in melanoma management

Do we need a new melanoma classification?
Yes: Claus Garbe
No: Jeffrey E. Gershenwald

The AJCC system assess the various stages of the disease (c: clinical, p: histological, yc or yp: post-therapeutic, r: at recurrence, a: at autopsy). The current AJCC system is the eighth edition, and in some respects it is out of step with the latest therapeutic discoveries and breakthroughs.
It is based on data from the International Melanoma Database and Discovery Platform (IMDDP) cohort (10 centres in Europe, the US and Australia collecting melanoma-specific survival information for Stage I to III patients from 1998 to 2013). It suffers from the under-reporting of specific deaths from melanoma, as this information is hard to collect. With current treatments, Stage IV survival curves have, in reality, increased significantly, rising from 5 to 50% at five years, for example since 2008, in particular the survival of patients with brain metastases.
A disadvantage of the current classification also lies in the fact that it is not easy to use in clinical settings, because it does not use digital apps for example.
Incorporating the new biomarkers that are available would make it more relevant, but none are currently validated or widely accepted.
Any changes made should maintain the universality of the classifications, which is their main asset.

Is adjuvant treatment of melanoma still needed?
Yes: Axel Hauschild
No: Alexander Menzies

Yes: if we look at the five-year survival curves of Stage III subgroups (A to D), the 25% mortality rate at best always justifies the proposal of adjuvant treatment.
None of the quality of life studies in the five pilot trials showed any negative impact of adjuvant therapy, despite the occurrence of side effects (3% of which were severe, unpredictable and sometimes irreversible, such as cardiological and neurological effects) and 15% treatment stoppages.
An indirect analysis of overall survival rates (from CK238 and EORTC 18071) showed 35% improvement with nivolumab versus the placebo and 43% improvement at three years with dabrafenib + trametinib combination therapy.
In real life, 75% of patients accept the risks associated with adjuvant therapy.

In reality, however, treatment only benefits around one in five patients, if we exclude: treated patients who still relapse and those who would never have relapsed in any event, for example.
Adjuvant treatment is given after lymph node surgery in Stage III patients, which does not prevent the risk of lymphoedema as it does not currently eliminate the need for dissection. The hope with

neoadjuvant therapy is to reduce or eliminate the need for surgery after achieving a response to initial immunotherapy.
We hope to exclude patients for whom adjuvant therapy is not appropriate by using immunohistochemical signatures, for example: patients who are negative for example for the immunoprint analysis have an estimated recurrence-free survival rate of 96% at 10 years.
However, we do not currently know how to identify patients who will benefit from adjuvant treatment.
The 20% early relapsers (those who relapse before they have had time to start adjuvant therapy after surgery) are de facto non-candidates.
The current indications for adjuvant therapy also leave out all the silent killers represented by thin melanomas with a high risk of recurrence, which have not been identified to date: 63% of current melanoma-related deaths were initially stage I melanomas!

Long-Term Management Strategy for LaBCC

A practical walk-through on the management of therapy with sonidegib for the treatment of LaBCC

First-line systemic treatment of LaBCC
Nicole Basset-Seguin

The majority of sporadic BCCs result from mutations in PTCH; a smaller number are due to SMO mutations. Two hedgehog pathway inhibitors are currently available. They bind to Smoothened to block proliferation.
Sonidegib is highly lipophilic. Skin concentrations are six times higher than plasma concentrations.
At 200 mg/day, the overall response rate is good (and confirmed in real life), at around 60%, with a 20% complete response rate. 1.5% of patients progress.
After a response, the longer the treatment can be continued, the longer-lasting the response will be upon stoppage. 60% of patients with a complete response relapse within three years (primarily when there is involvement of the trunk or limbs), and 85% respond completely again after resuming treatment.
35% of patients (and 40% of those with Gorlin syndrome) still have not relapsed three years after stopping.
In complete responders, a study is under way to test maintenance with two out of four weeks reduced to one out of three weeks in the event of a toxic response to treatment.
Another trial is investigating the effects of adjuvant radiotherapy following a complete response.
For partial responders, in real life, the median treatment period is seven months, with one third of patients stopping to undergo surgery when this is made possible by the partial response.
In practice and without any statistical evidence at present, the speakers try to treat small tumours with a complete response for at least six months in total; they treat the most massive tumours for 12 months. Obviously, this depends on the patient’s tolerance.

Optimal management of HHI therapy
Susana Puig

The effects of hedgehog inhibitors are well known: they include muscle spasms (30%), dysgeusia (15%), alopecia (5%), nausea, diarrhoea, and in the longer term, weight loss and fatigue.
In the event of toxicity with sonidegib, alternate-day dosing is expected and authorised and is probably preferable to therapeutic breaks (which need to be long – at least two to three months to be effective), given the high skin concentration, with comparable responses to the full dose. Beware of CYP3A4-inhibiting drugs such as everolimus, with which a dose reduction (directly this time) should

also be considered. Rotation may also be an option, both to reduce the side effects and to regain efficacy.
However, the quality of life of patients does not seem to be affected over time, and will be all the less so if they are supported and informed of the expected effects and if solutions are offered to combat these inconveniences (nutritional consultation and adapted recipes, hydration, twice-daily stretching, no sport in the evening to avoid night cramps, socio-aesthetic advice, minoxidil at three months of treatment).
The issue of teratogenicity is probably wrongly less discussed with elderly male patients.
BCCs that occur in patients with Gorlin syndrome have a lower mutation load and fewer UV-induced mutations; they have greater genomic stability, fewer SMO mutations and therefore lower intrinsic resistance to hedgehog inhibitors. For these patients, it is therefore all the more important to emphasise the need for excellent photoprotection to avoid UV damage that could increase the rate of resistance to treatment.

LaBCC treatment algorithm in practice
Ketty Peris

Second-line immunotherapy can currently be discussed despite low CD8 T-cell infiltration into tumours. The Phase 2 study testing cemiplimab reported an overall response rate of 30% including 9% complete responses.
The issue of post-hedgehog inhibitor (HHI) surgical margins is not clear-cut. Currently, the visible rather than the initial margins are often taken.

