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Efficacy of Individualized Cancer Management

Kangla Tsung[1*], Zhang Xu[2], Zhang Hui[3] and TANLUN Clinical Research Participants Group

[1]Department of Clinical Management of Cancer, Medical Research and Innovation, Co. Ltd., Beijing, China

[2]Department of Pathology and Immunology

[3]TANLUN, Department of Trauma Healing and Anti-Inflammation

ABSTRACT

Individualized cancer management is the opposite of the standardized care adapted for current clinical practice by the mainstream medicine. It is not a fancy concept but a logic and inevitable reality derived from the intrinsic characteristics of cancer and host antitumor response. The question is not whether it should be done but how it is done. One missing aspect of individualized management is how to measure its effectiveness. Unlike standardized management that compares therapy efficacy among different management plans by the statistical criteria on the entire groups of patients but not individual patient in the group, individualized management can measure the efficacy on individual patient. This is not only possible, but necessary. A true individualized cancer therapy is not only based on personal situation for each patient, but must also satisfy the criterion that the outcome of selected therapy is predictable for that patient, a feature that current standardized care does not have. Therapy selection based on the individualized assessment of the status of antitumor immunity in each patient is the essential part of individualized management. Thus, treating each patient according to the status of his antitumor immunity should be the most critical skills a physician needs to master when facing each individual cancer patient. In the past seven years, we have been exploring individualized management of cancer through recognizing and manipulating antitumor immunity in each patient. Our combined experiences indicate a significant benefit to patient survival with reduced costs even when such effort was not perfect in the past. With time and more learning, we see this practice becoming more and more practical in a clinical setting. When this individualized approach becomes guideline for cancer management, we will see a significant leap of clinical improvement on both patient survival and cancer cure rate.

*Corresponding author's

Kangla Tsung, Department of Clinical Management of Cancer, TANLUN Medical Research and Innovation, Co. Ltd., Beijing, China.

Individualized Cancer Management Must Be Predictable for Treatment Outcome

The current clinical management of cancer is based on three pillars: TNM staging, Standardized treatment plan and Evidence-based medicine. Why these three pillars are wrong and how to replace them have been discussed in a previous article [1]. Standardized treatment plan is applied to patients with the same TNM staging designation. In reality, these patients are widely different in terms of several aspects, such as mode of tumor replication, degree of malignancy, ability to metastasize and recognition and control by the host antitumor immunity. With so many differences, previous cancer management guideline recommended physicians to treat all patients with same TNM staging with one fixed plan, regardless other differences. This is the principle of standardized treatment for cancer management. The argument for such a "one plan for thousands" practice is that cancer is a complicated disease that most physicians lack the ability to select proper treatment plans for each individual patient, thus a pre-selected plan chosen by the top experts in the field would provide a good reference for the treating physician regardless his ability to choose complicated therapies. After all, the expert-selected plan had been shown to work best by clinical trials, a practice called evidence-base medicine. The problem with this argument as we had pointed out previously [1], is that the clinical study that the so-called best plan is based on never demonstrated that other treatment plans that failed to show highest response rate (thus not chosen as first line therapy) were not the best plan for those who responded to it. In reality, almost every therapy plan can find some patients who respond to it best, and there is no "one thing fits all" therapy that benefit every patient. If so, what is the logic behind treating thousand different patients with one fixed plan? There is none. For this argument, individualized cancer management would be one that treat each patient with a plan that likely to benefit that patient most. Naturally, such a plan is selected based on the special situation of the patient, not the common characteristics. One example is the selection of certain cancer patients for therapy targeting the specific mutated kinase responsible for uncontrolled replication of the tumor in those patients. This therapy clearly benefits those who had that mutated kinase, not others who do not have the mutation. By definition, any therapy selected based on the specific situation a patient occupies would satisfy the concept of individualized therapy. If a patient is treated by various therapies all of which are selected based his specific situation, then the management of that patient would be individualized management. But there is more to this definition. An individualized management must also eliminate uncertainty. Clinical observations show that patients with the same TNM staging do not respond same to the same therapy. Their clinical survival time varies widely. There is no satisfactory explanation for these variations. We all know that patients are actually different even grouped under the same TNM staging, but we don't know exactly what causes the difference. Many previous studies have looked into the differences between tumors from different patients. Pathology has identified many

different tumor structure and morphologies, but tumors with similar morphology still demonstrate different responses to the same treatment. More recent molecular biology analyses have identified differences in tumor genetic variation, for example some genetic mutations that drive tumor replication. This knowledge facilitated the development of targeted therapy that benefited those patients whose tumor growth could be inhibited specifically by small molecular drugs that target their tumor. Yet, among patients treated by such specific therapy, responses were also highly variable to the point that no one could accurately predict the outcome of the therapy in a given patient. If the outcome of a therapy cannot be accurately predicted, it cannot be called truly individualized management because it is not much different from standardized treatment in that we can only predict some patients may benefit but cannot say who it will be. In this regard, truly individualized management should meet one more criterion that it eliminates the unpredictability in therapy outcome.

