EUROPEAN LIQUID BIOPSY SOCIETY

26.09.2023

ELBS CLINAL WG MEETING – UVEAL MELANOMA WORKSHOP - MINUTES

WG leads: Christoffer Gebhardt, Nikolas von Bubnoff, Jean-Yves Pierga, Claus Lindbjerg Andersen
Speakers: Salvatore Grisanti, Jessica Hassel, Paul Nathan, Manuel Rodrigues

Key Take-Aways:

Challenges in early/localized disease:

1. Early detection to distinguishing UV from Naevi without biopsy and to prevent dissemination of tumor cells
2. Identify patients with higher risk of metastasis

Challenges in metastatic setting:

1. Decision making on which patients to treat and which not to treat
2. Decision on for how long and who should be continued on therapy? Treatment beyond progression?
3. Availability and reimbursement: LB is not available in the clinic yet. It is done for scientific reasons but would be needed at time point of staging, to decide whether or not to continue treatment, etc.

Biology and genetics:

- Currently there a no reliable, molecular, predictive markers for UM patients who will respond to immunotherapy.
- The presence of liver metastasis appears to have a great influence on response.
- There has been a positive TIL study in UM, there are follow-up studies being performed.
- There is little published data on the impact of clonal evolution in UM but more is coming

Next steps / ToDos:

All:

- Please check the discussion slide and let us know in which area you would see most potential. Open discussion is desired.
- Please indicate whether you would be interested in joining forced to set up a multi-centric study in UM

Christoffer and Nikolas:

- First rough, written idea collection for trials

Claudia:

- Will circulate minutes and slides.
- Will set up brainstorming call with all interested sites to continue discussion

1) DISCUSSION ON PRESENTATIONS

Early/Localized Disease

Nikolas: This is a rare and special disease; sometimes there is a situation where you have a suspected UM and there is a lack of sensitive and specific tests to diagnose.

Salvatore: It is treatable, but whatever we do we don't have impact on patient prognosis. Sometimes diagnosis is delayed, patients are told the observed lesion is a Naevus and to come back again in a few months for follow-up. At this point we do not whether it is melanoma are not treating it as such. Patients then return with a full-blown melanoma.
Also, less than 2 % of patients have clinically detected metastasic disease, meaning there are potentially already cells in the liver at point of diagnosis which will kill the patient one day. Biopsy from such small leasions in the eye is not trivial, you face the risk of making patients blind. It would be great to have a sensitive biomarker for melanoma even with small lesions. We know that tumors starting from 1 mm thickness can develop metastatic disease. Sometimes these lesions grow very slow, meaning we dismiss them as neoplasia since there is no change across many years. What we truly need is to detect these patients early. We might then decrease the number of metastatic disease patients.

Nikolas: This would also be helpful to identify patients with risk of early dissemination to the liver.

Klaus: Regarding early detection there are two CAVEATs, Naevi can have tumor-associated mutations (e.g. BRAF mutations) so we really have to make sure this is melanoma. The second thing is when we become very sensitive to detect these small lesions, we might run into the detection of CHIP mutations. We need to be careful not to create false positive results.
Second comment, regarding the dissemination potential. We want to be able to measure the change from dormant to active disease, therefore, even if you measure CTCs in "only" 50 % of the cases, this could be interesting in combination with ctDNA measurement. Maybe these are the 50 % of patients where the disease is already disseminating.

Nikolas: I agree, the time-point of dissemination might be extremely early. There might be a lead time of months and even years till you detect metastasis in the liver. Regarding driver mutations in melanoma, this is not massively overlapping with CHIP (maybe problematic for NRAS mutations) but for GNAq and GNA 11 these are not so often seen in CHIP.

Klaus: There are also new methods out that allow us to check methylation patterns to see whether CTCs have settled in the liver. These patterns seem to represent a liver specific response to the homing of tumor cells and might be interesting in UM.

Christoffer: We do not yet have a standard established protocol for follow up of uveal melanoma patients. This is becoming more and more important especially in context of the newly emerging assays. The future is the incorporation of MRD monitoring in follow up. Of course, clinical trials will be necessary to establish efficacy and clinical utility. This could be one field of interest for this WG.

Salvatore: It would be nice to compare different LB techniques in one patient to know the way forward.

