Viewpoint from a health care professional

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Possible Conflicts of Interest:

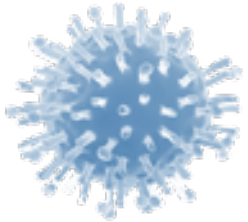
Speaker: Amgen, BMS, GSK, MSD, Novartis, Roche

Advisor: Amgen, BMS, GSK, MSD, Novartis, Roche

Research Support (to institution): Roche

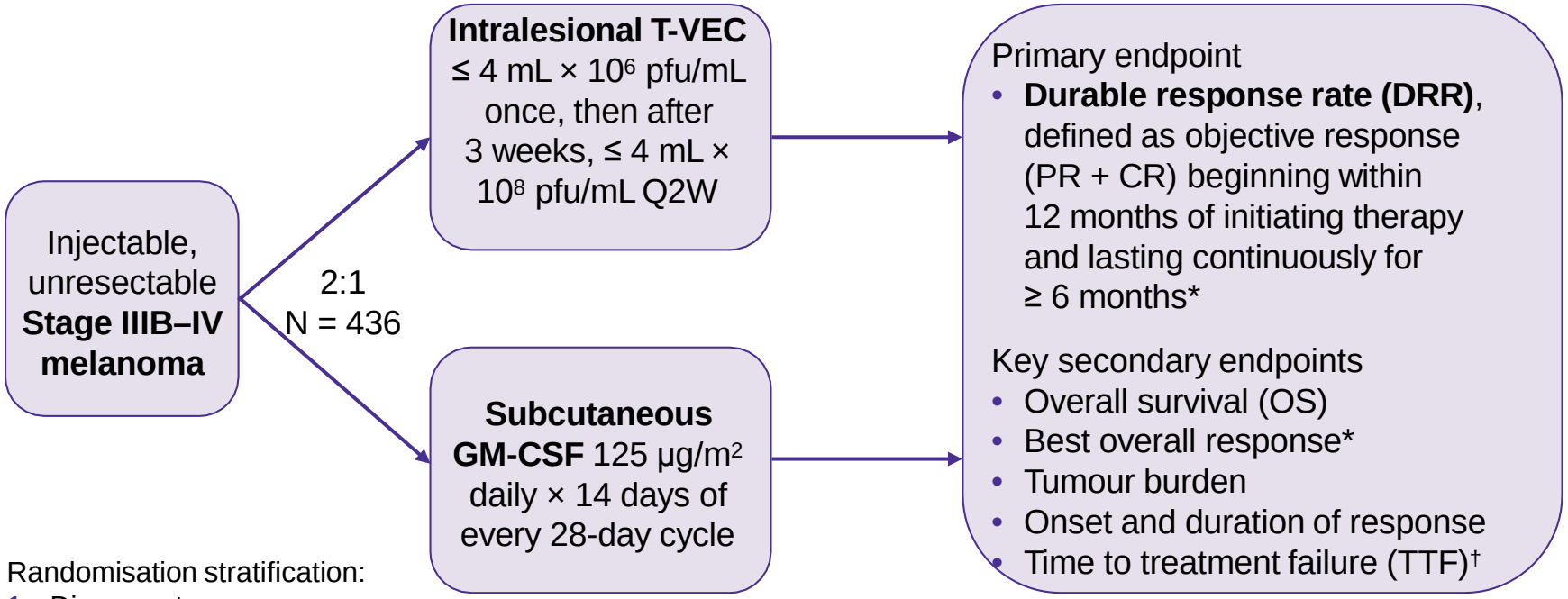
Study Fees (to institution): Amgen, Array, BMS, GSK, MSD, Novartis, Ribopharma, Roche

Talimogene-Laherparepvec (TVEC)



- An oncolytic immunotherapy based on a Herpes simplex Virus Type 1 strain (JS1) that was genetically modified to replicate preferentially in tumor cells and expresses human GM-CSF.
- It was recently approved for intralesional application in melanoma-patients with injectable locoregional and/or soft tissue metastases (AJCC stage III and IVM1a)

Phase 3 study in melanoma (OPTiM) – study design and endpoints



Randomisation stratification:

