PIONEER

innovative medicines initiative

PIONEER

IMI2 777492 – PIONEER

Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the Power of Big Data in EuRope

WP6 – HTA regulator – payer integration

D6.2 Prostate cancer reference models

efpia

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Contents

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Version	Date	Description
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Publishable Summary

The aim of this deliverable was to develop a publicly available, peer-reviewed reference model for health-economic evaluations for advanced prostate cancer, available online on the PIONEER website. The model can be used to analyze new and existing technologies for advanced prostate cancer at different points in the treatment pathway as well as different treatment sequences.

Based on previous work in PIONEER, the model includes metastatic hormone-sensitive prostate cancer (mHSPC), with subsequent health states. To inform the model development, a literature review of previous health-economic models of advanced prostate cancer was performed, including cost-effectiveness models published in peer-reviewed journals or used in HTA assessments.

The health-economic model was developed in Excel using Visual Basic for Applications (VBA). It is a patient-level state-transition model. The structure of the model is flexible and allows the user to include a sequence of up to five transitional health states representing different stages of disease and treatment lines and two absorbing health states representing cancer specific and non-cancer specific death. The model contains a comprehensive set of parametric functions which can be used to inform the transition probabilities, and it can easily be adapted with additional transition probabilities when survival analysis of time-to-event data is available.

The estimation of transition probabilities between health states in the model was based on Kaplan-Meier data for overall survival (OS) and progression-free survival (PFS) in clinical studies. In general, Kaplan-Meier data for OS and PFS does not provide sufficient information to derive relevant transition probabilities for health-economic modeling in a straightforward manner. Previous methods exist but have been restricted to the assumption of constant risk. To meet this challenge, a new method for estimating transition probabilities from Kaplan-Meier data for OS and PFS was developed. The method presented in this deliverable may provide a basis for further health economic modeling in settings where state transition models with time-dependent risks are needed, but analysts are limited to Kaplan-Meier data for OS and PFS.

Aim of the deliverable

Development of a publicly available, peer-reviewed reference model for health-economic evaluations for advanced prostate cancer. The model will be able to analyze new and existing technologies for advanced prostate cancer at different points in the treatment pathway as well as different treatment sequences.

Methods

A patient-level state-transition model with time-dependent risks was developed in Excel using Visual Basic for Applications (VBA). Patient-level simulation allows for keeping track of time spent in each treatment in a treatment sequence.

To inform the model development, a literature review of previous health-economic models of advanced prostate cancer was performed. The review included cost-effectiveness models published in peer-reviewed

journals or used in HTA assessments. The literature review allows us to build on existing knowledge and benchmark against previous models.

The estimation of the transition probabilities between disease states requires several definitions and datasets with detailed information. The required definitions concern clinically relevant disease states (i.e., mHSPC and mCRPC). Suitable datasets need to contain variables to determine different disease states and transitions between the disease states over time.

As specified in the study protocol, the data for the estimation of transition probabilities between health states in the model was planned to be derived from the PIONEER database. In addition, transition probabilities were also to be estimated from clinical studies to provide flexibility and fill data gaps. However, it was not possible to derive transition probabilities from PIONEER data due to challenges in phenotyping and cohort definitions. While cohort definitions for treatment groups of metastatic hormone-sensitive prostate cancer (mHSPC) were developed in PIONEER Studyathon 3, the same was not accomplished for the subsequent state metastatic castration resistant prostate cancer (mCRPC). Therefore, the estimation of transition probabilities relied on clinical studies as the only data source.

Results

Literature review

To inform the model development, a literature review of previous health-economic models of advanced prostate cancer was performed. The review included cost-effectiveness models published in peer-reviewed journals or used in HTA assessments. Searches were conducted in scientific (the PubMed database) and grey literature (the NICE appraisals database) in November 2022 to identify previous health-economic models of advanced prostate cancer. The PubMed search was based on search strings with relevant economic, treatment, and disease- specific terms and was limited to publications from the last 10 years. Secondary searches in reference lists of review articles identified in the search were also performed. The PubMed search identified 358 titles, of which 79 journal articles were selected for full-text review. The final sample consisted of 52 peer-reviewed articles with health-economic simulation models. The NICE appraisals search identified 16 appraisals, all of which were added to the final sample.

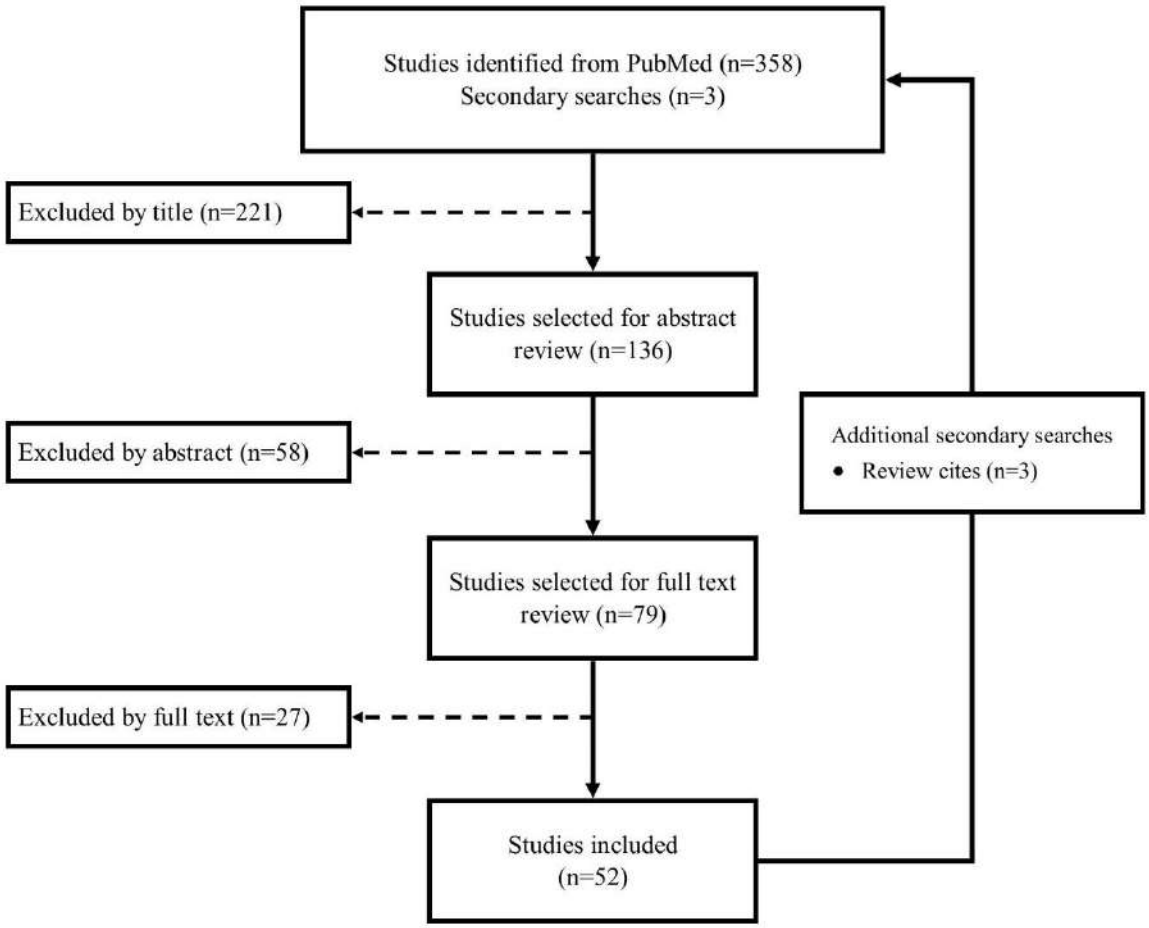

Figure 1. Literature review flow chart

The most common model type included in the literature search was Markov model (N=54), followed by partitioned survival (N=7). Among patient-level models, about half were Markov models (N=4) and the other half discrete event models (N=3).

Table 1. Model types included in the literature review

MODEL TYPES	COHORT-LEVEL	PATIENT-LEVEL	TOTAL
Markov	50	4	54
Discrete event	0	3	3
Decision tree	3	0	3
Partitioned survival	7	0	7
Other/unclear	1	0	1

The simulated cancer stage at baseline was nmHSPC in about half of the models (N=31), mCRPC in a third of the models (N=19), mHSPC in fifth of the models (N=15) and nmCRPC in three models. Among the models

simulating mCRPC, post docetaxel was the most common starting point (N=12). Two mCRPC models did not specify docetaxel history.

Table 2 Simulated baseline population in included models

BASELINE POPULATION	NUMBER OF MODELS
nmHSPC	**31**
Localised	25
Locally advanced	2
Biochemical recurrence	6
nmCRPC	**3**
mHSPC	**15**
mCRPC	**19**
Pre docetaxel	5
Post docetaxel	12
Unspecified	2

Model cycle length (where applicable) varied between weekly and yearly and were typically shorter for more advanced disease at baseline. Models simulating nmHSPC had longer model cycles, with 14 out of 26 using yearly cycles and shortest cycle length being monthly. Models simulating mCRPC had the shortest model cycles, with five out of 15 using weekly cycles, and the longest cycle length being monthly.

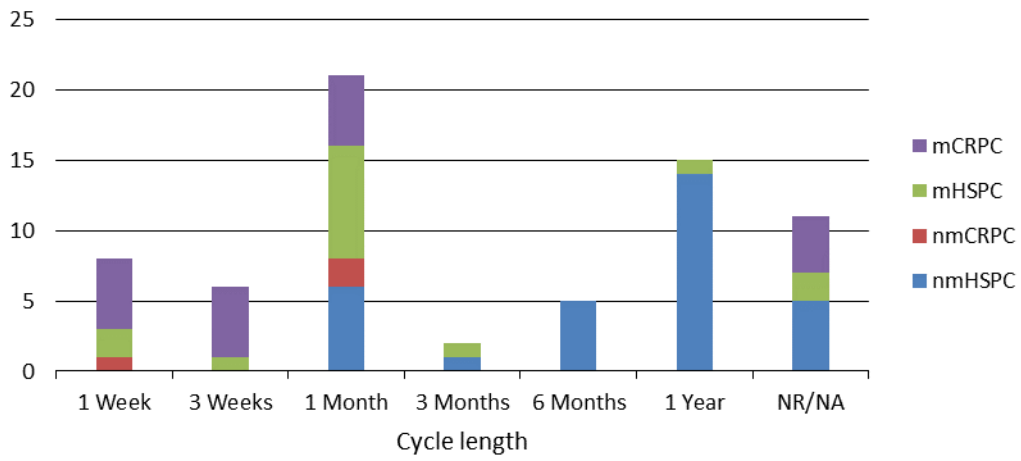

Figure 2. Number of models with different cycle lengths, depending on baseline population

There was a tendency to have more health states in models simulating earlier stages of disease at baseline. Most models with nmHSPC at baseline included four health states (10 out of 29), while mHSPC and mCRPC mostly included 3 health states (8 out of 14 and 16, respectively). Among models simulating nmHSPC at baseline, only one model reported stratifying subsequent metastatic health states into mHSPC and mCRPC.

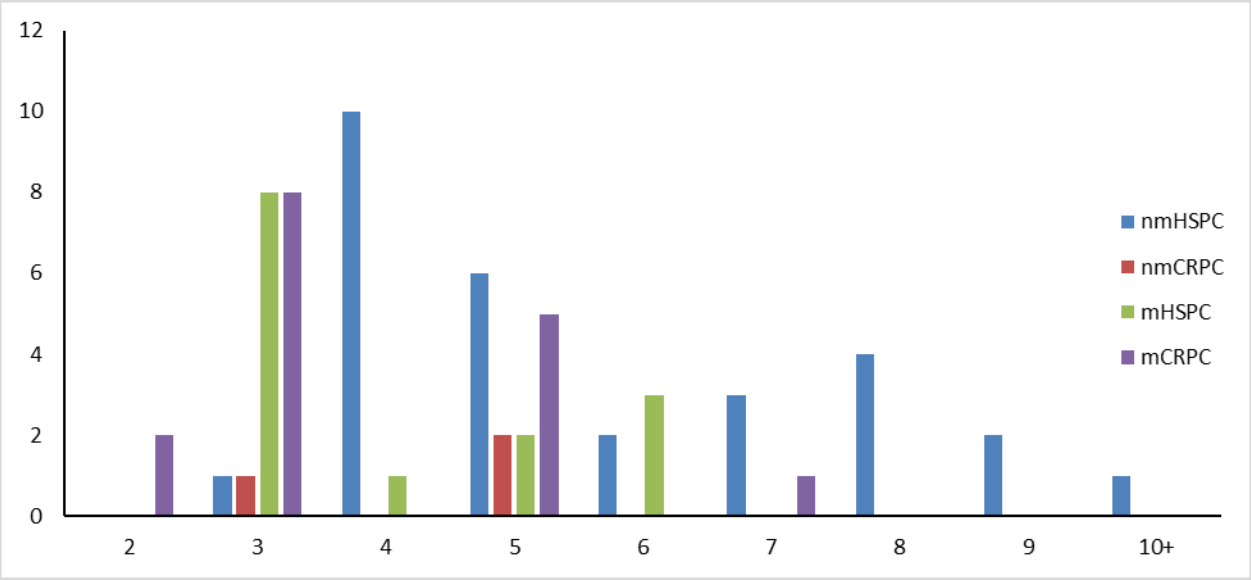

Figure 3. Number of models with different number of health states depending on baseline population

Model structure

The health economic model was developed in Excel using Visual Basic for Applications (VBA). It is a patient-level state-transition model. The structure of the model is flexible and allows the user to include a sequence of up to five transitional health states representing different stages of disease and treatment lines. The health states are mutually exclusive, and each state allows for transitions to the next state in the sequence. The model also includes two absorbing health states representing cancer specific and non-cancer specific death. Figure 4 shows the model structure with all health states included.

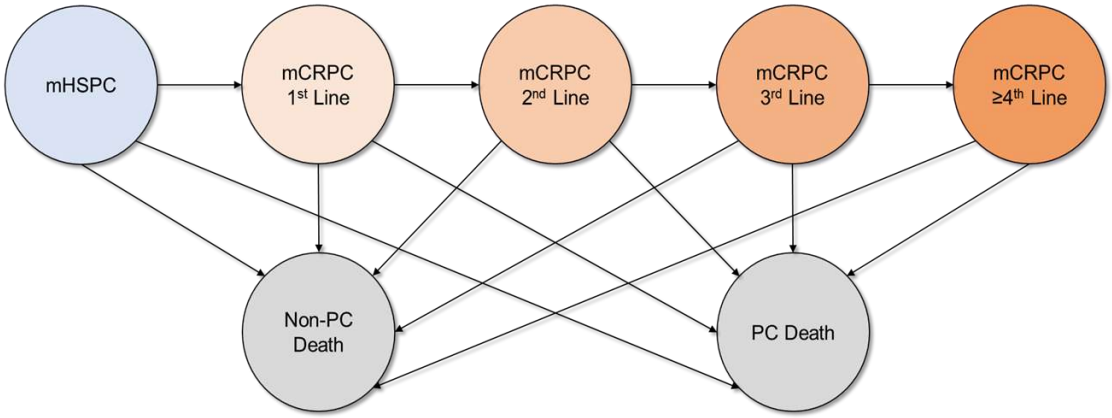

Figure 4. Model structure

The model simulates and compares two treatment arms with a user specified time horizon. Each hypothetical patient enters both treatment arms and progresses through the transitional health states until death or the simulation time horizon is reached. The model cycle length is one week (maximum 1,000 weeks). Once all patients have been simulated, simulation results from both treatment arms are aggregated and presented in Excel tables. The model applies discount rates to health and costs separately.

The model account for both stochastic uncertainty (first-order uncertainty) and parameter uncertainty (second-order uncertainty). Stochastic uncertainty relates to the random variability between patients (e.g., starting age and individual events). Parameter uncertainty relates to the estimation of parameters at the cohort level (e.g., transition probabilities, costs, and quality of life). Up to 1,000 cohorts and 10,000 patients per cohort may be included in a simulation, with larger number of patients and cohorts resulting in more stability in the simulation results, at the cost of a longer simulation time. The model structure used in the simulation is defined by specifying the starting health state (mHSPC or mCRPC) and total number of mCRPC states. The starting health state is the same for all patients. Inclusion of non-prostate cancer mortality is optional, and the risks of death are user specified by entering yearly mortality risks from standard life table data.

For each treatment arm and health state, transition probabilities are modelled by selecting a clinical trial arm and a parametric function (exponential, Weibull, Gompertz, log-normal and log-logistic) for progression and prostate-cancer mortality, respectively. The risks may be further adjusted by hazard ratios (exponential, Weibull and Gompertz) or relative risks (log-normal and log-logistic), to account for differences in baseline demographic and disease characteristics between the modelled population and the study population.

Costs

Cost inputs are defined by event and state costs, stratified by health state and treatment arm. Five types of costs are included: medication, administration, health care, adverse events and other. Event costs are applied in the first cycle of the health state, and state costs are applied each week spent in the health state. Event costs are applied to all transitional health states as well as to the absorbing health states non-specific and cancer-specific death.

Quality of life

Quality of life inputs are defined by event and state and stratified by health state and treatment arm. The model also allows for an underlying age-dependent quality of life, which is entered for each year of age.

Model outputs

Model outputs include graphical representation of overall survival and cumulative incidence of progression for each health state. Result tables present total discounted costs disaggregated by category, discounted quality adjusted life years and life years. Results are presented by treatment arm and as incremental difference between treatment arms, including ICER and net monetary benefit. The model also presents a cost effectiveness plane showing the costs and QALYs for each cohort and a cost effectiveness acceptability curve.

Transition probabilities

The transition probability is the risk of moving from one health state to another within a specific time-period. These probabilities are often derived from clinical studies, epidemiological data, or expert opinions. Clinical trials often report only OS and PFS, which is not sufficient information to derive relevant transition probabilities for health economic modeling in a straightforward manner. With only OS and PFS at hand, previous methods have been restricted to the assumption of constant risk [1].

An innovative method for estimating transition probabilities by utilizing publicly available Kaplan-Meier data on Overall Survival (OS) and Progression-free Survival (PFS) was developed. This method builds upon previous research involving the analysis of pseudo individual-level data [2, 3] and the estimation of simultaneous events [4]. Figure 5 provides a visual representation of how transition rates were estimated. Each step is explained in detail below. Statistical analysis was performed in STATA version 14.2.

