Combined androgen blockade and treatment of localized prostate cancer: a real hope when approaching the year 2000

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Introduction
Although much remains to be accomplished, the attitude towards prostate cancer has improved significantly over the recent years. The worst case attitude is that prostate cancer is not a serious problem, since it usually affects men in their 60s and 70s, at an age where other causes of death become frequent. This lack of interest derives from the erroneous impression that prostate cancer grows so slowly that other causes of death will usually occur before prostate cancer can lead to death. However, the fact that prostate cancer is the second cause of death in men certainly casts serious doubts about such thinking. Moreover, the observation that more than 70% of deaths from prostate cancer occur after the age of 70 years is not a valid reason not to exert our best efforts to avoid, as much as possible, the particularly serious suffering associated with prostate cancer death.

The two most important scientific facts which should be used as basis for a successful fight against prostate cancer are: the androgens acting in the prostate originate from two sources of approximately equal importance, namely the testicles and the adrenals, thus indicating the need for combined androgen blockade (CAB); the efficacy of androgen deprivation is almost certainly greater for localized than for metastatic disease, thus indicating the critical importance of early treatment.

Addendum to the androgens of testicular origin, the active androgens made locally in the prostate exert their action by interacting with the androgen receptor in the same cells where their synthesis takes place, without being released in the extracellular environment. Contrary to the previous more efficient treatment of early stage disease; endocrine therapy could thus be part of the therapeutic plan of any patient treated for prostate cancer at any stage of the disease.

Endocrinology of prostate cancer intracrinology
Following the observations of Huggins and his colleagues (1941), the next most important advance in our understanding of the endocrinology of prostate cancer is the observation that humans and some other primates are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroids, dehydroepiandrosterone (DHEA), its sulfate, DHEA-S, and some androstenedione (4-dione), which are converted into potent androgens in a large series of peripheral tissues, including the prostate (Fig. 1). In fact, plasma DHEA-S levels in adult men are 100 to 500 times higher than those of testosterone (Labrie et al. 1985), thus providing high levels of the substrate required for conversion into androgens in the prostate as well as other peripheral intracrine tissues.

Although orchiectomy, estrogens, or LHRH agonists or antagonists (through blockade of release of bioactive LH) cause a 90-95% reduction in testosterone concentration in the circulation (Labrie et al. 1980,1985 Waxman et al. 1983), a much smaller effect is seen on the only parameter directly reflecting androgenic action, namely the intraprostatic concentration of the potent androgen, DHT. In fact, intraprostatic DHT levels are reduced by only 50 to 70% following medical or surgical castration (Labrie et al. 1985, Bélanger et al. 1986).

Addendum to the androgens of testicular origin, the active androgens made locally in the prostate exert their action by interacting with the androgen receptor in the same cells where their synthesis takes place, without being released in the extracellular environment. Contrary to the previous
belief that the testes are responsible for 95% of total androgen production in men (as suggested by simple measurement of circulating serum testosterone), it is now well demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors, DHEA-S, DHEA, and 4-dione into the active androgens, testosterone and DHT. In fact, the prostate synthesizes its own androgens to a level comparable to that of the androgens of testicular origin.

Knowledge in this area has recently made rapid progress, with the elucidation of the structure of most of the tissue-specific cDNAs and genes that encode the steroidogenic enzymes responsible for the transformation of DHEA-S and DHEA into androgens and/or estrogens in peripheral tissues (Andersson & Russel 1990, Andersson et al. 1991, Labrie et al. 1992b, c, 1995a, c, 1996d, 1997b, Rhéaume et al. 1992, Bernier et al. 1994a, b, Luu-The et al. 1995a, b).

Combined androgen blockade

Metastatic disease

As indicated above, the discovery that the adrenals contribute 30-50% of total androgens in the human prostate (Labrie et al. 1985, 1993a) through local transformation of DHEA of adrenal origin into the potent androgen, DHT (Labrie 1991, Labrie et al. 1993a, c, 1996d, 1997b) clearly indicates that androgen blockade should be a two-way approach that includes: (1) elimination of testicular androgens by orchiectomy (Huggins & Hodges 1941) or an LHRH agonist (Labrie et al. 1980, Faure et al. 1982) combined, at start of treatment, with (2) blockade of the action of DHT made locally in the prostate cancer using a pure antiandrogen, such as flutamide (Eulexin) or one of its derivatives, namely nilutamide (Nilandron) or bicalutamide (Casodex) at the appropriate dose.

