Summer Project Report: PAH Panel activity and outcome analysis update (Ben Healey)

First established in 2009, the Pulmonary Arterial Hypertension (PAH) panel aims to ensure all patients receive PAH treatments appropriately and according to guidelines, with outcomes comparable to those seen internationally. The last analysis of panel decisions, patient treatment regimens and outcomes was undertaken in 2014. Subsequently, there were changes to panel processes and the passage of sufficient time to undertake patient outcome analysis extending to five years. Changes to the therapeutic mix (introduction of epoprostenol) and second-line approval process are also in progress. In this context, a more current overview of panel activity and outcomes was indicated.

Ben therefore updated and extended the 2014 analysis, producing 5-year survival curves for different treatment pathways and introducing international comparisons for incidence, prevalence, and survival rates. This involved working with staff in the medical directorate and other areas of Pharmac, in addition to communicating plans and results to panel members. The project spanned approximately four weeks over December 2017 and January 2018. Data for the analysis was compiled from MAD, the Special Authorities database and the Pharmaceutical Claims database.

The main project output was a presentation available under objective folder fA233314. A draft was distributed to panel members and Pharmac staff involved with the PAH panel, with suggestions incorporated into a final version (also distributed). The document was well received, with panel members indicating their intention to discuss the findings further at the next panel meeting.

Specific findings

Readers are directed to the presentation for detailed results and figures. Nevertheless, top-line findings include:

Trends in panel decisions:

- The introduction of indefinite renewal approvals for sildenafil in 2013/14 substantially reduced the administrative burden for that therapy, reducing the total number of decisions required by the panel
- Following the drop in 2014, the total number of decisions has steadily increased again. Initial applications have grown modestly, but most growth is from indefinite renewals for sildenafil and particularly annual renewals for other therapies as the cohort of patients managed by the panel increases in size.

Therapy mix for patients with PAH under the panel:

- sildenafil remains the most prevalent therapy, consistent with it being the accepted first-line
- sildenafil with an endothelin receptor antagonist (ambrisentan or bosentan) is the most prevalent dual-therapy; this has grown over time
- Together, the above comprise approximately 90% of total patient-year-equivalents for all PAH therapies

Therapeutic outcomes

- Survival times are not significantly different across therapy pathways, but are relative to age at commencement
- Overall survival for those who received therapy is similar to published rates internationally
- This is on a background of incidence and prevalence rates that are higher than in older reported data from other countries.
    - International comparisons are subject to a number of potential confounds, including panel geographical coverage, patient mix (eg, age cutoffs) and case definition.

Possible future PAH analysis

Should resources become available in future to extend the project, the following may be useful lines of enquiry to inform the panel's work and support dissemination of the NZ panel outcomes in the international literature.

- Detailed international comparisons
    - Attempting to account for cohort differences (age, aetiologies, etc.)
    - Including confidence intervals (currently only cohort sizes are noted)
- Investigations by PAH aetiology
    - Including assessment of state of data in the underlying panel database

- Detailed analysis of case disposal
    - Death, transplantation, approval declines, etc.
- Analysis of mortality rates compared to background NZ population mortality
    - Leading to calculation of relative risk by age group for PAH patients

