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ABSTRACT BOOK

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The role of industry and investigator driven trials in hematopoietic stem cell transplantation

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Over the last decades, hematopoietic stem cell transplantation (HSCT) has become an established procedure for many congenital or acquired severe disorders of the hematopietic system as well as for chemo- or radiosensitive malignancies. An estimated more than 50000 such procedures are performed annually worldwide with bone marrow, peripheral blood or umbilical cord blood stem cells from the patients themselves for autologous, with healthy donor cells for an allogeneic transplant (1). HSCT provides proof of principle that healthy stem cells can replace failed or missing organ function and serves as model of modern complex high cost medicine. As such, it appears to be a prime target for all, industry driven, investigator initiated or university sponsored research. A rapid superficial analysis supports this assumption. A search for "hematopoietic stem cell transplantation" at www.clinicaltrials.gov reveals 2454 hits with 1068 open and actively recruiting clinical trials; a search at PubMed identifies 31968 hits. These findings confirm the high current interest in research concerning the field of HSCT. Clinical trials are conducted worldwide. Of the 1068 listed open studies, there are 1 open access, 78 (7%) observational and 989 (93%) interventional studies. Of the 133 listed phase III interventional trials 19 (14%) are sponsored by industry, 26 (20%) by NIH and 88 (66%) by universities or local institutions. The analysis in PubMed reveals a quite different situation. 307 hits are produced for "hematopoietic stem cell transplantation AND phase III trial", only 3 of them are true prospective randomized trials. In addition, the high activity on the "clinical trials" webpage contrasts with the high current needs in HSCT. Best conditioning, best graft-versus-host disease prevention and treatment, best stem cell source or optimal unrelated donor selection still need to be defined; few comparative studies have established the role of HSCT compared to best non transplant strategy. Some considerations for these

deficiencies are warranted, literature about potential reasons is scarce. They might relate to the role of the industry, the role of the universities, the role of the individual investigators or to the procedure itself.

HSCT is a costly complex procedure with substantial inherent morbidity and mortality (2). The relative small numbers, the heterogeneity of the patient population and the many potential factors associated with outcome complicate any analysis and increase the risk of any registration trial. There is no drug which obtained registration by a trial in HSCT and use of most drugs in HSCT is de facto "off label". The majority of trials in HSCT relate therefore to supportive care issues; the design of such industry sponsored studies is such as to present the value of the drug, not of the procedure. There are other key deficiencies. A few studies have recently addressed the macroeconomic factors associated with the use of HSCT on a global level and the factors associated with the diffusion of HSCT technology (3,4). Three factors were found to be associated with the establishment of the technology: availability of resources (as measured by gross national income per capita), governmental support (as measured by governmental health care expenditures per capita) and access to the transplant (as measured by the number of teams per inhabitants). Four factors (4 "E") were found to be associated with the diffusion of technology: *e*conomical situation, *e*vidence, *e*xternal regulations and *e*xpectation of the responsible physicians. The latter explains some of the reasons for the absence of answers to critical questions in HSCT. Reduced intensity conditioning was introduced about a decade ago to improve outcome and to expand access to elderly patients or to those with co morbidities. To date, more than 50 different reduced intensity conditioning regimens are in use, none is proven to be superior in any condition, and no prospective controlled study has established preference of any approach. Transplant physicians just "believe" that their approach is best for their patients (5). They are hindered in addition to participate in multicenter prospective clinical trials by structural deficits in university or research agency funding. Participation amongst others in a clinical research project, if not as primary investigator, can be considered as "not innovative", therefore valued as "no priority for funding". Co-

authorship as seventh amongst 14 authors in a publication might not be considered as a positive publication track record in a university career.

What are the potential consequences and ways out of these dilemmas? First and above all, university and granting agencies must recognize the need and the value for supranational collaborative observational and interventional "science- driven" studies. Instead of a multitude of underpowered national or regional trials, coordinated European trials should prevail. They can be conducted as well in a reasonable time frame. They should originate with their key questions out from comprehensive observational studies. The World Health Organization WHO has stipulated in its guiding principles on organ, cell and tissue transplants that data collection, on donors and recipients alike, is essential in order to improve outcome and to safeguard patients and donors (6). Data collection and data analysis is integral part of therapy. The European Group for Blood and Marrow Transplantation (www.ebmt.org) has established a quality management system (www.jacie.org) and a standardized data reporting system. Recent data show that the introduction of such a quality management system was associated with improved outcome (6). Hence, standardized professional care with external review yields superior outcome than ad hoc treatment. These data pave the way for future fields of joint research with Health Technology Assessment. Standardized reporting of expensive complex procedures should be mandatory, within the framework of a quality management system. Such data form the basis for "generating evidence". Health Technology Assessment, quality control and science can thus be incorporated. The question should not be about quality and justification of Industry driven, investigator initiated or university sponsored research but integration within a broader framework. With such an approach, conduct and funding of independent research in medicine will remain possible.