Although 50-60% of androgens can be eliminated by orchiectomy or medical castration with an LHRH agonist, the best method available for interfering with the action of androgens produced locally in the prostate is the use of a pure antiandrogen, such as flutamide (Eulexin) or one of its derivatives, namely nilutamide (Nilandron) or bicalutamide (Casodex) at the appropriate dose.
Following our initial data (Labrie et al. 1982, 1985), a series of prospective, randomized and controlled clinical trials have demonstrated a prolongation of life following combined androgen blockade (CAB). Although the clinical data are not available for bicalutamide, the two antiandrogens flutamide and nilutamide have been shown, in prospective and randomized studies, to prolong life, to increase the number of complete and partial responses, to delay progression, and to provide better pain control (thus improving quality of life) in metastatic prostate cancer, when added to surgical or medical castration compared with castration alone (Crawford et al. 1989, Denis et al. 1993, 1998, Janknegt et al. 1993, Albersten et al. 1997, Caubet et al. 1997, Dijkman et al. 1997).

Analysis of all studies performed with flutamide and nilutamide associated with medical or surgical castration compared with castration plus placebo shows that overall survival is increased by an average of 3-6 months (Crawford et al. 1989, Denis et al. 1993, Janknegt et al. 1993, Prostate Cancer Trialists’ Collaborative Group (PCTCG) 1995, Caubet et al. 1997, Dijkman et al. 1997, PCTCG 1997, unpublished data). Since about 50% of patients at that age die from causes other than prostate cancer, this difference in overall survival translates into an average of 6 to 12 months of additional months for cancer-specific survival. One should remember that no survival advantage has yet been achieved in advanced breast cancer, thus indicating the particularly high level of sensitivity of prostate cancer to androgen deprivation, even at the stage of metastatic disease. Using the trials where sufficient published information was available to permit rigorous statistical analysis of the data, Caubet et al. (1997) have shown a relative risk of approximately 0.8 in favor of combination therapy for both time to progression and survival. In other words, the addition of a pure antiandrogen to castration decreases by approximately 20% the risk of progression of disease and overall death, compared with castration alone in advanced metastatic prostate cancer.

In the initial publication of a meta-analysis including all published and unpublished trials of variable size and quality with a short follow-up of 40 months, the difference in survival in favor of combination therapy did not quite reach the level of statistical significance in a two-sided test (PCTCG 1995). However, as was then predicted (Labrie & Crawford 1995), an analysis performed in 1997 (PCTCG 1997, unpublished data) of the same, but more mature data with the addition of some new data showed a statistically significant benefit on survival by adding a pure antiandrogen, especially flutamide, to castration compared with castration alone. Discussion and controversy about the benefits of CAB should now be something of the past: CAB adds an average of 6 to 12 months of cancer-specific survival in patients with metastatic disease. To the living population of males in the USA, where 3.0 million are expected to die from prostate cancer, 6 months of life saved correspond to the addition of 1.5 million years of life.

Although intermittent treatment with combined androgen blockade has become a subject of major interest, intermittent androgen blockade remains experimental and should not be used outside clinical trials. Patients who elect this possibility are encouraged to enter the current SWOG trial. Intermittent androgen blockade is largely based upon the control of prostate specific antigen (PSA). One should realize, however, that PSA, especially in localized disease, is exquisitely sensitive to androgen blockade. Its use can be extremely misleading and lead to a premature arrest of androgen blockade well before cancer itself is under control (Labrie et al. 1997a).

Stage C/T3 disease

We have taken advantage of the new developments in the endocrine therapy of prostate cancer and have studied the effect of long-term continuous treatment (median of 5.1 years, up to 12.9 years) of 115 evaluable stage C/T3 prostate cancer patients with CAB as first primary treatment. Of the 50 deaths, 24 (48%) were from prostate cancer and 26 (52%) from other causes. It can be seen in Fig. 2 that the probability of cancer-specific survival is 85.3% and 68.8% at 5 and 10 years, respectively.