Melanocytic naevi: biology and management

Atypical naevi: not just a skin phenotype
Veronique Bataille

Genome decoding is still in its infancy. Our speaker’s observations provided attractive genetic responses to existing phenotypic observations.
Does gender have an impact on naevi?
In women, certain loci have been found to be associated with the number of naevi and the risk of melanoma; they also influence the location of the naevi (legs vs arms vs head and neck vs torso). In Turner syndrome, there are many naevi on the trunk and there is a higher risk of melanoma.
The number of naevi is a major risk factor for melanoma, although of course, not all patients with atypical naevi syndrome will develop melanoma. The risk also increases when there is a family history of melanoma, and also of other cancers such as pancreatic, brain and kidney cancer. The NHS now offers genome sequencing for patients.
Telomeres are the non-coding structures at the ends of each chromosome. Their length at birth and the rate at which they shorten with age vary from one individual to the next. Short telomeres are associated with a risk of heart disease and chronic illness. Several studies suggest that increasing numbers of naevi are associated with high age-adjusted telomere length, good spinal mineralisation, and better cognitive function. Melanocytes and neurons may share common senescence pathways.

Atypical naevi and early melanoma: balancing between under- and over-diagnosis
Raymond L. Barnhill

Is melanoma over-diagnosed by pathologists, which could explain the continuous and growing increase in the incidence of melanoma observed since 1975, whereas mortality has fortunately

stagnated? This increase could be due to over-diagnosis (a higher rate of screening, more biopsies, more permissive histological diagnostic criteria) or a more effective therapeutic attitude.
It is important to be aware that for melanocytic lesions with moderate-severe atypia and thin melanomas up to 0.8 mm, reproducibility is poor (inter-operator 25 to 45% between expert dermatological-anatomical pathologists and intra-operator 35 to 63%!), more particularly for the category of naevi with moderate atypia.
Particularly delicate lesions include atypical naevi, dysplastic naevi, melanocytomas, and atypical Spitz tumours.
Doubt should be accepted, and certain criteria should not be dogmatically misinterpreted: for example, worrying pagetoid spread, involving the entire surface of the epidermis, is a classic and non-pejorative observation in pigmented spindle cell naevi where it is associated with a well-preserved peripheral arresting nest, symmetry, and sharp delineation.
What currently appears to be strictly within the domain of pathologists could, with non-invasive imaging, become a task for dermatologists who will also have to reason in this way!
The new MPATH-DX V2.0 classification will be included in the 5th edition of the WHO classification. The main change is the reclassification of the three categories of atypical naevi – mild, moderate and severe atypia – into two groups: mild (no need for revision surgery) or severe.

Diagnosis and management of atypical Spitz tumours
Daniela Massi

To diagnose a Spitz tumour, the following should be taken into account:
- the existence of overlapping clinical forms,
- changes in the histopathological criteria with age,
- the presence of major criteria: large size, ulceration, prominent appearance, high grade
- nuclear atypia, more than 6 mitoses/mm², hypodermal involvement and necrosis
- immunohistochemistry (IHC): clonal loss of p16 expression, deep HMB-45 staining, Ki67/MIB-1 greater than 20 (even more so in the presence of foci)
- VE1 positivity does not completely rule out the diagnosis

And in the event of criteria for an atypical Spitz tumour, the following should be discussed:
- additional IHC: ALK, ROS1, pan-TRK, p16
- FISH (MAP3K8)
- optional molecular testing if IHC and FISH are negative
- before diagnosing Spitz melanoma.

The term melanocytoma has changed and now refers to genetically intermediate lesions, unlike naevi which do not have a pathogenic mutation. We therefore now need to specify whether we are talking about a melanocytoma/deep penetrating naevus with WNT activation, a melanocytoma with BAP1 activation, or a Spitz melanocytoma.
Next-generation sequencing can rectify the diagnosis of Spitzoid melanoma.
For example, initially finding an MAPK8 fusion or a PTEN mutation in the TERT promoter is indicative of malignancy.
Therapeutic de-escalation in atypical Spitz tumours:
Recommended margins are 5 to 10 mm. 40 to 50% of patients with a positive sentinel node have not had a negative outcome, which raises the question of whether a sentinel node biopsy is appropriate for this indication. In any event, the decision should be made at a multidisciplinary meeting.

Updated management recommendations for congenital naevi
Cristina Carrera

A single naevus should be managed as an acquired naevus. Less than 30% of melanomas occur in pre-existing naevi, so systematic removal is not recommended. It should be performed in the presence of dermoscopic findings suggestive of melanoma in congenital naevi (atypical or negative network, bright white lines; angular grey lines) or if desired by the child and/or parents. The best cosmetic results are obtained with surgery and not with laser therapy (risk of repigmentation ++); on the other hand, adjuvant laser treatment of the scar further improves its appearance.
Specific features of the acral site in children:

- On palms of hands and soles of feet: benign parallel furrow pattern with globules on ridges ("peas-in-a-pod" pattern)
- In nail matrix naevi: frequent periungual involvement of the hypo and eponychium, or worrying appearance with irregular lines or Hutchinson's sign, distal fibrillar "brush-like" pattern
- The situation is different for large (adult size 20-40 cm), giant (40-60 cm), or multiple naevi. There is a mosaic RASopathy in 1/20,000 births with an NRAS mutation in 70% of cases. Two risks should be systematically investigated, proportional to the number and size of the congenital naevi:
- A neurocutaneous syndrome in 12 to 26% of cases: meningeal or parenchymal melanocytosis of varying expression, with or without melanin deposits, predictive of complications
- A risk of cutaneous, lymph node or CNS melanoma in 2 to 12% of cases

In the event of a giant naevus, the parents should be informed of the potential multinodular or hairy nature of the naevus and its extension (between x1.7 on the head to 2.8 on the arms and trunk and 3.3 on the lower limbs).
An early MRI should be proposed (ideally before the age of six months, before myelination) in the event of naevi whose estimated size in adulthood will be larger than 40 cm, multiple medium-size naevi or medium-size naevi associated with more than four small satellite naevi.
There is no need to rush to remove the lesions! Indeed, spontaneous lightening is possible (but unpredictable) regardless of size or colour during the first three months!
Moreover, studies have shown that other people perceive a large and prominent scar in the same way they do a naevus. Lastly, removal does not reduce the risk of subsequent melanoma.