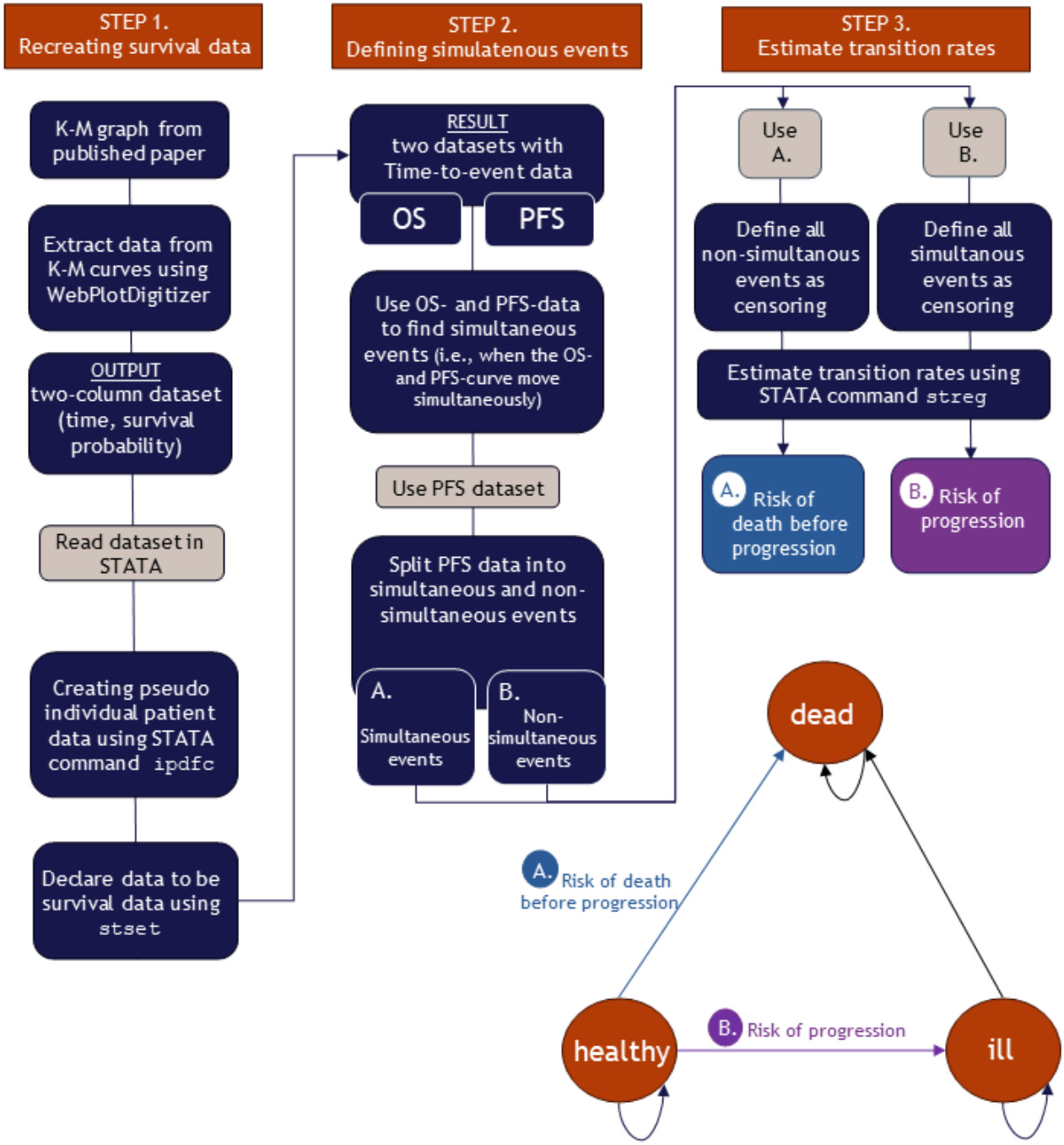

Figure 5. The flowchart of estimating transition rates from published K-M curves

Recreating survival data

Studies containing Kaplan-Meier curves of the endpoints Overall Survival (OS), and Progression-free Survival (PFS) were selected based on the results from Studyathon 3. Data points were extracted from these graphs using digitizing software. Individual-level time-to-event data were recreated using the ipdfc command in STATA, an approach developed by Wei et al. (2017)[3] based on previous work by Guyot et al. (2012)[2]. This

method uses Kaplan-Meier curves to create pseudo individual patient data (IPD), using patient counts from trial publications to determine relevant time intervals and correcting for data inconsistencies (e.g., monotonicity violations).

Defining simultaneous events

The reconstructed time-to-event data were then defined as survival data using the STATA stset command, separately for the two datasets (i.e., OS and PFS). Building on the approach proposed by Pahuta et al. (2019)[4], simultaneous events were defined as shifts that occur simultaneously in the OS-curve and the PFS-curve. All simultaneous events were assumed to be death before progression, and all non-simultaneous events to be progression. In the analysis of death before progression events of progression are censored and vice versa. The results are illustrated in Figure 6 with data from the PREVAIL study (Enzalutamide arm) and in Figure 7 (placebo arm). The reconstructed PFS-curve is shown in the graph to the left.

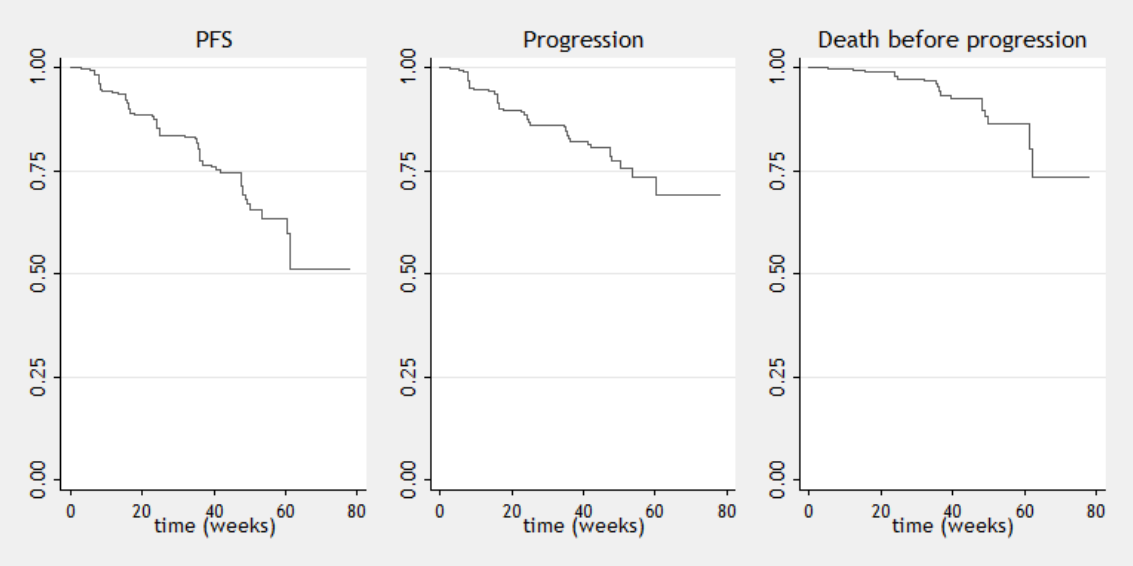

Figure 6. Progression-free survival, death before progression, and progression

Note: Data from the PREVAIL study (arm: Enzalutamide)

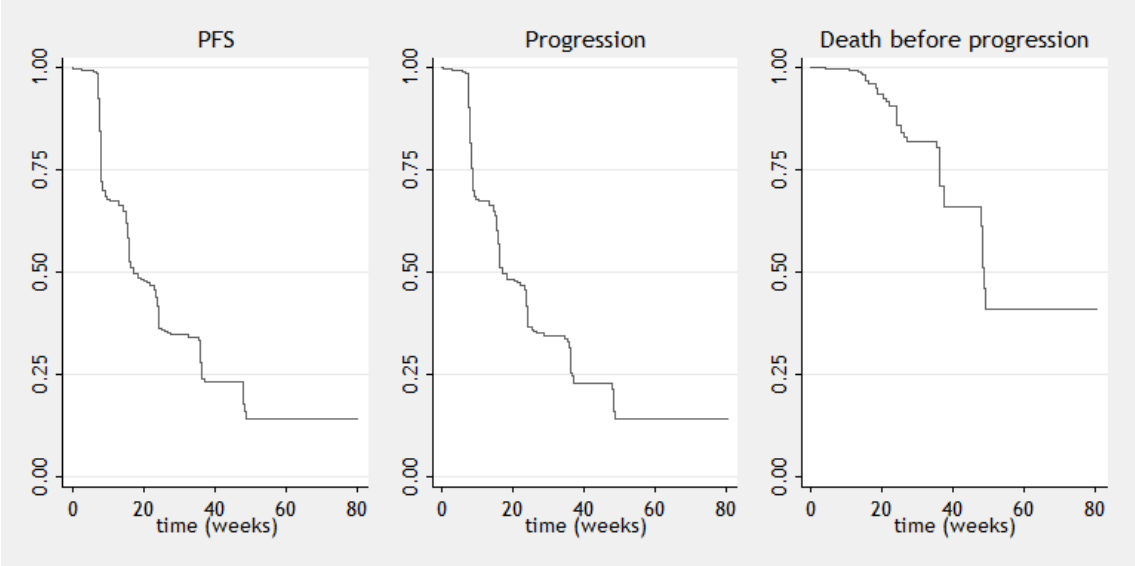

Figure 7. Progression-free survival, death before progression, and progression

Note: Data from the PREVAIL study (arm: placebo)

Estimating transition rates

Transition probabilities were estimated for the events progression, and death before progression. In survival analysis, two events can be considered competing if the probability for an individual to experience an event is related the occurrence of the other event. For example, if a patient experiences the event of progression they are no longer at risk of death *before* progression. The survival curve of time-to-progression based on data from the PREVAIL study (Enzalutamide arm) are shown in Figure 8. The corresponding figures for all clinical trials can be found in the supplementary material. The figure also shows four distributions that have been fitted to the data. Parametric estimates of the risk of progression for all studies included are displayed in Table 3 and standard errors in Table 4.

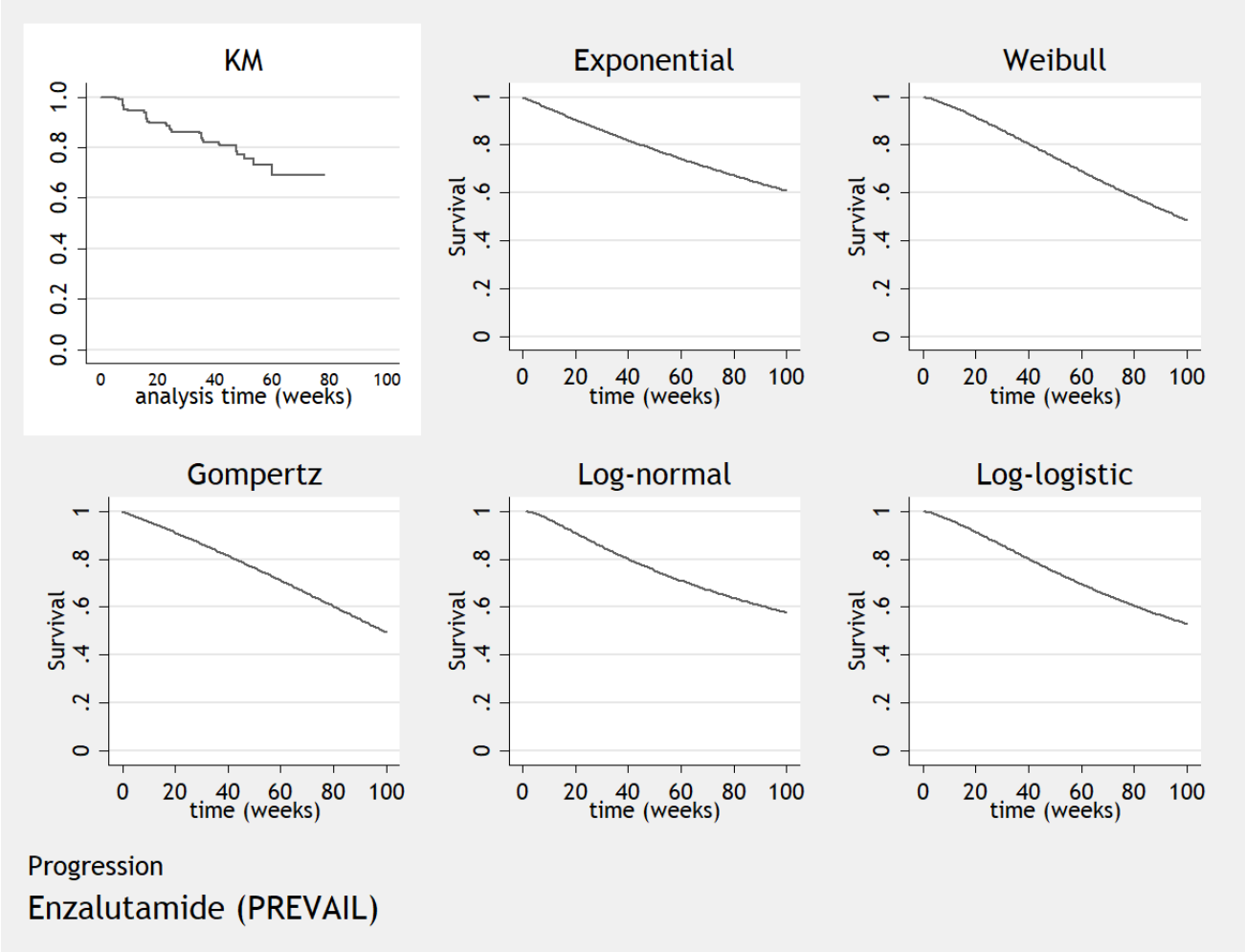

Figure 8. Time to progression, Kaplan-Meier data, and parametric fit

Table 3. Risk of progression: parametric estimates

		PARAMETRIC DISTRIBUTION								
		Exp	Weibull		Gompertz		Log-normal		Log-logistics	
STUDY	Drug	_cons	Shape (p)	_cons	/Gamma (γ)	_cons	Ln sigma (ln σ)	_cons	/ln Gamma (/ln γ)	_cons
PREVAIL [5]	Enzalutamide	-5.304	1.309	-6.355	0.01	-5.472	0.344	4.879	-0.33	4.691
PREVAIL [5]	Placebo	-3.471	1.46	-4.852	0.013	-3.629	-0.18	2.98	-0.743	2.935
TROPIC [6]	Cabazitaxel	-3.173	0.929	-2.945	-0.019	-2.911	0.337	2.662	-0.272	2.633
TROPIC [6]	Mitoxantrone	-2.808	0.864	-2.404	-0.037	-2.382	0.154	2.215	-0.353	2.105
AFFIRM [7]	Enzalutamide	-4.415	1.239	-5.308	0.003	-4.493	0.114	3.963	-0.392	3.956
AFFIRM [7]	Placebo	-3.582	1.299	-4.572	-0.005	-3.511	-0.244	3.122	-0.758	3.036
COU-302 [8]	Abiraterone	-4.817	1.174	-5.549	0.000	-4.809	0.204	4.408	-0.354	4.379
COU-302 [8]	Placebo	-4.177	1.048	-4.365	-0.007	-3.975	0.16	3.711	-0.343	3.685
ENZAMET [9]	Enzalutamide	-6.283	1.182	-7.186	0.000	-6.286	0.373	5.991	-0.254	5.86
ENZAMET [9]	BSC+ADT	-5.424	1.104	-5.924	-0.002	-5.323	0.272	5.043	-0.282	5.008
LATITUDE [10]	Abiraterone	-5.59	1.205	-6.552	0.002	-5.739	0.368	5.306	-0.316	5.166
LATITUDE [10]	Placebo	-4.948	1.269	-6.142	0.002	-5.059	0.063	4.497	-0.464	4.487
STAMPEDE[11]	Abiraterone	-6.465	0.979	-6.356	-0.003	-6.208	0.581	6.417	-0.059	6.241
STAMPEDE[11]	ADT	-5.448	0.657	-3.779	-0.012	-4.71	0.899	5.336	0.249	5.182
TITAN [12]	Apalutamide	-5.821	1.295	-7.139	0.006	-6.104	0.342	5.504	-0.336	5.329
TITAN [12]	Placebo	-5.136	1.171	-5.881	0.001	-5.199	0.27	4.763	-0.3	4.727
PETRYLAK*[13]	Docetaxel	-4.094	1.095	-4.46	-0.003	-4.021	0.2	3.666	-0.366	3.645
PETRYLAK*[13]	Mitoxantrone	-3.683	0.826	-3.053	-0.025	-3.178	0.342	3.119	-0.161	3.057
COU-301 [14]	Abiraterone	-4.095	1.216	-4.864	-0.005	-3.998	0.023	3.624	-0.451	3.598
COU-301 [14]	Placebo	-3.863	1.317	-4.939	0.001	-3.877	-0.108	3.378	-0.587	3.337

* Petrylak is the name of the first author, not a study name.

Table 4. Risk of progression: standard errors (SE)

		PARAMETRIC DISTRIBUTION								
		Exp	Weibull		Gompertz		Log-normal		Log-logistics	
STUDY	Drug	_cons	Shape (p)	_cons	/Gamma (γ)	_cons	Ln sigma (ln σ)	_cons	/ln Gamma (/ln γ)	_cons
PREVAIL [5]	Enzalutamide	0.106	0.399	0.112	0.172	0.007	0.168	0.08	0.142	0.085
PREVAIL [5]	Placebo	0.054	0.184	0.056	0.076	0.004	0.04	0.039	0.038	0.043
TROPIC [6]	Cabazitaxel	0.06	0.156	0.045	0.088	0.005	0.077	0.045	0.07	0.05
TROPIC [6]	Mitoxantrone	0.059	0.128	0.039	0.079	0.006	0.063	0.044	0.065	0.049
AFFIRM [7]	Enzalutamide	0.056	0.226	0.058	0.093	0.003	0.055	0.043	0.053	0.046
AFFIRM [7]	Placebo	0.067	0.229	0.065	0.095	0.004	0.046	0.05	0.047	0.055
COU-302 [8]	Abiraterone	0.065	0.285	0.066	0.109	0.002	0.07	0.05	0.065	0.055
COU-302 [8]	Placebo	0.058	0.2	0.049	0.087	0.003	0.059	0.043	0.06	0.047
ENZAMET [9]	Enzalutamide	0.086	0.477	0.095	0.156	0.002	0.126	0.071	0.109	0.078
ENZAMET [9]	BSC+ADT	0.063	0.303	0.062	0.106	0.001	0.073	0.05	0.067	0.054
LATITUDE[10]	Abiraterone	0.072	0.364	0.076	0.128	0.002	0.094	0.055	0.075	0.061
LATITUDE[10]	Placebo	0.061	0.291	0.063	0.101	0.002	0.057	0.046	0.055	0.05
STAMPEDE11]	Abiraterone	0.067	0.322	0.061	0.117	0.001	0.121	0.055	0.104	0.061
STAMPEDE11]	ADT	0.05	0.146	0.029	0.074	0.001	0.109	0.038	0.091	0.043
TITAN [12]	Apalutamide	0.092	0.498	0.109	0.177	0.003	0.13	0.074	0.108	0.083
TITAN [12]	Placebo	0.07	0.328	0.073	0.124	0.002	0.082	0.055	0.073	0.061
PETRYLAK*[13]	Docetaxel	0.072	0.257	0.064	0.109	0.003	0.077	0.054	0.072	0.059
PETRYLAK*[13]	Mitoxantrone	0.068	0.174	0.045	0.095	0.004	0.084	0.051	0.086	0.056
COU-301 [14]	Abiraterone	0.052	0.197	0.053	0.083	0.004	0.047	0.041	0.048	0.043
COU-301 [14]	Placebo	0.073	0.273	0.076	0.115	0.005	0.057	0.055	0.06	0.058

* Petrylak is the name of the first author, not a study name.

Figure 9 show survival curves of death before progression based on data from the PREVAIL study (Enzalutamide arm). Parametric estimates of risk of death before progression for all included studies is displayed in Table 5 and standard errors in Table 6.