The present study shows that CAB alone is an effective and well tolerated treatment for stage C/T3 prostate cancer. In fact, local control of the disease was initially achieved in all patients, with a corresponding long interval free of symptoms and signs of disease as well as good survival with minimum adverse effects and

Figure 2 Probability of cancer-specific survival in 115 patients with clinical stage C/T3 prostate cancer treated with long-term combination therapy alone. The probability of cancer-specific survival is 85% and 69% at 5 and 10 years, respectively.
morbidity. The excellent local control obtained in the present study is in agreement with our previous data showing that, in 17 patients with low urinary tract obstruction, such androgen blockade alone relieved the obstruction in 16 of 17 patients and only one patient relapsed locally during the course of the study (Emond et al. 1989).

Since no prospective randomized study has been performed, comparison with the large series available is thus the only possible way of evaluating the relative efficacy of the present approach. Accordingly, following the ‘Consensus statement in the management of clinically localized prostate cancer’ of the National Institute of Health (1987), which reviewed data from studies with reasonably large numbers of patients, one can conclude that the results of the most widely accepted therapeutic alternative for T3 prostate cancer, namely radiotherapy, indicate an overall survival of 64% at five years and 35% at ten years while, in our study, the five-year survival is 74.2% and 53.3% at 10 years. Moreover, the 74.2% survival at 5 years in the present study compares favorably with the 62% survival achieved with radiotherapy alone in a similar group of patients (Bolla et al. 1997). The benefits of long-term CAB observed in our series of stages C/T3 patients is even more encouraging when one realizes that 40% of our subjects had elevated PAP serum values at diagnosis. This feature suggests that our patients were more likely to have disseminated disease at diagnosis (Paulson 1980), thus removing surgery and radiation therapy as alternatives.

**Choice of treatment of localized disease**

Despite the fact that clinically localized prostate cancer has become the predominant stage at diagnosis, there is no randomized and prospective comparison of the efficacy of the available treatments (Consensus Conference 1987, Middleton et al. 1995). The only exception is the recent and most important demonstration that the addition of androgen blockade to radiotherapy prolongs disease-free survival and overall survival compared with radiotherapy alone in stage T3 patients (Bolla et al. 1997). This is the first demonstration that treatment can prolong life in localized prostate cancer and these important benefits have been achieved with androgen blockade.

The lack of sufficient scientific information makes difficult the choice of treatment for localized disease. However, based upon the most rigorous evaluation of the data available in the literature and our own experience, we will make the suggestions which, in our opinion, provide the best chance of controlling the cancer while minimizing the risk of progression to metastatic disease and the resulting death from prostate cancer. The complications associated with radical prostatectomy, radiation therapy and brachytherapy should also be taken into account in the...
choice made by the patient (Middleton et al. 1995). The most frequently reported complications are incontinence, impotence (erectile dysfunction), cystitis, rectal injury, bleeding as well as bladder neck and urethral stricture (Middleton et al. 1995).

The treatment options for localized disease are radical prostatectomy, external beam radiotherapy, brachytherapy and hormone therapy alone, a combination of hormone therapy with surgery, radiotherapy, brachytherapy or even deferred treatment (watchful waiting). Life expectancy, rather than the age of the patient should be the factor considered in treatment selection.

For a series of reasons previously described (Gann et al. 1995, Hugosson et al. 1995, Labrie 1995, Labrie et al. 1995b), watchful waiting is not, for almost all patients, an alternative to be considered, except in patients with a short life expectancy. The real problem with watchful waiting is that all cancers progress, albeit at a different rate, and will kill the patient if he lives long enough. As illustrated in Fig. 3, the best estimates of the probability of local progression, metastases (not curable), and death for a 70-year-old man during the next 10 years are 60%, 40%, and 18%, respectively (Labrie et al. 1995b). For a 55-year-old man, the risks of local progression, distant metastases, and death from prostate cancer are 90%, 70%, and 45%, respectively, if he lives up to the age of 70 years. The curves illustrated in Fig. 3 for a 55-year-old patient can be moved along the abscissa for any age at diagnosis in order to estimate, for each patient, the risk of serious complications (including cancer death) if the clinically localized prostate cancer is not treated immediately at diagnosis.