Intralesional therapy for non-melanoma skin cancers: past, present, and the future

Foundations of intralesional therapy for NMSC
Vishal A. Patel

Coley was the first to think of using intralesional injections to treat malignant tumours. He successfully injected streptococcus and then mixtures of bacterial products first into bone and soft tissue sarcomas, then into metastatic melanomas, with the rationale of stimulating the immune system. The technique was then discredited by the author's lack of scientific rigour, until the use of BCG therapy in 1975, which was hampered by its low efficacy and the occurrence of anaphylactic reactions and disseminated BCGitis.
It was not until the arrival of T-VEC (talimogene laherparepvec, an oncolytic immunotherapy derived from HSV1) that an intralesional agent capable of selective replication in the tumour became available.
The pivotal Phase III study on unresectable injectable Stage II to IV melanoma showed significant efficacy versus the GM-CSF comparator with complete responses in 10% of cases, but not in the Stage IV M1b/c subgroups.
Disappointingly, adding T-VEC to pembrolizumab did not lead to a significant improvement (KEYNOTE-034: T-VEC + pembrolizumab vs placebo + pembrolizumab).

In the treatment of non-melanocytic skin cancers, intralesional injections have also been reported in the literature with good results. Intralesional 5FU has been used since the 1980s. A recent review of the literature found pooled results with cure rates of over 90% for BCC (24 patients)! The same results were observed with bleomycin (11 patients) and with interferon alpha 2b (more than 70% in BCC and 90% in squamous cell carcinoma). All these results suffer from publication bias. Methotrexate has also been used intralesionally for keratoacanthoma.
Interferon has also been used intralesionally for BCC, showing an increase after treatment in all T cells, CD4 helper cells, cytotoxic CD8 cells and NK cells, with cure rates at five years of over 90%, which was comparable to surgery with a better cosmetic result.
Injections are performed with a 26 to 30 G needle and a 0.01 ml graduated syringe. The risk is the frequent loss of 30 to 50% of the injectate due to the friability of the tumours. One of three classic injection methods is used: in one or two sites until blanching or orange peel effect, by multiple peripheral injections more or less at the base, or by tangential injection of four equal aliquots in the quadrants plus one at the base. The angle to be adopted depends on the targeted structure: 10° for the dermis, 45° for the subcutaneous tissue, and 90° for the muscle.
For cytotoxic drugs, each quadrant is injected in series of 0.1 ml, with a maximum of 1 to 2 cc per session, two to four weeks apart; this may or may not be preceded by a reduction in tumour mass by shaving.

Advancements in intralesional therapy for NMSC
Michael R. Migden

Why complicate treatment with complex intra-tumour injections, when we can simply use topical agents (or the 500 Dalton rule – a substance needs to be smaller to penetrate the skin)? Topical patidegib 2%, a topical hedgehog inhibitor, is being used to treat BCCs and prevent new BCCs in at-risk patients (Gorlin syndrome) in Phase 2 and 3 studies with no systemic side effects. The intralesional use of hedgehog inhibitors may offer an increase in efficacy over topical therapy, while still avoiding the side effects associated with systemic absorption.
The Phase 1/2 IGNYTE study of RP1 +- nivolumab tested the combination of oncolytic immunotherapy with a checkpoint inhibitor – RP1 + anti-PD-1 therapy – in melanoma and non-melanocytic tumours in 15 patients. The overall response rate was 60%, including 46% complete responses.
CERPASS is a promising Phase 2 study testing cemiplimab alone, 350 mg every three weeks administered intravenously, or combined with RP1 (intratumoural injection every three weeks, eight administrations) in advanced cutaneous squamous cell carcinoma. The results are pending.
ARTACUS is testing RP1 alone in organ (kidney or liver) transplant recipients with advanced or metastatic squamous cell carcinoma.
SP002 is a new vector created from a deleted adenovirus with insertion of the interferon gene: transduced cells express interferon within two weeks. The idea is to combine it with hedgehog inhibitors to counterbalance their down-regulation of the interferon gamma response: Phase 2 trial combined with vismodegib.
Intralesional immunotherapy in non-melanocytic skin tumours aims to increase tissue concentrations while reducing systemic effects. The injection technique for immunotherapies is different from the injection of cytolytic agents or viruses: they are injected more like interferon, with a 1 ml syringe marked every 0.1 ml. They should be injected very slowly, every two to three minutes, in 10 µl increments. Do not inject them into the subcutaneous space as this may be ineffective (5 mg in the subcutaneous plane are lost!), and do not inject them into the ulcerated area. They should be injected into a dense tissue; otherwise, inject the edge of the tumour. Intratumourally, in the event of small lesions, the aim is to treat with the smallest possible dose to minimise the side effects; however, for large lesions, a full dose will be injected, with the same risk of side effects, but with the aim of increasing efficacy with an increased local concentration. A Phase 1 study tested intralesional

cemiplimab in patients with resectable recurring squamous cell carcinoma (250 µl per week for 12 weeks followed by surgery). The primary endpoint was the incidence, nature and severity of dose-limiting toxicities and treatment-related adverse events in the first 28 days and the incidence and severity of adverse events up to 90 days after the last dose. Systemic absorption was very low. At the lowest dose of 5 mg, 75% complete histological responses were observed, i.e. almost as many as with the highest dose of 44 mg, but with a much better safety profile (12% Grade 3 to 5 side effects resulting in a treatment delay only). New cohort studies are testing six weeks of injection for both squamous cell and basal cell carcinomas.

