Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome

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Background—Hutchinson-Gilford progeria syndrome is an ultrarare segmental premature aging disease resulting in early death from heart attack or stroke. There is no approved treatment, but starting in 2007, several recent single-arm clinical trials administered inhibitors of protein farnesylation aimed at reducing toxicity of the disease-producing protein progerin. No study assessed whether treatments influence patient survival. The key elements necessary for this analysis are a robust natural history of survival and comparison with a sufficiently large patient population that has been treated for a sufficient time period with disease-targeting medications.

Methods and Results—We generated Kaplan–Meier survival analyses for the largest untreated Hutchinson-Gilford progeria syndrome cohort to date. Mean survival was 14.6 years. Comparing survival for treated versus age- and sex-matched untreated cohorts, hazard ratio was 0.13 (95% confidence interval, 0.04–0.37; $P<0.001$) with median follow-up of 5.3 years from time of treatment initiation. There were 21 of 43 deaths in untreated versus 5 of 43 deaths among treated subjects. Treatment increased mean survival by 1.6 years.

Conclusions—This study provides a robust untreated disease survival profile that can be used for comparisons now and in the future to assess changes in survival with treatments for Hutchinson-Gilford progeria syndrome. The current comparisons estimating increased survival with protein farnesylation inhibitors provide the first evidence of treatments influencing survival for this fatal disease.

Clinical Trial Registration—URL:http://www.clinicaltrials.gov. Unique Indentifiers: NCT00425607, NCT00879034, and NCT00916747. **(*Circulation*. 2014;130:27-34.)**

Key Words: aging ■ atherosclerosis ■ Kaplan-Meier estimate ■ lamins ■ lonafarnib ■ prenylation ■ progeria

Hutchinson-Gilford progeria syndrome (HGPS) is a sporadic autosomal dominant segmental premature aging disease with an incidence of 1 in 4 million.[1] Cardiovascular (CV) disease in HGPS is characterized by early and pervasive vascular stiffening, along with later-stage arterial occlusive disease.[2–4] These factors are major contributors to an accelerated form of premature atherosclerosis that culminates in early death from heart attack or, less often, stroke.

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The genetic mutations causing HGPS are a series of silent point mutations in the *LMNA* gene that increase the use of an internal splice site[5,6] resulting in translation of the disease-causing abnormal lamin A protein progerin. The normal *LMNA* gene encodes lamin A, a principal protein of the nuclear lamina, which is a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin (for review, see Broers et al).[7] The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, and apoptosis.

Disease in HGPS is produced by a dominant-negative mechanism; it is the effect of progerin, not the diminution of lamin A, that causes the disease phenotype.[8] Progerin is found in increased concentration in skin and the vascular wall of normal older compared with younger individuals, suggesting a role in

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normal aging.[2,8a] Unlike lamin A, progerin lacks the proteolytic cleavage site required for removal of its posttranslationally attached farnesyl moiety.[6] Progerin is postulated to remain associated with the inner nuclear membrane, unable to be released for degradation because of persistent farnesylation.[9–12]

The pathological effects of progerin farnesylation form the central hypothesis underlying treatment protocols using protein farnesylation inhibitors in HGPS. Preclinical studies administering farnesylation inhibitors demonstrated positive effects on both in vitro[11,13,14] and murine in vivo[15–19] progeria disease models. The preclinical data in support of farnesylation inhibitors was encouraging but complicated. With treatment, HGPS fibroblasts displayed improved nuclear morphology, gene expression, cellular lifespan, and nuclear stiffness.[11,13,14,20] However, HGPS fibroblasts also exhibited the potential for alternative prenylation[18] and lack of improved sensitivity to mechanical strain[20] with farnesyltransferase inhibitor treatment. In vivo, several progeroid mouse models displayed improved phenotype[16,18,19,21] and, in some cases, extended lifespan.[16,18,21] However, some mouse models display bone or neurological morbidity without overt CV morbidity, and cause of death is undetermined for any mouse model. Given the complicated preclinical results, extended survival in humans could not be assumed and could only be tested with adequate human cohort numbers and treatment duration.

The first human clinical treatment trial for HGPS administered the protein farnesyltransferase inhibitor lonafarnib for 2 years.[22] CV and neurovascular results demonstrated evidence for decreased vascular stiffness,[22] incidence of stroke, transient ischemic attack, and headache.[4] There was also evidence for skeletal and audiologic benefits.[22] Improvements occurred in some but not all subjects, and some disease phenotypes were not improved with lonafarnib. Trial duration was inadequate to test influence on survival. The second and currently ongoing trial added 2 additional medications to lonafarnib, also aimed at inhibiting progerin farnesylation. The statin pravastatin inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase, and the bisphosphonate zoledronate inhibits farnesyl–pyrophosphate synthase[18]; each enzyme functions along the protein prenylation pathway (Figure 1).

Along with their influences on protein prenylation, both pravastatin and zoledronate affect disease in subjects without HGPS using mechanisms of action independent of the prenylation pathway. There exists both direct and indirect support for efficacy of these drugs specifically through inhibiting progerin prenylation in HGPS versus alternative mechanisms of action. In vitro, phenotypic improvements in progeroid mouse fibroblasts treated with pravastatin plus zoledronate are completely abolished when cells are allowed to specifically bypass the need for 3-hydroxy-3-methylglutaryl coenzyme A reductase and farnesyl–pyrophosphate synthase.[18] In vivo, statins were shown to exert beneficial CV effects through mechanisms distinct from their effect in lowering cholesterol and low-density lipoproteins.[23] Additional statin effects were demonstrated in pathways of inflammation, immunomodulation, and thrombosis. However, the usual target pathways of statins do not appear as significant components in the HGPS population. Children with HGPS exhibit normal values for serum total cholesterol and low-density lipoprotein, serum high-sensitivity C-reactive protein,[24,25] and arterial intima-media thickness[3,25] and demonstrate no overt evidence of endothelial dysfunction. Finally, zoledronate exhibits its major effects by decreasing bone resorption and ultimately improving bone density.[26] Although both bone density and skeletal morphology are affected in HGPS,[27] fracture rate is normal[28] and subjects do not die from bone disease. Thus, influence on HGPS lifespan in humans stemming from zoledronate would likely be attributable to effects outside of the skeletal system.

Assessing change in population survival attributable to treatment necessitates a robust analysis of the untreated HGPS comparison population. Two studies estimated mean survival for this disease group at 13.4[29] and 12.6[1] years based mainly on literature searches. Neither included subjects who were living or lost to follow-up (censored data), nor did they generate survival curves.