This high risk of complications and even cancer death in patients diagnosed with localized prostate cancer and who do not receive immediate treatment is due to the fact that approximately 50% of cancers are already outside the prostate at the time of diagnosis (Labrie et al. 1994, O’Dowd et al. 1997). Moreover, as mentioned above, approximately 20% of the patients having organ-confined disease when the prostate is surgically removed will show failure within 10 years. Taking into account the fact that the curative therapies will eliminate cancer only in patients having disease confined to the prostate, only 40% of the men diagnosed with localized prostate cancer are expected to be cured by surgery, radiotherapy or brachytherapy alone. The consequence is that 60% of men need systemic therapy in addition to local treatment. Another major but related problem is that one cannot distinguish with certainty which men diagnosed with localized prostate cancer have truly organ-confined disease (40%) from those who already have disseminated disease (60% of them).

High efficacy of combined androgen blockade alone in localized disease

It is pertinent to indicate that CAB alone is highly efficient in keeping localized prostate cancer under control. In a personal series of 26 stage T2-T3 patients who received flutamide and an LHRH agonist for up to 12 years (median, 7.1 years), a rise in PSA occurred in only one patient after 8 years and 4 months of treatment (Labrie et al. 1997a).

The side effects of CAB are well tolerated, namely hot flushes usually lasting for a few months at start of therapy, impotence, and loss of libido (Labrie et al. 1985, Crawford et al. 1989, Denis et al. 1993). Unlike estrogens, the combination of flutamide and a LHRH agonist leads to an improved lipid profile compared with orchiectomy (Moorjani et al. 1988).

The present data clearly indicate that androgen deprivation is extremely efficient for the treatment of clinically localized prostate cancer, its ability to control the disease in 26 patients for up to 8.3 years being possibly superior to that of radical prostatectomy and radiation therapy alone (Fig. 4). Although a 15 year follow-up is required to assess the long-term effect of treatment of localized prostate cancer, it is recognized that local recurrence and especially serum PSA can be used as an interim parameter to evaluate efficacy (Zietman et al. 1994b). Without a randomized study, however, it is not possible to strictly compare one clinical series with another. Despite these limitations, it is of interest to see in Fig. 4 that the 5-year actuarial rate of recurrence in a similar category of patients who had radical prostatectomy was 24% at the Johns Hopkins Hospital (Morton et al. 1991), while it was 57% at the Boston University Medical Center (Zietman et al. 1994a) and 31% in a comparable series at the UCLA Medical Center (Trapasso et al. 1994). In a series of stage T1-T2 prostate cancer at the Cleveland Clinic Foundation, the 5-year recurrence rate was calculated at 39% (Kupelian et al. 1996). Similarly, PSA failure after radiation therapy has identified a high level of cancer recurrence. Thus, following radical irradiation for T1 and T2 disease, the 4-year% actuarial rate of recurrence has been reported as 35% at the Boston University Hospital (Zietman et al. 1994b) and 59% at Baylor University (Goad et al. 1993). A 5-year recurrence rate of disease-free survival has been calculated at 40% at the MD Anderson Hospital (Zagars & von Eschenbach 1993, Labrie et al. 1997a).

Since serum PSA had remained undetectable up to a treatment duration of 11.8 years (median: 7.1 years) in all other 25 patients, treatment has been stopped in 17 patients of this group. These 17 patients have now been followed for a median duration of 2.0 years. As can be seen in Fig. 5A, only three patients have shown progression of serum
CAB was stopped in 44 stage T2-T4 patients treated for surgery or radiotherapy alone (Fig. 4). Moreover, when those obtained in comparable groups of patients treated by androgen blockade of much longer duration than one year after cessation of treatment, thus indicating the need for androgen blockade to be continued for several years, for example, for 5 years. At first PSA rise above 0.2 ng/ml (Hybritech assay or its equivalent), CAB should be started without interruption with serum PSA measured every 2 months as follow-up.

Figure 4 Comparison of the failure rate after combined androgen blockade (first failure at 8.3 years in this study versus failure rates of 24%, 57%, 31% and 39% at 5 years after radical prostatectomy and 35%, 40%, and 59% 4 years after the start of radiation therapy. (1- (Morton et al. 1991); 2- (Zietman et al. 1994a); 3- (Trapasso et al. 1994); 4- (Kupelian et al. 1996); 5- (Zietman et al. 1994b); 6- (Kaplan et al. 1993); 7- (Goad et al. 1993); 8- (Labrie et al. 1997a)).