Individualized Cancer Management is the Natural Result of Variable Antitumor Immunity
Current cancer management based on standardized "one plan for thousands" benefits some while harm others. To those who do not respond to the standardized treatments, the harm is at least the loss of opportunity to take other benefiting treatments, less to say that sometimes the standardized plan may cause uncontrolled tumor progression. Unfortunately, there are many in this category, often more than half of patients taking the standardized treatments. The only way to avoid the wrong treatment is to know that it is wrong for a given patient at that given moment. To know which treatment is right for which patient at which time is the basis of individualized management because it is based on personal information, based on the specific situation of a given patient. There are two most personalized pieces of information about a cancer: one is about the tumor; the other is about the host immune response against the cancer. Most people recognize the first one but not the second. While both aspects affect the prognosis of a case, the antitumor immunity from the host is a much more influential factor on prognosis, which has been evasive until recently. And, it is also the most variable one leading to the conclusion that cancer is an individualized disease and therefore need individualized treatment. The variable antitumor immunity in each cancer patient comes from the personalized genetic composition: tumor antigen in the form of 8-12 amino acid peptide is presented on personalized HLA molecule to personalized T cells receptor. This process determines that there is no common tumor antigen between two cancer patients with different genetic composition (which is always the case). As such, the molecular nature of a given tumor antigen (where the antigen is derived), the amount available antigen for presentation and the path it is released will all be highly variable even among different patients having similar tumor burdens, less to say between patients having different tumor burdens (mass and location). Together all of these factors contribute to the variability of antitumor immunity among patients. On the other hand, host factors also contribute to variation of antitumor immunity. For example, tumor micro-environment determines whether and when the released tumor antigen is picked up and presented to T cells. It also determines the direction of antitumor immune response (Th1 or other). Release of local accessary factors through Toll-like receptor on antigen-presenting cells is a complicated process that significantly impact the antitumor response and we know little about. It is not an exaggeration claim that no two patients will have identical antitumor immunity.

The contribution of antitumor immunity to the efficacy of various tumor reduction therapies is definitive as we have reviewed previously [2]. Because of this decisive role of antitumor immunity, the response to a tumor reductive therapy such as chemotherapy by a given patient is determined by two factors: the susceptibility of the tumor cells to the drug and the influence on antitumor immunity. The former contributes to the short-term tumor killing while the later contributes to long-term tumor control [3]. Every patient going through the same chemotherapy will have different combination of these two contributions to the final outcome. In one extreme, a patient with no antitumor immunity would exhibit only drug-mediated direct killing of tumor cells. A simple reflection of this short-term efficacy may be temporary tumor reduction followed by tumor relapse three weeks later. In another extreme, a patient with relatively strong antitumor immunity may exhibit temporary tumor rebound following chemotherapy due to the fact that tumor replication is severely suppressed by immunity and chemotherapy losses it's direct killing on tumor cells. But antitumor immunity could be temporarily suppressed by chemotherapy, thus tumor replication becomes active following chemotherapy (our unpublished observations). Many other responses fall between the two extreme situations. It is the variable antitumor immunity that often causes different responses by different patients to the same therapy. For example, a radiation therapy on one tumor nodule may kill the tumor cells and eradicate that nodule. The release tumor antigen form radiation may activate antitumor immunity. But persistent radiation may also suppress the concomitant immunity inside the tumor. The net effect on antitumor immunity could be activation of antitumor immunity (abscopal effect), or burst of distant metastasis that determines the subsequent clinical outcome and patient survival. What determines whether we have activation or suppression of antitumor immunity is a combination of factors, among them the strength and activation status of antitumor immunity (our unpublished observations).