PHARMAC
Pharmaceutical Management Agency

Pulmonary Arterial Hypertension Panel

After eight years of activity

Ben Healey
PHARMAC

New Zealand Government

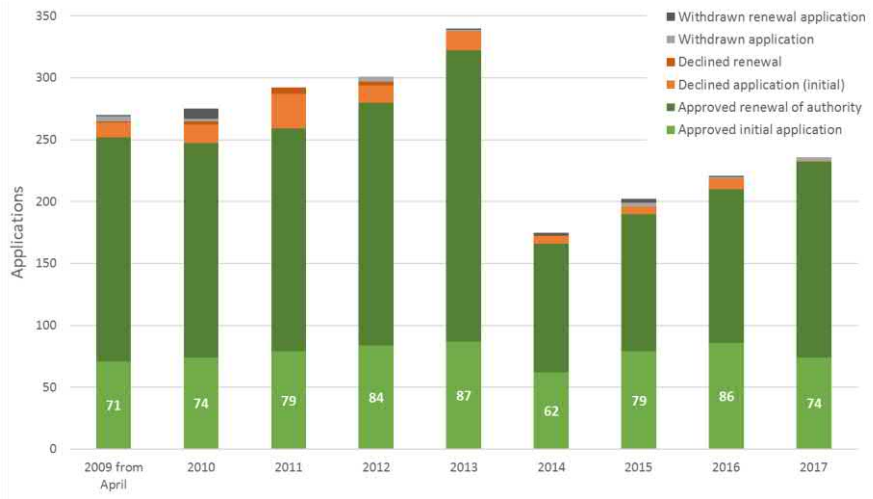
Pulmonary Arterial Hypertension Panel

- Established 2009
  - PHARMAC transferred management of drugs from hospitals
  - Applications started April 2009
  - Existing patients transferred by September 2009

- Data
  - Eight full years of new patients
  - Actual drug therapy determined from dispensing data in the *Pharmaceutical Claims* database

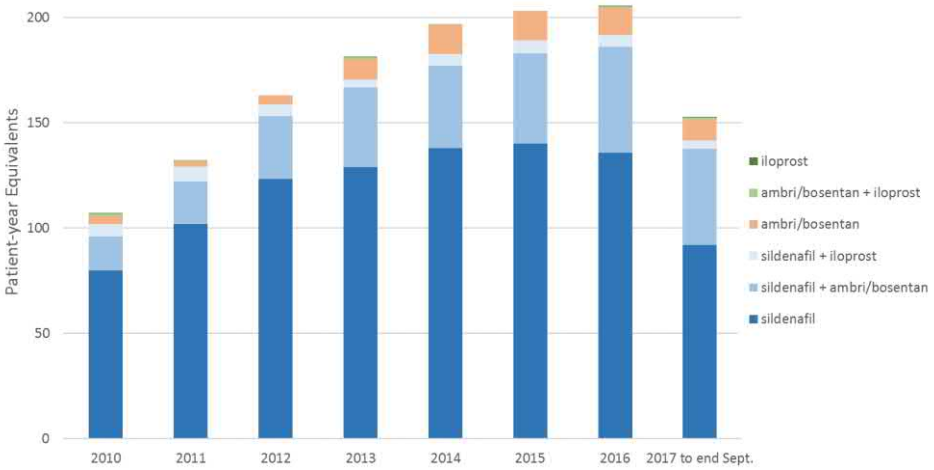
Panel application decisions

(April 2009 to December 2017)



