least threefold while the levels of 121 transcripts were reduced by one-third or more, with accompanying p-values less than 0.01. Most of these genes encoded proteins important for DC effector functions including cytokines, chemokines and receptors; antigen presentation; cell adhesion; and T cell activation. We observed a high level of expression of a novel member of the class A scavenger receptor family, MARCO. MARCO is thought to play an important role in the immune response by mediating binding and phagocytosis, but also in the formation of lamellipodia-like structures, of dendritic processes, and in cell trafficking. With respect to the latter, we have now shown in mice that approaches that block MARCO can have profound effects on DC migration from tumor vaccination sites to peripheral lymphoid tissues. Our future clinical vaccine trials in cancer patients may incorporate this strategy as well to enhance potency.

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Wednesday 29 September 10:15–12:00

WORKSHOP 6

Pharmaceutical industry, investigators and institutions: partners or tools? Practical issues in clinical cancer drug development

25 INVITED

Pharmaceutical industry, investigators and institutions: partners or tools? Practical issues in clinical cancer drug development. Erosion of the principal investigator in a climate of industry dominance

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Although institutional review boards, government agencies, and the scientific community consider the principal investigator as the individual who is ultimately responsible and accountable for the design, execution, and analysis of clinical trials of novel therapeutics, the role of the academic investigator is becoming dangerously ambiguous. There is no doubt that the phenomenon is largely due to the progressively greater control that the pharmaceutical and biotechnology industries are insidiously assuming behind the scenes. The heightened interests of the pharmaceutical and biotechnology industries in cancer therapeutic development, along with the somewhat seasonal interests of the investment community, have undoubtedly catalyzed cancer therapeutic development efforts over the last decade, but the notion of the principal investigator as the "captain of the ship" is drifting by the wayside. The pressures and inherent objectives of the "business of oncology" have interfered with the role of the principal investigator as the individual in charge, which is impacting on the optimal development of cancer therapeutics on both microscopic (individual studies) and macroscopic (overall drug development paradigm) scales. The early years of anticancer drug development in the United States were largely dominated by efforts sponsored by the National Cancer Institute (NCI). During this period, principal investigators became "attached" to therapeutics and the proponent for their optimal development, shepherding them through an unencumbered process. The NCI development process encouraged "foundation building", in which clinical scientists orchestrated clinical and translational studies autonomously, and the development of each subsequent study and clinical developmental stage was based on bedside and laboratory investigations performed during the previous stage. Compared to the present, the investigator was truly the "captain of the ship" and intimately understood the therapeutic-maximal efficiency. The investigator held clinical data close to hand; the investigator was aware of all pharmacokinetic and translational data generated at the site; and results were discussed and debated in an unimpeded, uncensored fashion at major meetings.

However, a brave new world is upon us. At present, the principal investigator performs even the most uncomplicated phase 1 trials as a cog in a clinical trial machine, often dominated by large Clinical Research Organization (CRO) and multiple autonomous factions of pharmaceutical companies (e.g. experimental medicine, product oriented medicine, marketing, regulatory, business unit, pharmacology, quality assurance, and imaging groups), each of which enacts its own standard operating procedures and insists that the investigator work according to their directives. This fractionation has result in a true loss of control and the overall principal investigator (principal responsible investigator) is often unnamed and assigned by default on the basis of maximal patients accrued. For the individual investigator, even trying to grasp the organizational aspects of the pharmaceutical sponsor and contend with the paperwork have become inordinate tasks. Although the organizational structure of less complex, smaller biotechnology companies might be much easier to grasp, the overall "investment side" ramifications of the project are always close at hand to the academic scientists. Concerns about investor perception of the new therapeutic are progressively dominating early clinical trials and these pressures are pressures are palpable to the investigator, even at the earliest developmental stage. Although the participation of patient populations with refractory cancers known to have excellent performance status and once considered ideal for the evaluation of toxicity in phase 1 studies, are now considered suboptimal since subliminal corporate pressures have shifted towards the maximizing the potential to demonstrate clinical activity to prop up the drug's perception for investment community. Such efforts, which are often based on teleological reasoning and misperceptions about the mechanism of action of new drugs, impede the achievement of the toxicological objectives.