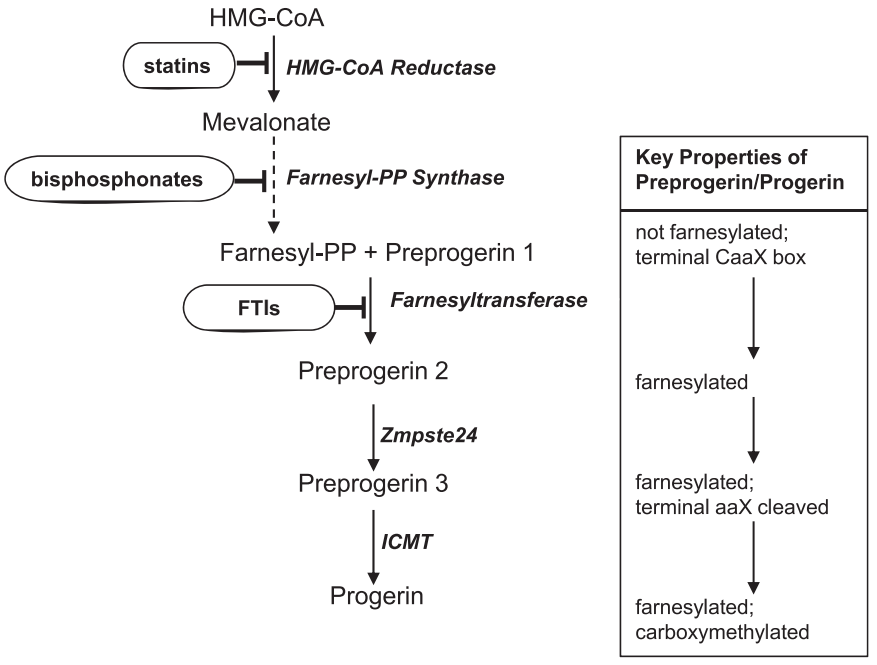

Figure 1. Current HGPS treatment strategies aimed at preventing formation of progerin protein by inhibiting posttranslational farnesylation of preprogerin. Enzymes facilitating each step are italicized. Dashed line indicates that multiple steps in the pathway are not shown. Medications aimed at inhibiting protein farnesylation are circled. ICMT indicates isoprenylcysteine carboxyl methyltransferase.

We developed Kaplan–Meier curves and survival estimates for a large untreated HGPS cohort. To assess whether treatment has an influence on survival for children with HGPS, we provide comparisons between this untreated cohort and a treated cohort that received HGPS-specific treatments during clinical trials. A robust comparison required subject matching with regard to age, sex, dates, and other potential confounding factors.

Methods

Inclusion Criteria and Demographics

This project was approved by the Rhode Island Hospital Institutional Review Board. Some data were obtained through a Data Use Agreement between the Progeria Research Foundation, Rhode Island Hospital, and Brown University. The clinical trials were approved by the Boston Children's Hospital Committee on Clinical Investigation.

Study subjects were identified using the Progeria Research Foundation International Registry (www.progeriaresearch.org), published scientific and news articles, and publicly available databases. Minimum inclusion criteria were as follows: (1) phenotype confirmation by study investigators; (2) living age or age of death; (3) inclusion history in progeria clinical trials (at clinicaltrials.gov) NCT00425607 (lonafarnib monotherapy) and NCT00879034 and NCT00916747 (lonafarnib, zoledronate, and pravastatin combination therapy); and (4) treatment duration. Because of institutional restrictions, 10 subjects with HGPS included in an open-label clinical trial conducted in Marseilles (registered at clinicaltrials.gov as NCT00731016) were unavailable for inclusion in this study (Dr Nicolas Levy, personal communication).

Untreated subjects had not received clinical trial medications within any clinical treatment trial for HGPS. Treated subjects received trial medications for any length of time; treatment initiation and duration varied.

HGPS was defined by clinical phenotype, which is consistent and unique from non-progerin–producing progeroid laminopathies. The main differential diagnosis for HGPS includes mandibulo-acral dysplasia and restrictive dermopathy, which are both attributable to alternative mutations in LMNA. These are both quite distinct in appearance, so there is little possible confusion with the classic HGPS.[30] When genotype was known, all positive cases by phenotype contained a progerin-producing mutation in the *LMNA* gene. Although exclusion of non-progerin–producing laminopathies is reliably accomplished using phenotype in the absence of genotype, there are cases in which the splicing mutation yields very low levels of progerin and a clinically different phenotype that is not categorized as HGPS.[31,32] These subjects were not included in the analysis because they are considered non-HGPS by phenotype.

Statistics

Drs Massaro and D'Agostino performed all statistical analyses. Demographic characteristics are presented with counts and percentages and compared between groups using Fisher's exact test. Untreated patient survival age was estimated by the Kaplan–Meier method. Untreated subjects living as of the start of data analysis and subjects appearing in a published report living at the time of the report but then lost to follow-up (see Table I in the online-only Data Supplement) were censored at the time of their last-known living age. Treatment trial subjects were included as part of the untreated cohort until age of treatment initiation.

Cox proportional hazards regression was used to compare treated and untreated (ie, never treated) groups for survival. To control for potential confounding variables, sex and age matching was performed, and the untreated subject pool included only those born on or after 1991, the year on or after which all treated subjects were born. For every treated patient, all untreated subjects of the same sex who were alive at the age when the treated patient began treatment were identified; from this group of untreated subjects, 1 was randomly selected and used as the matched untreated patient in the analysis. Once an untreated patient was matched to a treated patient, the untreated patient was no longer available for matching. Patient follow-up began at time 0, in which time 0 is set to the age of treatment initiation for the treated patient in the matched pair. Supportive analyses were performed in which all subjects were followed from birth and placed at risk at the age of treatment initiation. Age, sex and continent of residency were included as covariates in these Cox models.

Treated and untreated subjects born on or after 1991 were compared using treatment (yes/no) as a time-dependent covariate, in which all treated subjects were considered untreated until time of treatment initiation and in which sex and continent of residence were included as covariates. For at least the first 2 years of age, all subjects are untreated, yielding 0 treated subjects during this timeframe and 8 treated subjects through approximately ages 0 to 4 years. In other words, although all subjects (treated and untreated) are theoretically placed at risk for mortality at birth in the time-dependent analysis, in reality, the treated subjects are only truly at risk at the age they began treatment, which was at least 2 years of age for all treated subjects, theoretically yielding a survival advantage in at least the first 2 years of life for the treated patients over the untreated patients. The survival advantage was not large, because only 1 untreated patient born after 1991 died before 2 years of age; nevertheless, for this potential bias in favor of the treated group, we considered the time-dependent analysis as supportive.

Hazard ratios (HRs) and their 2-sided 95% confidence intervals (CIs) for mortality in treated versus untreated were calculated. Sensitivity analyses were conducted by removing or censoring subjects with various confounding variables listed in Results.

Estimated extension in mean survival with treated versus untreated subjects was calculated by comparing areas under the treated and untreated Kaplan–Meier curves for the matched sample set.

Statistical analysis was performed using SAS version 9.3 and STATA version 12. *P* values are 2 sided and deemed significant at 0.05.

Results

Patient Characteristics

Overall, 161 untreated subjects and 43 treated subjects (100% of HGPS clinical trial subjects) were eligible for analysis. Subject sources are detailed in the online-only Data Supplement Appendix. For matched analysis of untreated versus treated cohorts, sex (P=1.00), continent (P=0.39), and known mutation subgroups (P=0.16) were similar (Table).