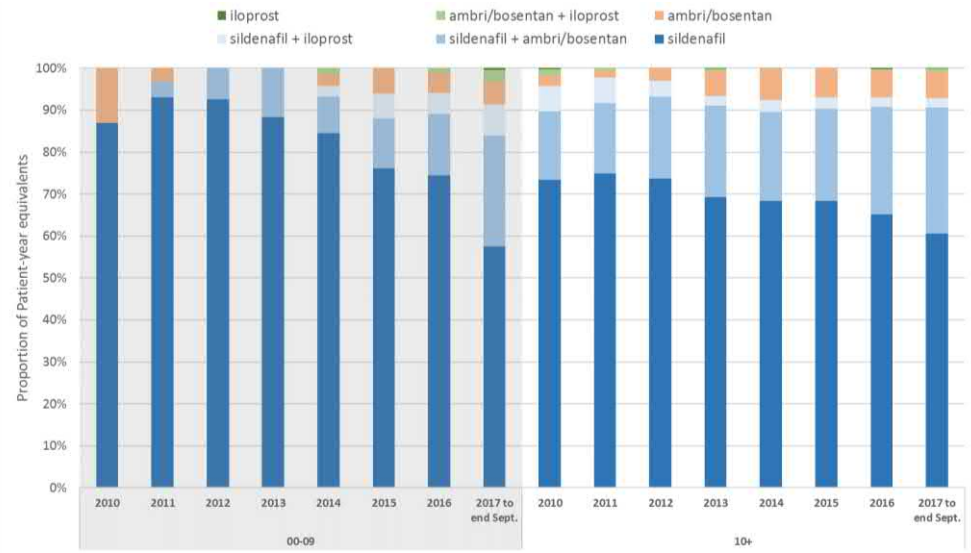
PAH therapies

as patient-year equivalents



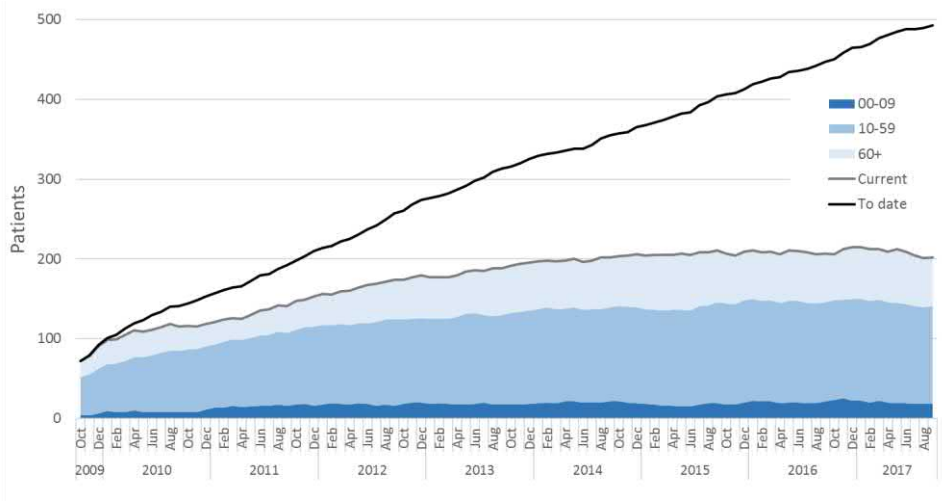
PAH therapies

by age classification



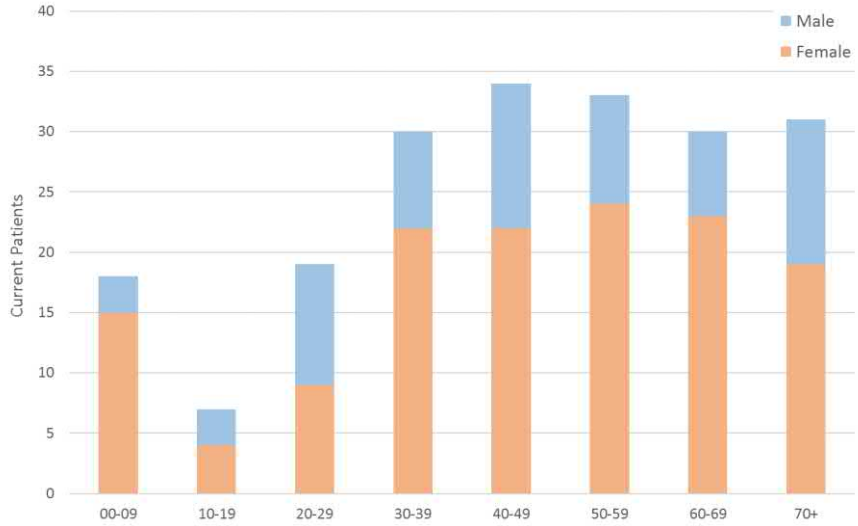
Time series of patients treated

(point-prevalence by month)