Another example is the recently developed immune checkpoint inhibitor (ICI) therapy. This treatment may bring dramatic and durable antitumor responses leading to clinical cure in some patients, but it may also bring accelerated tumor progression leading to shorter survival [4]. The reason why the same therapy has such totally opposite responses in different patients is not fully known. We have investigated this issue and presented our explanation [5]. The working mechanism of ICI therapy is through partial depletion of PD1-positive T cells followed by homeostasis-driven activation of residual T cells. When this depletion goes too far to complete depletion of antitumor immunity, a total loss of tumor control takes place. Whether under the same dosing schedule of antibody a partial or complete depletion will take place is determined by several factors including the structure of the tumor, the number of antitumor T cells, the location of these infiltrating T cells, and the status of PD1 expression on these T cells. All of these are highly variable and personal. Only by looking into these factors, one can be sure that a patient will benefit or be harmed by the same ICI therapy. This process of obtaining the personal information is part of the individualized management. Without it, we only know that among 100 patients, how many are likely to benefit, but we do not know who exactly. To be sure, we need individualized management. In other words, individualized management for cancer patients is needed because it eliminates guessing and gambling on patients' lives.

How is Individualized Management Achieved?

Like mentioned above, the process of obtaining personal information is the first part of individualized management before selecting therapy for treatment, Without the personal information, especially the status on antitumor immunity, one cannot select a therapy treatment with certainty on its outcome. Besides detailed knowledge on the patient's tumor and his antitumor immunity, one needs to know among all of the available means, which one will be best to achieve the goal. But what is the goal? There are short-term and there are long term goals. Different means may serve different goals. For example, a patient has a primary tumor in the lung with 1-2 bone metastases. What is the short-term and long-term goals? Can this case be cured? If so, the long-term goal would be to achieve the cure. What determines whether this case can be cured? It is often the status of antitumor immunity. With a decent antitumor immunity present, one can expect this immunity to control new metastasis and to limit the progression of the primary tumor. This allows time to eradicate existing tumor burden. If at the same time of tumor burden reduction, the antitumor immunity can be enhanced to a level that it will provide adequate protection against further establishment of new metastasis, this case will likely achieve clinical cure with removal of all existing tumor burden. This can be done and has been done in many cases. When this path is designed after the determination of antitumor immunity but before therapy begins, it is individualized management because it is designed before-hand based on the specific information from the patient and because that its outcome is relatively certain. Thus, the long-term goal is certain, and along the way, there are short-term goals at each stage to be achieved in order to achieve the long-term goal. For example, we have to eradicate the bone metastases. We need to select a treatment to achieve this goal. But we have to consider the impact on antitumor immunity when selecting. Usually we choose radiation, but the therapy details will be selected to meet the short-term goal of local tumor eradication. The impact on concomitant immunity has to be considered to make sure that antitumor immunity is preserved or activated, but not suppressed. Only when all of these considerations are put together before-hand, we have a true individualized management in place. It is true that no one can guarantee success of each step. For example, radiation could not eradicate the local bone metastases. But this is no reason not to plan and try to carry out the plan. There are a number of alternative choices that one can take at almost any time along the path to achieve what could be achieved for the patient. With more and more experiences, the fine tuning on short-term therapy tends to get more and more reliable in terms of achieving the predicted outcome (see below).

The most critical step towards achieving individualized management is gathering personal information, especially information about the status of antitumor immunity. As discussed above, information about the tumor has been the focus of many current analyses including routine pathologic and immunopathologic analyses by the hospital, and genetic analysis on tumor driver genes, tumor suppressor genes and other prognostic genes by commercial services. These analyses often provide detailed information on the tumor. The purpose of these analyses is to search for a potential matching to an established therapy or treatment plan such as guideline recommended plans. Such a one-to-one matching has been pre-determined by the guidelines. For example, certain type of lung cancer with certain TNM stage has a matching treatment plan. If this cancer has specific mutation in one of the known common driver genes (for example, EGFR gene), then it is matched to a specific targeted therapy. If no genetic mutations are found to match to available drugs, there will be other set of guideline-recommended plans such as chemotherapy with certain first-line drugs, second-line drugs, etc. This practice has been going on in the clinic for the past 4-5 decades. Now, we have another set of information that is as critical as, if not more than, the information from tumor aspect. That is the information about the antitumor immunity. This is the information on the troop we have to rely on when battling cancer. The presence of such a force against cancer has long been recognized, but its clinical utilization has long been ignored until recently with the development of immune checkpoint inhibitor (ICI) therapy. For, example, the status of antitumor immunity has not been considered in any clinical decision-making such as cancer surgery, chemotherapy and other tumor reductive therapies. But as we have pointed out [2], antitumor immunity is behind all of these therapies for responses. The true reason that it is not part of the clinical decision-making is the lack of recognition of its importance by the clinicians, even though tumor immunology researchers have long recognized its critical role [6]. Despite that many prospective studies have shown that presence of T cells in the tumor is responsible for better survival, for delayed post-surgery recurrence and many other aspects of cancer prognosis [7-14], no current clinical decision-making has incorporated the status of antitumor immunity into consideration. In order to let clinicians recognize the importance of antitumor immunity for their patients, we need a way to show and to measure this antitumor immunity in the clinical setting. Thus far, we do not have such measurements available to the clinicians even if they want to look into this. To overcome this restriction, we have developed some practical ways to measure the levels of antitumor immunity. The most direct way is to look into a tumor tissue for the presence and status of immune T cells [15]. In addition, we have proposed to follow sensitive tumor markers to reflect the change of antitumor immunity with therapy (manuscript in preparation). The history of a case, its tumor distribution in relation to time, development of patient symptoms, all of these are also indirect evidence that reflect the status of antitumor immunity. If one wants to find it, he will find it because it is there and exerting most critical influence on every cancer case.