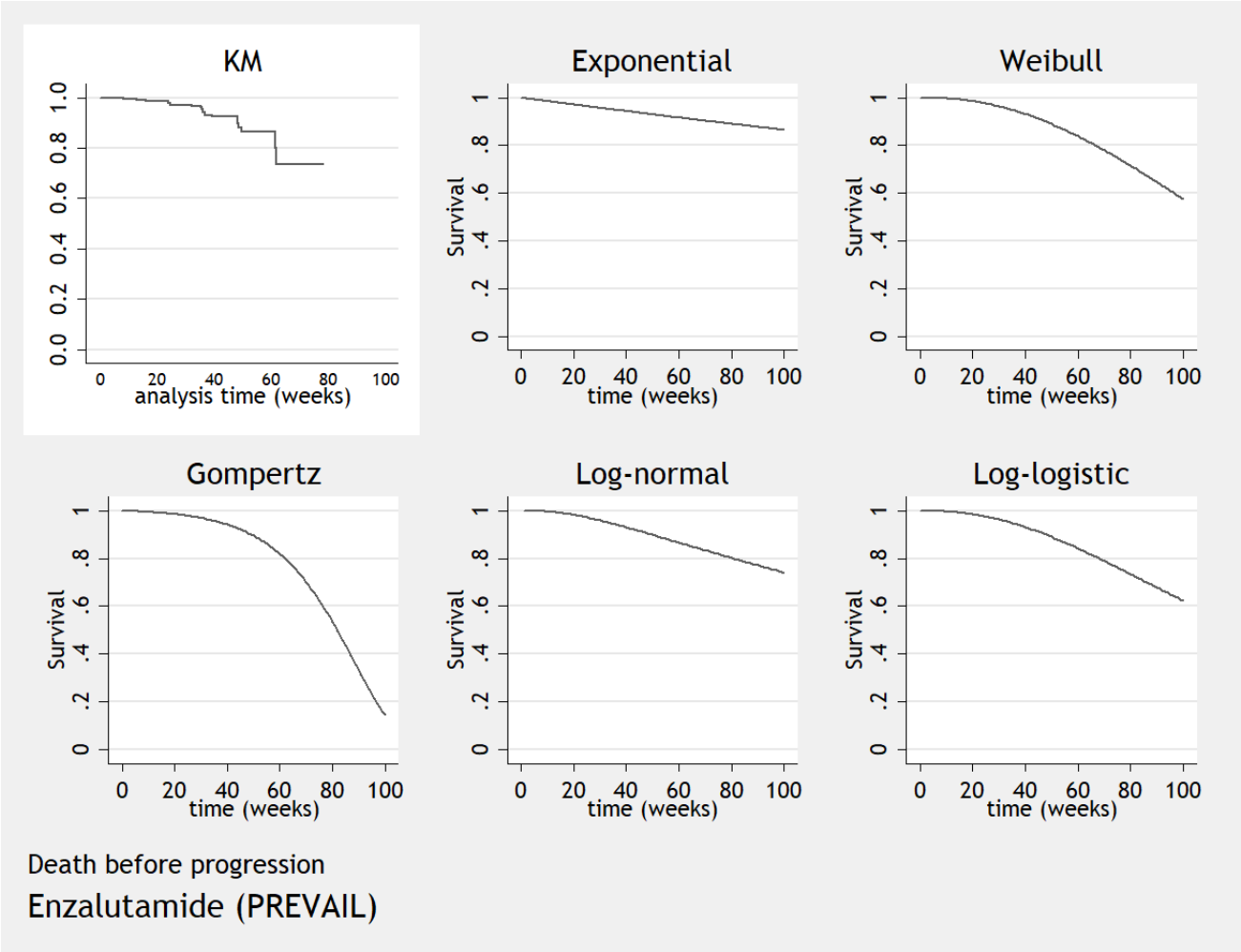

Figure 9. Time to death before progression, Kaplan-Meier data, and parametric fit

Table 5. Risk of death before progression: parametric estimates

		PARAMETRIC DISTRIBUTION								
		Exp	Weibull		Gompertz		Log-normal		Log-logistics	
STUDY	Drug	_cons	Shape (p)	_cons	/Gamma (γ)	_cons	Ln sigma (ln σ)	_cons	/ln Gamma (/ln γ)	_cons
PREVAIL [5]	Enzalutamide	-6.535	-10.916	2.241	-7.828	0.056	5.315	0.095	4.826	-0.829
PREVAIL [5]	Placebo	-5.471	-9.929	2.389	-6.262	0.048	4.057	-0.329	3.951	-1.045
TROPIC [6]	Cabazitaxel	-4.32	-7.358	1.886	-5.392	0.05	3.787	-0.015	3.731	-0.761
TROPIC [6]	Mitoxantrone	-4.181	-6.887	1.809	-4.657	0.025	3.492	-0.332	3.47	-0.935
AFFIRM [7]	Enzalutamide	-4.92	-8.546	1.951	-5.82	0.032	4.254	-0.167	4.206	-0.802
AFFIRM [7]	Placebo	-4.335	-7.528	1.923	-4.887	0.026	3.662	-0.315	3.612	-0.982
COU-302 [8]	Abiraterone	-6.661	-11.273	2.071	-7.675	0.022	5.59	-0.012	5.365	-0.77
COU-302 [8]	Placebo	-6.214	-10.943	2.148	-7.334	0.028	5.136	-0.104	4.997	-0.821
ENZAMET[9]	Enzalutamide	-7.662	-10.753	1.621	-8.516	0.01	7.397	0.472	6.576	-0.505
ENZAMET[9]	BSC+ADT	-6.659	-10.177	1.724	-7.293	0.008	5.938	0.082	5.77	-0.614
LATITUDE[10]	Abiraterone	-7.056	-8.377	1.281	-7.355	0.005	6.957	0.533	6.441	-0.278
LATITUDE[10]	Placebo	-6.085	-10.137	1.893	-6.936	0.014	5.289	-0.076	5.209	-0.726
STAMPEDE[11]	Abiraterone	-8.601	-7.948	0.873	-8.121	-0.006	10.368	1.033	9.047	0.126
STAMPEDE[11]	ADT	-6.955	-9.013	1.41	-7.092	0.002	6.404	0.26	6.24	-0.404
TITAN [12]	Apalutamide	-7.648	-16.968	3.053	-9.477	0.031	5.764	-0.32	5.523	-1.139
TITAN [12]	Placebo	-7.048	-9.577	1.575	-7.851	0.016	6.722	0.449	6.021	-0.476
PETRYLAK*[13]	Docetaxel	-4.614	-7.68	1.774	-5.282	0.02	4.115	-0.118	4.099	-0.785
PETRYLAK*[13]	Mitoxantrone	-4.53	-7.036	1.65	-5.07	0.017	3.997	-0.094	3.985	-0.732
COU-301 [14]	Abiraterone	-4.697	-7.902	1.878	-5.607	0.037	4.088	-0.091	4.032	-0.759
COU-301 [14]	Placebo	-4.282	-7.291	1.862	-5.145	0.04	3.704	-0.19	3.702	-0.794

* Petrylak is the name of the first author, not a study name.

Table 6. Risk of death before progression: standard errors (SE)

		PARAMETRIC DISTRIBUTION								
		Exp	Weibull		Gompertz		Log-normal		Log-logistics	
STUDY	Drug	_cons	Shape (p)	_cons	/Gamma (γ)	_cons	Ln sigma (ln σ)	_cons	/ln Gamma (/ln γ)	_cons
PREVAIL [5]	Enzalutamide	0.196	1.18	0.316	0.391	0.011	0.276	0.135	0.191	0.143
PREVAIL [5]	Placebo	0.147	0.708	0.198	0.219	0.007	0.106	0.091	0.087	0.096
TROPIC [6]	Cabazitaxel	0.107	0.522	0.142	0.202	0.006	0.095	0.07	0.073	0.08
TROPIC [6]	Mitoxantrone	0.117	0.48	0.13	0.172	0.005	0.074	0.076	0.069	0.084
AFFIRM [7]	Enzalutamide	0.072	0.433	0.109	0.138	0.003	0.055	0.052	0.047	0.057
AFFIRM [7]	Placebo	0.098	0.441	0.117	0.144	0.004	0.064	0.063	0.055	0.07
COU-302 [8]	Abiraterone	0.164	1.195	0.269	0.338	0.005	0.193	0.122	0.154	0.13
COU-302 [8]	Placebo	0.16	1.069	0.247	0.32	0.005	0.151	0.109	0.12	0.116
ENZAMET[9]	Enzalutamide	0.171	1.265	0.25	0.369	0.003	0.381	0.137	0.267	0.154
ENZAMET[9]	BSC+ADT	0.117	0.835	0.168	0.227	0.002	0.138	0.09	0.114	0.097
LATITUDE[10]	Abiraterone	0.149	0.801	0.167	0.275	0.003	0.326	0.118	0.257	0.129
LATITUDE[10]	Placebo	0.108	0.736	0.157	0.207	0.002	0.099	0.078	0.083	0.083
STAMPEDE[11]	Abiraterone	0.196	0.84	0.16	0.325	0.004	0.958	0.169	0.752	0.182
STAMPEDE[11]	ADT	0.107	0.638	0.124	0.188	0.002	0.153	0.082	0.132	0.087
TITAN [12]	Apalutamide	0.229	2.717	0.588	0.615	0.008	0.244	0.183	0.195	0.192
TITAN [12]	Placebo	0.183	1.12	0.249	0.378	0.006	0.385	0.142	0.279	0.158
PETRYLAK*[13]	Docetaxel	0.093	0.496	0.119	0.153	0.003	0.073	0.064	0.061	0.073
PETRYLAK*[13]	Mitoxantrone	0.104	0.485	0.118	0.166	0.003	0.084	0.068	0.073	0.077
COU-301 [14]	Abiraterone	0.071	0.386	0.101	0.134	0.004	0.059	0.049	0.048	0.055
COU-301 [14]	Placebo	0.09	0.453	0.123	0.167	0.005	0.066	0.061	0.059	0.068

* Petrylak is the name of the first author, not a study name.

Calculating transition probabilities

The transition probabilities are calculated using the methodology described by Briggs et al. (2006)[15]. The estimated parameters in Table 3 and Table 5 are used to calculate the survival function $S(t)$ for any distribution (exponential, Weibull, Gompertz, lognormal or log-logistic) as described in the STATA reference manual. Then, the transition probability between two time points t_O and t is calculated as

$$tp = 1 - \mathrm{S}(t)/\mathrm{S}(t_O).$$

Using the Gompertz distribution as an example, the survival function is

$$\exp\left[-e^{cons}\gamma^{-1}(e^{\gamma t} - 1)\right].$$

Thus, the transition probability is calculated as

$$tp = 1 - \exp\left[e^{cons}\gamma^{-1}(\exp(\gamma t_O) - \exp(\gamma t))\right].$$

Discussion

A reference health-economic model for advanced prostate cancer was developed, with a flexible model structure and a comprehensive set of parametric functions for modeling different treatment sequences. The model will be a useful tool for analyzing new and existing technologies for advanced prostate cancer at different points in the treatment pathway as well as different treatment sequences.

Although it was not possible to estimate transition probabilities from PIONEER data, the challenge of using Kaplan-Meier data for OS and PFS from clinical trials to estimate relevant transition probabilities resulted in the innovative method presented in this report. The problem of estimating transition probabilities with limited information is described in the review by Woods et al. (2020)[1]. In brief, clinical trials often report only OS and PFS, which is not sufficient information to derive relevant transition probabilities for health economic modeling in a straightforward manner. With only OS and PFS at hand, previous methods have been restricted to the assumption of constant risk [1]. The method presented in this report may provide a basis for further health economic modeling in settings where state transition models with time-dependent risks are needed, but analysts are limited to Kaplan-Meier data for OS and PFS.

It should be noted that caution must be taken before setting up scenarios evaluating drugs using the included parametric functions directly. Firstly, the clinical trials underlying the parametric functions included in the model may not be comparable due to differences in study design, protocol, and settings such as baseline demographic and disease characteristics. Furthermore, the method for separating PFS and OS into risks of pre-progression death, progression, and post-progression death is at an experimental stage and further research is needed to validate its results.

The model was developed with focus on metastatic disease, as specified by the study protocol. The scope was

defined in conceptualization meetings with the study group. It was motivated by results of the PIONEER Studyathon 3 developing definitions for treatment groups of mHSPC, and the anticipated corresponding work with mCRPC in mind. In decision problems where an earlier stage of disease needs to be analyzed, the current model may be adapted to incorporate earlier stages. The model can also easily be extended with additional transition probabilities when survival analysis of time-to-event data is available.

Conclusion

A reference health-economic model for advanced prostate cancer was developed, with a flexible model structure and a comprehensive set of parametric functions for modeling different treatment sequences. The model will be a useful tool for analyzing new and existing technologies for advanced prostate cancer at different points in the treatment pathway as well as different treatment sequences.

References

1. Woods, B.S., et al., *Partitioned Survival and State Transition Models for Healthcare Decision Making in Oncology: Where Are We Now?* Value Health, 2020. **23**(12): p. 1613-1621.
2. Guyot, P., et al., *Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves.* BMC Med Res Methodol, 2012. **12**: p. 9.
3. Wei, Y. and P. Royston, *Reconstructing time-to-event data from published Kaplan-Meier curves.* Stata J, 2017. **17**(4): p. 786-802.
4. Pahuta, M.A., et al., *A technique for approximating transition rates from published survival analyses.* Cost Eff Resour Alloc, 2019. **17**: p. 12.
5. Beer, T.M., et al., *Enzalutamide in metastatic prostate cancer before chemotherapy.* N Engl J Med, 2014. **371**(5): p. 424-33.
6. de Bono, J.S., et al., *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.* Lancet, 2010. **376**(9747): p. 1147-54.
7. Scher, H.I., et al., *Increased survival with enzalutamide in prostate cancer after chemotherapy.* N Engl J Med, 2012. **367**(13): p. 1187-97.
8. Ryan, C.J., A. Molina, and T. Griffin, *Abiraterone in metastatic prostate cancer.* N Engl J Med, 2013. **368**(15): p. 1458-9.
9. Davis, I.D., et al., *Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer.* N Engl J Med, 2019. **381**(2): p. 121-131.
10. Fizazi, K., et al., *Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer.* N Engl J Med, 2017. **377**(4): p. 352-360.
11. James, N.D., et al., *Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy.* N Engl J Med, 2017. **377**(4): p. 338-351.
12. Chi, K.N., et al., *Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer.* N Engl J Med, 2019. **381**(1): p. 13-24.
13. Petrylak, D.P., et al., *Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.* N Engl J Med, 2004. **351**(15): p. 1513-20.
14. de Bono, J.S., et al., *Abiraterone and increased survival in metastatic prostate cancer.* N Engl J Med, 2011. **364**(21): p. 1995-2005.

15. Briggs, A.H., K. Claxton, and M.J. Sculpher, *Decision modelling for health economic evaluation*. Oxford handbooks in health economic evaluation. 2006, Oxford: Oxford University Press. x, 237 p.

Repository for primary data[1]

[1] Suggested headings

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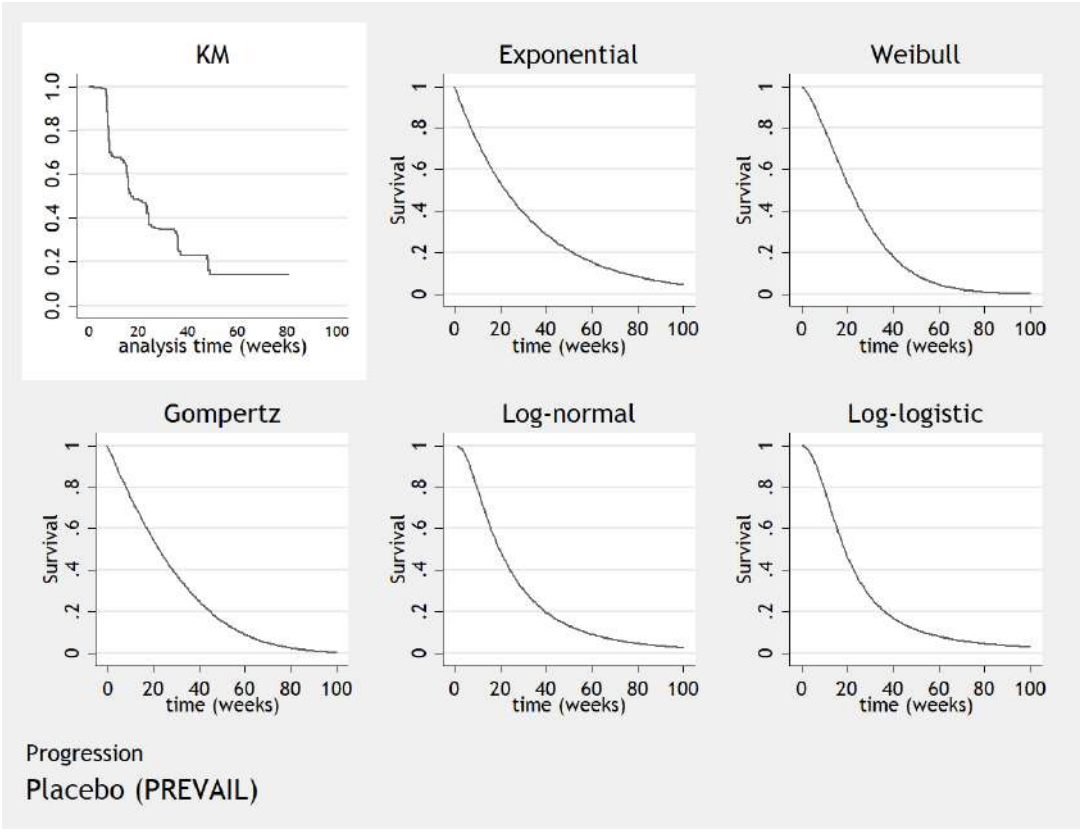
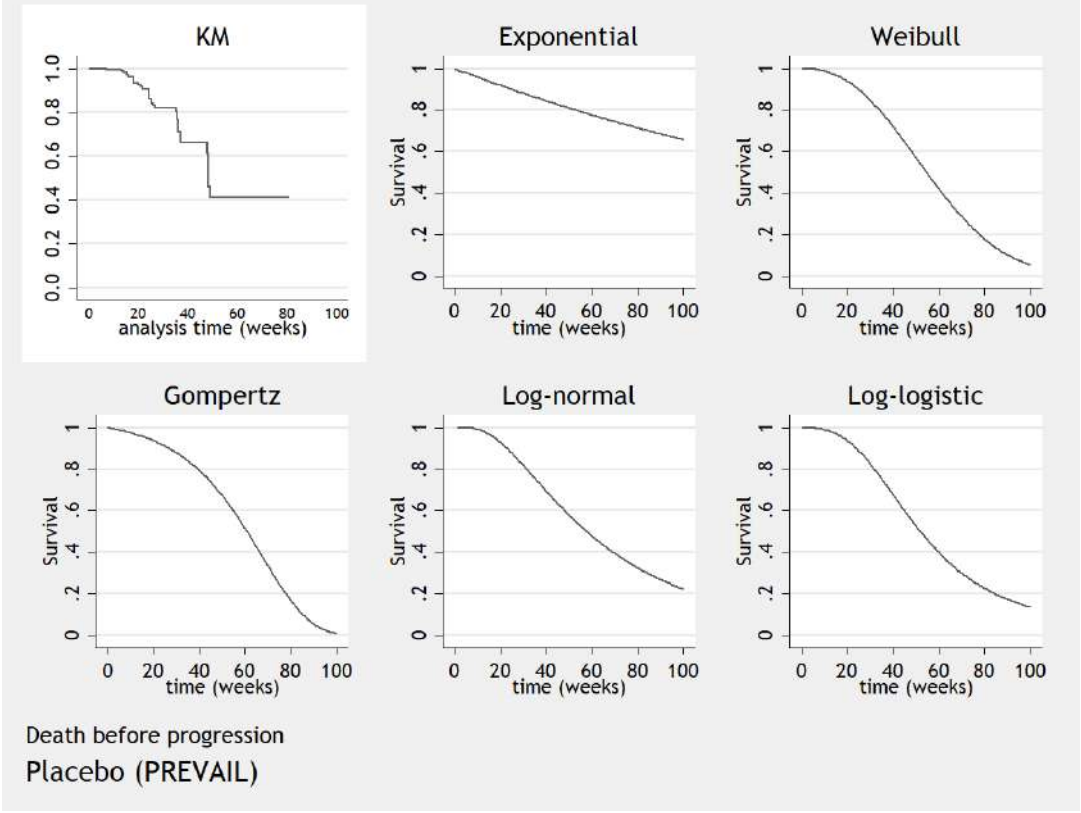
Supplementary material