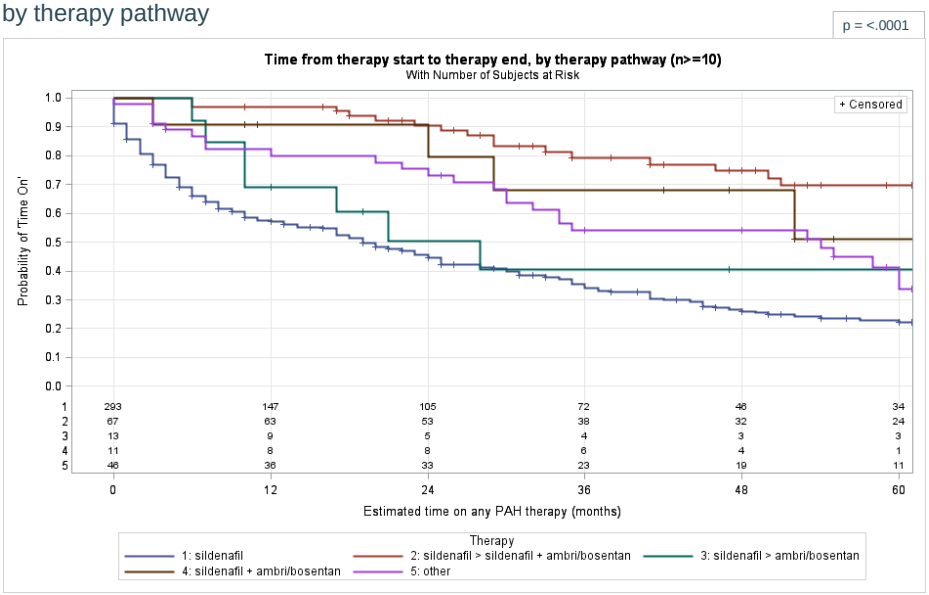
Current patients by age and gender

(as at September 2017)