PSA. Including the median posttreatment follow-up of 2.4 years (up to 4.2 years) in the 17 patients who stopped CAB, median overall follow-up is 8.9 years, ranging from 2.8 to 14.1 years. One patient died at 8.4 years from a noncancer related cause. When treatment is restarted in such patients, it is usual for the PSA to return to undetectable levels.

Figure 6 shows the dramatic effect of the duration of CAB on the PSA failure rate after cessation of endocrine therapy. Treatment had been given for one year only in a series of T2 patients, the serum PSA did not remain undetectable for one year in any of the 11 patients. However, in 14 of 17 patients with category T2 disease treated for 7 years and 22 of 26 patients with T3 disease, treated for 10 years the PSA remained undetectable for 2.4 and 1.8 years of follow-up.

Such data obtained with CAB alone are superior to those obtained in comparable groups of patients treated by surgery or radiotherapy alone (Fig. 4). Moreover, when CAB was stopped in 44 stage T2-T4 patients treated for a median duration of 8-10 years, a PSA rise was seen in only 6 of them (14%) during a two-year follow-up period. Most importantly, PSA then returned to undetectable levels in all patients when CAB was reinstituted. On the other hand, when CAB was stopped in 11 T2 patients treated for only 1 year, a PSA rise was observed in all patients within 1 year after cessation of treatment, thus indicating the need for androgen blockade of much longer duration than one year.

Such data, combined with those of the 3-year treatment period of Bolla et al. (1997) and the results obtained following 10.5 months versus 3 months of CAB associated with radiotherapy (Laverdiere et al. 1997) as well as the benefits of 5 years of Tamoxifen as adjuvant to surgery in breast cancer compared with 2 years (Swedish Breast Cancer Cooperative Group 1996), indicate the importance of administering CAB as neoadjuvant (before surgery or radiation therapy) and/oroadjuvant for a continuous period of a few years, probably five years (Labrie et al. 1997a). In agreement with these findings, randomized and prospective international studies comparing an LHRH agonist and flutamide (CAB) associated with prostatectomy, radiation therapy or brachytherapy performed at 6 months followed by continuation of CAB for 4.5 additional years compared with CAB alone for 5 years are now opened for accrual in Canada. Based upon the above-summarized data, we estimate that a total period of 5 years of CAB is the best choice for the duration of androgen blockade.

Combined androgen blockade alone or in association with surgery or radiotherapy

In men unable to receive curative therapy or having a less than 10-year life expectancy, combined androgen blockade alone appears as a highly efficient means of controlling localized prostate cancer.

Based upon the most encouraging data obtained in patients with stage T2 disease (Labrie et al. 1997a), CAB alone is a valid alternative, especially for patients aged 70 years or more and for those having a life expectancy of less than 10 years.

For younger men having a more than 10-year life expectancy, the best approach, however, is likely to be the association of long-term combination therapy (probably 5 years) with surgery, radiotherapy or brachytherapy.

Our own belief, based upon the data summarized above, is, for young patients, to use CAB for 6 months before surgery and to continue CAB after surgery for a total of 5 years following cessation of CAB. A rise of PSA above 0.2 ng/ml should be a signal to immediately reinstitute CAB for 3 years. For patients having the best prognosis, radical prostatectomy alone can be performed with serum PSA measured every 2 months as follow-up. At first PSA rise above 0.2 ng/ml (Hybritech assay or its equivalent), CAB should be started without interruption for 5 years.

With the information summarized above and the recent demonstration that androgen blockade for 3 years combined with radiation therapy leads to a 45% improved survival at 5 years compared with radiation therapy alone (Bolla et al. 1997), it seems logical to recommend the association of CAB for 5 years when radiation therapy is used, at least in stage T3 patients. In fact, the 45% overall survival advantage obtained by adding 5 years of androgen blockade to radiotherapy was in clinical stage T3
disease (Bolla et al. 1997). However, as mentioned above, since approximately 60% of clinical stage T2 cancers are in fact pathological stages T3 or even T4 cancers, it would appear reasonable to apply the same strategy of CAB to external beam radiation therapy for both stages T2 and T3 disease.