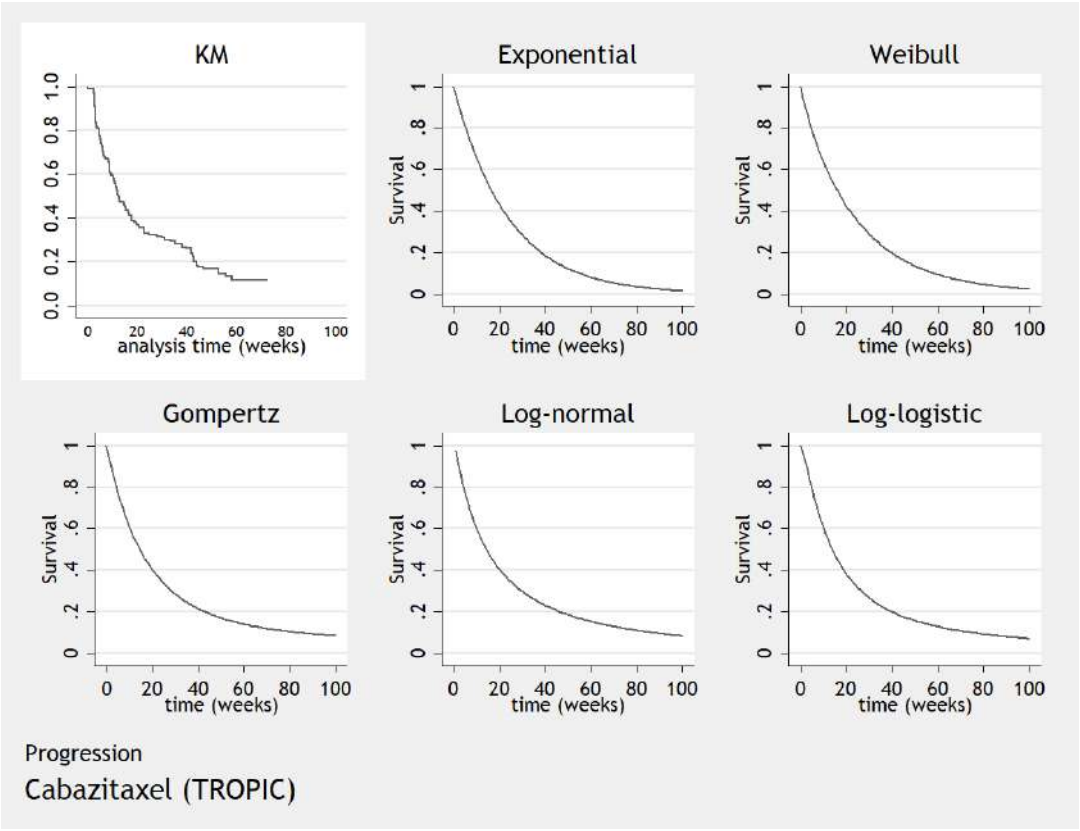
Progression

Placebo (PREVAIL)



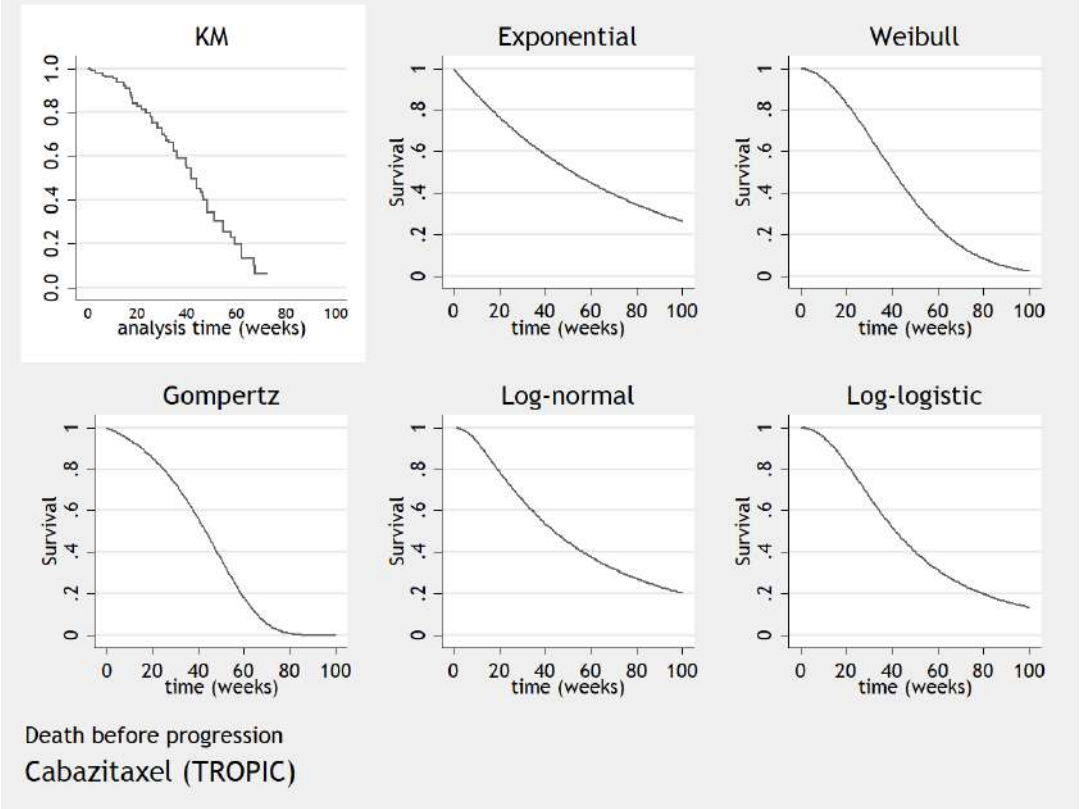
Death before progression

Placebo (PREVAIL)



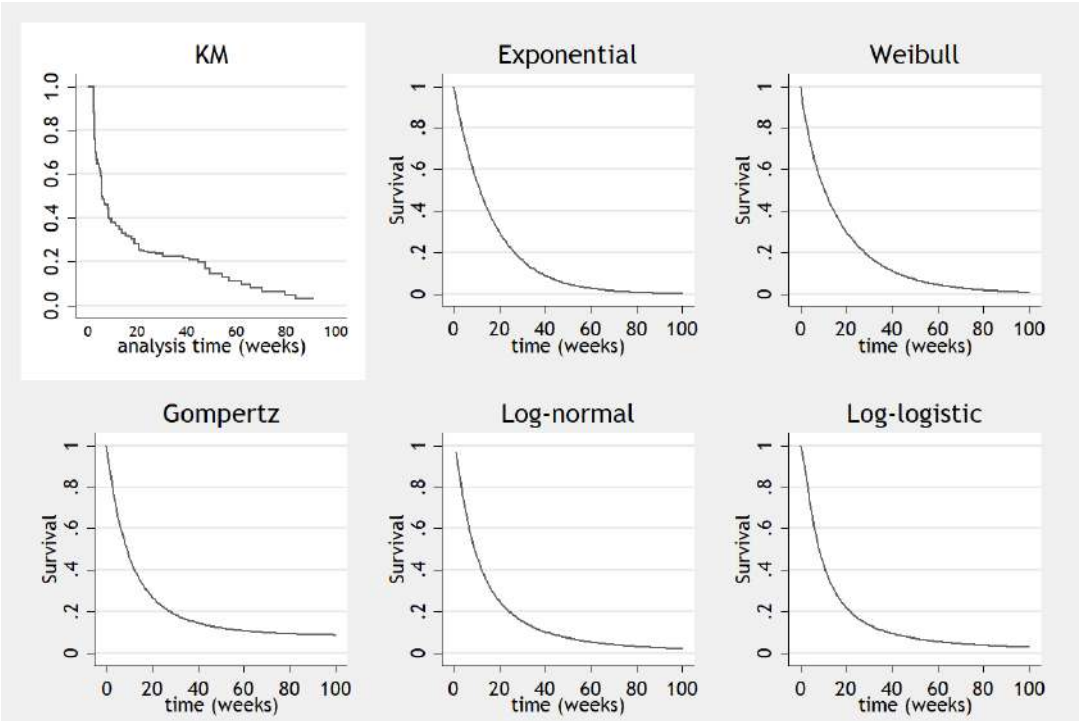
Progression

Cabazitaxel (TROPIC)



Death before progression

Cabazitaxel (TROPIC)



Progression

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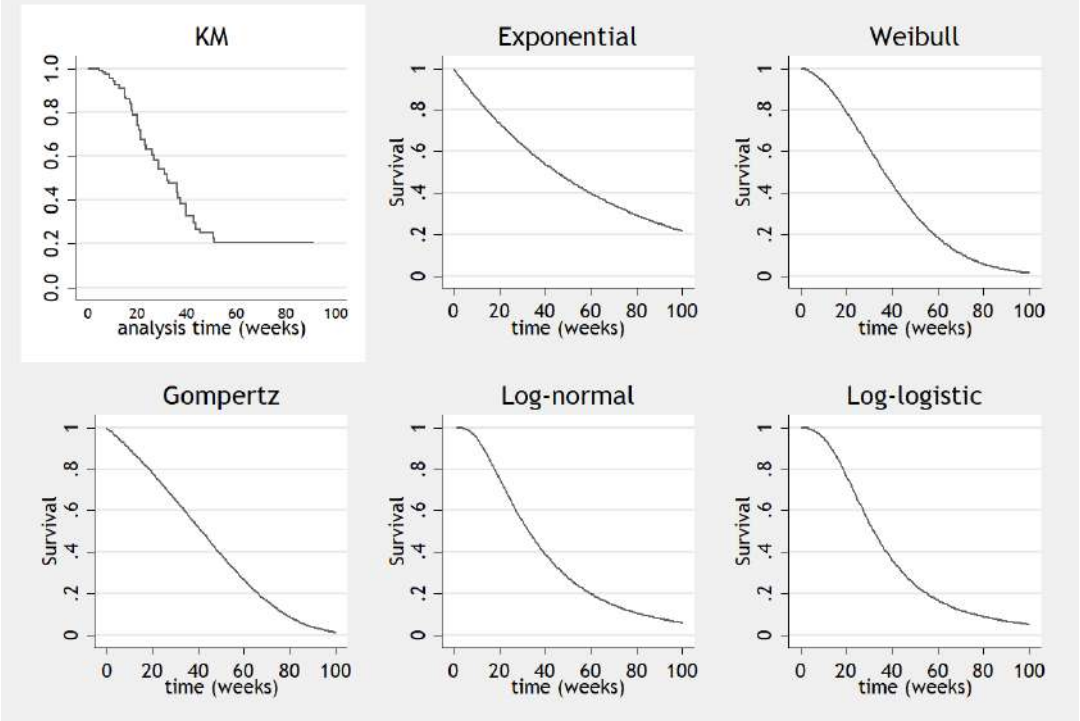

Death before progression

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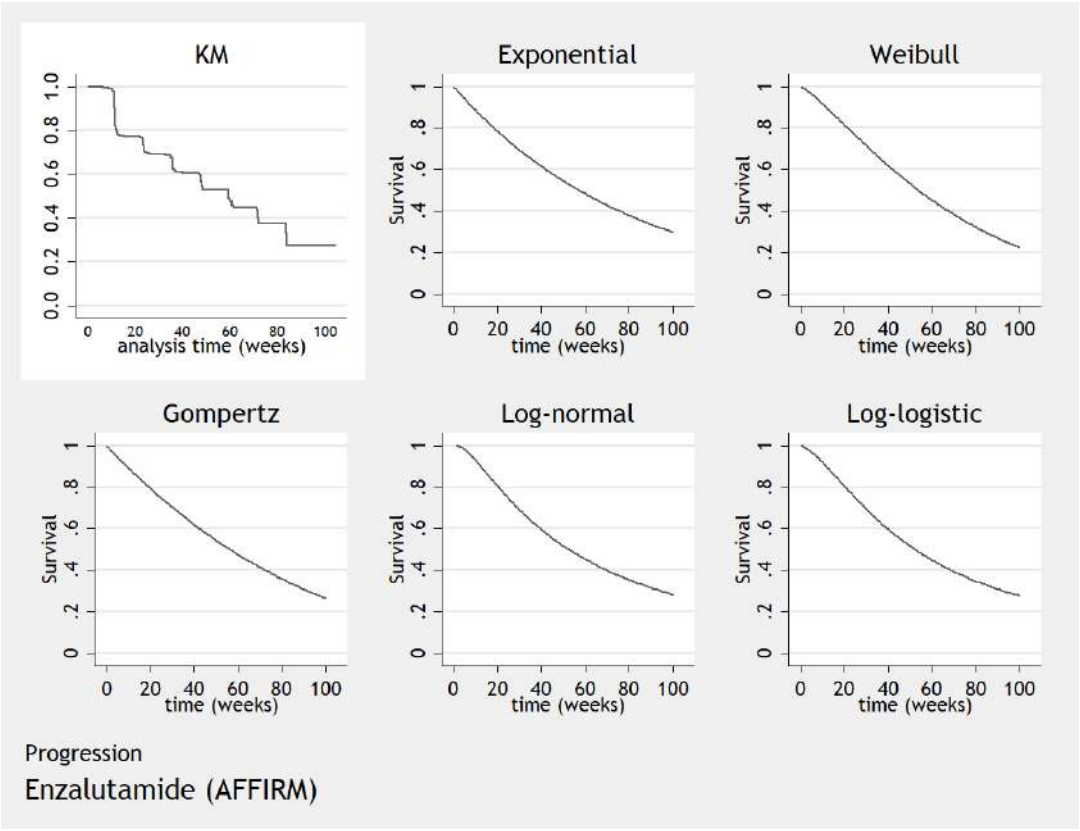
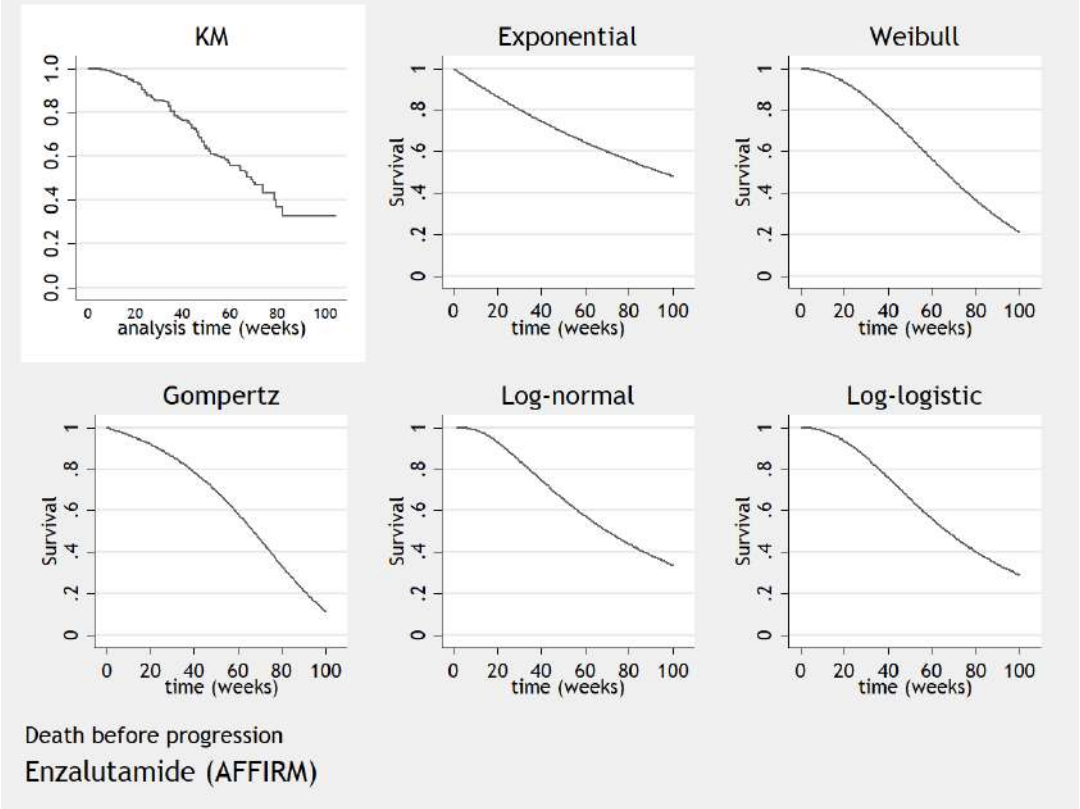


Progression

Enzalutamide (AFFIRM)



Death before progression

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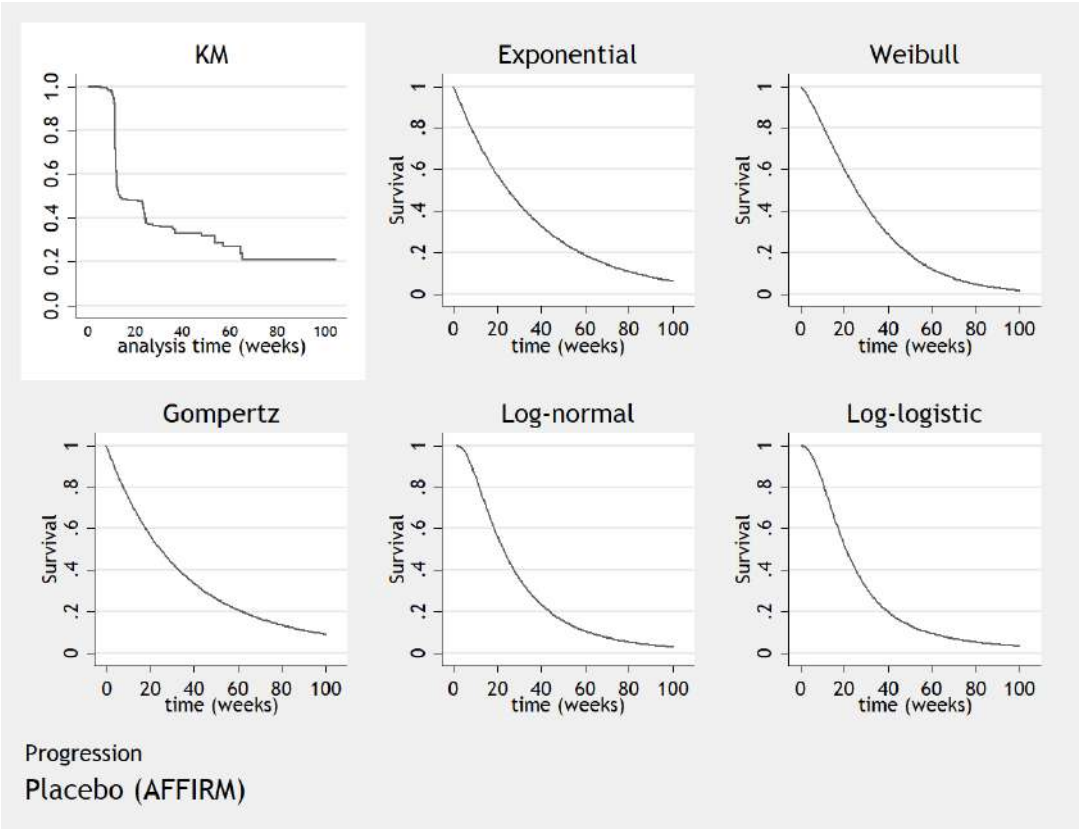