Time on any PAH therapy

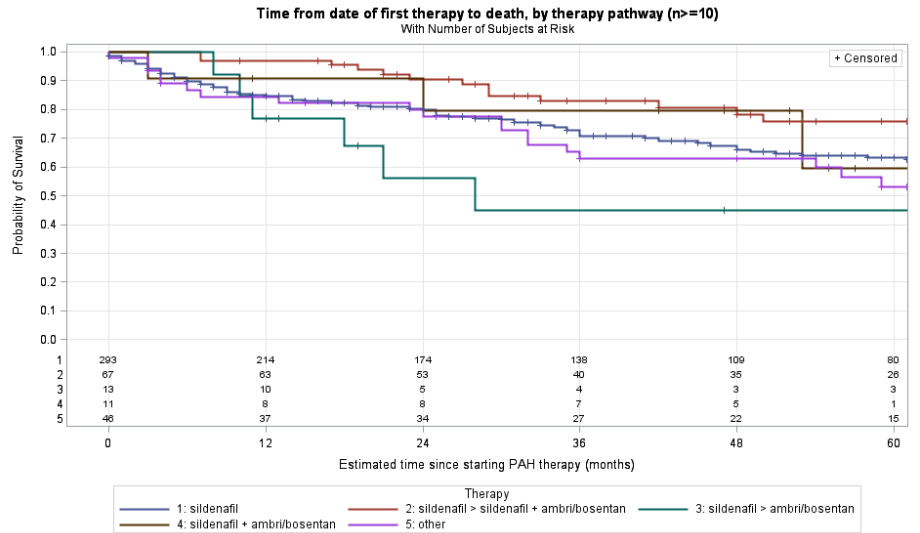
by therapy pathway



Overall survival

by therapy pathway

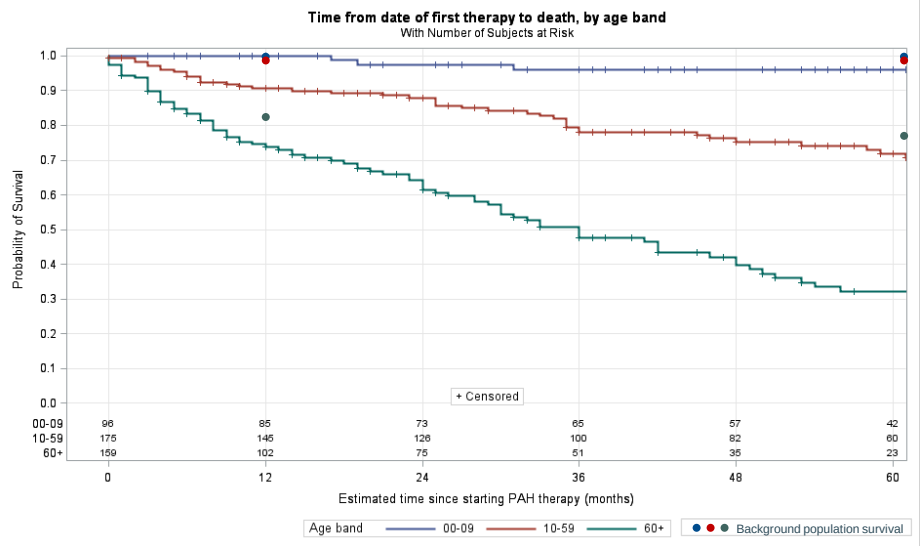
p = 0.0843



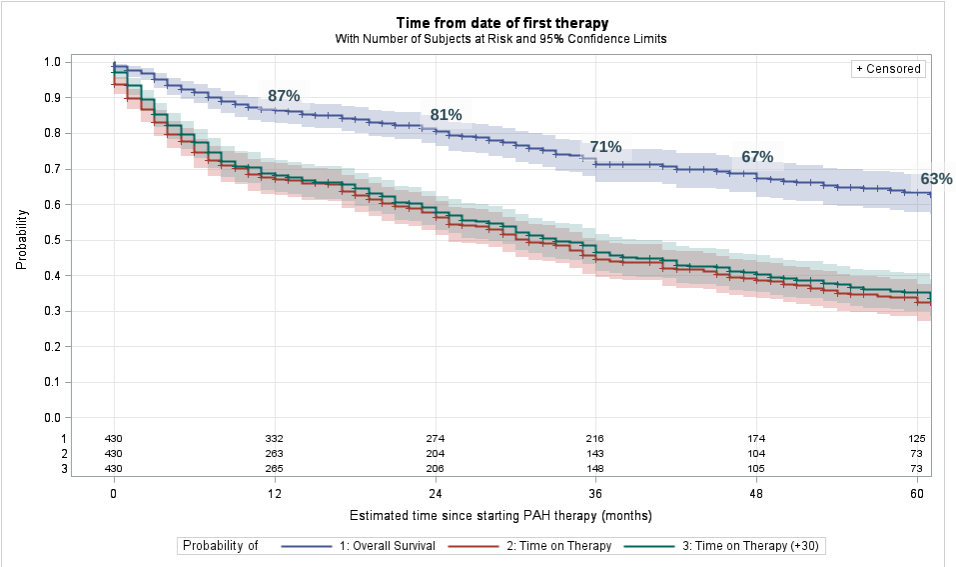
Overall survival

by age at therapy start

p = <.0001



Time on any PAH therapy vs. Overall survival



Overall survival: International comparators

Source	Country	Data coverge (years)	Cohort Size (patients)	% Survival at year 1	2	3	4	5	Notes
NZ Panel	***New Zealand***	***2009 – 2017***	***430***	***87***	***81***	***71***	***67***	***63***	***Incident cases.***
Kane et. al. (2010)	United States	1995 – 2004	*484*	81		61		48	Incident and prevalent cases.
Thenappan et. al (2013)	United States	1991 – 2007	*576*	86		69		61	Incident and prevalent cases.
McGoon et. al. (2013)*	United States	2006 – 2009	*3,515*	85		68		57	Incident and prevalent cases.
Humbert et. al (2010)	France	2002 – 2003	*121*	88	65	51			Incident cases, 'all cohort' patients.
Escribano-Subias et. al. (2012)	Spain	2007 – 2008	*167*	88		74			Incident cases, 'all cohort' patients.
Wensel et. al. (2011)	Germany	1996 – 2008	*69*	97	87	84		70	Incident cases, idiopathic, familiar or anorexigen-associated PAH.
Jansa et. al. (2014)	Czech Rep.	2007 – 2007	*91*	89	78	74			Incident cases.
Ling et. al. (2012)	Uk, Ireland	2001 – 2009	*482*	93	84	73		61	Incident cases.
Mueller-Mottet et. al. (2015)	Switzerland	2000 – 2012	*493*	87	77	69	^73		Incident cases.
Chung et. al. (2015)	Korea	2008 – 2011	*297*	91	88	84			Incident cases. Group 1 PH only.
Alves Jr et. al. (2015)	Brazil	2008 – 2013	*178*	93	80	74			Incident cases.

* Reporting on various REVEAL studies published after 2010
^ for years 2009 - 2012 only. Other figures for all incident cases, and not significantly different across years.