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Results of independent and company driven trials: colon and other solid cancers

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Company driven research (or profit research) has as its main objective permission for the marketing of a new drug for a particular indication. At present, regulatory agencies approve the new anti-neoplastic agents especially on the basis of a surrogate endpoint (response rates and, more frequently, progression-free survival) with evidence of activity of the new drug. The consequences of this policy are that no data on efficacy and long-term toxicity are available when the drug comes on the market. Between 1990-2002 only 18/57 (32%) of approved drugs increased survival (1). The FDA, in the case of accelerated approval, requires that the company subsequently produce results showing the impact on survival or on quality of life of these drugs, but such studies are reported only years after the drug has been reimbursed by the National Health System (see bevacizumab in the treatment of metastatic breast cancer). Furthermore, often these drugs present only marginal benefits with respect to the treatments already available and at very high costs for the National Health System. Examples of drugs thus approved with doubtful efficacy are cetuximab and panitumumab for metastatic colorectal cancer. In fact: - cetuximab in combination with FOLFIRI as first-line chemotherapy for metastatic colorectal cancer increased progression-free survival (PFS) by 0.9 months with respect to FOLFIRI alone (2); - cetuximab in combination with irinotecan as second-line chemotherapy increased PFS by 1.4 months with respect to irinotecan alone (3); - cetuximab as third-line therapy increased overall survival by 1.5 months with respect to the best supportive care (4). Similar results have been obtained with panitumumab as third-line therapy which increased PFS by 0.7 weeks with respect to the best supportive care (5). When these results were reanalyzed in KRAS wild type patients (the subgroup for which the two drugs are now approved on the basis of retrospective subgroup analyses) the benefits were marginal: in different studies cetuximab versus no cetuximab treatment increased PFS from 0 to 1.8 months

and panitumumab versus no panitumumab from 1.2 to 2.0 months. Finally, as an example of a drug showing a statistically significant difference but also a clinically irrelevant difference in a randomized clinical trial we have erlotinib. This drug has been approved for metastatic pancreatic cancer on the basis of the results of a study in which, when compared with gemcitabine alone, it increased overall survival by 0.3 months (6).

Independent research has as its main objective the clarification of the role of the new drug that has been approved by the regulatory agencies. We have two types of independent research: the first is that which is totally or partially supported by pharmaceutical companies but designed and realized by the various oncological research groups world-wide. Generally, this research has been previously agreed on with the companies and, of course, answers questions considered important both to academics and to the pharmaceutical companies. The other type is that totally supported by institutions such as the National Health System, Regions, University, Italian Drug Agency, National Research Council, etc. This latter research is the only one that has an interest in evaluating the real impact of the new drug (or its combination) on the overall survival or on the quality of life of cancer patients. However, independent research could plan studies of new combinations of anti-neoplastic drugs or new indications (rare tumors) or to define the drug's optimal dose with a large patient population, studies on predictive factors, pharmaco-economic studies, pharmaco-epidemiologic studies (suitability of prescriptions and effectiveness) and non-pharmaco-centered studies (diagnostic approaches, screening tests, follow-up tests) to answer important clinical issues.

Unfortunately, this research today presents ever-more difficulties after the introduction of the "European Directive related to the application of the Good Clinical Practice guidelines in the execution of clinical trials" that is the discipline regulating clinical research in effect since 2004 in Europe. The official goals of the Directive were to improve the protection of patients and the reliability of research reporting and to harmonize and increase the competitiveness of European clinical research. Instead, this Directive dramatically increased the documentation required to start a clinical trial and the cost of setting up, running, and closing down trials increased some four-fold without

increasing the protection of patients. Furthermore, there have been fewer trials to offer patients, and answers to important clinical questions have been significantly delayed or remained unanswered. Consider that the number of new trials of EORTC fell from 19 in 2004 to 7 in 2005 (63%) and a third fewer patients were enrolled; that trial costs increased by 85% and insurance costs from 70m to 140m Euros, that trial initiations were about 5 months slower than in 2004 (7). To make things worse in Italy, it has been decided that insurance is obligatory for studying drugs already on the market. Due to all these problems, there is a real risk that the only clinical studies in existence will be those run by the pharmaceutical industry. In fact, only a few ongoing trials will answer the several problems of sponsored research (i.e., the TAYLOR and the Short HER2 studies) and probably no studies will be carried out to prospectively evaluate the role of cetuximab and panitumumab in KRAS wild type metastatic colorectal cancer.

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Transplant immunosuppression: less is more, but where have the academics gone?