Progression

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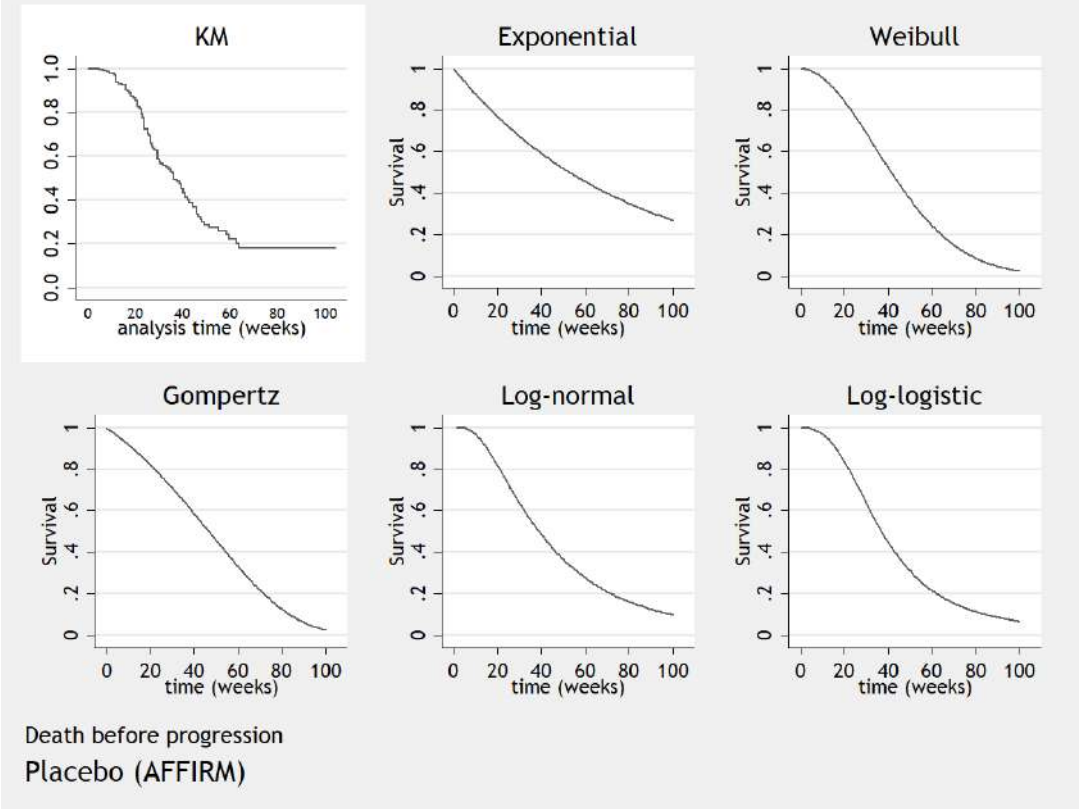

Death before progression

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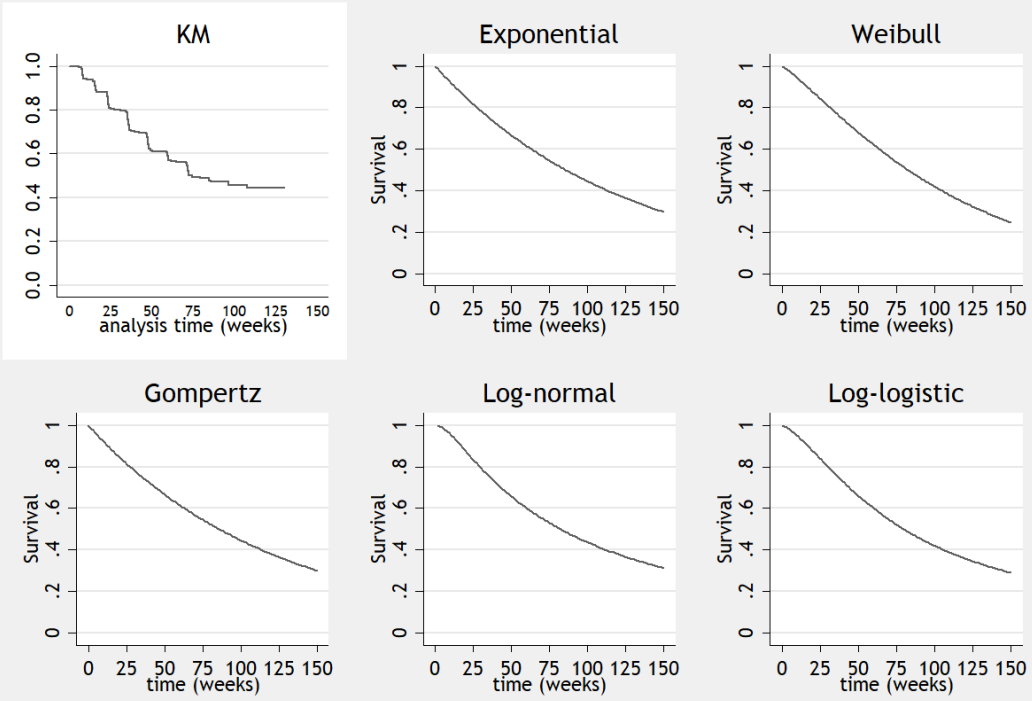
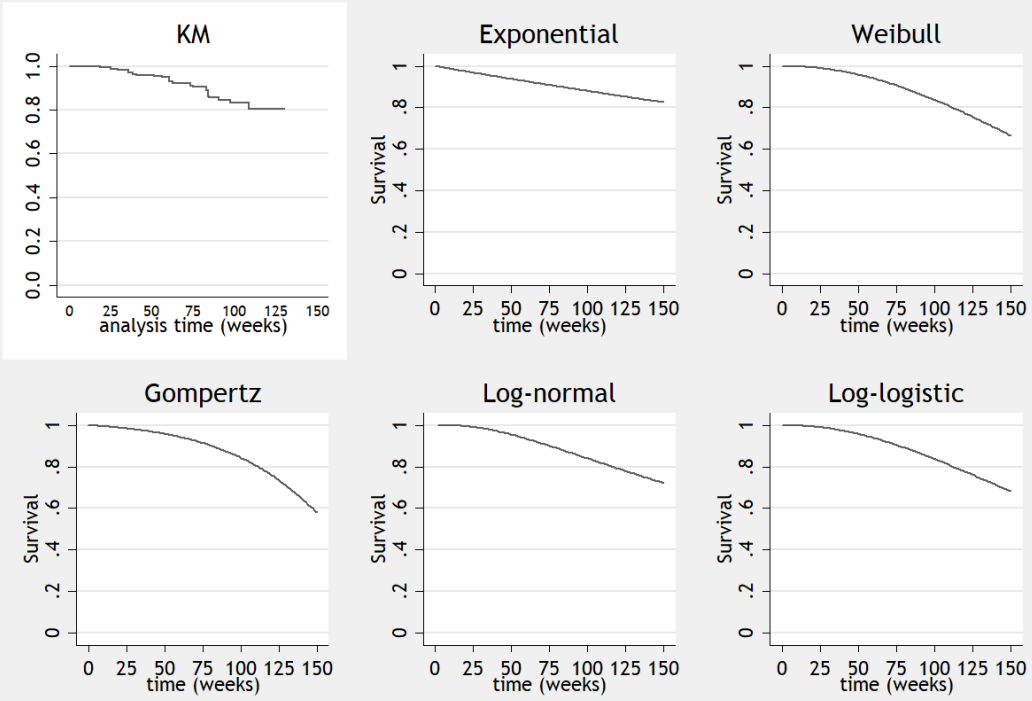


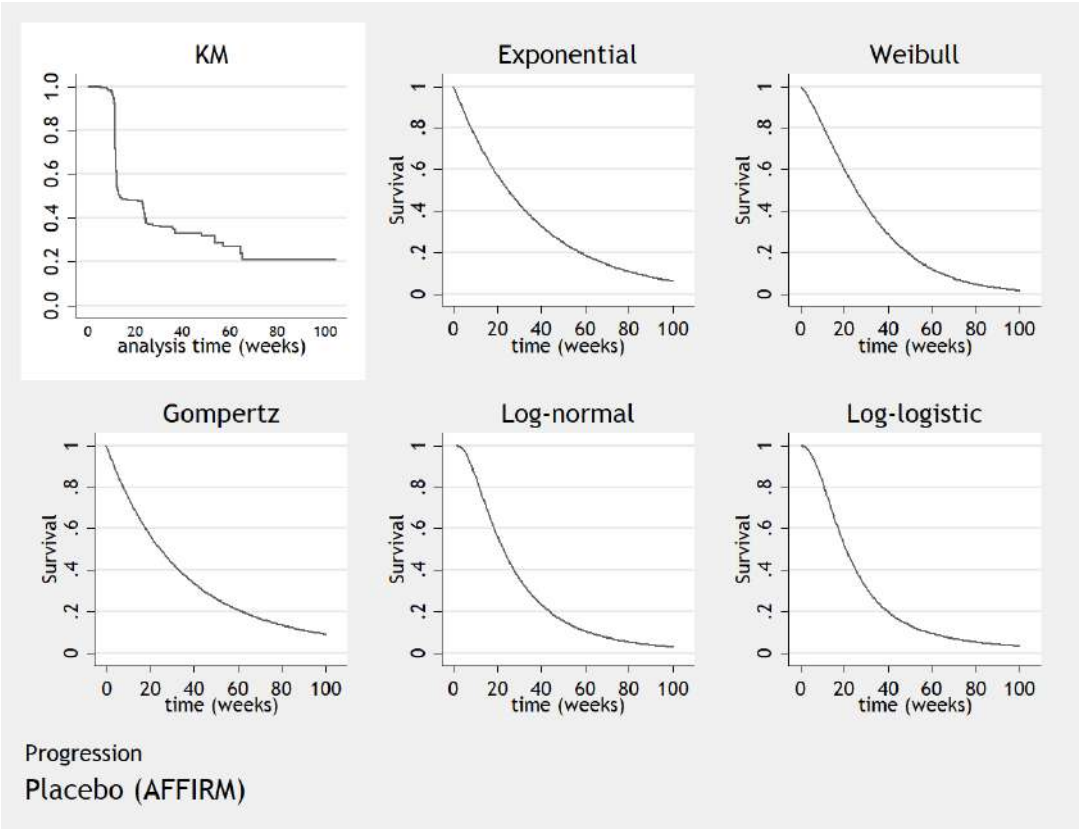
Progression

Abiraterone (COU-302)



Death before progression

Abiraterone (COU-302)



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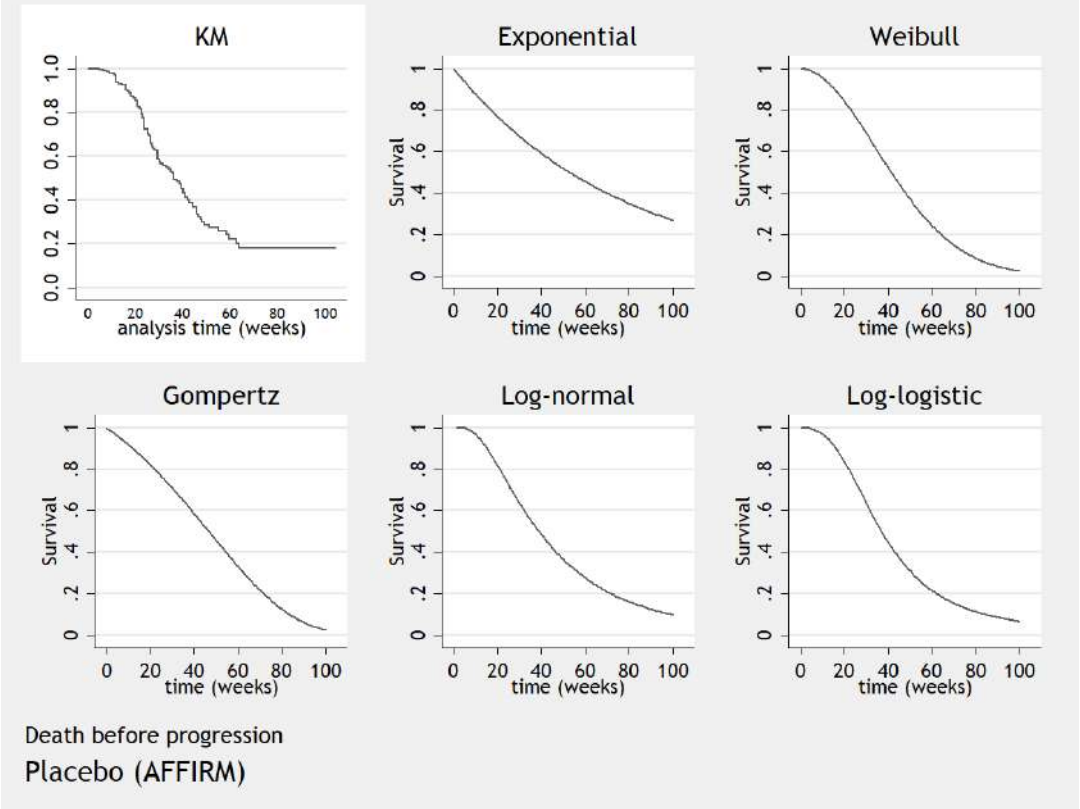

Death before progression

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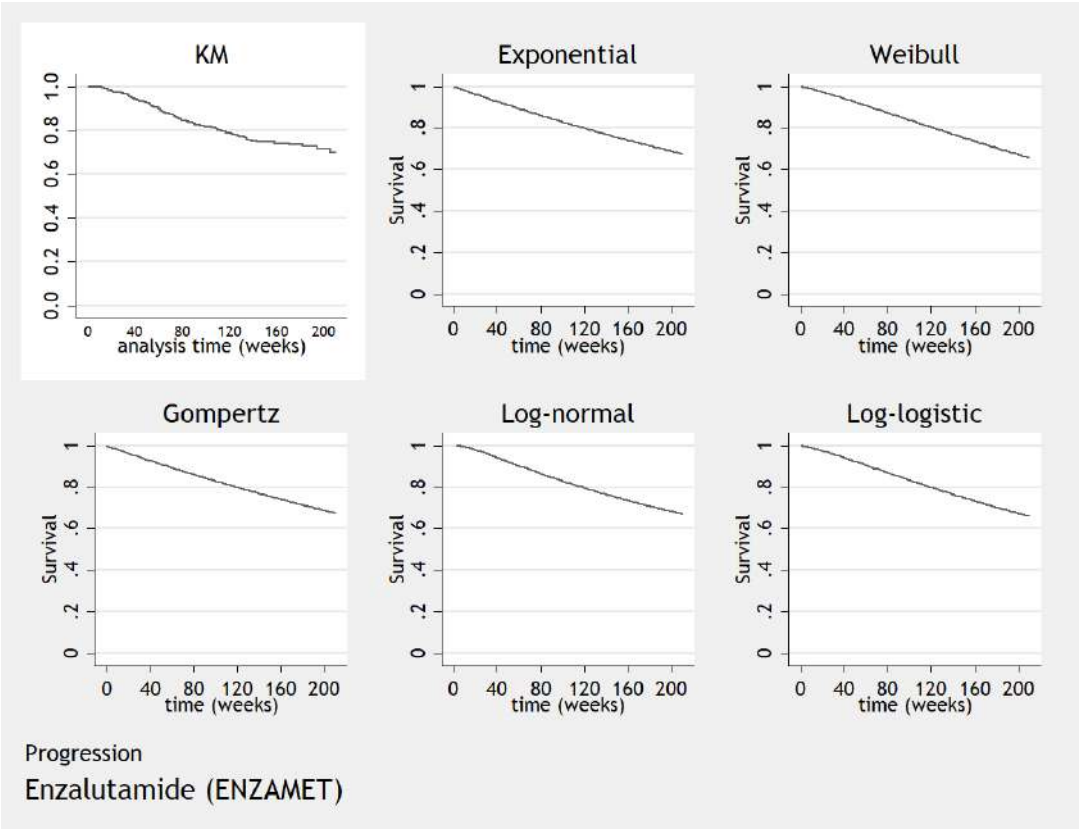
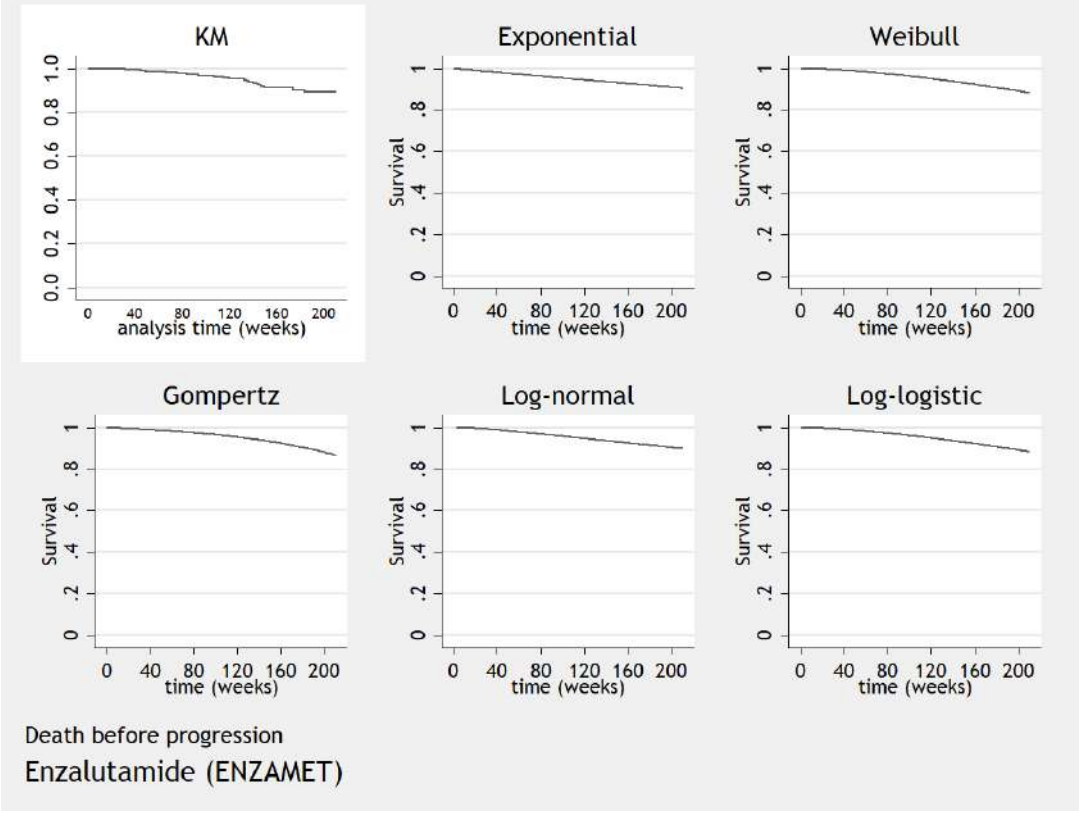


Progression

Enzalutamide (ENZAMET)