Management of rare malignant skin tumours

Pitfalls in the diagnostics of rare skin malignancies
Petr Arenberger

Difficult-to-treat cases with rare sarcomas
Judit Oláh

Unfortunately, there are no recommendations or consensus for all these rare skin tumours.
There continues to be a patchwork of case reports and non-standardised treatments that are not advancing the community as a whole. It would have been nice to know if there are other rare skin tumour networks like Caraderm.
It is regrettable that the topic does not seem to be motivating the crowds at the moment, as this was a final conference session without any scoops or many attendees.
Zsuzsanna Lengyel's session on "Difficult-to-treat cases with rare adnexal tumours" did not take place.
So there was not much to take away from the first presentation, unless you had missed the session on Merkel cell carcinoma and the 2022 recommendations: the 80% of Merkel cell carcinomas positive for polyomavirus DNA are associated with fewer lymph node locations at diagnosis, are often located on the lower limbs, metastasise less frequently and have a lower mutational burden; excision with 1 cm margins + adjuvant radiotherapy (unless there are anatomical constraints) or, failing that, 2 cm margins; Mohs surgery is also possible; and indication for a sentinel node biopsy, followed by 50-55 Gy radiotherapy of the lymph node area in the case of positivity, +- dissection.
Rare cutaneous sarcomas are often diagnosed late, as their clinical presentation is not typical and initial surgical management is rarely appropriate, leading to incomplete resection.
Currently, for the rare skin tumours that are encountered, and depending on local possibilities, once the classic iterative surgical management approaches with the associated radiotherapies and classic cytotoxic agents are out of the way, we can hope to try an anti-PD-1 therapy, based on the various clinical cases reported here and there in the literature.
For example, the speakers presented some cases of epithelioid angiosarcoma expressing PD-1, which were treated with a good response. Similarly, a malignant peripheral nerve sheath tumour (MPNST) in a context of Li-Fraumeni syndrome with a p53 mutation was successfully treated. This will be all the more expected if there is a high tumour mutational burden (TMB) or microsatellite instability (MSI-H) or a defective DNA repair system (dMMR).
There is still a long way to go before these patients can be properly managed: this will involve a systematic review by expert pathologists, the systematic holding of multidisciplinary meetings, exhaustive data collection and molecular testing by NGS to identify therapeutic targets (useful in maybe 60% of cases? and sometimes leading to appropriate treatment, such as tazemetostat in epithelioid sarcoma).

Rare tumours of the anogenital area
Erika Varga

Here as well, there are problems of diagnostic and treatment delays for these hidden locations for which patients are slow to consult.
The speaker drew our attention to several cases of acquired circumscribed lymphangioma. This disorder affects the genital region and occurs in the aftermath of or concomitantly with certain situations of chronic inflammation – tumours or radiotherapy, infections (herpes, erysipelas, lymphogranuloma venereum), or Crohn's disease – during which extensive fibrosis leads to localised lymphatic anomalies. The treatments to be proposed are conservative (proportional surgery, laser therapy, sclerotherapy, etc.).

Report written by

Dr Oriol Yélamos

Dermatologist, Spain

Sequential treatments for metastatic melanoma

Dr Paolo Ascierto

With time we have learned that even in cases of BRAF mutant melanoma it's better to start with antiPD1 than to start with BRAF inhibitors. Also, some studies have shown that patients with resistance to BRAF treatments also show resistance to immunotherapy. This is due to the fact that BRAF inhibitors change the tumor microenvironement which makes the tumor resistant to immuotherapy. This may explain why it's better to start treatment of metastatic melanoma with immunotherapy rather than targeted therapy.

Another reason for antiPD1 resistance is the presence of mutations in JAK2, which induces loss of interferon gamma signaling (Zaretsky et al. NEJM 2016).

Interestingly, in cases where you give immunotherapy first, then if they relapse you can give them targeted therapies and they do better than if you give them immuno alone. So, it may be good this sequential approach, but maybe it's also a good option to give all the drugs at the same time (triple therapy). However, so far triplet therapy has not been shown to be better than immuno alone, although we don't have long term follow-up data.

Interestingly, some patients with high LDH may benefit from a short pulse of targeted therapy before, later immunotherapy. Probably, the negative effect of BRAF inhibitor on drug resistance happens with time, so short pulses of initial treatment may be benefitial. We will have some more data in the future since there are some clinical trials ongoing to study this issue.

Melanoma models for the next generation of melanoma therapies

Dr Liz Patton

Although new treatments appeared recently in melanoma, there are some key challenges:
- Metastasis and tumor dormancy
- Drug resistance
- The melanoma immune response
- Aging and the microenvironment
- Rare melanoma subtypes

These challenges are key targets for new drugs. Dr Patton's group is studying mainly melanoma heterogeneity and that's why her group is using zebrafish to study it. The advantages of zebrafish is that it allows fast melanoma models (3 weeks is what it takes in this model to develop a melanoma).
What they are studying is:
- Map and discover melanocyte subpopulations and developmental lineages
- Understand how melanocytes lineages contribute to melanoma heterogeneity
- Develop therapies to target heterogeneity in residual disease and drug resitance

It's very interesting to use zebrafish since we can use not the adult but also the embryo to allow the identificariom the melanocyte migration in the embryo.

They have shown that a subset of melanoma cells can persist if certain treatments are given, and these cells are positive for tfap2b. These cells are called persister cells. Hence, since Tfap2 is overexpressed in persister cells, this is a potential treatment pathway for perister melanoma cells.

Another potential pathway is ALDH1. If this pathway is overexpressed is pro-tumorogenic. Interestingly, ALDH1 is elevated in patients who have progressed to antiBRAF treatments.