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Organ transplantation has proven to be an effective therapeutic for a large variety of disease states, but the chronic immunosuppression required for allograft survival increases the risk for infection and neoplasia. In the past 50 years, a wealth of experimental data has accumulated relating to strategies to preserve function and prolong graft survival. These strategies operate by inducing peripheral or central tolerance to the allograft, with protocols based on regulatory T cell induction as the most promising ones. However, as these protocols move into the clinic, there is recognition that little is known as to their efficacy when confronted with the human immune system: pre-existing memory T cells and 'heterologous immunity' in Ag-experienced humans but not in immunologically naive rodents, infections and early activation of innate immune response and the related inflammation-induced cytokine milieu that inhibit Treg activity while augmenting the T effector response, all pose significant barriers to tolerance induction.
A better understanding of cellular and molecular mechanisms by which memory T cells and innate immunity modulate transplantation tolerance and detailed immunological studies of the rare 'spontaneous tolerant' patients may lead to development of combined strategies that target and modulate the immune system at multiple levels.
Since the first successful renal transplantation in Boston in 1954, more than a million such procedures have been performed worldwide. By strikingly minimizing the incidence of acute rejection, immunosuppressive drugs have led to overall improvements in allograft and patient survivals. However, the improved short-term survival rates have come at a cost: these drugs generally need to be given for the entire life, induce many indirect and direct side-effects and pose an increased risk of life-threatening complications, infections

and malignancies. Furthermore these therapies have had little effect on the inexorable loss of transplanted organs because of chronic allograft rejection.

Recent trends in long-term survival rates have indicated a progressive improvement of renal allograft half-lives, but this has been only observed in patients who never had an acute rejection episode. These data emphasize the critical role of the recipient's alloimmune response as a major determinant of transplant outcome and highlight the need to develop novel strategies to induce immunologic donor-specific tolerance defined as a lack of a destructive immune response towards the graft in the presence of generalized immune competence. Ideally, tolerance should also translate into a lack of chronic rejection and late graft loss.

Collaborative Clinical Trials

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Future improvements in health care will require the introduction of new therapies following their evaluation in clinical trials. Indeed, progress in medical research and innovations among pharmaceutical and device manufacturers have produced unprecedented opportunities for new therapeutics. However, there is a crisis in the clinical trials environment produced by burgeoning costs, burdensome regulatory requirements and other factors, and this reduces the likelihood of successfully completing the critical clinical trials that are essential. The problems with clinical trials have been the topic of reviews (1), and they must be approached on a broad societal basis with input from government, pharmaceutical and medical device industries, academia and patient advocacy groups. Many changes will be needed. However, a simple change in structure of late phase clinical trials for some categories of drugs and devices could result both in greater efficiency and better information from the studies generated and deserves consideration (2).

Pharmaceutical and device companies usually sponsor targeted, disease-specific clinical trials to obtain selective regulatory approval to market their products for a particular indication. They select the patient population for the trial and define study procedures and endpoints, seeking to optimize the likelihood of a positive outcome. This approach is costly as it requires establishment of a clinical trials infrastructure, and expenses to develop new pharmaceuticals may reach several hundred million USD. Study enrollment is frequently slower than expected if the target population is limited and if there are concomitant competing trials by other companies in the same area. It is likely that this problem will worsen as more devices and drugs are brought to late phase clinical trials often with very similar agents competing for the same population. Further, the available populations for clinical trials are likely to become smaller as targeted therapies are directed toward smaller and better defined subsets of patients with

common illnesses. For example, new targeted therapies in cancer therapeutics such as inhibitors of epidermal growth factor can only be tested in a small subset of lung cancer patients with the appropriate mutation. As the pathobiology of common diseases is better understood, including more detailed analyses of complex genetic contributions, new therapies may be applicable to increasingly smaller subsets of patients, and this will make enrollment in trials more challenging and limit the number of possible competing trials.

There are examples of the impact of these problems in the recent development of both new medical devices and pharmaceuticals. For example, many new anticoagulants have been tested in the past decade and some introduced into clinical practice, typically following a predictable pattern of clinical trials. Initial phase 3 studies are conducted to demonstrate effective prevention of venous thromboembolism following major orthopedic surgery because the high rate of objectively-determined venous thrombosis allows for defined endpoint with a very small sample size, and also the risk of bleeding caused by the new agent can be assessed following surgery. Several companies have conducted separate phase 3 trials in knee replacement and hip replacement. This has resulted in a need for very large overall patient populations to be included, and there has been competition among concurrently conducted trials for enrollment sites and patients. This is inefficient, increases costs and can delay completion of the trials. Furthermore, there are always variations in study design between trials including differences in patient selection and definitions of thrombotic and bleeding endpoints which make it difficult to compare results across trials. Therefore, we often have little comparative information about the relative benefits of these agents. Very recently, tens of thousands of patients with atrial fibrillation have been entered into at least 3 large international randomized prospective trials evaluating new oral anticoagulants (3-5). Again, these studies have run independently with similar but slightly different designs. They have produced important new findings, but as in the past, we have no information regarding the comparative effectiveness of these new agents.