Cause of death was identified for 50 of the 102 deceased untreated subjects and was attributed to CV failure (n=40; 80%), head injury or trauma (n=5; 10%), stroke (n=2; 4%), respiratory infection superimposed on CV disease (n=2; 4%), and complications from anesthesia during surgery (n=1; 2%). Similarly, cause of death in the 5 deceased trial participants was CV failure (n=3; 60%), head injury (n=1; 20%), and stroke (n=1; 20%).

Trial Medication Side Effects

Notable lonafarnib monotherapy-related side effects included the following: (1) mild diarrhea; (2) fatigue; (3) nausea; (4) vomiting; (5) anorexia; (6) transiently elevated aspartate aminotransferase and alanine aminotransferase; and (7) depressed serum hemoglobin. All generally improved with time and are detailed by Gordon et al.[22] Because the combination trial is ongoing, a detailed account of toxicities is not available. However, to date, the most notable side effects include zoledronate-related postinfusion flu-like symptoms,[33] pravastatin-induced transient muscle discomfort, and mildly elevated creatine phosphokinase.[34]

Survival Analysis for Untreated Group

Analysis of the full untreated cohort (n=204), including treatment trial participants censored at the time of treatment

Table. Patient Characteristics

Variable	All (n=204)	Untreated (n=161)	Treated* (n=43)	Matched Untreated (n=43)
Females	98 (48.0)	72 (44.7)	26 (60.5)	26 (60.5)
Males	106 (52.0)	89 (55.3)	17 (39.5)	17 (39.5)
Born on or after 1986	136 (66.7)	93 (57.8)	43 (100.0)	43 (100.0)
Born on or after 1991	118 (57.8)	75 (46.6)	43 (100.0)	43 (100.0)
Known genotype	105 (51.5)	62 (38.5)	43 (100.0)	24 (55.8)
Continent				
Africa	10 (4.9)	5 (3.1)	5 (11.6)	1 (2.3)
Asia	37 (18.1)	30 (18.6)	7 (16.3)	9 (20.9)
Australia	2 (1.0)	2 (1.2)	0 (0.0)	0 (0.0)
Europe	45 (22.1)	35 (21.7)	10 (23.3)	11 (25.6)
North America	78 (38.2)	63 (39.1)	15 (34.9)	12 (27.9)
South America	32 (15.7)	26 (16.2)	6 (14.0)	10 (23.3)
Mutation subgroup†				
c.1824 C>T; p.G608G	89 (84.8)	50 (80.6)	39 (90.7)	18 (75)
c.1822 G>A, p.G608S	5 (4.8)	3 (4.9)	2 (4.7)	1 (4.2)
Intron 11, c.1968+1 G>C	2 (1.9)	2 (3.3)	0 (0.0)	1 (4.2)
Intron 11, c.1968+1 G>A	5 (4.8)	4 (6.6)	1 (2.3)	2 (8.3)
Intron 11, c.1968+2 T>A	2 (1.9)	2 (3.3)	0 (0.0)	1 (4.2)
Intron 11, c.1968+2 T>C	1 (1.0)	1 (1.6)	0 (0.0)	1 (4.2)
Intron 11, c 1968+5 G>C	1 (1.0)	0 (0.0)	1 (2.3)	0 (0.0)

Values are shown as n (%).

*There were no significant differences when comparing treated versus matched untreated cohorts for sex, continent of origin, birth year, or known mutation subgroups.

†Percentages of known mutations.

initiation, provided a Kaplan–Meier survival curve for HGPS (Figure 2A). Mean and median survival were 14.6 and 14.5 years, respectively.

Subgroup comparisons were conducted, with no significance found (see Table II in the online-only Data Supplement). These included male versus female and known versus unknown genotype. The possibility that general medical advances over time would improve survival for more recent subjects was addressed by comparing subjects born before 1986 with those born on or after 1986 (~50% of subjects). The possibility that healthier subjects would be removed from the untreated cohort as they enrolled in treatment trials was addressed by censoring the entire patient cohort at the clinical trial initiation date, May 2007.

For use in future comparison studies by other investigators, data elements for all subjects are provided (see Tables I and III through V in the online-only Data Supplement).

Association Between Farnesylation Inhibitors and Survival

There were 5 of 43 (11.6%) deaths in the treated group and 21 of 43 (48.8%) deaths in the matched untreated group. Median follow-up from time of treatment initiation in both treatment groups (untreated subjects matched to treated subjects) is 5.3 years (quartiles of 3.3–5.5 years).

Kaplan–Meier estimates demonstrated increased mortality for the untreated cohort over the treated cohort when follow-up begins at age of treatment initiation for the treated patient in the matched pair (age- and sex-adjusted $P<0.001$; Figure 2B). Age-, sex-, and continent-adjusted HR for mortality of treated subjects in the matched analysis was 0.15 and therefore positively associated with survival (95% CI, 0.04–0.43). Kaplan–Meier estimates similarly demonstrated increased mortality for untreated when follow-up begins at birth with subjects placed at risk at the age of treatment initiation for the treated patient in the matched pair ($P<0.001$; Figure 2C). Time-dependent analyses on patients born after 1991 yielded increased survival with $P=0.017$ and sex- and continent-adjusted HR=0.28 (95% CI, 0.10–0.79; Figure 3).

During the first 6 years after treatment initiation for the treated patient in the matched pair, extension in mean survival with treatment was 1.6 years, with a 95% CI of 0.8 to 2.4 years ($P<0.001$). There was a 33% increase in Kaplan–Meier area under the curve for treated versus untreated. To account for potential confounding variables within comparisons between untreated and treated cohorts, a sensitivity analysis that either excluded or censored specific subjects was conducted as follows. Two prospective subjects could not enroll because of health issues and were omitted from the untreated group. Five trial subjects taking recombinant growth hormone were omitted from the treated group. Clinical trial subjects did not generally receive clinical care at the trial hospital site, because clinical care was the responsibility of the subjects' home physicians. However, 1 trial patient received clinical care from the clinical trial group starting at age 18.4 years because of urgent clinical need while at the trial site. This subject returned home after care was completed and subsequently passed away at home at age 20.3 years. To account for this trial site clinical care, sensitivity analysis was performed where this patient was censored at age 18.4. Other than these variables, there were no known differences between subjects who enrolled and those who did not enroll in the clinical trials. Results of this sensitivity analysis were similar to those described above.

Discussion

This study demonstrates that, without treatment, HGPS survival distribution is stable and independent of sex or medical advances, because males compared with females, as well as pre-1986 compared with post-1986 Kaplan–Meier curves, were similar. This implies that the progerin-associated morbidity is the overriding factor in survival. The quality and quantity of data for the reference population are key to current and future success in assessing changes in survival. Given that the estimated prevalence of HGPS is currently 1 in 18 million,[35] this study captured a significant portion of the population.