The proper way to use this information about the individualized antitumor immunity is different from the way we use information gathered from tumor. Instead of matching to an established treatment (drug or plan) like we do with the information on tumor, we first assess the general or long-term best prognosis of a case, before we design a treatment plan that may bring us there. The reason that we can assess the general prognosis of a case is because that degree of malignancy and levels of antitumor immunity are the two most critical prognostic factors determining the outcome of a case. Information gathered on tumor alone cannot point out the outcome of a case because even a not so malignant tumor will likely progress without the control of antitumor immunity less to say a more malignant tumor. On the other hand, as long as there is a strong antitumor immunity, regardless the malignancy of a tumor, the prognosis is generally good. So, between these two factors, antitumor immunity is more influential. The actual assessment may need some experiences because one needs to collect actual data on antitumor immunity and prognosis in many patients to learn what levels of antitumor immunity can be considered strong or week. This can be done with time and cases. This can be done even with artificial intelligence. The design to achieve short and long-term goals in a given case is the second step once we have a general assessment. This could be a complicated step requiring flexibility and experience, but certainly have some rules to follow. Take the above example of a stage IV cancer of a primary tumor with a bone

metastasis, when this is a case with decent antitumor immunity, we know that is it potentially curable. But how to achieve this potential will require some manipulations. Clearly, we cannot do direct surgery on the primary tumor leaving the bone metastasis. This has proven fatal in the past and has been the reason that guidelines do not recommend or even forbit surgical approach on stage IV cases. The short-term goal in this case will be first to elevate antitumor immunity, followed by eradicating the bone metastasis, and then to achieve tumor-free state through final surgery to remove the primary tumor. Once we have a goal, we select means to achieve it. In theory, all treatment options are open for this selection. But in reality, we know that chemotherapy usually is good enough for this purpose [3,16]. Whether the goal of elevating antitumor immunity is achieved through chemotherapy can be determined by follow the change of sensitive tumor markers. Once this goal is achieved through 1-2 cycles of chemotherapy, we can move to eradicate the bone metastasis. The reason that we need to elevate antitumor immunity before radiation therapy to eradicate the bone metastasis is that radiation often suppress immunity and a stronger antitumor immunity is likely to survive the suppression by radiation (our unpublished observations). The success of eradication of bone metastasis by radiation is a high possibility by experience and that is the reason we choose to do so. There are other ways, however, to eradicate bone metastasis including bone surgery and fracture cementing (vertebroplasty). Which method is selected should be based on the specific situation of the patient. But regardless, all of these methods will rely on the presence of antitumor immunity to assist the eradication of any residual tumor cells not eliminated by the therapy. Occasionally, eradication of bone metastasis may even activate antitumor immunity, which is a welcoming effect that cannot be expected for sure. Upon the eradication of bone metastasis and the elevation of antitumor immunity, the final step of removing the primary tumor can be carried out. This will ensure to reach a tumor-free state. This state alone does not guaranty a clinical cure, it is the continued maintenance of this state that secures a clinical cure. For a systemic disease such as cancer, post-surgery maintenance of tumor-free survival is best achieved with the function of antitumor immunity left in place before removal of primary tumor [15]. This is the reason why we emphasizing on elevation of antitumor immunity with tumor burdens present because tumor antigen is needed to activate antitumor immunity. Alone the same line of thinking, this is also the reason why tumor vaccine may play a critical role to maintain antitumor immunity after removal of all tumor burdens. For the past 7 years, we have been not only looking for the sings of antitumor immunity, but also been using this immunity in the management of every cancer case that went for us for help. After all these years and hundreds of cases, we now know that it is possible to follow the status of antitumor immunity in any cancer case and it is possible to make the best use of it to achieve maximal clinical benefit for the patients.