Sponsors have become obsessed with meeting timelines and milestones and this obsession is indeed coming at a cost. The single institution, single principal investigator trial is becoming archaic because of the notion that time-lines are much more likely to be met by using more investigators and institutions, even when it is clear that the bottleneck is study design, not patient accrual. Championed by the pharmaceutical and biotechnology industries, the growing trend in the conduction of phase 1 studies is in the direction of large, multi-functional evaluations in lieu of smaller, more intimate trials that have been traditionally conducted at a single institutions and strictly focused on dose finding and characterizing the toxicological and pharmacological profiles of new anti-cancer therapeutics. This trend undoubtedly stems from mounting competitive pressures in these industries, resulting in a quest for maximal efficiency in patient resource utilization and a strict adherence to often-unrealistic management-driven timelines. These competitive corporate pressures have been progressively shifted over the years to the clinic and are now being observed downstream at the earliest phase of therapeutic evaluations, which were once considered immune from any study design imperfection that would even slightly increase the risk for patients, since the overriding theme in the design and conduction of the phase 1 studies has always been related to minimizing risk and the principal dictum has been to cut no corners and leave no stones unturned. Phase I studies of anti-cancer agents, which have much narrower therapeutic margins and higher risk-benefit ratios have traditionally been performed by a small number of experienced investigators at a maximum of one or two highly specialized sites. These practices encouraged investigators to become intimate with their clinical and pharmacologic data, whereas current multi-institutional practices encourage investigators from different sites to compete with one another for treatment slots. Similar to good laboratory practices, which mandate the use of the fewest well calibrated instruments as possible to minimize experimental variability due to instrumentation, the seemingly minor, albeit powerful, characteristic of the intimate study has traditionally facilitated the acquisition of expertise by both investigators and research staff since it enables them to make detailed observations over the entire

range of dose levels. Not only does the resultant intimacy enhance the ability of investigators to detect subtle, albeit potentially consequential, adverse effects, and to readily compare toxicities from dose level to dose level, patient to patient, and schedule to schedule, but the geographic concentration of adverse events has undoubtedly accelerated the derivation of measures to minimize adverse effects, which would have otherwise led the development of many important therapeutics astray for many years or possibly forever. In essence, this rather low-tech approach to phase I evaluations has resulted in the accurate, safe, expedient, and successful characterization of the toxicological and pharmacological profiles of a multitude of anti-cancer agents over the last several decades.

Even more concerning is the lack of real-time sharing of data by sponsors who insist on the use of central laboratories and do not permit investigators to perform pharmacokinetic and translational analyses at the site under the guise of the somewhat questionable need for data analysis at commercial laboratories that abide by "GLP" when the real issues are control and confidentiality. Furthermore, such information is often held "close to chest" until the guise of irrelevance or until the data itself are irrelevant. Shouldn't the "captain of the ship" make the decision about the relevance of all study data in a real-time fashion. In some cases, sponsors have even refuse to disclose chemical structures and preclinical information construed as highly proprietary to principal investigators, but it is more concerning that investigators no longer question these practices even though they bear the ultimate responsibility for the conduction of the trial. In some case, they fear that future relationships may depend on their perception as well behaved and not prone to troublemaking behavior.