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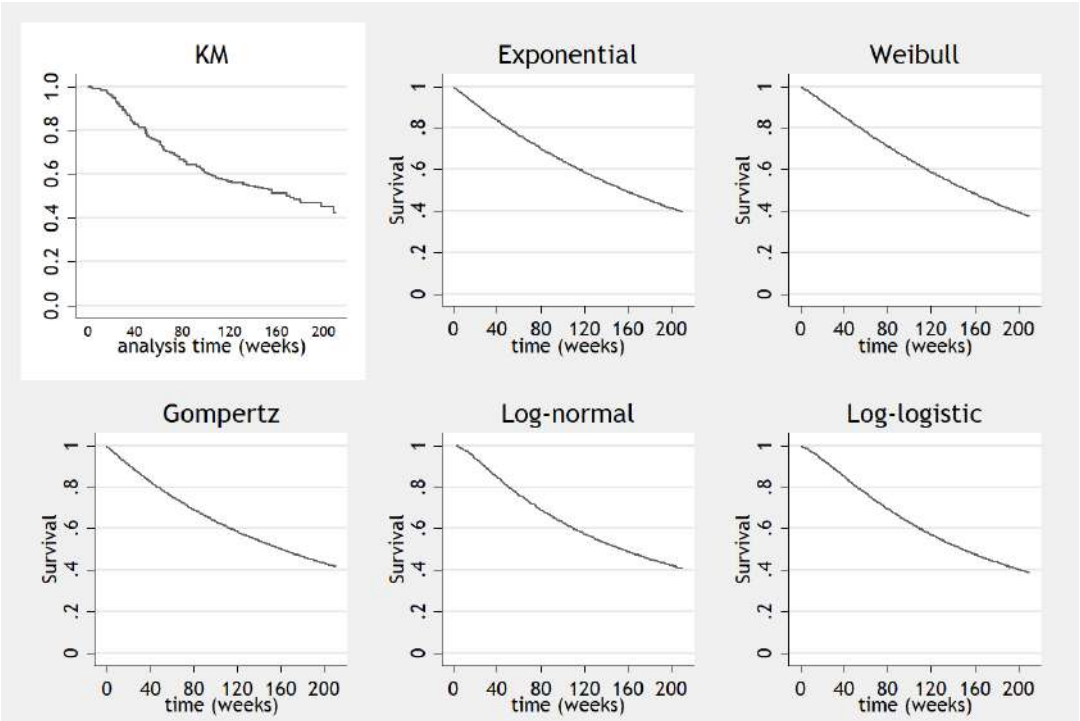

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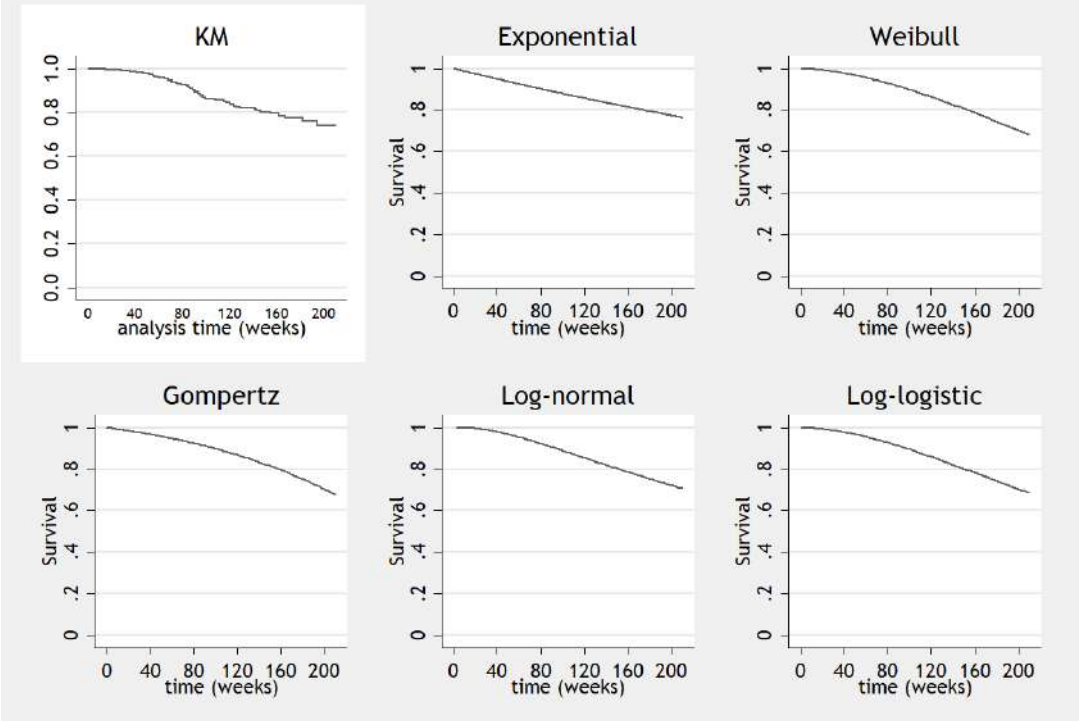

Death before progression

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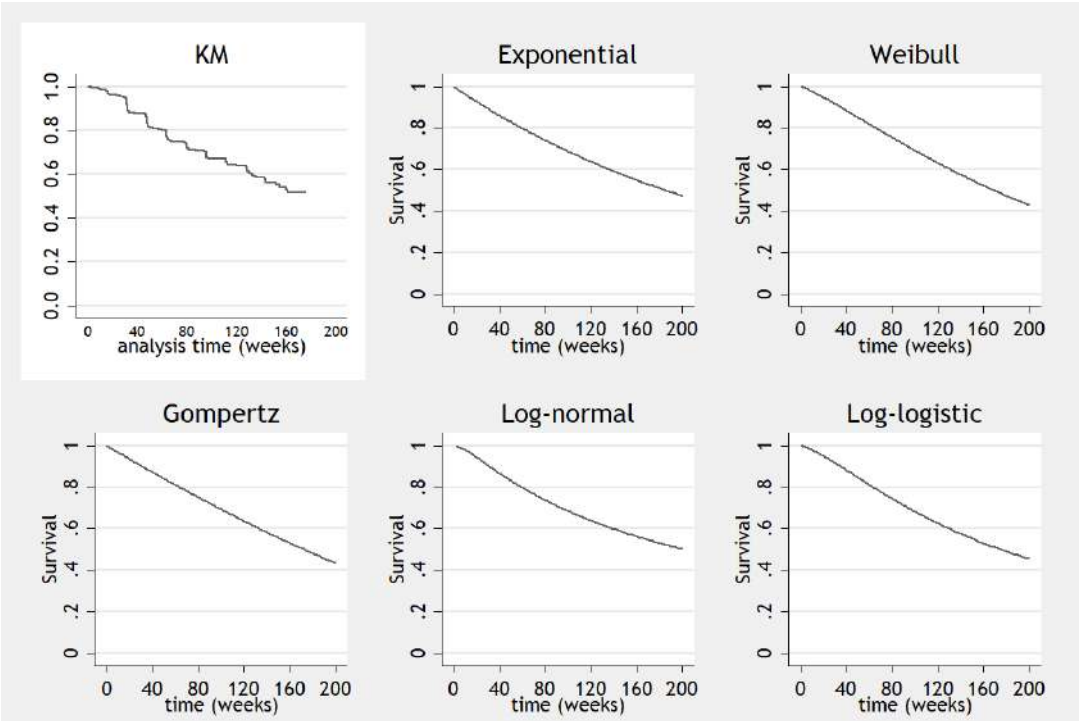
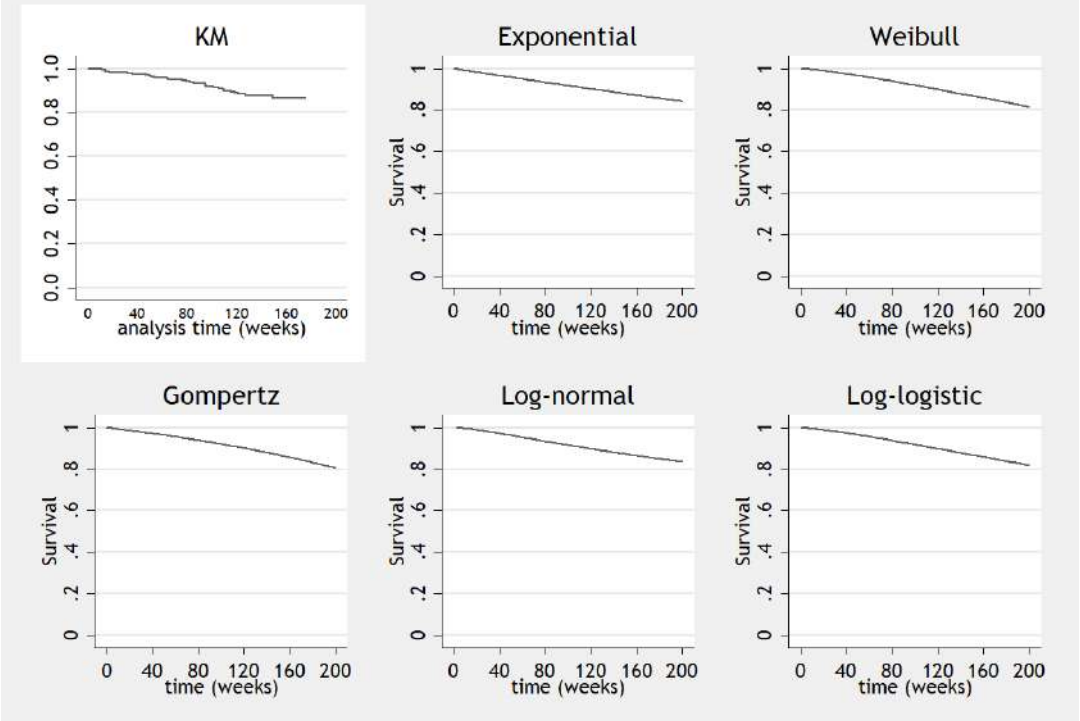


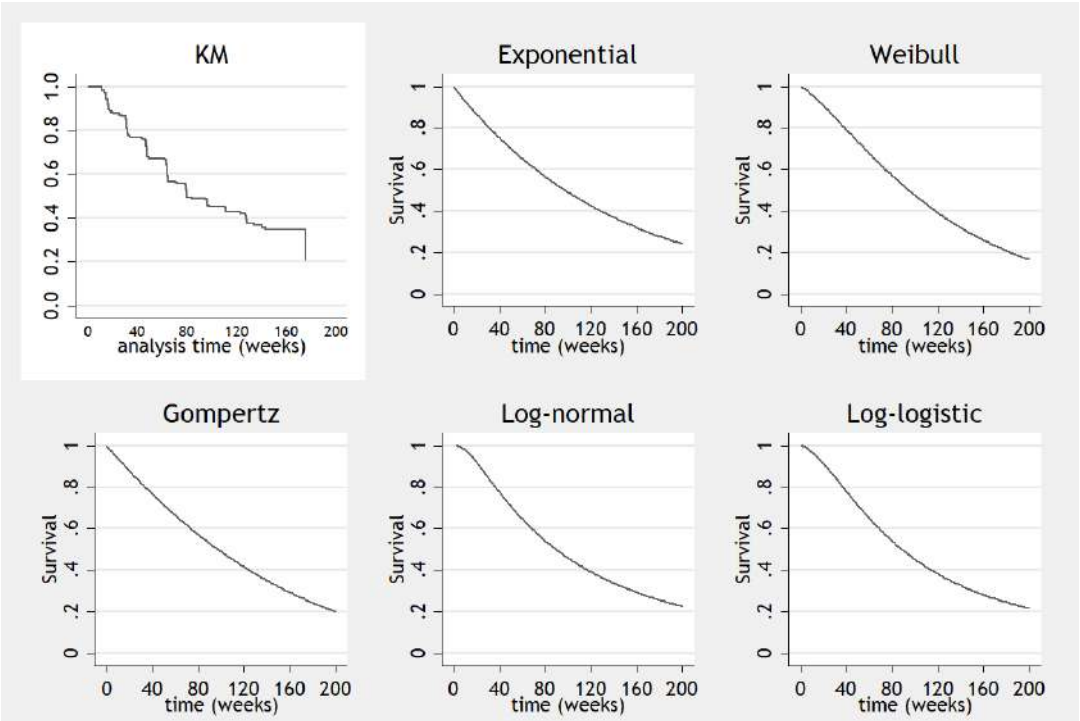
Progression

Abiraterone (LATITUDE)



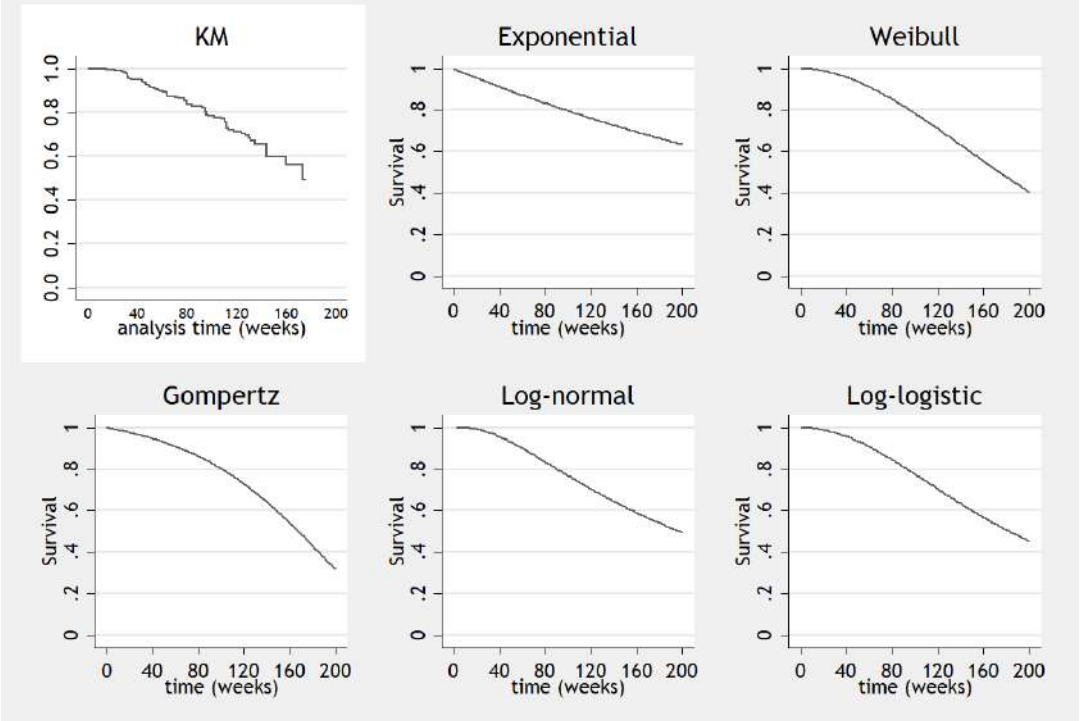
Death before progression

Abiraterone (LATITUDE)



Progression

Placebo (LATITUDE)



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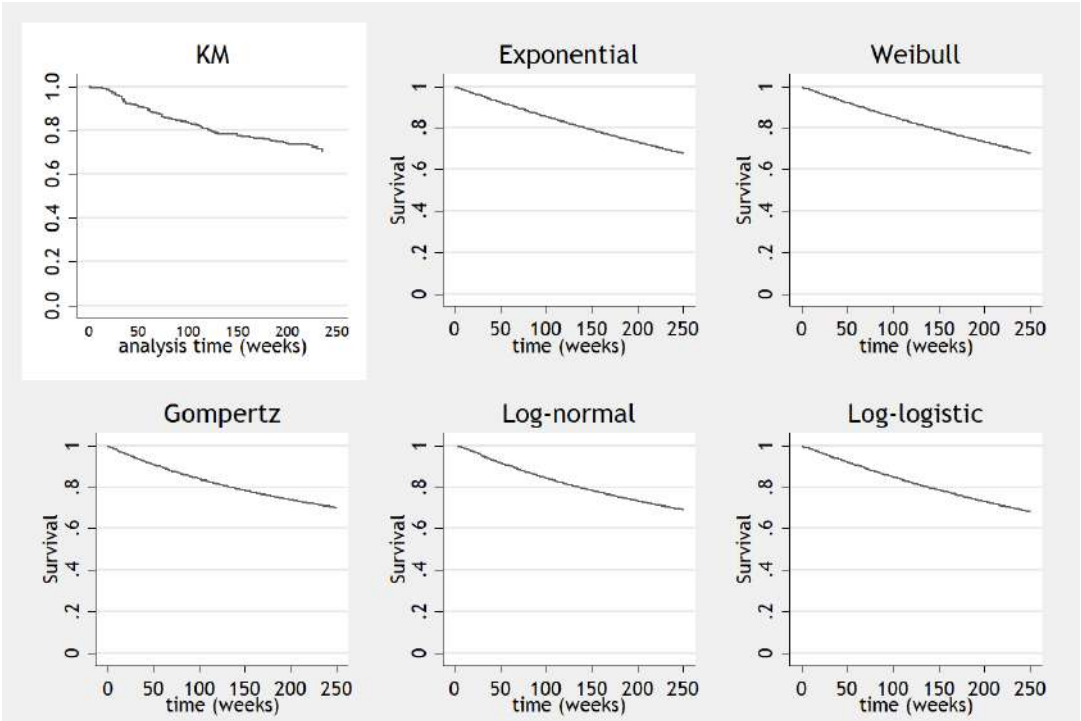
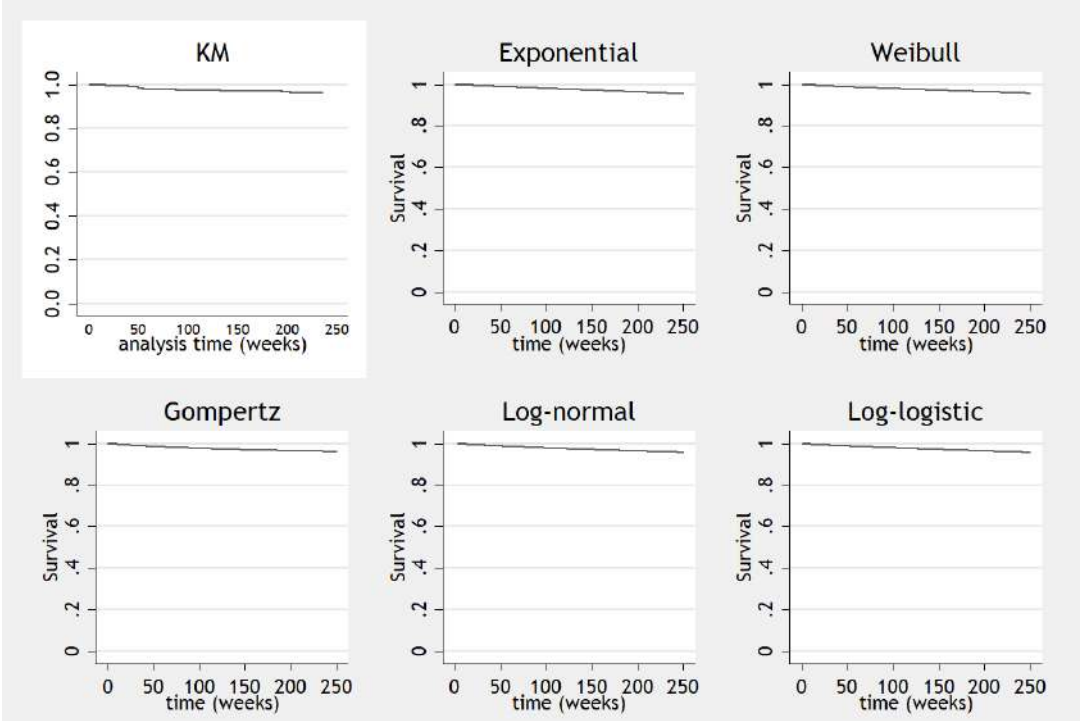