What Would be the Benefit of Individualized Cancer Management?

Strangely as it may seem, there is no established criteria to measure whether a management on an individual cancer patient is "successful". The current guidelines on cancer management are derived from clinical studies that compare different treatment regimens for the group of patients with same TNM staging. Patients respond to these treatments differently and their survival periods vary widely. Does that mean those who survived the longest

under the given therapies benefited most from these therapies? From individualized angle to look carefully into each case, no such statement can be made. Take the example of our previous stage IV case of a primary tumor with a bone metastasis, current guideline depicts a treatment plan that is only able to maintain a tumor-carrying state. The actual survival time for the patient is determined by the status of his antitumor immunity and may vary between hospitals and physicians, but most likely no clinical cure could be achieved. In such a case, regardless how long this patient survived, his treatment under the standardized management cannot be "successful" because he should be cured to begin with. Any non-cure outcome would be failure as long as this patient is considered. As such, the measurement of benefit of a therapy must be considered under the status of antitumor immunity in each patient. Because the status of the antitumor immunity is the most critical prognostic factor influencing patient survival, patient with a weak antitumor immunity and shorter survival may actually benefited from a therapy more than a patient with a strong antitumor immunity and longer survival under the same therapy. Theoretically, a patient with a set of tumor and antitumor immunity under current available treatment selection must have a maximal survival time if everything goes right for that patient. This may be a cure, or may be only few months of survival, depending on the malignancy of the tumor and the levels of antitumor immunity. In this view, whether a patient has benefited from a management can be measured by how close the actual survival time to the maximal theoretical survival time. Figure 1 is an illustration of this view. Thus, under this measurement, not only effectiveness on individual patient can be measured, the superiority of certain management entities (for example, hospitals) can also be compared directly to see which one has the best record for approaching the maximal survival of each patient. As can be seen, the accuracy of such a measurement system depends heavily on assessment of the theoretical survival time, which is totally new concept to the mainstream medicine. However, through the practice in the past 7 years, we have recognized that this assessment is highly possible and, with accumulation of experiences, is gradually more and more accurate. At present, our individualized management system could achieve a level of >80% effectiveness, meaning more than 80% of patients treated by our individualized management reached within 80% of their potential survival time as assessed before treatment begin. We will be presenting some of these cases of individualized management in a subsequent publication to illustrate how it was done.
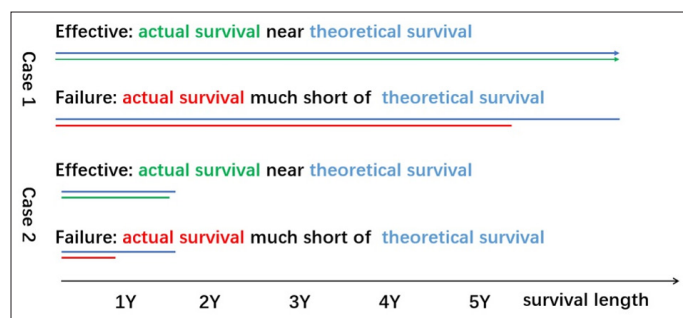

Figure 1: Examples of effectiveness of individualized treatment. Effectiveness is measured not by the absolute length of the survival time, but the closeness of actual survival time (green or red bar) to theoretical survival time (blue bar).

Note that in case 1 even the failed outcome has longer survival time than the successful outcome of case 2.