This study is the first to demonstrate a positive effect of any treatment on estimated survival in HGPS. Results were

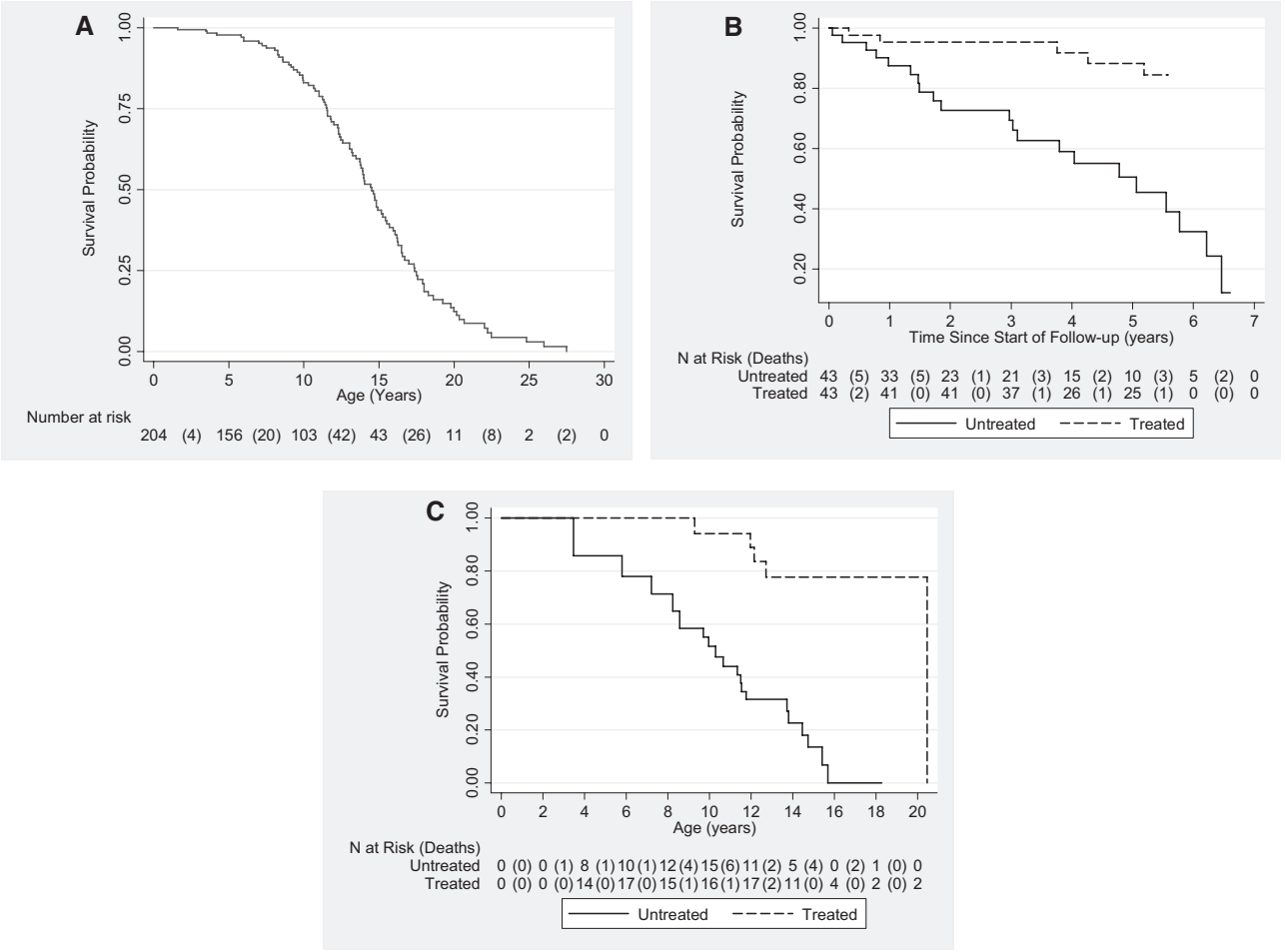

Figure 2. Kaplan–Meier survival estimates for untreated and treated HGPS cohorts. The number of patients at risk are presented below the *x* axis. Numbers in parentheses are number of deaths during that time interval. **A**, Untreated cohort. Treated subjects were included but censored at age of treatment initiation. Mean and median survival were 14.6 and 14.5 years, respectively. **B**, Kaplan–Meier survival estimates comparing untreated (solid line) with treated (dashed line) cohorts using matched analysis (age-adjusted $P<0.001$) in which time 0 on the *x* axis (ie, beginning of the patient being at risk) is defined for each matched pair as the age of treatment initiation for the treated patient in the matched pair. **C**, Kaplan–Meier survival estimates comparing untreated (solid line) with treated (dashed line) cohorts using matched analysis (unadjusted $P<0.001$) in which time 0 on the *x* axis (ie, beginning of the patient follow-up) is defined as patient birth and the subject becomes at risk at the age of treatment initiation for the treated patient in the matched pair.

consistent across 8 different possible confounding variables (sex, continent of origin, mutation status, birth year, medical advances, growth hormone treatment, failing health, trial site clinical treatment), and various analytic methods, strengthening our assertion that farnesylation inhibitors positively influenced patient survival. Because these children die from sequelae of a pervasive premature, progressive form of atherosclerosis, we speculate that extended survival is attributable to CV and possibly cerebrovascular benefits. This premise is supported by secondary outcomes showing evidence for decreased pulse wave velocity, carotid artery wall echodensity, and incidence of stroke, headache, and seizures in subjects treated with lonafarnib monotherapy.[4,22]

Because each treatment trial was sequential and of relatively short duration (2 years on lonafarnib monotherapy and 3.5 years on combination therapy), the analysis did not distinguish individual drug influences on longevity. Because lonafarnib is the drug to which all subjects have been exposed and for the longest period of time in most instances, we speculate that this drug is primarily responsible for the estimated life extension. This speculation takes into account the CV and neurovascular systems being responsible for most deaths and the improvements seen in some CV and neurovascular properties with lonafarnib treatment. To evaluate further whether addition of zoledronate and pravastatin may be beneficial, neutral, or harmful to morbidity and mortality, it will be crucial to compare CV and other clinical changes with combination therapy with those of lonafarnib monotherapy, once the combination therapy trial is completed.

In the treated group 5 of 43 subjects died compared with 21 of 43 in the untreated matched comparison group, both with median follow-up of 5.3 years. Treatment group inclusion was independent of duration of treatment, age, or stage of disease at treatment initiation. The HR of 0.13 indicates that, given a specific point in time, subjects with HGPS receiving farnesylation inhibitors demonstrated an 80% reduction in risk of death compared with untreated subjects. Interpretation of this effect is complicated by the longitudinal nature of the Kaplan–Meier curve and variable treatment times for different subjects. The estimated 1.6 years of extended survival