For stages T1-T2 disease, one possibility is to perform radiotherapy or brachytherapy first after 6 months of CAB and then start CAB for 5 years only if PSA rises. Serum PSA should be measured every 2 months. An increase of serum PSA of 0.5 ng/ml within 12 months or an increase above 1.0 ng/ml should be the signal to reinstitute CAB for 3 years followed by the same follow-up of serum PSA measurement every second month.

Because the aim of androgen blockade is to cause a maximal reduction in prostatic androgen levels in order to induce maximal atrophy, apoptosis, and death of prostate cancer cells, combined androgen blockade using a pure antiandrogen (Labrie et al. 1982, Labrie et al. 1985) in association with an LHRH agonist or surgical castration is the most logical approach.

Summary and conclusions
The present data show that an optimal use of the available diagnostic and therapeutic approaches can have a major impact on quality of life and survival in prostate cancer. The only way to have a major impact on prostate cancer death is clearly treatment of localized disease. Moreover, it has become clear that, in analogy with breast cancer where significant survival benefits were obtained only after 2-5 years of adjuvant Tamoxifen therapy, combined androgen blockade must be administered for much longer periods than done so far, most likely up to 5 years.

Although PSA shows unique usefulness as an early sign of recurrence of cancer after any form of therapy, its high sensitivity to androgen deprivation needs caution. In fact, serum PSA decreases to undetectable levels much before generalized apoptosis or control of cancer proliferation is achieved. In other words, an undetectable serum PSA is not equivalent to cancer cell death. It should be remembered that the only form of endocrine therapy demonstrated to prolong life is the one where androgen blockade was administered continuously for years without interruption. Before being recommended, intermittent therapy needs to be proven in large randomized trials as being equivalent to continuous treatment on survival, the prime and essential objective of prostate cancer therapy. It is pertinent to remember that continuous androgen blockade is the only treatment shown to prolong life in both metastatic and localized disease.

The important benefits of androgen blockade in localized prostate cancer are in agreement with the well known observation that, in patients with metastatic disease treated with CAB, progression occurs almost always in the bones and not in the prostate, thus clearly indicating that prostate cancer localized to the prostatic area is highly sensitive to androgen deprivation. All available means should be taken to prevent prostate cancer from migrating to the bones, where treatment becomes extremely difficult and cure or even long-term control of the disease is no longer possible.

A major source of controversy concerning early diagnosis and treatment of prostate cancer is that, until recently, no prospective and randomized trial had shown statistically significant benefits of treatment of localized prostate cancer on survival (Kolata 1987). The absence of data from well designed clinical trials was erroneously interpreted as negative data. Most fortunately, two
prospective randomized trials have recently demonstrated for the first time that not only quality of life but, most importantly, prolongation of life could be achieved in localized prostate cancer patients treated with androgen blockade. In the EORTC trial performed in stage T3 patients, survival at 5 years was increased from 62% in the group of patients who received radiation therapy alone to 79% (45% difference) in those who received androgen blockade using an LHRH agonist for 3 years and an antiandrogen for one month in association with radiotherapy (Bolla et al. 1997). A similar observation has been made in RTOG trial 83351 in the subgroup of high Gleason score patients (Pilepich et al. 1997). No valid reason remains to doubt that treatment of clinically localized prostate cancer can prolong survival.

In addition to the major impact on prostate cancer deaths, the economic savings on health care costs has been previously discussed (Labrie et al. 1993b,d, Littrup et al. 1994, Aus et al. 1995). The calculations performed leave little doubt that the strategy based upon efficient screening and treatment, namely androgen blockade, surgery, radiotherapy or brachytherapy alone or in combination with androgen blockade should play a key role in the successful fight against prostate cancer while decreasing the costs for the health care system and society (Labrie 1994, Labrie et al. 1995b).

Major progress has been made by many groups during the last decade in the field of early diagnosis and early treatment (surgery, radiotherapy, brachytherapy, and hormonotherapy) of prostate cancer while our understanding of the endocrinology of this disease has also made significant progress, including the most important demonstration that androgen blockade prolongs life in both localized and advanced prostate cancer. There is no doubt, however, that only a concerted effort of urology, endocrinology, radiation therapy, and many other specialties can set the stage for the most successful fight against this most devastating disease. The significant progress made, however, is a stimulus to move forward at an even more accelerated pace.

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