On the other hand, main stream medicine only recognize statistical data to draw conclusion on which therapy is "better". With large number of patients, we could compile a survival curve to reflect the overall survival data, but that does not mean much from the angle of individualized management as discussed above. Short survival does not mean we did not achieve the maximal benefit for that patient. But if individualized management is superior to standardized care, then we should expect to see in many patients a longer survival under individualized management. As such, the compiled overall survival for individualized care must reflect this expectation. Only in this aspect that we can use the statistical survival curve from a group of patients under individualized management to make a statement whether it is superior to the standardized care. In order to make that argument, we have compiled the survival curve from a group of late-stage lung cancer patients under individualized management it is in the past 9 years. The selection of lung cancer is because that is the largest group of patients we have managed, so that we will have sufficient number of patients to show. This set of data is a real-world study, not a clinical trial. All patients who followed our suggestion and went through individualized care are included, regardless of the status of the antitumor immunity. Only so-called late-stage cancer patients, Stage IIIb-IV, are selected because these are the patients need individualized management most. We also compiled the data from all subtypes of lung cancer including small cell lung cancer patients in the analysis. In general, small cell lung cancer is more "lethal" than other types of lung cancer. As comparison, we searched real-world studies that listed late-stage non-small cell lung cancer for the survival data. Quite a large number of such date can be found to provide comparison to our data. Figure 2 is the data selection process. During the period of 2014/2/1 to 2023/1/31, six hundred fourteen (614) lung cancer cases have contacted us for help. Two hundred thirty-three (233) of these cases are the so-called late-stage TNM cases (including recurrences). Among these, 156 cases had followed our individualized management suggestions. Most of these cases are adeno and squamous cell carcinoma, 9 cases are extensive small cell lung cancer, 12 cases are recurred cancer from previous early-stage surgery cases. Ten of these cases went to other therapy (most likely immune checkpoint therapy) during their treatment and lost contact.
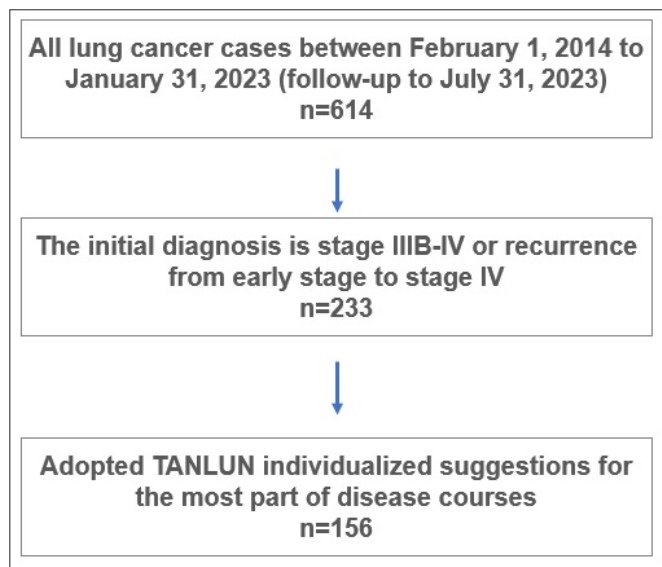

Figure 2: Case selection process for figure 3 data

Figure 3 is the Kaplan-Meier survival curve of these 156 patients. From this curve, we find a median survival time of 42 months and a five-year survival rate of 33%. How is this compared to the real-world survival by standardized care? We have searched extensively to match the patient composition to our study and compiled the data from multiple studies in Table I. As Table I shows, all outside real-world survival data have a median survival time ranged between 3-14 months with most of them fell in the range of 8-11 months. This is highly consistent among all published real-world studies for the late-stage lung cancer patients. The difference is usually the sample size and the inclusion of Stage IIIa patients. Even compared to controlled clinical trials, our record stands out significantly. For example, the best therapy breakthrough in recent years has been the Immune Checkpoint Inhibitor (ICI) therapy which was first developed in late-stage lung cancer patients. Most of these clinical trials with strictly selected patients showed a median survival time of 12-14 months for chemotherapy control groups and 18-22 months for ICI therapy groups [17,18]. The best reported median survival time for the best responders of ICI therapy with tumor PDL1 expression >50% has 26-28 months [19,20], still far short of our record of median survival of 42 months in non-selected real-world cancer patients mostly not treated by ICI therapy or targeted therapy. In addition, no study had included patients from extensive stage of small cell lung cancer. Had small cell lung cancer been included, the survival time would definitely be shorter as small cell lung is much more lethal than non-small cell lung cancer. In contrast, our data show that we have a median survival time of 42 months, much longer than the survival time from all outside studies.
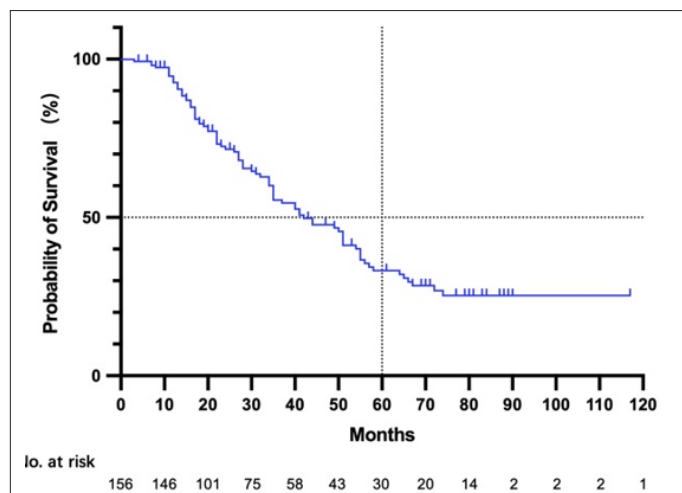

Figure 3: Kaplan-Meier survival curve of the 156 patients selected from the process described in figure 2.