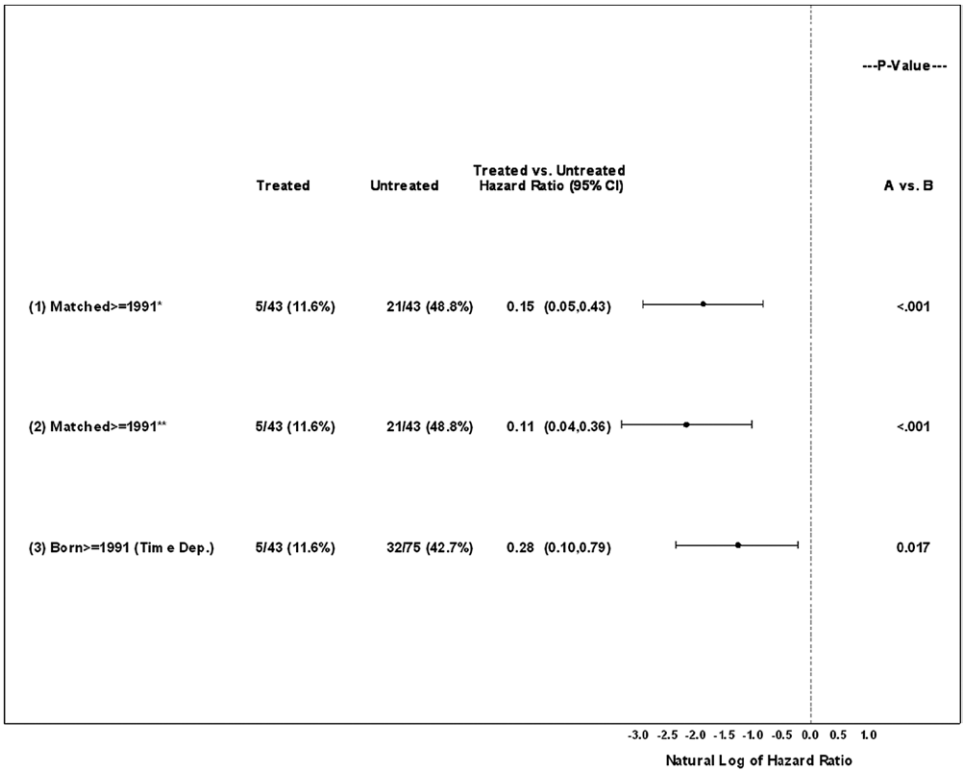

Figure 3. Hazard ratios (HRs) comparing untreated with treated cohorts using matched analyses and time-dependent analysis for patients born on or after 1991. HRs and *P* values were generated from Cox proportional hazards regression and adjusted for sex and continent. *For each matched pair, follow-up begins at time 0 defined as the age of treatment initiation for the treated patient in the matched pair; HR and *P* value further adjusted for age at risk. **For each matched pair, follow-up begins at birth, and the patient is placed at risk at the age of treatment initiation for the treated patient in the matched pair; HR and *P* value further adjusted for age at risk.

may be conservative because many subjects started treatment late in their disease course and may potentially benefit from earlier initiation of farnesyltransferase inhibitor therapy and given that most subjects were still living at the time of analysis because of the short follow-up time. This is a statistical estimate; it will take ~6 years until a true extension in mean survival can be determined from actual treated cohort age.

This study was limited by the use of an external untreated control group. For HGPS and other ultrarare, fatal pediatric diseases with no known treatments, only single-arm clinical trials have been conducted to date and are therefore the sole source of data to demonstrate safety and efficacy of any potential new treatment. We attempted to address this issue by using a matching statistical analysis and integrating potential confounding variables.

There are no previously established life-extending treatments for HGPS. Farnesylation inhibitors are clearly not curative, because many features of disease persist despite treatment.[22] However, evidence suggesting that survival may be improved by these medications offers a first step in recognizing that treatments aimed at further reducing progerin could thwart its fatal effects.

Appendix

Drs Gordon, Massaro, D'Agostino, Campbell, Brazier, Kleinman, and Kieran are Progeria Clinical Trials Collaborative members. Additional participating Progeria Clinical Trials Collaborative investigators include the following (in alphabetical order): W. Robert Bishop, PhD (Merck Research Labs, Kenilworth, NJ), Robert H. Cleveland, MD (Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, MA), Marie Gerhard-Herman, MD (Department of Cardiology, Brigham and Women's Hospital, Boston, MA), Catherine M. Gordon, MD, MSc (Department of Pediatrics, Hasbro Children's Hospital and Warren Alpert Medical School of Brown University, Providence, RI), Susanna Y. Huh, MD, MPH (Division of Gastroenterology and Nutrition, Boston Children's Hospital and Harvard Medical School), Marilyn Liang, MD, Division of Dermatology, Boston Children's Hospital and Harvard Medical School, David T. Miller, MD, PhD (Division of Genetics and Laboratory Medicine, Boston Children's Hospital and Harvard Medical School), Marsha Moses, PhD (Department of Surgery, Boston Children's Hospital and Harvard Medical School), Ara Nazarian, PhD (Center for Advanced Orthopedic Studies, Department of Orthopedic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA), Susan Riley (Department of Physical Therapy, Boston Children's Hospital), V. Michelle Silvera, MD (Department of Radiology, Boston Children's Hospital and Harvard Medical School), Leslie Smoot, MD (Department of Cardiology, Boston Children's Hospital and Harvard Medical School), Brian D. Snyder, MD, PhD

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Disclosures

Dr Gordon is the parent of a child who participated in the study. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Hutchinson-Gilford progeria syndrome is an ultrarare segmental premature aging disease uniformly resulting in early death from heart attack or stroke. There is no approved treatment and no proven strategy for extending lifespan. Recently, several clinical trials administered drugs that interfere with protein farnesylation aimed at reducing toxicity of the disease-producing protein progerin. We conducted a study to ask whether estimated lifespan is extended as a result of 1 or more these treatments. We first established a robust analysis of an untreated Hutchinson-Gilford progeria syndrome population to generate Kaplan–Meier survival curves that can be used henceforth for treatment comparisons. Survival was distributed normally; the mean was 14.6 years. We then conducted a series of survival comparisons with the treated populations, accounting for age, sex, and 8 additional possible confounding variables. The hazard ratio was 0.13 (95% confidence interval, 0.04–0.37; $P<0.001$), with median follow-up of 5.3 years. There were 21 of 43 deaths in untreated versus 5 of 43 deaths among treated subjects. The analysis did not distinguish individual drug influences on longevity. The study provides the first evidence of treatments influencing survival for this fatal disease. Because lonafarnib is the drug to which all treated subjects have been exposed and for the longest period of time in most instances, we speculate that this drug is responsible for the largest proportion of estimated life extension. Farnesylation inhibitors are clearly not curative, because most features, including cardiovascular disease, persist despite treatment. However, this study offers a first step in recognizing that treatments aimed at further reducing progerin could thwart its fatal effects.

Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome

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Supplementary Appendix

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Subject Sources

Overall, 161 untreated subjects were eligible for analysis: 102 deceased and 59 living or lost to follow-up. Of the deceased subjects, 82 were identified through The Progeria Research Foundation International Registry and Database. Twenty-six of these 82 subjects were also described in published studies. Twenty subjects were identified solely through published studies. Of the 59 subjects living or lost to follow-up, 35 untreated currently living subjects who had not been enrolled in a treatment trial were identified through The Progeria Research Foundation International Registry and Database. Twenty-four subjects were identified from case reports as living at the time of the case report. These subjects were considered lost to follow-up and censored, though publication dates would imply that they are deceased at this time. There was no overlap between these 24 case report subjects and any other subjects included in the study; this was confirmed by comparison between identified cases and properties such as the gender, age, and dates of publication. In summary, there were 34 cases that overlapped between The Progeria Research Foundation International Registry and published articles; 9 cases that overlapped between publications. In addition, 8 articles and the cases described therein were excluded as it was determined that there was too much possibility for overlap. When overlap was

identified, the oldest living age or age at death was counted, and the overlapping case report was omitted from the analysis.