A change in the conduct of clinical trials to a more collaborative approach could overcome some of these problems. The cooperative development and conduct of trials in which pharmaceutical or device companies share costs, enrollment is expedited, and the duration of the trials shortened while using a common protocol with well defined endpoints would be the result.

There are important successful examples of this approach. The Cardiac Arrhythmia Suppression Trial (CAST), sponsored by the National Institutes of Health, tested 3 anti-arrhythmic drugs from different pharmaceutical companies with a common placebo-controlled protocol to determine whether one or more of the drugs would reduce the rate of death from arrhythmia (6). This study showed that 2 approved anti-arrhythmic agents resulted in excess mortality, and these findings changed practice. If separate studies had been done, they would have taken much longer, and it is unlikely that such a clear result would have been obtained. Also, the importance and benefit of collaboration has been demonstrated recently by therapeutic trials related to multiple myeloma (7) and Alzheimers disease sponsored by the Foundation for the National Institutes of Health (8).

There are limitations to such an approach. Such studies are only possible when several similar therapies are available for testing at the same time. New regulations from regulatory agencies might be required to impose a clinical trial structure on companies with competing products and a desire to get to market first. However, individual corporate expenditures would be reduced, and the results would be more definitive than if each company functioned alone. The result would be that new therapies could be developed faster and comparisons among competing, similar therapies would be more straightforward. Additionally, there are trust and patent issues associated with such collaborative trials that would require negotiation or possibly new legislation.

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Outcome research in melanoma: do clinical trials are the answer to better understand the patients' outcome in melanoma?

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One of the important issues for a phase III trial is the external validity of the study. This criterion allows one to understand the generalizability of the results, and relates to whether the study patients may be similar to those evaluated in one's own practice. To better understand the results of a clinical trial the readers should first know further details of the recruitment process. The first question is as follows: overall, how many patients have been evaluated in the context of a clinical trial? In particular among patients meeting the inclusion criteria, what is the eligibility fraction (patients meeting eligibility criteria/patients meeting inclusion criteria)? These data may be important for critical patients such as metastatic melanoma cancer patients. The eligibility fraction gives important data and details of the overall population we see in clinical practice, and allows one to understand the fraction of patients who really can receive and potentially benefit from chemotherapy. A recent revision of the Consolidated Standards of Reporting Trials guidelines suggests that authors should include the number of the potentially eligible patients assessed for eligibility [1]. Patients enrolled in clinical trials may not represent those we see in the daily practice.
IL-2 is one of the drug approved by FDA for clinical use in advanced melanoma. Recently a phase II randomised study has been reported in the New England Journal of Medicine. No data are available regarding the elegibility fraction (2). Since IL-2 therapy may be offered only for patients with excellent performance status, in absence of comorbidities, we lack the opportunity to better understand the external validity of this study.
Furthermore in the adjuvant seTting, considering the minimal contribution of IFNalpha 2B, in the last 10 years only 3 out of 12 studies reported the Consort diagram.
Overall the se data indicate that there is a terrific need to report all the useful and informative details of the studies in melanoma cancer patients. The role of the outcome research is demonstrated by considering disease-related prognostic factors and patient-related socioecomic features, which may influence the breslow thickness, the disease free and overall survival.
With regards to disease-related prognostic factors, the role of mitotic rate has been reported for the first time in an outcome study, which

changed the TNM staging system in melanoma patients with stage I-II according to the AJCC classification (3).
There is evidence that cancer patients coming from more disadvantaged SES have a higher risk of death as a result of their disease compared to patients with advantaged SES. However, most of the studies reported only general demographic characteristics such as age, sex, racial and ethnicity. They lack important information regarding education, current employment or occupational status, and family context.
In a recently reported trial, our group investigated the correlation between SES, education, family context and Breslow, disease free and overall survival in AJCC stage I-II melanoma cancer patients (4). By using a prospective electronic data base, with individual data concerning pathological and epidemiological features, we were able to demonstrate that gender, age, SES and family context are the strongest correlates of Breslow, the most important prognostic factor. Furthermore, in our study, the risk of melanoma death was 7 times higher in patients with low SES and living alone and almost 2 times higher in patients with low socio-economic status but not living alone. Our data have clinical implications for the design of future melanoma prevention campaigns in order to reduce cancer disparities and improve the prognosis of more socioeconomically disadvantaged melanoma patients.
All the above data demonstrate that there is a terrific need to performe outcome research study to better understand patients' outcome in the real medical world.