Metastatic setting

Christoffer: Paul, the Tebe-MRD trial uses ctDNA, did you include other analytes such as CTC or EVs in this analysis?

Paul: You are correct it is only ctDNA. The panel is not commercially available but an academic panel from Oxford.

Jessica: One question regarding the sensitivity of your assay. In the original study 40 % of patients with measurable disease had no measurable ctDNA. Will you need to be much more sensitive to find and identify patients with molecular relapse?

Paul: I do not have the exact numbers of the relative sensitivity of the panel in oxford compared to the commercially available one. However, there are two issues to consider. One is the sensitivity of the test, the second is the biology. The 40% that were ctDNA negative with macroscopic disease, their OS was 90%. That is very interesting and far superior to the rest of the group. Also ctDNA cleared patients had similar OS to patients that were initially ctDNA negative.

Jessica: Have you started recruiting yet? If so, how many patients are included so far?

Paul: The study is open, however, I cannot share the detailed numbers yet.

Nikolas: According to your experience, if a patient who is cleared experiences a "LB-relapse" what are the dynamics and lead time between ctDNA progression and image-based progression?

Paul: We cannot answer that from the former studies. I believe the academic study Jessica has presented will be exactly right to answer this question. For the Tebe-MRD study we will also be able to get some difference in kinetics between radiologic and ctDNA relapse.

Jessica: Will you biopsy the liver upon relapse?

Paul: Yes, that is standard of care, we will do that.

Jessica: So just in the blind because you don't have anything on RECIST?

Paul: Oh I see. So no, we do not have ethical consent to biopsy liver that is normal looking. But of course this would be really nice to have as that kind of biopsy would be very instructive on dormancy in UM.

Klaus: I was just wondering. What are the target genes of your panel and what is the lowest level of detection (VAFs)?

Paul: The panel is very similar to that of the 202 study. So its basically GNAQ, GNA 11, SF3B1, IFAX and a couple of others. The thing with UM is, you need only about 6 targets.

Biology and Genetics

Nikolas: A quick question on immunoincology in UM. Are there biomarkers that are able to predict response? Is there a fingerprint of patients responding to therapy?

Christoffer: There is some data presented on this topic. TNF-alpha and associated factors have been demonstrated in patients who are non-responsive to IT in UM. I am pretty sure common resistance mechanisms to IT in other solid tumors also play a role in UM. However, why the tumors to not respond so well is quite clear, this is a cold tumor, where resistance mechanisms play a much larger role. Also probably the lack of neoantigens.

Paul: We don't really have useful molecular predictive markers for who will respond to IT. From the data of two small phase II single arm studies, it looks as if the group who benefits most from epi-

nevo are the group who have extrahepatic metastases only. In our tebe study, that makes up around 7% of the patients, so it is a very small group. In the studies there was a high representation of patients who had extra-hepatic disease only. The odds ratio for benefit for epi-nevo was only increased for these patients, not for those with hepatic metastases. The question remains, what do we know about the biology about these patients? There has been a suggestion that they are more enriched for a group that have more SF3B1 driver mutations and we know that the tumors are a little more indolent.

Jessica: And from another perspective as well we know patients with CM and liver metastasis also don't tend to respond as well to ICI. It might be something in the microenvironment of the liver that adds to this effect. Of course TNB is one big story and the localization in the liver might be an important added factor.

Paul: Plus, there is a positive TIL study in UM. There are tumor-responsive TILs in UM that under the right circumstances can have an anti-tumor effect.

Jessica: Do you know Paul where they took the metastasis from for the TIL therapy? Was it from the liver? Or was it cutaneous mets – then it might be patients with extra-hepatic disease as well.

Paul: I know that a follow up study is coming for this.

Christoffer: I agree that cellular IT may be a very interesting therapy option for UM in second line. Maybe also vaccination, we will see about that, probably more in an adjuvant setting, right after high-risk resection or radiation.

Nikolas: Are there adjuvant trials around?

Paul: Hopefully soon

Jessica: There is one with dendritic cell vaccination in Erlangen

Nikolas: Is there a liquid biopsy program running there in parallel?

Jessica: I do not think so.