The Progeria Research Foundation International Registry (www.progeriaresearch.org) is an official HGPS patient registry. It currently captures an estimated 30% of the world's population of those living with HGPS, from 39 countries. Based on an estimated prevalence of 1 in 18 million, the database has captured all children living with HGPS in the USA since its inception in 1999. All subjects are followed until they are deceased.

Table S1: Censored Subjects

Censored Untreated Subjects

Study ID	Sex	Mutation	Age (Y)	Study ID	Sex	Mutation	Age (Y)
HGPS116	M	c.1824C>T, p.G608G	4.86	HGPS146	F	c.1824C>T, p.G608G	2.82
HGPS117	M	c.1824C>T, p.G608G	12.87	HGPS147	F		5.82
HGPS118	M	c.1824C>T, p.G608G	15.05	HGPS148	M	c.1822G>A, p.G608S	1.30
HGPS119	M	c.1824C>T, p.G608G	1.80	HGPS149	M	c.1824C>T, p.G608G	0.77
HGPS120	M	c.1824C>T, p.G608G	10.12	HGPS150	M		4.5
HGPS121	F	c.1968+1 G>A	12.40	HGPS151	M		21.3
HGPS122	M	c.1824C>T, p.G608G	16.89	HGPS152	F		4.7
HGPS123	F		8.46	HGPS153	M		7.8
HGPS124	M	c.1824C>T, p.G608G	3.33	HGPS154	M		14.5
HGPS125	M	c.1824C>T, p.G608G	7.92	HGPS155	M		8.5
HGPS126	F	c.1824C>T, p.G608G	3.36	HGPS156	M		4.25
HGPS127	M	c.1824C>T, p.G608G	6.73	HGPS157	F		6.5
HGPS128	M	c.1824C>T, p.G608G	1.42	HGPS158	F		3.5
HGPS129	F	c.1968+2 T>A	2.46	HGPS159	M		5.5
HGPS130	F	c.1824C>T, p.G608G	7.13	HGPS160	F		10
HGPS131	M	c.1824C>T, p.G608G	3.71	HGPS161	M		3
HGPS132	M	c.1824C>T, p.G608G	0.74	HGPS162	M		6
HGPS133	M	c.1824C>T, p.G608G	2.29	HGPS163	F		4
HGPS134	F	c.1968+1 G>A	3.06	HGPS164	F		8
HGPS135	F	c.1824C>T, p.G608G	3.20	HGPS165	F		12
HGPS136	F	c.1824C>T, p.G608G	15.51	HGPS166	F	c.1824C>T, p.G608G	12
HGPS137	M	c.1824C>T, p.G608G	2.69	HGPS167	M		4
HGPS138	M	c.1968+2T>C	8.46	HGPS168	F		12
HGPS139	F	c.1824C>T, p.G608G	4.91	HGPS169	M	c.1824C>T, p.G608G	10
HGPS140	F	c.1824C>T, p.G608G	15.29	HGPS174	M		4
HGPS141	M	c.1968+1 G>A	7.18	HGPS299	F		14
HGPS142	F	c.1968+2 T>A	1.42	HGPS300	M		7
HGPS143	F	c.1824C>T, p.G608G	11.86	HGPS301	M		7
HGPS144	F	c.1824C>T, p.G608G	10.13	HGPS302	M		6.8
HGPS145	F		12.56				

Treated Subjects Censored At Age of Treatment Initiation

Study ID	Sex	Mutation	Age (Y)	Study ID	Sex	Mutation	Age (Y)
HGPS182	F	c.1824C>T, p.G608G	6.00	HGPS204	F	c.1824C>T, p.G608G	9.47
HGPS183	F	c.1822G>A, p.G608S	6.78	HGPS205	F	c.1824C>T, p.G608G	2.08
HGPS184	F	c.1824C>T, p.G608G	3.08	HGPS206	F	c.1824C>T, p.G608G	4.94
HGPS185	M	c.1824C>T, p.G608G	17.50	HGPS207	F	c.1822G>A, p.G608S	11.90
HGPS186	F	c.1824C>T, p.G608G	8.99	HGPS208	F	c.1824C>T, p.G608G	7.40
HGPS187	F	c.1824C>T, p.G608G	3.18	HGPS209	F	c.1824C>T, p.G608G	10.83
HGPS188	M	c.1824C>T, p.G608G	11.63	HGPS210	M	c.1824C>T, p.G608G	2.24
HGPS189	M	c.1824C>T, p.G608G	10.61	HGPS211	F	c.1824C>T, p.G608G	3.33
HGPS190	F	c.1824C>T, p.G608G	4.04	HGPS212	M	c.1968+5G>C	6.79
HGPS191	M	c.1824C>T, p.G608G	8.73	HGPS213	M	c.1824C>T, p.G608G	3.24
HGPS192	F	c.1824C>T, p.G608G	8.97	HGPS214	M	c.1824C>T, p.G608G	8.39
HGPS193	F	c.1824C>T, p.G608G	4.24	HGPS215	M	c.1824C>T, p.G608G	10.83
HGPS194	M	c.1824C>T, p.G608G	3.52	HGPS216	F	c.1824C>T, p.G608G	16.19
HGPS195	F	c.1824C>T, p.G608G	7.22	HGPS217	M	c.1824C>T, p.G608G	9.68
HGPS196	F	c.1824C>T, p.G608G	3.90	HGPS218	F	c.1824C>T, p.G608G	3.52
HGPS197	M	c.1824C>T, p.G608G	2.56	HGPS219	M	c.1824C>T, p.G608G	8.95
HGPS198	F	c.1824C>T, p.G608G	8.90	HGPS220	M	c.1824C>T, p.G608G	4.76
HGPS199	F	c.1824C>T, p.G608G	3.70	HGPS221	M	c.1824C>T, p.G608G	3.19
HGPS200	F	c.1824C>T, p.G608G	4.32	HGPS222	F	c.1824C>T, p.G608G	6.19
HGPS201	F	c.1824C>T, p.G608G	11.13	HGPS223	M	c.1824C>T, p.G608G	2.51
HGPS202	M	c.1824C>T, p.G608G	9.08	HGPS224	F	c.1968+1G>A	2.31