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From clinical research to real life "Outcome Research": Breast cancer

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Breast cancer is the most frequent malignant disease in women and it accounts for more than 2 millions new cases per year in the world.
The incidence of the disease is in continuous increase, however fortunately mortality decreased in most of the Western countries by about 20% during the last 20 years, probably due to better screening and early detection procedures and due to new therapeutic options available nowadays.

Already two centuries ago it was known that the ablation of the ovaries (performed for the first time toward the end of 1800 y a German surgeon named Schinzinger and developed further by Thomas Beatson) could induce remissions in a certain percentage of patients and during the following decades the role of hormones in breast cancer became evident and allowed the development of several compounds.
The aera of chemotherapy started about 60 years ago also introduced in the armamentarium against breast cancer a number of possibilities that are still growing.
During the last years the better understanding of the biology of the disease allowed the development of new compounds (e.g. tyrosine kinase inhibitors, antibodies) that gave rise to huge hope among patients and professionals.

The development of these new therapeutic agents has been largely performed in universities and by the pharmaceutical industry, frequently in cooperation.
During the last years the costs of development of a new compound have been massively increasing and it is estimated that at the time being they are around 1 billion per compound that comes to

due to the magnitude of the financial investments (including the costs of all compounds that do not make it to real life) this effort can only be afforded by large companies that are I full control of the process.

In breast cancer about 10 years ago academia decided to start a new initiative in order to become a partner of the industry and in order to be able to perform trials which are meaningful for the patients and do not only respond to the requirements of registrations agencies (FDA, EMA, etc.): the Breast International Group was founded. Its purpose is to perform large trials in a possibly short time (therefore favoring the needs of pharma companies involved in the process) but to have the control on the conduct of the trials and in particular on the data-base, the outcome, the toxicities, the statistics and the reporting of the results of such trials.
The Group has performed already several trials that have been conducted under these auspices, allowing therefore to avoid the frequent problems observed in trials performed exclusively under the control of the pharma industry:

- Lack of central/independent review of outcome values (should be mandatory)
- Reporting of toxicities as non related to treatment or not reported at all
- Another frequently observed issue is the non-reporting of trials that show uninteresting results for the pharmaceutical industry (for example low dose of Letrozole?). The obligation to register all trails to the NCI data-base will be surely palliating to this problem.

In conclusion independent academic clinical research in breast cancer is nowadays nearly impossible due to the exorbitant costs. One of the possibilities is to develop a partnership between academia and pharmaceutical industry which should allow having a reasonable certitude that the reported outcome and toxicities of a new compound correspond to reality.

Insights from population-based registry studies with a focus on myeloproliferative neoplasms and chronic myeloid leukaemia

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Background. By taking advantage of high-quality population-based Swedish registries including Swedish Cancer registry, Swedish Population registry, Swedish Multigenerational registry, Swedish Inpatient and Outpatient registers, national disease specific registers and also local registries at all major hematology/oncology units we have addressed several issues related to patients with hematological malignancies. The information achieved through this kind of research is in this report exemplified by studies on familial aggregation and risk factors for leukemic transformation in patients with myeloproliferative neoplasms (MPNs). In addition, we present patterns of relative survival among large cohorts of patients with MPN and chronic myeloid leukemia (CML).
Patients and Methods. In the study of risks of MPN among relatives to patients with MPNs we used a cohort of 11,039 patients and their 24,577 first-degree relatives and compared risks with first-degree relatives (n=99,542) of matched controls **(I).** Based on this nationwide MPN cohort we conducted a nested-case control study including 162 cases with a subsequent acute myeloid leukaemia (AML; n=153) or myelodysplastic syndrome (MDS; n=9) and 242 matched control patients. For all patients we obtained clinical and MPN treatment data **(II)**. In studies on relative survival we identified 9,384 patients with MPNs diagnosed 1973-2008 with follow up 2009 **(III)** and 3,173 patients with CML **(IV)** diagnosed between 1973 and 2008 with follow-up also end of 2009.
Results. *Familial aggregation **(I)***. Relatives of MPN patients had significantly increased risks of polycythemia vera (PV) (relative risk (RR) and 95% confidence intervals (CI) = 5.7; 3.5-9.1), essential thrombocythemia (ET) (RR = 7.4; 3.7-14.8), and MPN unclassifiable (NOS; RR = 7.5; 2.7-20.8). Analyses stratified by type of first-degree relative revealed consistently higher risks for siblings, compatible