Paul: The point is a good one, I think every new adjuvant trial needs to include LB, it is an obvious choice.

Lars: Regarding TILs we are right now running a trial in Gothenburg where we include patient with liver mets only, isolate TILs and use the bioreactor from Miltenyi to treat these patients with hepatic-artery infusions, so we infuse the TILS directly into the liver circulation. We are now running the 3rd patient we will see. Regarding the TIL study, I believe they did not publish were they extracted the TILs from.

Nikolas: Is there data on the significance of clonal evolution in UM? Do you see a switch of driver mutations or additional of mutations in UM?

Lars: That is something that is ongoing at the moment, so I will update you soon.

Paul: There is a little published but more is coming.

Past and Current studies at Institut Curie

Manuel: Yes regarding the predictors of response, we published a study a few years ago of a cohort of about 300 patients with 4% response to PD1 directed therapy and of these patients there were some with a MBD4 mutation which induces a hyper-mutated phenotype which is clonal. This is associated with about 1/3 of the responders in our institute.

Christoffer: Very nice outlook on this great cohort of the SALOME study, which seems to be ideal for translational projects. May I ask you how you funded this study?

Manuel: For SALOME as well as the other trials I showed they are publicly funded

2) Possible Ideas for LB-based studies

Christoffer: At this moment we have only limited adjuvant trials coming. This from my point of view would be the most exciting niche to fill, probably by MRD detection using ctDNA.
When it comes to therapy response and detection of resistance, the metastatic situation makes more sense. However, at this moment it is difficult to predict which drug-combination would be the next one to be approved. At this moment its only Tebe and CPI available. This would be something only Immunocore might be interested in and they already decided on the TEBE-MRD trial in the UK.

Jessica: Well I guess they have interest. However, we need a test that we can use in clinical routine, meaning the test would already need to be commercially available. The treatment is approved and we would need something in the clinics now. I would not be interested in a trial that takes very long. That might be scientifically interesting, but will not help us now in the clinic.

Christoffer: I completely agree, I assume that everyone of us is interested in getting data fast and quick transferability.

Nikolas: I think we alredy have these tests in our hands. ddPCR is robust, cheap fast and sensitive. The spectrum of mutation in UM is feasible with ddPRC. In parallel we could go for more investigational tests (methylation, CTCs, fragmentation).

Christoffer: Good idea to use an academically validated test that is available and that can then rapidly be applied to all centers of interest. However, the issue of course with a collaborating industry partner is that we would rely on their technology and their level of development. When this is in the hands of the investigators, a test can be adapted, modified and optimized during the protocol.

Nikolas: We have experience with about 30 cases from the Erlangen study in which ddPCR was nicely feasible. However, this was only a small amount of cases.

Christoffer: Yes, but I believe most of us have experience with limited cases, which makes it even more important to join forces. There is no center with hundreds of metastatic UM patients.

Nikolas: This is an excellent point and I believe it would be highly valuable to join forces. For this it would be great to know whether this group would be willing to contribute samples to a common strategy and study design?

Klaus: This are all excellent ideas of investigation. We should now check the newest EU calls and see which activities would best fit in and also get in contact with suitable industry partners. The most important thing is truly to put together specific work packages and somebody has to take the lead to draw a 1- 2 page proposal on each of these areas so we can see what we can do.

Christoffer: It would be valuable to brainstorm on all of these areas. Clinical follow-up is very interesting but may take a long time to get data. The adjuvant setting might be more feasible.

Klaus: For the call, UM is a rare disease which makes it necessary to work together on a European level, we have experts here who have done excellent work in the field. If we have a two stager,

the first step is a concept paper, which needs to be anonymous. Nikolas and Christoffer would you like to take the lead here and write a first draft?

Christoffer and Nikolas: Yes, we would be happy to do that

Klaus: the 8th of November is very sportive, but the funding is probably quite nice

Nikolas: We should get feedback and vote on which way to go and see who would be interested in participating.

Christoffer: Nikolas and I will write something quick and dirty for the group and then have a brainstorming call with input from the group.

Nikolas: We can circulate the slides and please be very direct and honest and let us know what you like and don't like as experts in the field.

Klaus: Thank you very much, it was a very informative and productive meeting and I am very positive that we have a strong group here to tackle this tumor