Summary:
- Tfap2b marks a melanocyte stem cell population in embryos that patterns adult zefbrafish skin
- These stem cell states specifically emerge in a subpopulation of persister cells at tbe site of residual disease
- Targeting persister cells can extend melanoma free survival following targeted therapy in pre-clinical animal models

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Management immune related adverse events

Dr Caroline Robert

Immunotherapy can be very helpful to fight tumor cells. However, sometimes this response can be to strong. However, we know that these immune related adverse events (irAE) are expected so what we need to to is treat them correctly.
The most irAE are fatigue, skin ones and fortunately the most severe are rare (cardiac, renal...). Additionally, these irAE can overlap and make things more complicated.
Multiple guidelines describe how to treat these irAE. In general (foto):
1. Promt detection and grading of irAE
2. Detection potential alternative etiologies and give symptomatoc review
3. Hold or discontinue ICI therapy and give symptomatic treatment
4. Think alternative treatments beyond corticosteroids
5. Consult with organ specialists in case of severe irAE

Management starts with providing adequate information to the patient before giving the drug, orally and written. Also, make sure the patient can contact the medical team.

Skin irAE: the most common is maculopapular rash. Can be mild even if BSA >30: even if a lot of the skin is affected can be managed with topical treatment and doesn't require ICI withdrawal. This needs to be taught to oncologists so they don't initiate systemic steroids fast and they don't stop the ICI. Other skin irAE need dermalogical referral: bullous pemfigoid, psoriasis...

Fatigue is very common but can also mask other more severe irAE. We need to perform ECG, thyroid studies...

Thyroid irAE are generally irreversible.

Hypophysitis is an irAE that can be a vital emergency. It can be challenging to identify since it can present with mild fatigue.

Hepatotoxity tends to be asymptomatic, so we identify it with blood tests. We need to take into account other drugs patients take, including herbs or alcohol. Also take into account viral infections.

Colitis and pneumonitis can be common and the problem is ruling out infections.
A special type of lung irAE is sarcoid-like granulomatosis, that if mild doesn't need drug withdrawal.

Myocarditis is a severe irAE. If suspected (with troponin elevation), rapid referral to cardiology and initiation of steroids.

If a patient has had irAE, can we rechallenge the treatment? It depends on the severity and the patient profile (previous autoimmune diseases... Fotos!), and also if you give the same treatment or a different one: if same antiPD1 treatment there's around 50% chances to have irAE, from antiCTLA4 to antiPD1 21% grade 3, from antiPD1 to antiCTLA4 34% grade 3.

It seems that some genetic variants in IL7 are associated with higher rates of irAE.

What do we need to do before we treat a patient (in bold, what doesn't need to be repeated):

- Medical history: autoimmune disease, recent infection, comorbidities, ongoing treatments
- Complete physical exammination, weight, height
- ECG +- echocardiogram
- Bood tests: CBC, electrolytes, T3, T4, TSH, cortisol, ACTH, liver tests, creatinin, glucose, A1C Hb, ferritin, amylase, lipase, fibrinogen
- Auto-Ab if autoimmune disease
- Urinary tests: glysoruria, urine sediment, proteinuria
- Infection: quantiferon,HBV, HCV, HIV, HTLV
- Resting oxygen, saturation, PFT if needed

Melanoma research

ATAD2 biomarker
Dr Arianna Bagliollini

ATAD2 is expressed in primary melanoma and is correlated with worse survival.
ATAD2 is sufficient and required for melanoma formation.

GDF15 biomarker

Dr Jörg Wischhusen

GDF15 has multiple functions:
GDF-15 induces anorexia and cachexia.
Also GDF-15 seems predictive of potentially failing pregnancy.
GDF15 also correlates with poor survival in cancers

Why does it have different effects? It's because GDF15 impairs adhesion on endothelia and on ICAM1. So, it impairs T cell adhesion and priming.
In cancer GDF15 contributes to antiPD1 resistance. So, blocking GDF15 reduces this resistance.
Similarly, responders to antiCTLA4 drugs have low levels of GDF15.
Visugromab (antiGDF15) seems to be a promising drug in phase I trials for multiple cancers, and it seems very safe.
Neutralizing GDF15 restores the ability of immune cells to extravasate blood vesels and enter the tumor microenvironment in vivo.

Metabolism and melanoma
Dr Alpaslan Tasdogan

Metastasis, although lethal, they are a highly inneficient process in which most cancer cells don't survive. Why do some metastatic cells survive and some others don't? One of the explanation is alterations in metabolism (alterations in glucose, lactate...). These changes in metabolomics define how metastases will behave. And in fact, metabolic profiles are different from brain, liver or lung metatases:

- Brain and lung tumors are oxydative
- Clear cell renal cell carcinomas are glycolytic

However, studying the metabolism cannot be done in cell cultures. It needs in vivo models.

Skin cancer guidelines and updates

Actinic keratosis (AK) guidelines
Dr Lidia Kandolf

AK risk transformation into SCC is low but should be suspected in cases of ulcerated, painful or indurated lesions.
This risk is higher in immune suppressed patients, so in these patients we always have to treat AKs.
In immune competent patients, of isolated small lesions it's also OK to recommend patient self-examination.

The best trestment is combining cryotherapy with topical treatments.
Regarding field treatments, there's a novel approach using 5FU + calcipotriol in a short course of trestment. Also, a novel treatment is tirbanibulin 1%, being approved for non-hypertrophic lesions.
When we compare all these treatments, 5FU (5% > 4%) is the most effective treatment, followed by ALA-photodynamic therapy.

Squamous cell carcinoma (SCC) guidelines
Dr Alexander Stratigos

Risk factors in SCC are somehow different in different guidelines, but some are common:

- Clinical Tumor size 2-4 cm
- Thickness >6mm
- Poor differentiation
- Perineural invasion >= 0.1 mm
- Desmoplastic

Regarding diagnosis, it's very important to obtain clinical images.
Regarding pathology reports, it is important to report standardized data.
Regarding management, surgery is the standard of care (ideally with microscopic control). Regarding initial margins, there are differences but it ranges from 4-6 mm margins in low risk SCC, and 6-10mm for high risk SCC.
For high risk SCC, patients need to be staged with CT scans and ultrasonography, and eventually MRI in cases of soft tissue or bone involvement.
Regarding SLNB, there's limited evidence when to perform it, since positive SLNB patients do not perform worse than negative SLNB, the European guidelines do not recommend SLBN.