with a model of recessive genetic inheritance, which can be confirmed only by identifying the susceptibility gene(s). Mean age at MPN diagnosis was not different (P = .20) for affected relatives of cases (57.5 years) versus controls (60.6 years), and risk of MPN by age was not different for parents versus offspring of MPN cases (P = .10), providing no support for anticipation. Relatives of MPN patients had a borderline increased risk of CML (RR = 1.9; 0.9-3.8; P = .09). *Risk factors for transformation in MPN* ***(II)***. 41 of 162 (25%) MPN patients with AML/MDS development were never exposed to alkylating agents, radioactive phosphorous (P^{32}), or hydroxyurea (HU). Compared to MPN patients who were not exposed to HU, the odds ratios (and 95% confidence intervals) for 1-499 g, 500-999 g, >1000 g of HU were 1.5 (0.6-2.4), 1.4 (0.6-3.4), and 1.3 (0.5-3.3), respectively for AML/MDS development (not significant). MPN patients who received P^{32} >1000 megabecquerel and alkylators >1 g had a 4.6-fold (2.1-9.8; p=0.002) and 3.4-fold (1.1-10.6; p=0.015) increased risk of AML/MDS, respectively. Patients receiving two or more cytoreductive treatments had a 2.9-fold (1.4-5.9) increased risk of transformation. *Relative survival in MPNs* ***(III).*** A total of 9,384 MPN patients were identified; PV=4,389, ET=2,559, PMF=1,048, and MPN NOS=1,288; 47% were males and the median age at diagnosis was 71 years. Relative survival ratios (RSR) and excess mortality ratios (EMRR) were computed as measures of survival. Patients of all MPN subtypes had inferior RSRs compared to the general population. Ten-year RSRs for PV, ET, PMF and MPN NOS were 0.64 (95% CI 0.62-0.67), 0.68 (0.64-0.71), 0.21 (0.18-0.25) and 0.49 (0.44-0.53), respectively. Relative survival was significantly decreased during all calendar periods. However, survival rates improved significantly with time and the highest RSRs were seen in the most recent calendar period. Relative survival was analyzed by subtype before and after 1993 when MPN NOS was introduced in the classification. Before 1993, ET had a significantly lower relative survival compared to PV, 10-year RSR being 0.43 (0.38-0.47) compared to (0.60 (0.57-0.63). However, after 1993 the relationship was the opposite reflected in a 10-year RSR of 0.83 (0.79-0.88) for ET and 0.72 (0.67-0.76) for PV. Thus, survival rates improved with time for patients with PV and ET. PMF on the other hand had poor survival rates throughout the study

period. *Relative survival in CML **(IV)***. Relative survival improved with each calendar period with the greatest improvement 2001-2008. Five-year cumulative RSRs (95% CI) were 0.21 (0.17-0.24), 0.23 (0.20-0.27), 0.37 (0.33-0.41), 0.54 (0.50-0.58) and 0.80 (0.75-0.83) in the five (1973-1979, 1980-1986, 1987-1993, 1994-2000 and 2001-2008) calendar periods, respectively. This improvement was confined to age groups < 79 years. The 5-year RSRs for patients diagnosed 2001-2008 were 0.91 (0.85-0.94) and 0.25 (0.10-0.47) for patients <50 and > 79 years, respectively. Males had inferior outcome. The up-front overall use of imatinib mesylate (IM) increased from 40% (2002) to 84% (2006). Only 18% patients > 80 years received IM as first-line.

Conclusions. *Familial aggregation **(I)***. Our findings of 5- to 7-fold elevated risk of MPNs among first-degree relatives of MPN patients support the hypothesis that common, strong, shared susceptibility genes predispose to MPN, and possibly CML. *Risk factors for transformation in MPN **(II)***. The risk of AML/MDS development following MPN diagnosis was not significantly associated with HU treatment but with high exposures of P^{32} and alkylators. 25% of MPN patients who developed AML/MDS were not exposed to cytotoxic therapy, supporting a major role for non-treatment related factors. *Relative survival in MPNs **(III)***. We found all MPN subtypes to have a significantly decreased life expectancy compared to the general population. However, survival of MPN patients improved over time in all age groups. This may reflect in part the earlier establishment of a MPN diagnosis in more recent years but also the introduction of more effective treatment strategies and better supportive care. *Relative survival in CML **(IV)***. This large population-based study shows a major improvement in outcome of CML patients up to 79 years of age diagnosed 2001-08 mainly caused by an increasing use of IM. The very elderly still do poorly partly due to a limited use of IM.

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International networks and the safety of drugs

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Why speaking about international networks for drug safety at an oncologic meeting?
There are at least two good reasons. A first one, focuses on the increasing number of new medications which may have a potential for inducing cancer; it is the case, for example, of several biological agents, such as tumor necrosis factor-alpha (TNF-alpha) antagonists, used in rheumatology, gastroenterology and dermatology [1]. Cancers are rare events and only international cooperation may enable to properly estimate risks. It is obvious that even a small increase in the risk of selected cancers may significantly modify the benefit-risk profile of the involved drug. A second reason partly related to the previous one, is the higher risk of developing specific cancers one can observe in pharmacologically immune-suppressed patients such as organ transplanted patients [2]. Again, only an international cooperation could enable to assess risks in these groups of patients with uncommon conditions and to find ways to minimize risks. Cancer induction differs from other adverse events, since it may have a latency of several years for development, and may result from interaction between different environmental risk factors and genetic background. The skin may function with regards to cancer risk as a sentinel organ. Keratinocyte derived skin cancers (namely, basal cell and squamous cell carcinomas) are the most common cancers in humans with incidence rates in the order of one per thousand per year. Quite remarkably, skin cancer is associated with several solid cancers of internal organs [3]. Hence, a documented increase in the incidence of skin cancer may alert about an increased risk of internal organs as well.