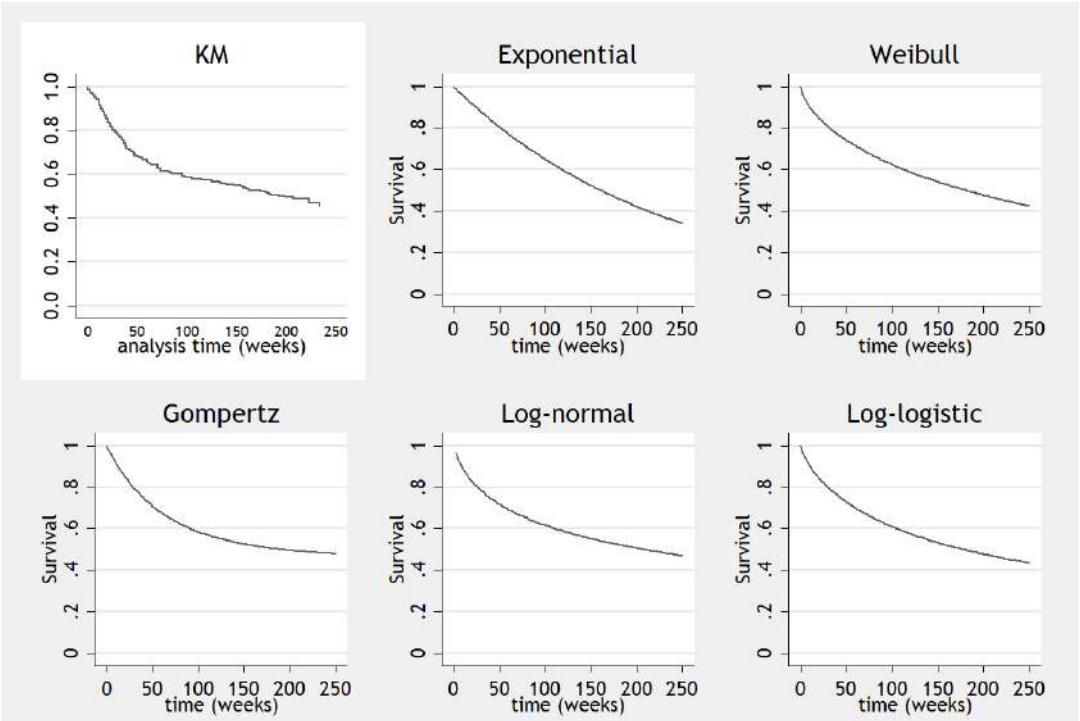
Progression

Abiraterone (STAMPEDE)



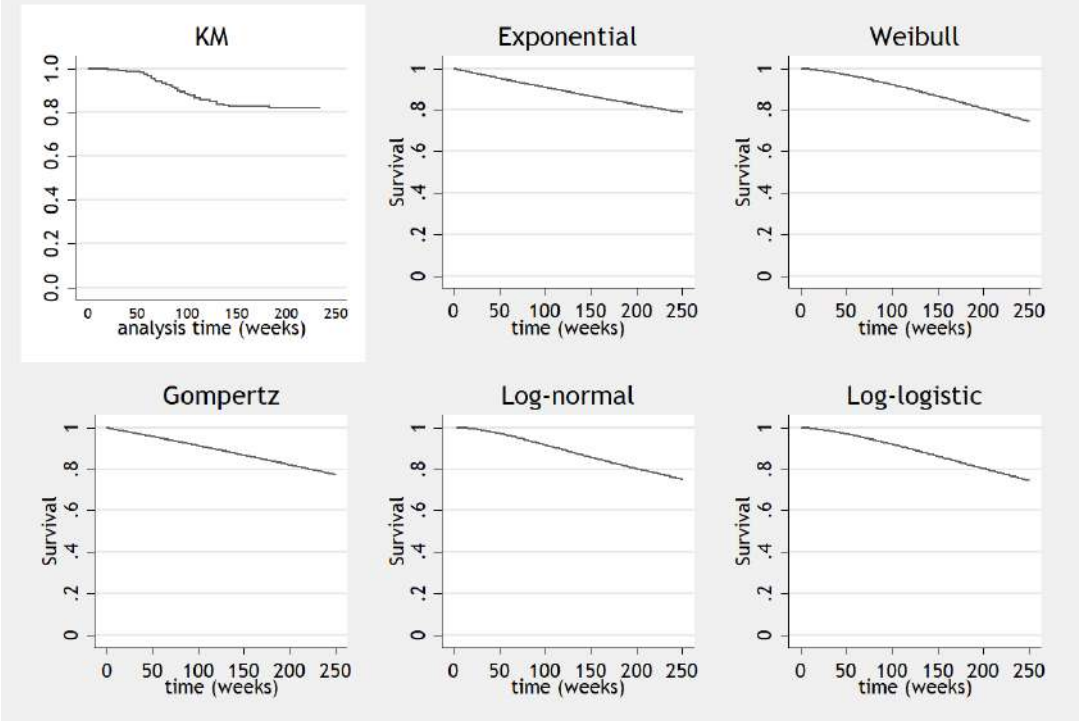
Death before progression

Abiraterone (STAMPEDE)



Progression

ADT (STAMPEDE)



Death before progression

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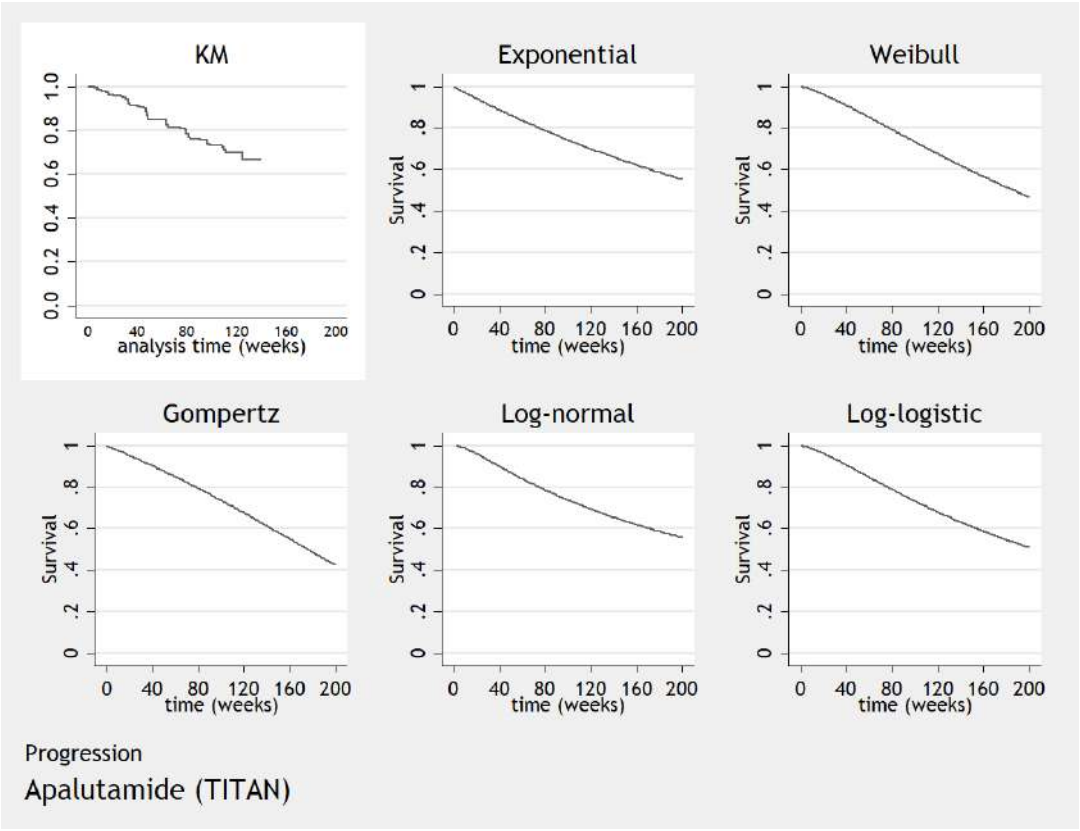
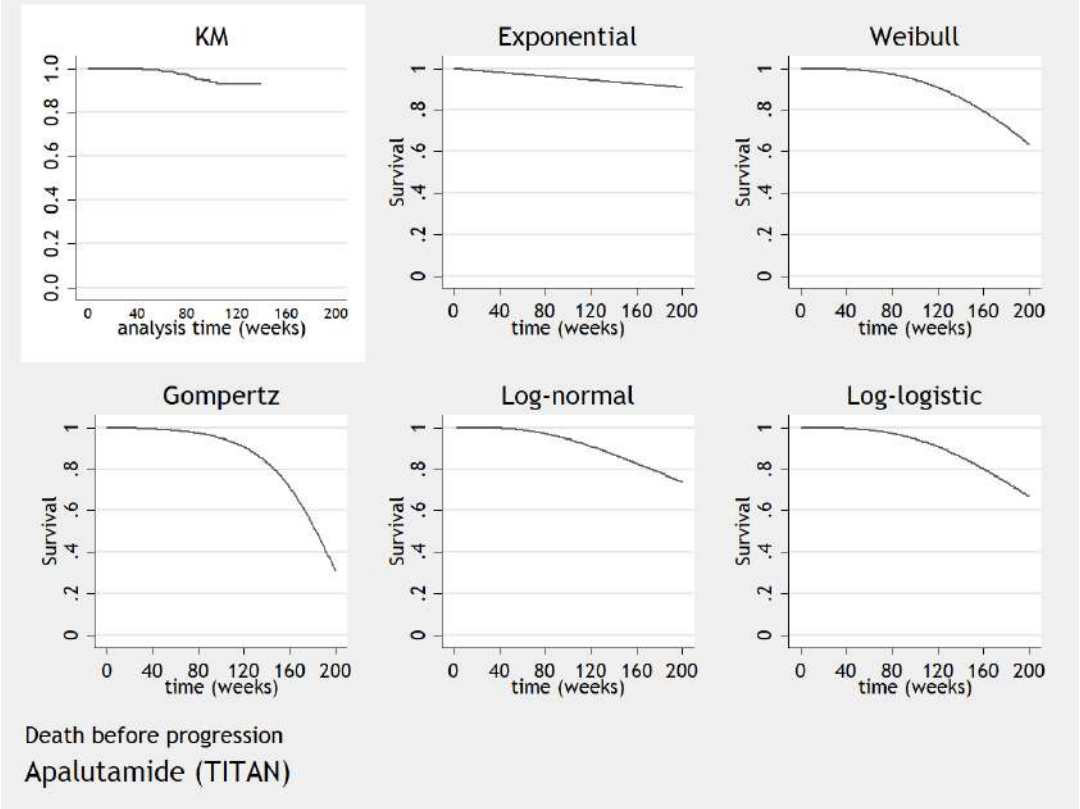


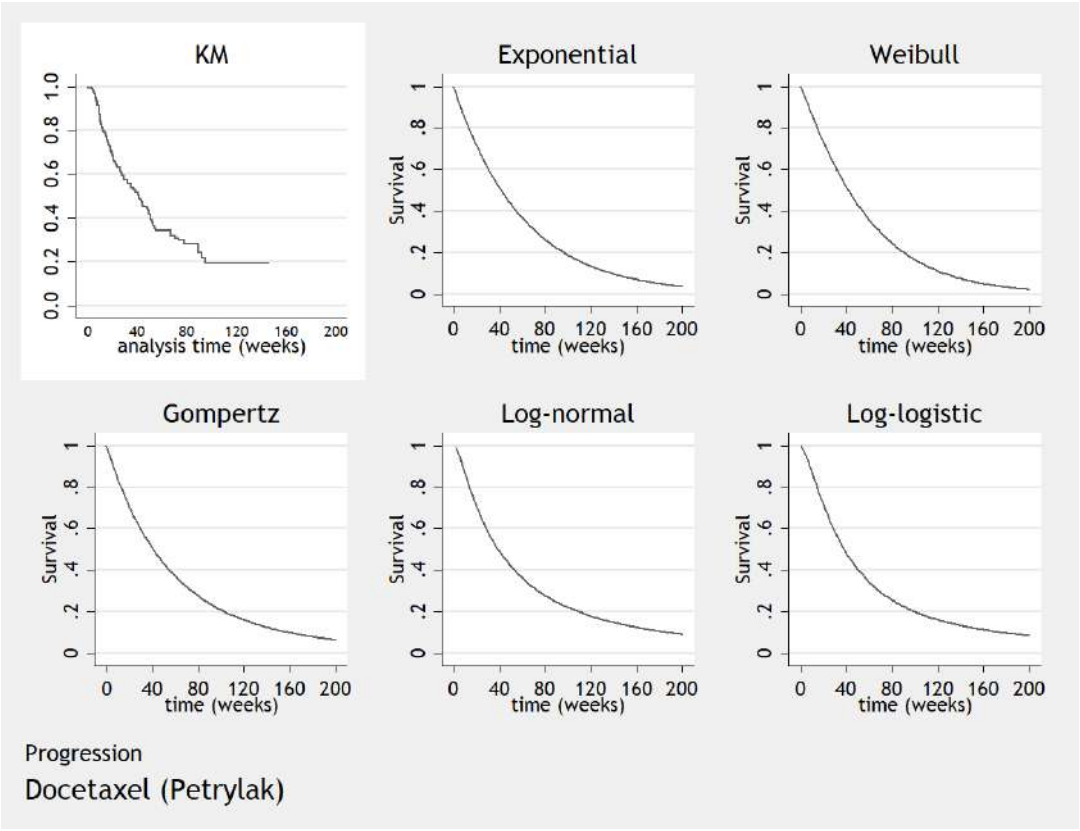
Progression

Apalutamide (TITAN)



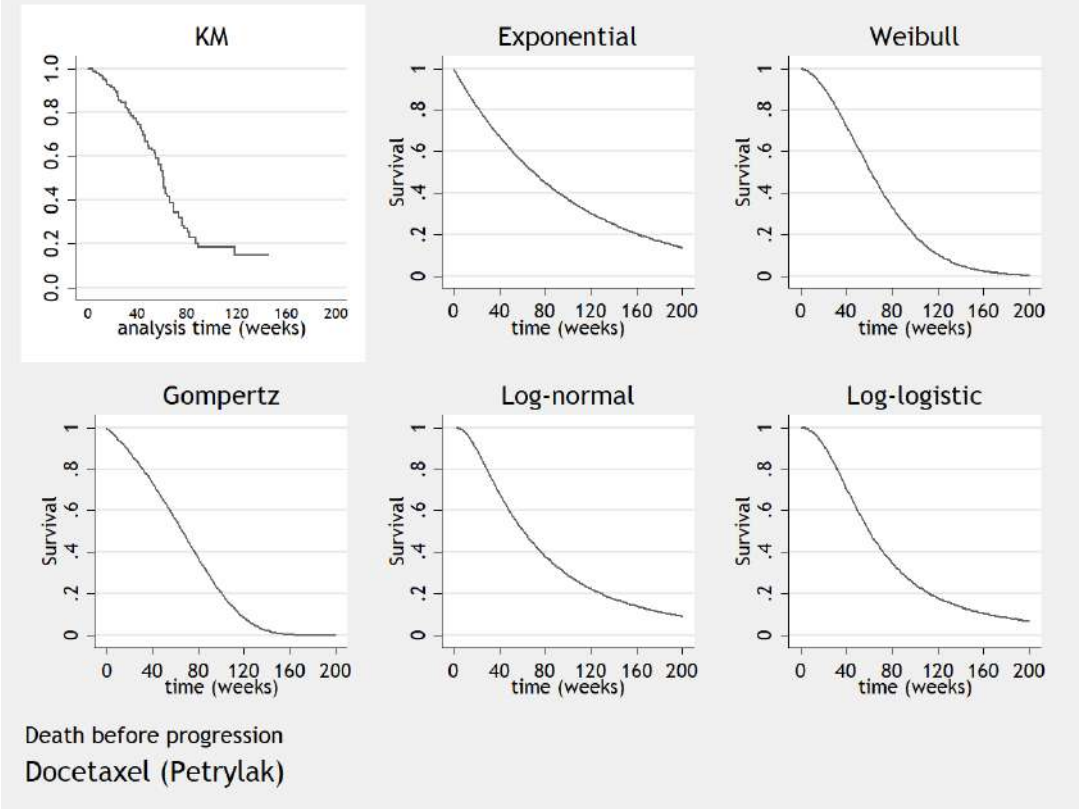
Death before progression

Apalutamide (TITAN)



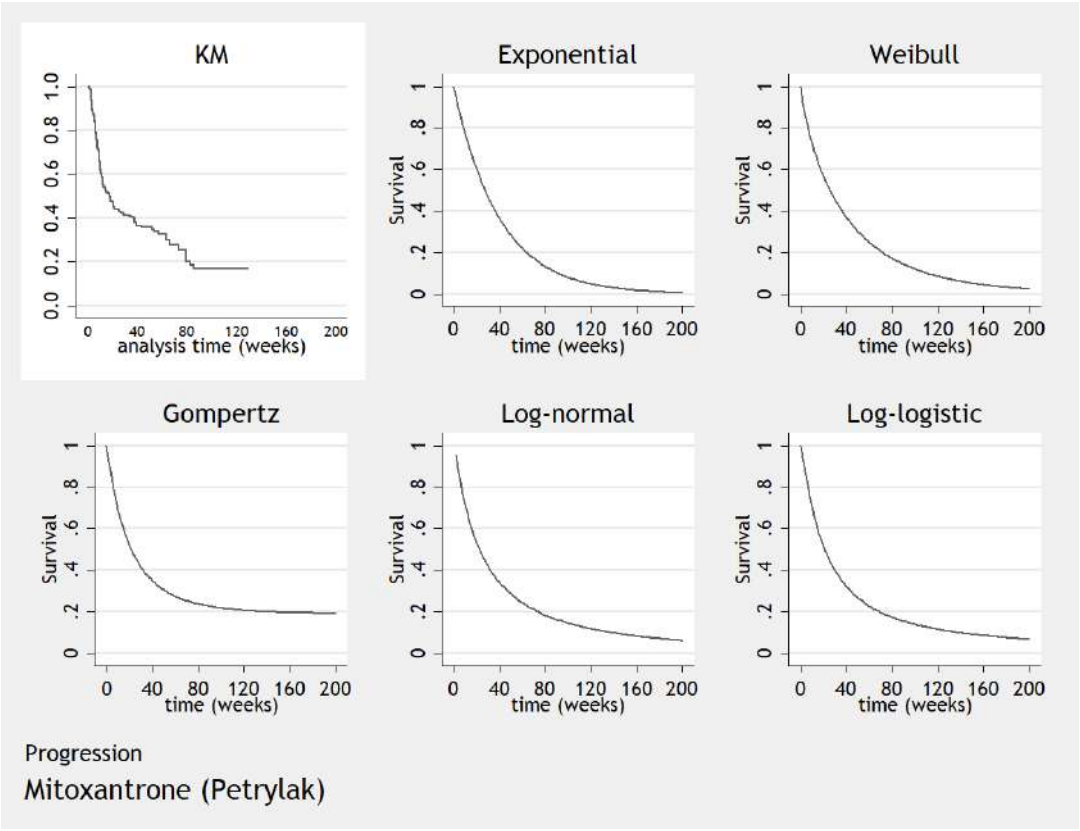
Progression

Docetaxel (Petrylak)