Radiotherapy can be used in 3 settings:

- When surgery cannot be performed
- Post-surgery: when positive margins and surgery is not possible to be performed again
- Adjuvant: when multiple high risk SCC (perineural invasion is found, large size...) but each case needs to be discussed individually
- Follow-up for SCC:
- Low risk SCC: every 6-12 months for 5 years. No imaging recommended.
- High risk primary:

Every 3-6 months with lymph node ultrasound for 2 years. Later, every 6-12 months without imaging up to 5 years, later once yearly

- Locally advanced or metastatic:

Every 3-6 months with lymph node ultrasound for 5 years, and with imaging (CT, MRI, PET) every 3-6 months for 3 years and later basedon individual risk. Later, every 6-12 months with ultrasound up to 5 years, later once yearly

- Immunosuppression: every 3-6 months lifelong depending on patients

Regarding prevention, sun protection is crucial, and current guidelines recommend nicotinamide 500mg bid in immunocompetent patients.

Basal cell carcinoma (BCC) guidelines
Dr Ketty Peris

Regading diagnosis, clinical examination with dermoscopy is, in most cases, enough to diagnose and predict BCC subtype.
The main novelty is the definition of advanced BCC, since this can also include common BCC located in difficult to treat locations. In these cases, hedgehog inhibitors may be helpful. Also, in this setting it's possible to use these drugs before surgery, in a neoadjuvsnt approach.

Melanoma guidelines
Dr Claus Garbe

Dermoscopical examination should always be performed when suspecting melanoma.
With patients with positive SLNB, lymphadenectomy shouldn't be performed and adjuvant therapy should be offered.
Lymphadenectomy should be performed when macrometastases are identified, clinically or using imaging techniques.

In stage IV patients, immunotherapy should be offered in all patients, irrespective to BRAF status. In some scenarios in which we need fast response (symtomatic metastases) we can offer BRAF inhibitors in first line.

Merkel cell carcinoma (MCC) guidelines
Dr Celeste Lebbé

There are two types of MCC: one associated to Merkel polyomavirus and one not associated to it.
MCC typically grows rapidly, mostly on subexposed areas.
Histologically they are CK20+ and TTF1 negative.

When to perform staging?
- Tumor size >= 2cm
- Immunosuppression
- Head and neck
- Positive SLNB

What needs to be performed?
- Whole body examination
- Ultrasonography of nodal basin
- If available, PET-CT

Managament of the primary tumor
- Surgery of the primary tumor with clinical safety margin of 1cm followed by post-operative adjuvant radiotherapy on the tumor bed (expert opinion, no trials)
- Adjuvant radiotherapy should be performed within 8 weeks of surgery
- SLNB is recommended

Management of regional disease
- If positive SLNB: adjuvant radiotherapy is preferred over lymphadenectomy
- If macroscopic nodal disease: lymphadenectomy

Management of locally advanced or metastatic MCC
- AntiPD1: Pembrolizumab: not approved in Europe
- AntiPDL1: Avelumab approved in Europe

Dermatofibrosarcoma protuberans (DFSP)
Dr Philippe Saiag

It doesn't have risk of distant metastases unless it undergoes fibrosarcomatous transformation (occurs in 15-20% patients).
Although it's rare, it's the most common skin sarcoma.
It is characterized by a translocation in 17q22 and 22q13 which results in a fusion protein COL1A1-PDFGB.
Pathologically, it shows spindle cells CD34 positive.
There's no need to perform imaging staging.
Prognosis: local recurrences were very common with previous convencional surgery, but it is less if Mohs surgery is performed.
The treatment is mainly surgical, and you need to remove the tumor completely. Margins should include the deep fascia and laterally you need 1-1.3 cm margins with microscopically-controlled surgery. If no microscopically-controlled surgery is available, 3cm margins are needed.

Medical treatment with Imatinib is approved in inoperable primary DFSP or metastatic DFSP.

Controversies in melanoma management

Do we need a new melanoma classification? Yes
Dr Claus Garbe

The current AJCC classification has many limitations in different stages.

Limitations for stage I-II:
- Does not provide reliable prognostic information and is misleading for therapeutic decisions
- The explanation for this miscalculation is probably underreporting of melanoma-specific deaths.
- There is an urgent need for a new AJCC melanoma classification with calculation of MSS, OS, and RFS

Limitations for stage IV:
- The current AJCC version 8 melanoma classification does not reflect the dramatic changes in therapeutic efficacy in metastatic melanoma.
- There is an urgent need for a new AJCC melanoma classification which incorporates the new treatment successes.

Regarding clinical clarity:
- The current classification uses complicated constructs to define substadia that are not reproducible on top of your mind
- A clinical classification should be developed to be able to learn by heart.

Do we need a new melanoma classification? No
Dr Jeffrey E. Gershenwald

We know that staging classifications are be imperfect but we need a balance between complexity with simplicity which allows generalizability.
The current classification is a common language that facilitates worldwide consistency.
However, it is true that heterogeneity is the main problem of melanoma.
Regarding the N status, SLNB still has a point in regards to prognostic information.
Another good thing about the current classification is the advent of nomograms, which can be carried on the phone or computer without any need to memorize them.
Other additions in the current classification that help decision making are the addition of brain mets (M1D) and LDH levels.
And although tumor burden and mitoses are not included in the AJCC, they are recommended to be taken into account, and they are being studied and used in some nomograms such as the one from the melanoma Institute of Australia.
Regarding the addition of treatment into the calculation for survival, it may be useful in developed countries, but may not be applicable where immunotherapy or targeted therapies are not available.

Do we need adjuvant treatment? Yes
Dr Axel Hauschild

All trials using adjuvant therapies in melanoma have increased progression free survival, wih an estimated cure rate of 17%.

So, it is highly effective in high risk patients but it has some risk of severe side events. So, what's more worrisome, disease relapse or treatment adverse events? It's unknown, but the key is to correctly select the patients at risk of disease relapse by using gene expression profiling (GEP) tests. Which are the alternatives to current adjuvant treatments? Improved selection of high risk patients who need adjuvant therapy (GEPs), neoadjuvant treatment with or without posterior adjuvant treatment.