Mounting an international network is not an easy task. I will discuss the issue by making reference to my experience with the organization of an international registry of patients with psoriasis being treated by systemic agents, the Psonet collaboration. The armamentarium of systemic treatments for psoriasis greatly enlarged in recent years with the introduction of biological agents targeting cytokines such as TNF-alpha, and the p40 subunit of interlukin 12-23. New drugs are also expected to be delivered soon, e.g., antagonists of interlukin 17, Janus kinase 3 (JAK3) inhibitors and apremilast, among the others. An issue which was discussed at an early phase of drug delivery of new biological agents was their potential for inducing cancer. Since psoriasis is a chronic long-lasting disease, data on long-term effectiveness and safety are requested. Patient registries associated with cohort surveillance are especially suited to provide these data, and several European countries have established such registries. Combining the results from nation-based registries would increase power and may enable to conduct investigations that would not be feasible at a single country level. This is particularly relevant when studying rare or delayed adverse events such as cancer [4]. Psonet is an investigator-initiated, international scientific network of coordinated population-based registries of systemic treatment for psoriasis, which has been supported for its establishment by a grant from the Italian Drug Agency (AIFA) and is coordinated by Centro Studi GISED in Italy. The initiative started in January 2005 [5]. Eleven European registries at different stages of development are associated in Psonet to date. A total of about 25,000 patients have been enrolled. The Psonet members agreed early in time on a common set of variables and procedures to be included and implemented in the national registries. Thus, entry criteria, clinical and socio-demographical characteristics, major outcomes, and follow-up schedules are harmonized between registries. Among the others, deliverables of the Psonet collaboration would include: 1. comparative data on treatment strategies for psoriasis in Europe; 2. rapid alerts on newly recognised unexpected events; 3. regular reports on effectiveness and safety data, 4. analyses of risk factors for lack of response as a preliminary step to identifying relevant biomarkers. The network documents the feasibility of data combination at an

international level, moreover, Psonet could be linked with other registries, e.g., rheumatologic registries, to increase power when assessing rare events such as cancer.

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Long term outcomes in Lymphoma

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Novel drugs developed over the last decade are going to markedly change the prognosis for both non-Hodgkin's (NHL) and Hodgkin's (HL) Lymphomas **(1-3)**. These novel drugs are mainly monoclonal antibodies, to be employed either naked or as immunoconjugate, and they usually display potent anti-lymphoma activity along with reduced short-term toxicity. However, prolonged follow-up is still required to verify: i. the real impact of the new agents on disease curability; ii. the possible toxicities that may arise at mid- and long-term from the extensive use of the novel drugs, either alone or in association with chemotherapy. Indeed, further and prolonged studies are needed in order to define the optimal therapeutic strategy for lymphoma patients, i.e. the ideal combination of novel drugs with well established and conventional treatments. We here report two studies of outcome research, demonstrating the value of prolonged follow-up in the evaluation of treatment programs for lymphoma patients. Both studies addressed the issue of autotransplant-based approaches with and without the anti-CD20 Rituximab monoclonal antibody. The long-term outcome evaluation allowed to define both the therapeutic efficacy in term of disease curability and the risk of mid/long-term toxicities of the treatments assessed in our independent clinical research.

The first outcome research is an update on three consecutive prospective trials performed in Italy over the last 18 years, to verify the efficacy of the use of High-Dose Sequential Chemotherapy (HDS) and autograft as first-line therapy for high-risk Follicular Lymphoma (FL) <60 yrs. Indeed, we started early in 1990, developing a scheme derived from the HDS schedule designed by Massimo Gianni, with the aim to exploit the possible in-vivo purging effect operated by