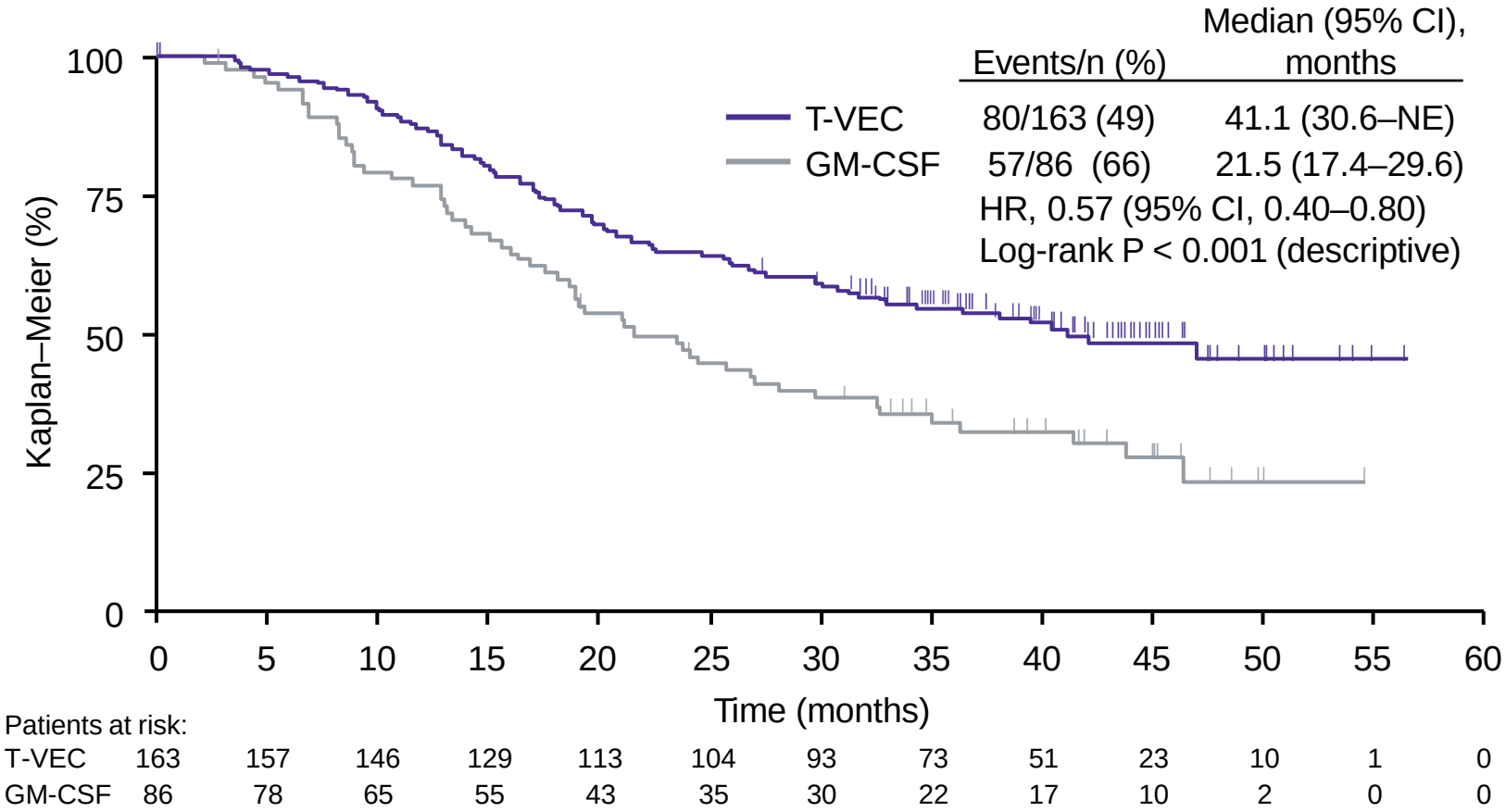
1. Disease stage
2. Prior non-adjuvant systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

Patients enrolled between May 2009 and July 2011. Discontinuation of treatment because of progressive disease per response assessment criteria was not required before 24 weeks unless alternate therapy was clinically indicated.