Do we need adjuvant treatment? No
Dr Alexander Menzies

Adjuvant therapy has improved recurrences but has it improved overall survival? Not in most cases. In around 40% of patients adjuvant therapy doesn't work, in around 40% of other patients there are no differences with placebo meaning that if we didn't give the drug these patients would have survived as well. And there's only 1/5 of cases in which there is a benefit, but at very high economic cost (around 100.000€per year including drug costs, monthly visits, trimestral scans...) and potential toxicities (which could be spared in non-responders). Also, it is very frustrating for the patient and for the doctor to administer adjuvant treatment since we don't have biomarkers (blood, imaging...) that can tell us if the treatment will work or no, resulting in important anxiety between follow-ups.

Also, now we give adjuvant therapy to advanced melanomas, but most deaths occur in thinner melanomas to which we are not giving them any adjuvant treatment.

So, what do we do to improve overall surivival? Neoadjuvant treatment!
Neoadjuvant treatment has many advantages: has better efficacy and survival, provides tailored prognosis, tailored treatment (we can avoid lymph node disecction even in macroscopic disease if they have responded, we can perform biomarker analysis, we know who responds since we can assess pathological response...), and allows rapid development of drugs.

Biomarkers for melanoma

Dr Reinhard Dummer

It would be great to have biomarkers but it's extremely complex since melanoma is very heterogeneous.
Two biomarkers have been studied in the COMBI-AD trial: tumor burden and inflammation. What is associated with better responses to adjuvant treatment is a low tumor burden and high inflammation.

Similarly, data from other trials have shown the importance of the microenvironment (PIK3CA, erbb2...). Patients with mutations in PIK3CA mutations or with erbb2 expression will do worse when using BRAF/MEK inhibitors and may benefit from the addition of other treatments.

The problem is that tumors are heterogenous and what may be true for some melanoma subtypes may not be true for others, so it's important to develop biomarkers for the different subsets of melanomas. Another thing that adds even more complexity is that melanoma mutations are dynamic, and they change over time.

Maybe the future is integrating all the information available such as pathological data, dermoscopy, mutation information...

Neoadjuvant treatment for melanoma

Dr Georgina Long

We are facing an unbelievable moment in melanoma with the advent of neoadjuvant treatment. With the neoadjuvant approach we are seeing flat Kaplan Meyer curves when treating advanced melanomas for the first time in history. This is because treatment given prior to surgery allows a better immune response against the tumors, and since we can study the tumor after being treated, we are learning which patients are best candidates to receive treatments.

The advantages of neoadjuvant treatment are multiple (5, summarized below), besides the fact that we use drugs for less time, which that it's cheaper, less toxic...

The 5 advantages of neoadjuvant therapy in melanoma are:

1. In increases the anti-cancer immunity compared with adjuvant treatment (there's enough data coming from multiple trials such as as the OPACIN, Nadine...). Here the key feature is that we give the drug before surgery, later we remove the lymph node or primary tumor, and analyze the pathological response.
2. Has great patient feedback (patients love it since this will reduce morbidity related to surgery), and provides a refined prognosis
3. It tailors surveillance and allows us to identify who is going to benefit from additional adjuvant therapy and who won't
4. It's a great translational platform since we can study biomarkers and study the biology of drug resistance
5. It allows rapid drug development since most neoadjuvant schemes can be completed between 4 to 6 weeks, compared the 1 or 2 years needed in the adjuvant setting. This also allows us to select drugs which may work and which ones won't work way faster.

Regarding point number 1, it's important to report correctly the pathologic response and there are white papers stating what needs to be described in the path report and how to process the tissue. So, it's crucial to talk with the pathologists to make sure they are aware of these challenges.

Interestingly, there are different outcomes whether what's used is immunotherapy or targeted therapy (TT): if you don't get complete pathological response in TT, you can have relapses, whereas with immunotherapy you can do well even with a partial response, although the goal is to have a major pathological response (MPR) which includes completely pathological response (100% of tumor is gone) or nearly pathological tumor response (less than 10% of viable tumor is left).

Non melanoma skin cancers

Dr Iris Zalaudek

There are differences in prognosis of NMSC between men and women. There are multiple explanations for these: the sun exposure may be higher in men (but it's not really true since women tend to like sunbathing more), also maybe the chronic use of NSAID in women may improve the prognosis of NMSC... But probably there are more explanations.

We don't know if we have to treat all patients with AK even if they don't have any risk factors. Conversely, sometimes we don't treat the cancerization field in patients who have had an SCC removed. We need to focus our attention and effort to the patients who need it.

Also now we have drugs for advanced NMS, so we have to work more in a multidisciplinary approach. But it's probably not enough, and we need to continue working to improve the care of high risk patients, we need to perform research in field treatment of transplant patients, we need to implement dermatology services capable of dealing with new drug toxicities (antiPD1 are being increasingly used in NMSC) and we need to determine who needs to be followed up and who can do self-examination.

The role of local therapies in the interdisciplinary management of keratinocyte carcinomas

Exclusive radiotherapy
Dr Luca Tagliaferri

For BCC the classic treatment is surgery, especially Mohs surgery. However, some patients may not be willing to undergo surgery and a very good alternative is radiotherapy (RT).
When looking at systematic reviews, RT has the same recurrence rate as Mohs surgery (around 3%). Also, the esthetic results tend to be good, especially with newer RT techniques. So, RT can be used as a primary treatment with very good results.
In addition, in locally advanced BCC, RT can also be used in the neoadjuvant or adjuvant setting.
Also, which is the future of RT? Probably is image guided RT (guided with ultrasonography, OCT...), so multidiscipliary decisions are crucial.