Table I

Comparison of patient survival data between our study and other published real-world studies. The median survival of 8-12 months for late-stage lung cancer (non-small cell lung cancer) is consistently seen in all previously published analyses. These analyses usually exclude patients who die fast (within 14 days) after first therapy. Some studies did not include patients who were treated by TKI therapies. Of note are analyses that include or focused on patients receiving ICI therapies. The survival times are not much better than patients treated by other means (mainly chemotherapy), certainly worse than what was claimed in clinical trials. Both the median survival time (42 months) and 5-year survival rate (33%) standout much better than the numbers from all other studies. The much smaller sample size from our study

is not the result of careful selection of patients as we try to include any patients who came to use for help regardless of their survival potential as long as they followed our individualized suggestions for the most part (>70%) of their disease course.

Study	Sample size	Stage	Median OS (95% CI)	5-year Survival Rate	Note	references
Peng H et al.	1742	IV: 100%	10.0 (9.5-10.5)	6%	Chinese patients with 62% adeno carcinoma, 17% squmous cell carcinoma.	22
Adrian G. Sacher et al.	8113	IV: 100%	3.3 - 16.2		Patients using TK inhibitor therapy not included for analysis. Untreated patients had median OS=3.3 months.	23
Jason C Simeone et al.	9656	IV: 100%	11.7 (11.3–12.0)		Patients using TK inhibitor therapy not included for analysis.Chemotherapy combined with ICI therapy had the longgest median survival time of 17 months	24
Sean Khozin et al.	5257	IIIb-IV	9.3 (8.9-9.8)		Real-world outcome of ICI therapy. The worst survival is associated with EGFR mutation group (mOS=4.6 months), possible result of hyper-progression	25
Mark Stewart et al.	6,924	III: 7%-23% IV: 62%-91%	8.58-13.50		Real-world outcome of ICI therapy pooled from 6 data sets.	26
Sandra D. Griffith et al.	30,276	III: 20.4% IV: 65%	10.98 (10.79-11.18)		Short survival of 14days or less after first treatment was excluded	27
Jason Lester et al.	1003	IV: 100%	9.5 (8.8-10.7)		mOS for chemotherpay group= 8.1 months , ICI therapy group=14.0 months, TKI hterapy group= 20.2 mothss	28
Waterhouse et al.	4271	III: 8% IV: 81%	squamous: 10.6 (9.3–11.8) non-squamous: 12.0 (11.2–12.8)		Among 1597 patients accepting ICI therapy, 1153 patients had PDL1 expression≥50%, mOS =18.9 months, contradicting the mOS=30 months from KEYNOTE-024 trial.	29
Rebecca L. Siegel et al.	>1million	IV: 100%		7%	Historical data among 27% US population	30
TANLUN	156	III: 16% IV: 84%	42 (32.7 - 50.6)	33%	See text for description and discussion	this study

Several points should be discussed. First, most late-stage cancer patients went to us because that treating hospitals had already given up on them, usually because they had exhausted most effective therapies such as stable targeted therapy that may maintain a stable disease for 2-3years. Our study does not include such stable cases, or else they would not search around online to found us on the internet and went through all of the inconvenience to materialize our suggestions by their local hospitals. Their cases are generally more "difficult" than patients going to their reginal hospitals routinely. We never refuse to help any patient as long as they were willing to carry out suggestions based on their specific situations. Secondly, many times, because the actual treatments were not given by us and were not exactly as we wished, the outcomes often were not fully satisfactory. Even so, we still managed these cases to obtained much better outcomes in terms of survival time. If all of these patients were under our direct care like in a hospital, we believe that the outcome could be even better with improved rate of clinical cure. Thirdly, this set of data mostly are derived from previous 9 years, when our individualized management was in a state of development. With improvement of the accuracy of individualized management, we expect further improvement of the actual survival time. On the other hand, as discussed above, the survival curve in Figure 3 is determined by the variable antitumor immunity hidden behind each case. No matter how improved the survival will be, it is only going to be close to the theoretical survival in each case, and as in a real-world mixed group of late-stage lung cancer patients, the theoretical survival would be something close to what we see in Figure 3. Any significant change of that curve will come from therapies to alter the immune recognition in those short survival cases where there was no antitumor immunity. Other trend-breaking therapies are also possible if rapid tumor genetic variation can be effectively managed and controlled. Fourthly, the direct cost of our individualized management is much lower than that occurred with standardized care. On average, our patients spent about half amount of money on treatment-related cost to obtain much longer survival. The reason behind this low-cost management is that our individualized management focused on activation of antitumor immunity. Once this was achieved, it usually lasted several months to keep tumor under control. In other cases, tumor reduction through surgery was carried out when adequate protection could be established by antitumor immunity, and such manipulations obtained much longer progression-free survival. Regardless who