*Responses were determined using modified WHO criteria by a blinded EAC;
†TTF was defined as time from baseline to first clinically relevant disease progression for which no objective response was subsequently achieved or until death.
EAC, endpoint assessment committee; OPTiM, OncoVEX^{GM-CSF} Pivotal Trial in Melanoma, pfu, plaque-forming unit. PR, partial response.

Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

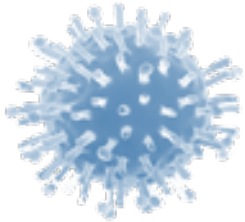
Exploratory subgroup analysis – OS in the Stage IIIB/C, IV M1a subpopulation*



*Due to the exploratory nature of the analysis and based on the current evidence, it has not been established that T-VEC is associated with an effect on OS.

Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

Talimogene-Laherparepvec (TVEC)



- An oncolytic immunotherapy based on a Herpes simplex Virus Type 1 strain (JS1) that was genetically modified to replicate preferentially in tumor cells and expresses human GM-CSF.
- It was recently approved for intralesional application in melanoma-patients with injectable locoregional and/or soft tissue metastases (AJCC stage III and IVM1a)
- It is a Gene Therapy Medicinal Product as defined in part IV of annex I to directive 2001/83/EC
- Our center is involved in a single agent biomarker study as well as in a combination study with the PD-1 antibody Pembrolizumab and has treated the first patient outside of a clinical study in Europe

Obstacles in the clinical development of ATMPs

- Regulatory
- Hands on use

Regulatory obstacles – GMO Approvals

- At study start-up it is expected that you can set up all formal requirements (ethics and health authorities approval, contracting) within 3-4 months
- With ATMPs the approval for the use of a genetically modified organism takes at least 6 months
  - It took more than 12 months to even receive a statement of receipt from the ministry of health for the first application for the use of Talimogene Laherparepvec in a clinical study in Austria
  - For every study, despite the use of the same drug a separate application for every center is necessary

Regulatory obstacles – Lack of clear EU/National Guidelines

- Bio-Safety Levels attributed to TVEC were completely different between countries and between the use in clinical studies and following approval
- For TVEC a bio-safety level 2 designation was used e.g. in Austria and Germany, bio-safety level 1 e.g. in Spain
  - While well defined for laboratory research no information is available on the requirements for bio-safety level 2 for the hands-on work with patients
  - Required “biological safety committees” were not established for clinical use of a BSL-2 drug. Necessary Qualifications were not defined
  - Study start up was markedly quicker in countries without BSL 2 designation

Regulatory obstacles - Lack of clear EU/National Guidelines

- Nearly every center has different requirements on:
  - where (laboratory, pharmacy, clinic room) TVEC will be prepared for use
  - how it has to be transported to the treatment room
  - which safety measures are necessary for patients and personnel
  - how clinical material that was used with TVEC should be disposed
- Current work by the national dermatooncology group (AMDO) focuses on harmonization of these processes

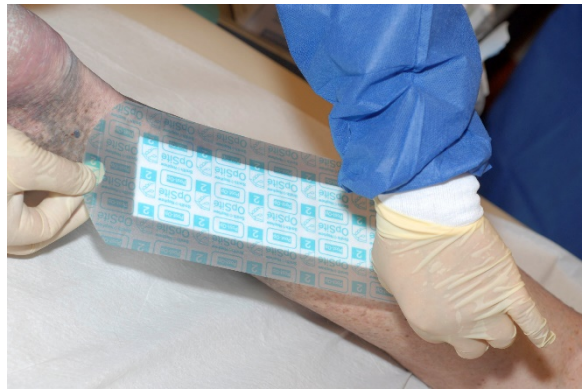
Hands on use of an ATMP - TVEC

- Has to be done after all other patients have left the clinic
- Pharmacy will only prepare the drug once all other drugs have been prepared
  - In some centers the hospital pharmacy is not willing to prepare this drug at all and it has to be done by MDs in a “research” lab
- Has to be transported in special protective containers
  - Some centers require special “back-alley” transportation

    or the use of full protective gear
- Requires a dedicated outpatient room
  - Some centers use surgical theaters for the application