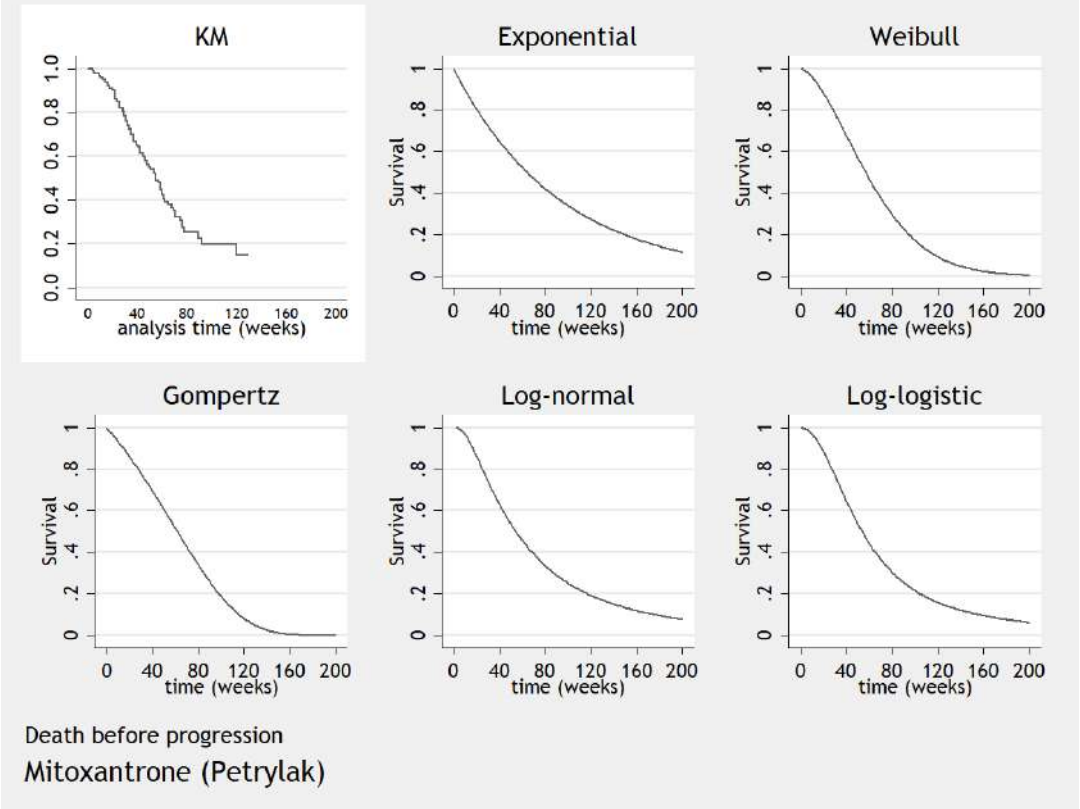
Death before progression

Docetaxel (Petrylak)



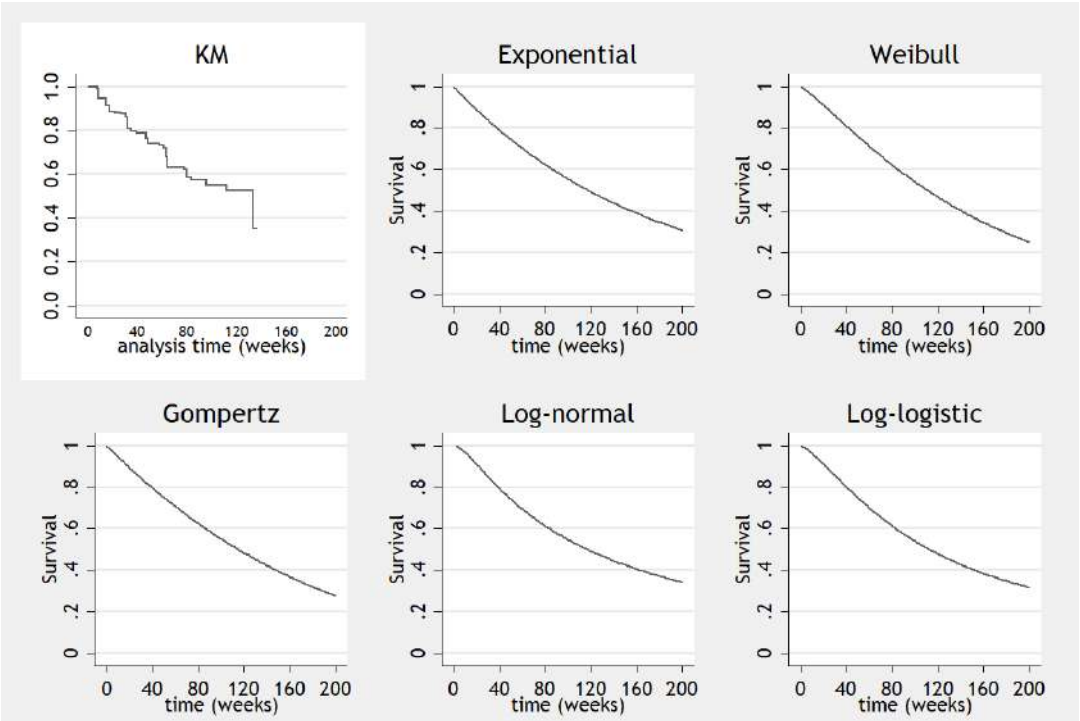
Progression

Mitoxantrone (Petrylak)



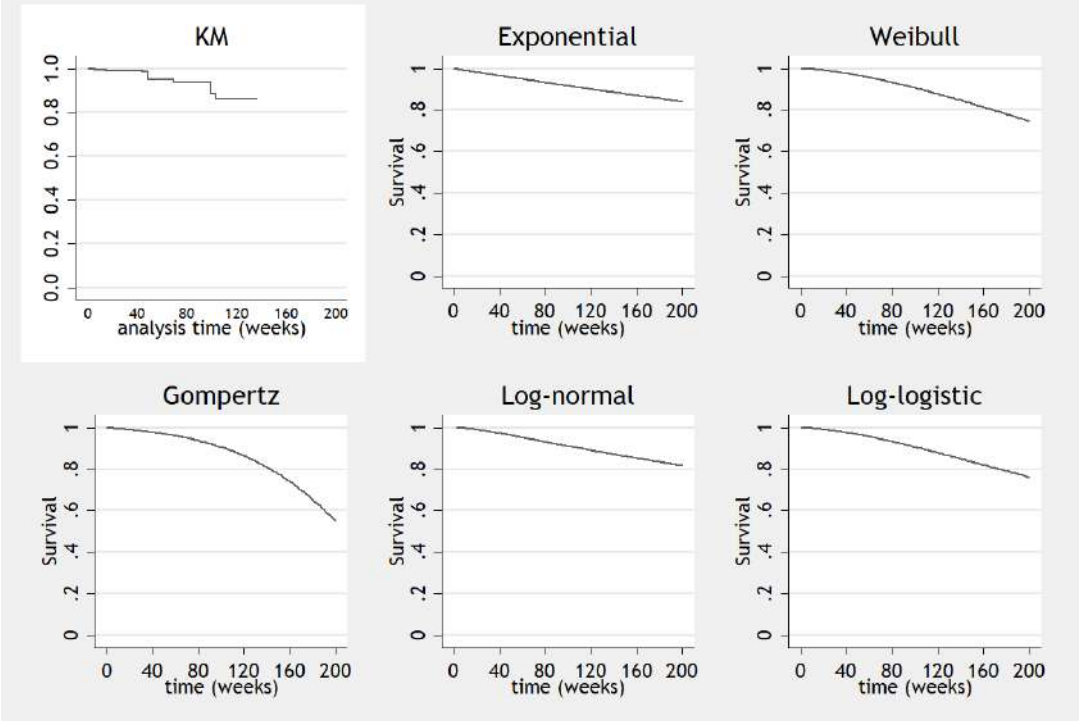
Death before progression

Mitoxantrone (Petrylak)



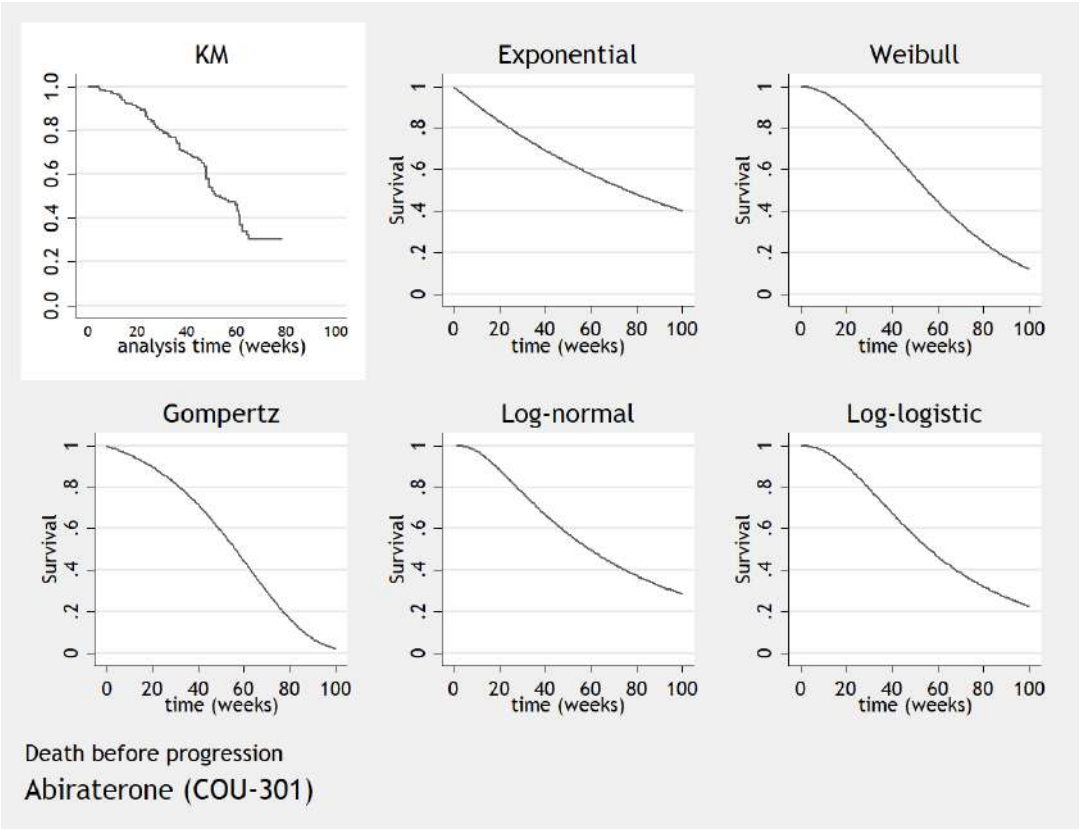
Progression

Placebo (TITAN)



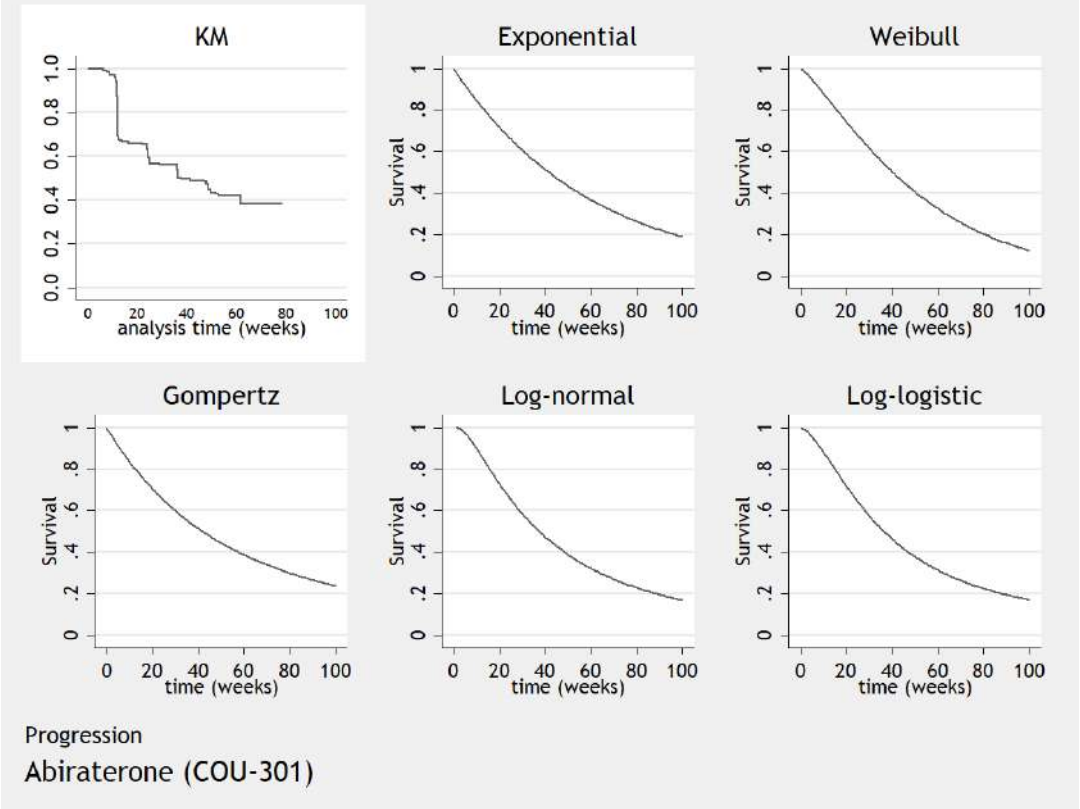
Death before progression

Placebo (TITAN)



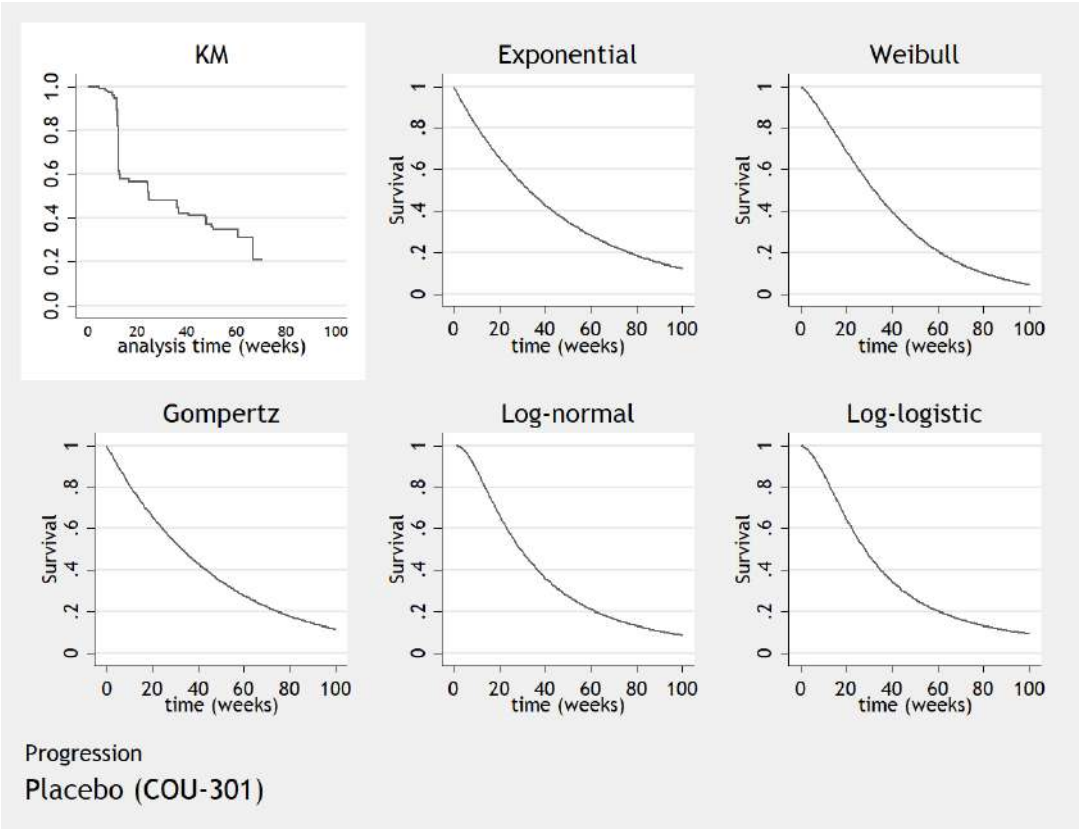
Death before progression

Abiraterone (COU-301)



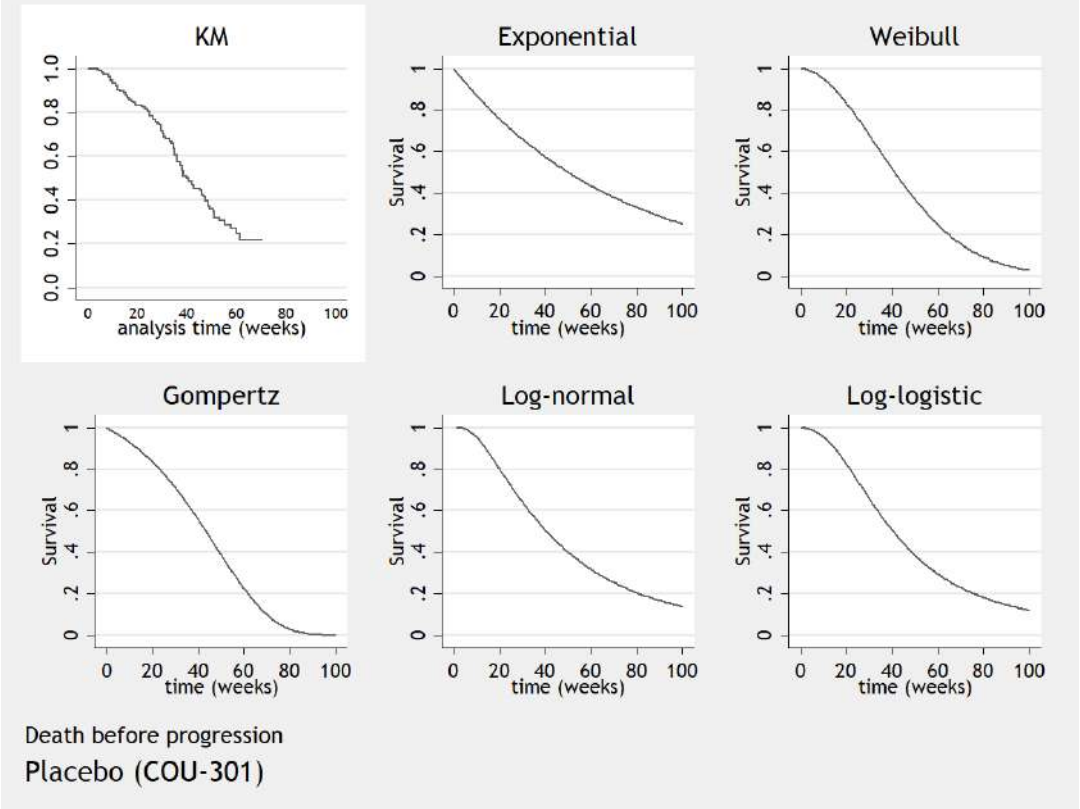
Progression

Abiraterone (COU-301)



Progression

Placebo (COU-301)



Death before progression

Placebo (COU-301)