Sponsors may truly be the proprietors of novel therapeutics and have fiduciary responsibilities to their stockholders, however, there are ethical and moral questions about whether their obligations extend to society at large, particularly when their proprietary technologies may portend reasonable benefit to cancer patients. As a society, we must address whether sponsors of precious medical commodities like cancer therapeutics should be allowed to make irresponsible developmental decisions, strictly based on financial and proprietary concerns. Should the ramifications of such decisions be considered similar to those of companies that produce and inappropriately develop and market cogs and widgets? Or, should pharmaceutical sponsors be held to a higher level of responsibility for decisions that ultimately lead to suboptimal results in terms of delayed remedies for the ailing and suffering? On the flip side, should they their rewards be disproportionately greater than sponsors of other products if they are to be considered disproportionately more culpable? Sponsors and investors formulate commitments with investigators and institutions with the underlying assumption that they will fulfill the principal goals of the studies, but the "small print" often gives them "an easy way out" (i.e. early study termination) when the "going gets rough" – when developmental risks appear inordinate, when agents do not appear to be suited for the "big 4" tumor types, or even when there are no responses in phase 1 evaluations. Do sponsors and investigators have underlying commitments, as well, to study patients to meet the overall study goals? Premature study termination based on fiduciary concerns should be construed as a violation of this unwritten contract. Certainly, the pockets of the pharmaceutical and biotechnology industries are limited, but potentially active drugs should not be put on shelves solely due to financial and proprietary concerns. Perhaps, mechanisms should be formulated and even mandated whereby individuals, institutions, and government agencies can further study such therapeutics, with partial licensing rights retained by the original sponsor. Once a compound becomes a "therapeutic" with a reasonable potential to benefit even patients with orphan diseases, sponsors should assume heightened responsibilities and obligations. Investigators must speak up when such issues occur and must never allow themselves to become complacent when faced with the erosion of their responsibilities in true spirit of a principal investigator. It is clear that a committed principal investigator who is truly aware and responsible for all aspects of their clinical trial will benefit patients, institutions, sponsors, and overall therapeutic development against cancer.

26 INVITED

The difficulties industry is experiencing with investigators

G.R.P. Blackledge. *AstraZeneca, Clinical VP Oncology, Cheshire, UK*

The title of this talk is confrontational. Reality is different. Certainly it is true that what drives investigators and what drives industry are different at the first level, but at a second level the objective is the same: through good preclinical and clinical research and with sound manufacturing processes all aim to provide improved new treatments for the prevention and treatment of patients with cancer.

With this, it is instructive to see where differences exist in the agendas of the two parties. Progression in academia where many investigators exist is by publication, citation indices and quality of research. For most in industry these are not primary drivers and factors such as team working, delivery focus around New Drug Applications and the amount of money that a new drugs makes are criteria of success. These different agendas can lead to distrust.

This presentation will focus on the 'hot spots' of disagreement with the industry and investigators. It will also propose solutions to these pressures. The relationship can and should be a good one if both sides understand the other and particularly do not try to do each other's job.

Wednesday 29 September 14:40–15:00

Keynote Lecture

27 INVITED

Highlights from the 3rd EORTC–NCI International Conference on Cancer Molecular Markers: From Discovery to Clinical Practice

R. Schilsky. *University of Chicago, Pritzker School of Medicine, MC 1000 Biological Sciences Division, Chicago, USA*

This meeting was the third in a series initiated in 2000 in Nyborg, Denmark. 210 scientists from North American and Europe participated in 6 sessions on topics including molecular profiling of tumors, trial design for marker studies, circulating markers, development of clinical laboratory tests and individualizing treatment. Nearly 100 abstracts were presented in oral or poster presentations. Carlos Arteaga presented the keynote address on clinical development of tyrosine kinase inhibitors and reviewed lessons learned from development of EGFR inhibitors. Gene expression profiling to refine prognosis of women with node negative breast cancer was discussed in depth and the design of definitive EORTC and NCI-sponsored clinical trials to prove the utility of this approach was presented. The importance of uPA/PAI-1 as an established prognostic factor in breast cancer was reviewed and the limitations of this approach, particularly in the US, were discussed. The potential of circulating tumor cells and bone marrow micrometastases as prognostic markers in breast cancer was described. The statistical pitfalls in analysis of expression arrays were reviewed and the sample size requirements for definitive marker studies were examined in detail. Among the lessons learned at the meeting were: a good technology does not guarantee a good study; context is important in both the cell and the clinic; a biomarker is only as good as the perceived clinical need, therefore clinical methods must be as rigorous as lab methods in biomarker studies; variability is everywhere so quality control is vital; prospective marker validation trials require thousands of patients, years of follow-up and millions of euros; a little promiscuity is a good thing for targeted therapies; the biology and prevalence of a marker must be well understood to successfully pursue enrichment strategies in clinical trials of targeted agents; and successful biomarker development requires a close working relationship of clinicians, laboratory scientists, statisticians and regulatory authorities. Better molecular diagnostics are necessary to inform the next generation of cancer treatment and prevention trials as biomarkers are essential to assess risk, refine prognosis, evaluate treatment effects, predict response and improve diagnosis.