Adjuvant radiation therapy
Dr Agata Rembielak

RT can be delivered in different ways for skin cancers: externally (the most common way), or unsing skin catheters (brachytherapy).
Skin eadiotherapy is al excellent alternative to surgery especially in elderly patients, but it requires multiple visits.
In which situations is RT useful:

- Primary treatment

Inclompletely excised
Closely excised
Completely excised: adjuvant RT

- Lymph node metastasis
- Distant metastases

For cutaneous SCC some patients may benefit from adjuvant RT, but which patients? Different guidelines differ but thye typically recommend adjuvant RT when positive surgical margins, or high risk SCC (perineural invasion...). The problem is that we don't have good quality data, and in this sense in th UK will now conduct a prospective study analyzing adjuvant RT vs observation in high risk SCC.

Electrochemotherapy
Dr Martina Ferioli

Electrochemotherapy (ECT) is a local treatment which requires delivering a drug (typically bleomycin or cisplatin) and later apply an electric flow through the tumor. This can overcome drug resistance and be used in nearly in all tumors.

This treatment can be used in multiple skin tumors such as melanoma, Merkel cell carcinoma, Kaposi sarcoma, metastases... But also there's evidence in BCC and SCC
It can induce an overall response rate about 80% with complete responses in 60-70% in tumors less than 3cm. The maximal therapeutic effect is obtained after 6-8 weeks. Cycles are spared 4 weeks if bleomycin is used.

We think about ECT when surgery is not possible or is contraindicated, lesions resistant to chemotherapy or radiotherapy, or in the palliative setting. But the truth is that ECT can be successfully used in BCC, SCC... However, guidelines do not recommend ECT as first line treatments and they leave more towards in the refractory or palliative setting. Probably, ECT may be also suitable in difficult to treat BCC or SCC.

New developments in radiotherapy
Dr Angela Hong

Due to COVID19 pandemic, different strategies were developped in the RT world. One was performing hypofractioned schemes (higher doses but less days). They adapted these schemes according to ECOG status and patient age. Also, they have been using topical RT with topical rhenium-188 brachytherapy. With these schemes they have shown very good results with less visits. However, with these hypofractionated schemes the cosmesis is a bit worse, with more hypopigmentation and other skin side effects.

Another new development include the use of 3D printed bolus (like a mould) to treat difficult to treat surfaces such as the nose.

Cutaneous lymphomas

Dr Emmanuella Guenova

There have been some changes in then latest cutaneous lymphoma classification, especially the change of name of marginal zone lymphoma which now is named marginal zone lymphoproliferative disease. Why did they change the name? Because this entity is so indolent that some authors thought it was not a real lymphoma.
Switching to cutaneous T cell lymphomas (CTCL), it is important to know that the classic presentation of mycosis fungoides is actually not the most common, so we need to know that there"s clinical heterogeneity.

There have been updates in the staging of mycosis fungoides which now is linked to prognosis, but there is some overlap in survival in advdanced stage II patients and early stage III, so this classification will be refined over time.

Regarding treatment, one interesting addition is the use of topical pimecrolimus in patch and thin plaque stages (data coming from a randomized clinical trial), showing efficacy and that there's no need to be scared of using topical calcineurin inhibitors in cutaneous lymphomas besides the black box warning published long time ago (which was actually removed).

Other drugs licensed for CTCL are mogamulizumab (anti CCR4 drug) and brentuximab in CD30 positive CTCL. Other drugs include HDAC inhibitors such as romidepsin which have modest effects.
Which are the unmet needs in cutaneous lymphomas? As opposed to melanoma in which immunotherapy has been developed, in cutaneous lymphomas the cancer cell is actually the immune cell, so drugs need to be selective to kill the cancer cells and not the normal immune cells.
In fact, some trials used immune checkpoint inhibitors in cutaneous lymphomas and some patients respond but others don't. It's postulated that non-responders cannot mount an effective immune response, but the exact biomarkers to know responders are unknown. Other explanations are differences in phagocytosis response.
So, maybe other ways to modify the immune response would be benefitial in cutaneous lymphomas. For example, one interesting approach is the inhibition of the JAK/STAT pathway with specific drugs such as tenslisib or cerdulatinib.

Newer drugs are focusing in maintenance treatments and probably will be newer HDAC drugs.
Also, we should't forget that in some mild cases, watchful observation is also an option, and on the other hand, in advanced cases the only curative treatment is bone marrow translplant.

Primary prevention of skin cancer. What the world can learn from Australia

Dr David Whiteman

Australia is an example of primary prevention for melanoma. In Australia, before the 1930s, people didn't get sun exposed. After the 30s, it started being trendy to be tan and Australians got to the beach with no sunscreen. Since the majority of people populating Australia came from England and Wales (fair skinned) and Australia is close to the equator, people got easily sunburnt. Later in the 50s, Australian epidemiologists saw a dramatic increase in melanoma mortality but nothing was done to address this. In the 80s, there was enough epidemiological data that UV radiation was responsible for this melanoma increase and the Australian authorities started doing something to revert the situation.

To do so, Australia has implemented educational, campaigns, changes in the law, regulations, tax changes among others. Regarding educational campaigns, in the 80s in Australia there was a big campaing called Slip Slop Slap in which people were told about the dangers of sun bathing and the relationship with melanoma. This campaign was very successful and nowadays people are not really seeking a tan. However, now the focus is on reducing daily sun exposure.
Regarding law changes, some Australians with melanoma have sued their companies because they developed melanoma and their employers didn't offer anything to protect them. This has created some changes in the laws and regulations of Australia and for example now people who work on the sun must wear wide brim hats, sun protective clothing... And they should be provided by the employer. Also, there have been regulations regarding sunscreens to make sure they work. Interstingly, in Australia, workers who need to be in the sun and need to wear sunscreen, can deduct the cost of sunscreen in their taxes. Also there have been regulations in terms of the use of shade, and schools, universities... need to have sun sheltered areas. Finally, Australia has also banned tanning beds. But are all these measures working? If we look at mortality, no, but probably because this public health campaings require decades to work. However, if we look at number of melanomas, it seems that the incidence of melanomas is decreasing i. the generations born after the slip slop slap campaign in the 80s.

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