HGPS203	F	c.1824C>T, p.G608G	6.94				

Table S2: Comparative Cohort Survival Analyses				
	Grouping	**Mean (95% CI)**	**Median (95% CI)**	**Log-Rank P-Value**
Untreated Whole Cohort Comparisons	Female Male	13.9 (12.9, 15.0) 15.0 (13.8, 16.3)	14.5 (13.1, 15.3) 14.8 (12.5, 16.5)	0.15
	Known Genotype Unknown Genotype	15.3 (13.6, 16.9) 14.4 (13.3, 15.4)	14.9 (13.5, 18.0) 14.0 (12.6, 15.3)	0.37
	<1986 >=1986	14.8 (13.4, 16.2) 14.1 (13.2, 15.0)	14.8 (12.3, 16.3) 14.0 (13.5, 15.3)	0.34
	Whole Cohort Censored May 2007	14.6 (13.7, 15.5) 15.0 (14.0, 16.0)	14.5 (13.7, 15.4) 14.8 (13.3, 16.2)	Not Applicable
Untreated *Sensitivity Comparisons	Female Male	13.9 (12.9, 15.0) 14.9 (13.6, 16.2)	14.5 (13.1, 15.3) 14.8 (12.5, 16.5)	0.20
	Known Genotype Unknown Genotype	15.1 (13.4, 16.8) 14.4 (13.3, 15.4)	14.9 (13.2, 18.0) 14.0 (12.6, 15.3)	0.48
	<1986 >=1986	14.8 (13.4, 16.2) 14.0 (13.1, 14.9)	14.8 (12.3, 16.3) 14.0 (13.1, 14.9)	0.26
	Whole Cohort Censored May 2007	14.5 (13.6, 15.4) 14.9 (13.9, 15.9)	14.5 (13.3, 15.2) 14.5 (12.3, 16.5)	Not Applicable
Untreated+ Treated Whole Cohort Comparisons	Female Male	14.2 (13.2, 15.2) 15.5 (14.2, 16.8)	14.6 (13.1, 15.5) 15.4 (13.8, 17.0)	0.13
	Known Genotype Unknown Genotype	16.0 (14.5, 17.5) 14.4 (13.3, 15.4)	16.0 (14.0, 18.3) 14.0 (12.6, 15.3)	0.07
	<1986 >=1986	14.8 (13.4, 16.2) 14.7 (13.8, 15.6)	14.8 (12.3, 16.3) 14.7 (13.8, 15.7)	0.89
	Whole Cohort Censored May 2007	14.9 (14.1, 15.8) 15.0 (14.0, 16.0)	14.7 (13.9, 16.0) 14.8 (13.3, 16.2)	Not Applicable
Untreated+ Treated *Sensitivity Comparisons	Female Male	14.2 (13.2, 15.2) 15.2 (13.9, 16.5)	14.6 (13.1, 15.5) 14.8 (12.5, 16.5)	0.24
	Known Genotype Unknown Genotype	15.8 (14.1, 17.5) 14.4 (13.3, 15.4)	15.7 (13.5, 18.3) 14.0 (12.6, 15.3)	0.15
	<1986 >=1986	14.8 (13.4, 16.2) 14.4 (13.5, 15.4)	14.8 (12.3, 16.3) 14.5 (13.5, 15.4)	0.67
	Whole Cohort Censored May 2007	14.8 (13.9, 15.7) 14.9 (13.9, 15.9)	14.7 (13.7, 15.7) 14.8 (13.3, 16.2)	Not Applicable

* To account for potential confounding variables within comparisons between untreated and treated cohorts, a sensitivity analysis which either excluded or censored specific subjects was conducted as follows: Two prospective subjects could not enroll due to health issues and were omitted from the untreated group. Five trial subjects taking recombinant growth hormone were omitted from the treated group. Clinical trial subjects did not generally receive clinical care at the trial hospital site, as clinical care was the responsibility of the subjects' home physicians. However, one trial patient received clinical care from the clinical trial group starting at age 18.4 years due to urgent clinical need while at the trial site. This subject returned home after care was completed, and subsequently passed away at home at age 20.3 years. To account for this trial site clinical care, sensitivity analysis was performed where this patient was censored at age 18.4. Other than these variables, there were no known differences between subjects who enrolled and those who did not enroll in the clinical trials.

Table S3. Deceased Untreated Cohort*

Study ID	Sex	Mutation	Age at Death (Y)	Study ID	Sex	Mutation	Age at Death (Y)
HGPS1	F	c.1824 C>T, p.G608G	11.35	HGPS52	F	c.1824 C>T, p.G608G	11.55
HGPS2	F	c.1968+1 G>C	5.81	HGPS53	M	c.1822 G>A, p.G608S	3.48
HGPS3	M		11.50	HGPS54	F		16.72
HGPS4	M		18.00	HGPS55	M	c.1968+1 G>A	3.55
HGPS5	M	c.1824 C>T, p.G608G	14.92	HGPS56	F		22.22
HGPS6	F	c.1968+1G>C	1.60	HGPS57	M		22.02
HGPS7	M	c.1824 C>T, p.G608G	10.66	HGPS58	F		14.03
HGPS8	M		9.57	HGPS59	M		19.78
HGPS9	M		26.00	HGPS60	F		14.81
HGPS10	F		12.38	HGPS61	M		11.57
HGPS11	M		11.76	HGPS62	M		22.48
HGPS12	M	c.1824 C>T, p.G608G	13.19	HGPS63	M		13.98
HGPS13	F		13.76	HGPS64	F		14.73
HGPS14	M		18.61	HGPS65	M	c.1824 C>T, p.G608G	17.99
HGPS15	F	c.1824 C>T,p.G608G	13.48	HGPS66	F		12.57
HGPS16	M	c.1824 C>T,p.G608G	13.91	HGPS67	M		20.68
HGPS17	F		16.56	HGPS68	F	c.1824 C>T, p.G608G	14.61
HGPS18	M	c.1824 C>T,p.G608G	24.81	HGPS69	M		15.42
HGPS19	M		8.25	HGPS70	F		8.06
HGPS20	M		8.58	HGPS71	M	c.1824 C>T, p.G608G	14.83
HGPS21	F	c.1822 G>A,p.G608S	6.00	HGPS72	M	c.1824 C>T, p.G608G	12.46
HGPS22	M		9.15	HGPS73	F		13.73
HGPS23	F	c.1824 C>T,p.G608G	7.21	HGPS74	M		16.07
HGPS24	M	c.1824 C>T,p.G608G	11.57	HGPS75	F	c.1824 C>T, p.G608G	9.92
HGPS25	F		9.97	HGPS76	F		15.25
HGPS26	F		16.21	HGPS77	M		16.21
HGPS27	M		4.19	HGPS78	F		13.04
HGPS28	F	c.1824 C>T,p.G608G	15.69	HGPS79	F		20.35
HGPS29	M		17.58	HGPS80	F		12.31
HGPS30	F	c.1824 C>T,p.G608G	9.30	HGPS81	M		17.33
HGPS31	M		12.26	HGPS82	M		7.50
HGPS32	M		13.93	HGPS83	F		13.25
HGPS33	F		16.27	HGPS84	M		8.33
HGPS34	M		16.99	HGPS85	M		16.50
HGPS35	M		8.63	HGPS86	M		11.25
HGPS36	M		9.70	HGPS87	F		11.83
HGPS37	F		15.15	HGPS88	F		10.75
HGPS38	M	c.1824 C>T,p.G608G	15.95	HGPS89	F		7.00
HGPS39	F		13.05	HGPS90	F		15.50
HGPS40	M		9.94	HGPS91	F		19.25
HGPS41	M		13.80	HGPS92	M		11.42
HGPS42	M		20.00	HGPS93	M		16.50
HGPS43	F		17.91	HGPS94	M		27.5
HGPS44	F		12.30	HGPS95	F	c.1824 C>T, p.G608G	17.37
HGPS45	F		14.69	HGPS96	F		6
HGPS46	F		8.27	HGPS97	F		9
HGPS47	F	c.1824 C>T, p.G608G	20.17	HGPS98	M		11
HGPS48	M	c.1824 C>T, p.G608G	14.01	HGPS99	M		12
HGPS49	M	c.1824 C>T, p.G608G	18.27	HGPS100	M		11
HGPS50	F		14.45	HGPS172	M		14.52
HGPS51	M	c.1824 C>T, p.G608G	10.29	HGPS298	M		17.5

*For 9 deceased individuals whose years of birth or death was not known, we used year of publication as year of death, and year of publication minus age at death was used for year of birth.