pays for the medical costs, our management may help to save tremendous resources while keeping maximal benefits.

Finally, we have established something new here to measure the effectiveness for individual cancer patient. As mentioned above, there is no such concept for individualized measurement of treatment effectiveness, less to say the actual method to do so. The scientific reasoning behind this measurement is based on a real-world observation that there are some fundamental differences between cases that make them different in responding to same therapy treatments and survival. In a way, it is like "fate", one cannot easily change but to go along with it. Our contribution here is to point it out that it is the personal characteristics about tumor and antitumor immunity that determine everything for that patient, including set the limit of survival under current therapy scopes. Once that is determined, the goal of management is for reaching the maximal survival for each cancer patient. If a selected therapy shortens the actual survival (for example, causing hyper-progression and early death), then it is bad for that patient, but not necessarily bad for another patient. In this regard, this personalized measurement may not be used for drug development where the purpose is to see how many patients in a real-world mix would respond to that drug with tumor reduction that translate to benefit to survival [1]. But it is a fair way to compare the management levels among medical institutions, between treatment plans, especially between the mainstream guideline-recommended standardized care and individualized care as we discussed here. For any care provider in a comparison, the ratio of actual to theoretical survival time (ATS ratio) can be measured, and the measurement can be graded to reflect this outcome. For example, one should be able to see how many patients under that care have reached maximal benefit defined as the ratio >0.9; how many have fared satisfactorily defined as the ratio between 0.8-0.9; how many faired so-so defined as the ratio between 0.6-0.8; and how many fared badly as ratio fell below 0.5. Then patient would be able to pick the institute they prefer not necessarily based on which one has the largest and most modern facility, or most expansive service charge, but on their ability and track-record to help patients reaching maximal survival time. By this measurement, our individualized management is at a level that >80% of late-stage cancer patients reached satisfactory range (ATS ratio >0.8-0.9). By the same measurement, >80% of late-stage cancer patients under all standardized care facilities and plans have an ATS ratio

below 0.6. For early-stage cancer patients who are often cured by surgery, the ATS ratio my be similar and satisfactory even under standardized care. It does not mean that standardized care is good for these patients. It is the combination of less malignant tumor and strong antitumor immunity that determine the good outcome in these cases. The huge difference is for late-stage cancer patients like those we listed in Figure 3. In this area, guideline-depicted standardized care only benefited very few while indiscriminately harmed majority patients. We have witnessed many such cases coming to us after being wrongly treated by the mainstream medicine. We will present some of these cases in a future article.

Individualized management for cancer patient is not a fancy concept but a highly needed practice. The fact that cancer is an individualized disease with variable tumor and antitumor immunity in each case is the reality whether we want to accept or not. Accepting this reality and gather the individualized information on tumor and antitumor immunity as we have discussed here, we will be able to greatly improve the outcome of cancer management and achieve more cures. Refusing to accept such a reality as the current mainstream medicine insists, we will continue to explore in the dark as it was 70 years ago [21]. This article has discussed the concept of individualized management, the scientific reasoning behind this concept, the method to carry out this management in the real world and the outcome of such practice. In a coming article, we will present detailed cases to demonstrate how was personal information collected and analyzed. How was general prognosis assessed and the path to reach maximal survival designed based on the information and analyses. How were therapies selected based on the path design and how was therapy outcome predicted and matched to the actual result. The goal is to make such a management known and become commonly accepted in hospitals at large. This is no easy task as mainstream medicine has long adopted certain principles that are difficult to challenge including the way to present and judge clinical data [1]. But the crux of medical care for cancer is maximal survival for patients. Anything that helps to reach that should be considered including our practice. With that, we present our view and data here for consideration.

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