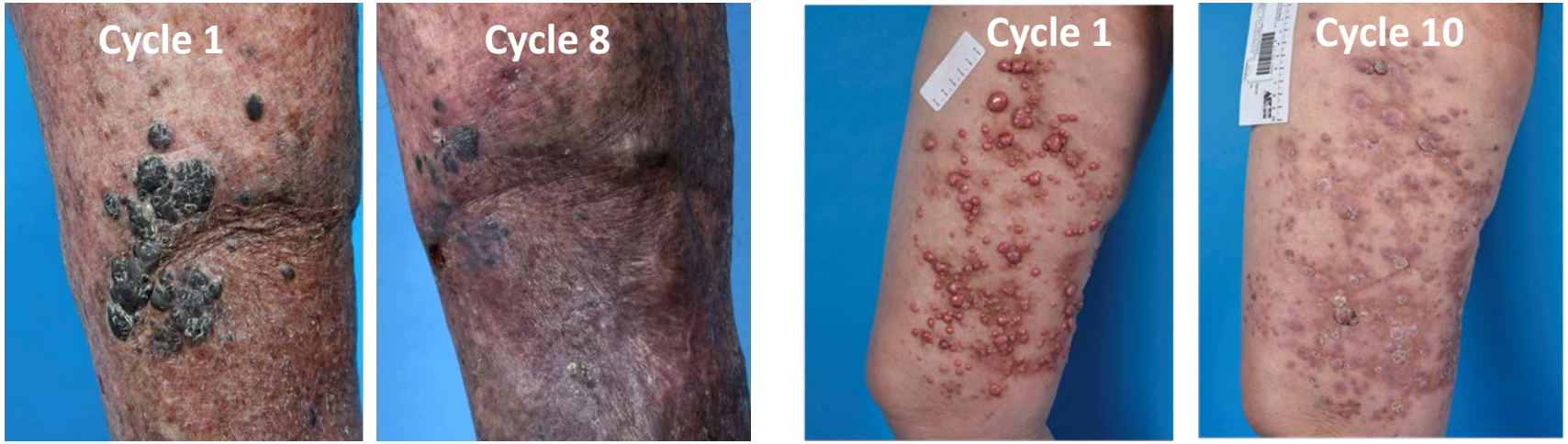
Hands on use of an ATMP - TVEC

- Nurses and doctors have to use protective gear during the application
  - In some centers routine personnel is not willing to assist and study teams still perform the application
- Patients need to use fluid impermeable dressings for one week following application and should avoid any contact of the treated area with other persons
  - Special issue with elderly patients who are dependent on health-care providers at home, patients with small kids….
  - Many questions arise on risk for children, partners – e.g. Do we have to set up a separate living area within the household?



Hands on use of an ATMP - TVEC

- The use of these drugs can have a major positive impact for patients



Patients with melanoma metastases treated with TVEC, bot patients have previously progressed on other approved treatments

- The safe and correct use of such a drug in daily routine requires a significant amount of time and personnel
  - At the same time resources are being significantly reduced in many European countries

Ways to improve the development/use of ATMPs

- Include stake holders from different regions early during development to actively approach the more complicated regulatory and practical aspects
- One European-level application/approval that can be used as a blue-print for approval at the national level
  - Larger pool of real experts available than on the national level
  - Should include a common recommendation for bio-safety level
  - Should include a clear and understandable risk assessment for better information of all health care professionals (nurses, technicians, pharamcists, general MDs)
- Option to amend existing approvals for the use of ATMPs
- Clearly defined, easily applicable regulations on the use of ATMPs, including clear and understandable recommendations for the use in the clinic

Access to ATMPs across European Countries

- AMTPs are mostly very high cost drugs, that put health systems, even in richer countries under significant financial stress
- Patients in many European Countries do not have access to these drugs, and are often still treated with therapies that have never shown a survival benefit in clinical trials
- Solving these inequalities is even more important than solving regulatory and practical use aspects of these drugs

Thank you for your attention!

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