Table S4: Citations Used for Untreated Cohort*				
Deceased Subjects			**Censored Subjects**	
Patient ID	**Reference**		**Patient ID**	**Reference**
HGPS13	Nelson, 1965 [1]		HGPS150	Thomson and Forfar JO, 1950 [23]
HGPS79	Delahunt, et al, 2000 [2]		HGPS151	Plunkett, et al, 1954 [24]
HGPS81 HGPS298	Gilford, 1904 [3]		HGPS152	Djupesland, 1962 [25]
HGPS82	Talbot et al, 1945 [4]		HGPS153	Margolin and Steinbach, 1968 [26]
HGPS83 HGPS84	Cooke, 1953 [5]		HGPS154 HGPS155	DeBusk, 1972 [10]
HGPS85	Doub, 1953 [6]		HGPS156	Bajoghli, 1976 [27]
HGPS86	Atkins, 1954 [7]		HGPS157	Chawla, et al, 1986 [28]
HGPS87	Rosenthal, et al, 1956 [8]		HGPS158	Erdem, et al, 1994 [29]
HGPS88	Macnamara, et al, 1970 [9]		HGPS159	Alghamdi, 1995 [30]
HGPS89	DeBusk, 1972 [10]		HGPS160	Mitchell and Goltman, 1940 [31]
HGPS90	Ghosh, 1973 [11]		HGPS161	Keay, et al, 1955 [32]
HGPS91	Meme, et al, 1978 [12]		HGPS162	Steinberg and Szeinberg, 1957 [33]
HGPS92	Shozawa at al, 1984 [13]		HGPS163	Sahni, et al, 1990 [34]
HGPS93	Chandravanshi et al, 2011 [14]		HGPS164	de Paula Rodrigues, et al, 2002 [35]
HGPS94	Schippers, 1916 [15]		HGPS165	Nair, et al, 2004 [36]
HGPS94	Manschot, 1940 [16]		HGPS166	Mutesa, et al, 2007 [37]
HGPS94	Manschot, 1950 [17]		HGPS167	Agarwal, et al, 2010 [38]
HGPS95	Nakamura, et al, 2007 [18]		HGPS168	Hanumanthappa et al, 2011 [39]
HGPS97	Curtin and Kitzen, 1929 [19]		HGPS169	Kalil and Fargalley, 2012 [40]
HGPS98	Reichel et al, 1971 [20]		HGPS299	Bhakoo, et al, 1965 [41]
HGPS99	Brown, et al, 1978 [21]		HGPS300 HGPS301	Viegas, et al, 1974 [42]
HGPS100	Wesley, et al, 1979 [22]		HGPS302	Erecinski, et al, 1961 [43]
*1432 published articles related to progeria were reviewed. Several subjects required multiple references to obtain complete inclusion information and therefore patient IDs may appear in multiple references				

Table S5: Treated Cohort Details

Study ID	Sex	Mutation	Age (Y)	Lonafarnib Monotherapy Trial Participation	Triple Therapy Trial Participation
HGPS182	F	c.1824C>T, p.G608G	8.81		X
HGPS183	F	c.1822G>A, p.G608S	11.96	X	X
HGPS184	F	c.1824C>T, p.G608G	8.30	X	X
HGPS185	M	c.1824C>T, p.G608G	20.34		X
HGPS186	F	c.1824C>T, p.G608G	14.15	X	X
HGPS187	F	c.1968+1 G>A	6.22		X
HGPS188	M	c.1824C>T, p.G608G	17.00	X	X
HGPS189	M	c.1824C>T, p.G608G	16.11	X	X
HGPS190	F	c.1824C>T, p.G608G	7.04		X
HGPS191	M	c.1824C>T, p.G608G	14.22	X	X
HGPS192	F	c.1824C>T, p.G608G	9.29	X	
HGPS193	F	c.1824C>T, p.G608G	7.23		X
HGPS194	M	c.1824C>T, p.G608G	8.80	X	X
HGPS195	F	c.1968+2 T>A	12.32	X	X
HGPS196	F	c.1824C>T, p.G608G	9.37	X	X
HGPS197	M	c.1824C>T, p.G608G	6.24		X
HGPS198	F	c.1824C>T, p.G608G	14.24	X	
HGPS199	F	c.1824C>T, p.G608G	9.15	X	X
HGPS200	F	c.1968+1 G>A	7.36		X
HGPS201	F	c.1824C>T, p.G608G	16.49	X	X
HGPS202	M	c.1824C>T, p.G608G	14.38	X	X
HGPS203	F	c.1824C>T, p.G608G	12.51	X	X
HGPS204	F	c.1968+2T>C	15.00	X	X
HGPS205	F	c.1824C>T, p.G608G	5.20		X
HGPS206	F	c.1824C>T, p.G608G	10.22	X	X
HGPS207	F	c.1824C>T, p.G608G	12.73		X
HGPS208	F	c.1822 G>A,p.G608S	12.83	X	X
HGPS209	F	c.1824C>T, p.G608G	13.69		X
HGPS210	M	c.1824C>T, p.G608G	5.91		X
HGPS211	F	c.1824C>T,p.G608G	8.77	X	X
HGPS212	M	c.1968+5G>C	9.85		X
HGPS213	M	c.1824C>T, p.G608G	6.20		X
HGPS214	M	c.1822G>A, p.G608S	12.15	X	X
HGPS215	M	c.1824C>T, p.G608G	16.27	X	X
HGPS216	F	c.1824C>T, p.G608G	20.45	X	X
HGPS217	M	c.1824C>T, p.G608G	15.09	X	X
HGPS218	F	c.1824C>T, p.G608G	6.83		X
HGPS219	M	c.1824C>T, p.G608G	14.47	X	X
HGPS220	M	c.1824C>T, p.G608G	10.25	X	X
HGPS221	M	c.1824C>T, p.G608G	8.52	X	X
HGPS222	F	c.1824C>T, p.G608G	11.76	X	X
HGPS223	M	c.1824C>T, p.G608G	6.20		X
HGPS224	F	c.1968+1 G>A	5.98		X

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