chemotherapy before stem and progenitor cell (PBPC) collection for autograft. The first trial was a single Center phase II study exploring both feasibility and efficacy of the HDS program as first line therapy in advanced-stage indolent lymphoma (1991-1998, 26 FL patients) **(4-5)**. A multicenter phase 2 trial was then launched among GITMO (Gruppo Italiano Trapianto Midollo Osseo) Centers, to verify the efficacy of HDS in advanced-stage FL in a multicenter setting (1996-1999, 92 patients) **(6)**. More recently, due to the availability of Rituximab, a randomized phase 3 study was launched together with GITMO and IIL (Intergruppo Italiano Linfomi) Centers, comparing Rituximab supplemented HDS (R-HDS) vs. CHOP-R in aaIPI 2-3 FL (2000-2005, 68 patients in the R-HDS arm) **(7)**. Overall, 186 have been treated with HDS, updated results on their long term outcome has been obtained for 170 of them. They all had a diagnosis of FL (grade 1-2: 71%) and presented with advanced stage, their median age was 48 yrs., high LDH was recorded in 48%, bone marrow involvement in 77%. Overall, 141 patients (83%) went into Complete Remission (CR), while treatment failed in 17% of patients, including early toxic deaths (3.6%), Partial Remission (4.8%) and no response (8.3%). The long-term outcome shows that 120 patients out of 170 are presently alive. A few deaths occurred, 25 due to lymphoma but unfortunately 7 and 11 due to peri-transplant and late toxicities, mainly secondary neoplasms. Despite the late toxicity onset, the survival projection curve indicate that at a median follow up of 10 years, the median survival has not yet been reached, with 82 patients (approximately 50%) presently in their first continuous complete CR. Indeed, 47 of them are in their first CCR at 8 up to 15 years since HDS. The results indicate that a prolonged survival is achievable also in poor risk FL and the survival curve obtained in our setting may represent a useful comparison for the novel chemo-immunotherapy approaches now commonly employed as first-line treatment in FL patients. Moreover, the approximately 50% of patients still alive without any sign of disease up to 15 years since HDS suggest that disease eradication and possibly the cure seem achievable at least in a subset of high-risk FL patients.

The occurrence of secondary leukemia has been of major concern in our outcome research on HDS in FL patients. Thus, we planned to perform a wide analysis of secondary neoplasms, in a large series of lymphoma patients treated with HDS, with and without Rituximab, and followed at very long-term. In this analysis we took advantage of the registry of the multicenter GITIL (Gruppo Italiano Terapie Innovative Linfomi) group, with the reports of most patients managed with HDS over the last two decades. Thus, a long-term follow-up survey has been performed on 1,347 lymphoma patients treated between 1985 and 2005 with a HDS program and autograft by 11 Centers associated to GITIL. Patient median age was 46 yrs, the vast majority of them were at high risk: more than half of the patients received HDS as salvage for refractory or relapsed disease; for patients treated at diagnosis, poor prognosis was due either to histology, namely mantle-cell and T-cell lymphoma, or to the clinical presentation. Overall, their median life expectancy could not be expected to exceed 5 years. The overall survival was good for such a series of poor risk patients, with projection, at a median follow-up of 7 years, of 63% at 5 and 56% at 10 years, respectively, and a median survival projected to be of more than 16 years. Patients receiving HDS supplemented with Rituximab had a definitely improved outcome compared to those receiving HDS without Rituximab, as already observed in a previous study on a selected group of patients **(8)**. However, the main issue of this outcome research was the incidence of secondary neoplasia. Unfortunately there have been 53 cases of secondary myelodysplasia/acute leukemia (sMDS/AL), with a crude incidence of 3.9%. Their median time of occurrence was 3.3 years, and it is definitely of concern the occurrence of some late sMDS/AL, up to 13 years following autograft. Overall, the cumulative incidence at 5 and 10 years of sMDS/AL were 3.09% and 4.52%, respectively. Advanced age, male gender and the use for autograft of PBPC collected after multiple high-dose chemotherapy shots were the three factors associated with a higher incidence of sMDS. In our outcome research, we also recorded 65 solid tumors among long-term survivors following HDS. The period of occurrence (median: 5.5 years) was delayed compared to sMDS and the cumulative incidence rates were 2.54% and 6.79%, at 5 and 10 years, respectively. Factors found to be

associated with solid tumor occurrence were advanced age, post-HDS radiotherapy, and rituximab addition to HDS **(9)**. The ultimate question regards the real risk for these patients of developing a second malignancy compared to what is expected in the control population. Thus, we calculated the standardized incidence ratio, that showed that our patient series had a 2.6 fold higher risk of sMDS/AL development and 3.2 fold higher risk for solid tumor compared to the age-matched Italian population.

In conclusion, the two studies here presented confirm the value of the outcome research to define the therapeutic efficacy of innovative treatment strategies for lymphoma patients.

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Independent as a redundant and misleading qualification of research

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The points which are discussed, with a comparative reference to the regulatory, methodological, bioethical literature include:

1) the origins and the implications of the term "independent" as currently used to qualify RCT (and more broadly research);

2) the misleading diversification/dissociation (in concepts and in practices) between care and experimental protocols;

3) the critical importance of a re-definition of the rules and practices related to insurance, monitoring, informed consent, to make research fully accountable to the rights of patients and society.