Incidence and prevalence

			*Per Million Inhabitants/Year^*	
Source	**Country**	**Year**	**Incidence**	**Prevalence**
New Zealand Panel	New Zealand	2014	13.6	52
		2015	14.6	54
		2016	14.5	55
McGoon et. al. (2013)*	United States	2006-2009	^2.0	^11
Humbert et. al (2010)	France	2002-2003	^2.4	^15
Peacock et. al. (2007)	Scotland	2002	^7.1	^52
Hurdman et. al. (2012)	UK (Sheffield)	2009	6.1	-
Ling et. al. (2012)	UK/Ireland	2009	1.1	7
Escribano-Subias et. al. (2012)	Spain	2007/8	-	^16
Jansa et. al. (2014)	Czech Rep.	2007	^10.7	^22

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^ Figures for Per Million *Adult* Inhabitants, for studies with a lower bound age cut-off (various)

Key points from the New Zealand data

- The introduction of indefinite renewal approvals for sildenafil substantially reduced the administrative burden for that therapy
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Possible future work

- Detailed international comparisons
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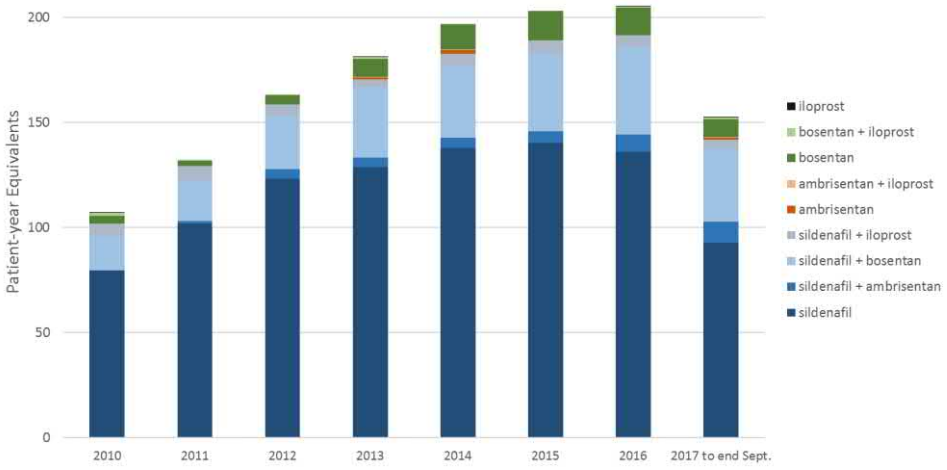
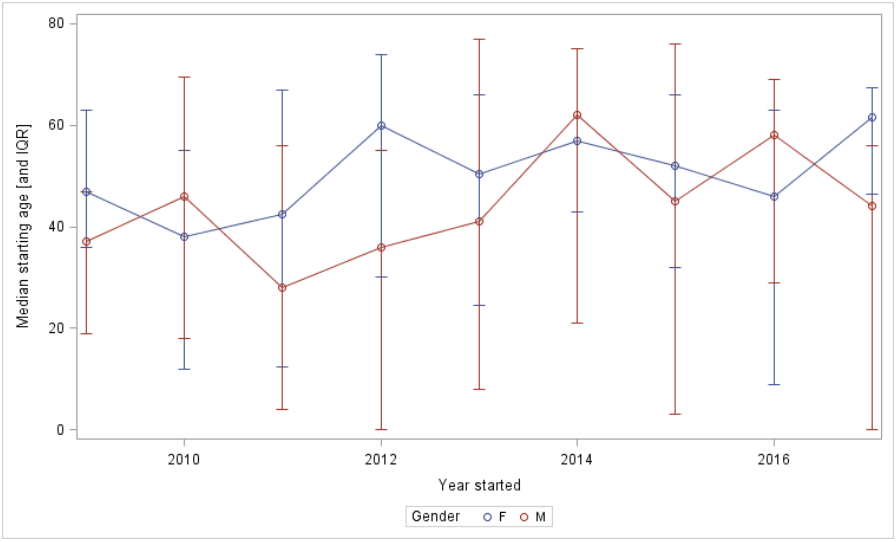
PAH therapies

as patient-year equivalents, endothelin receptor antagonists separated out



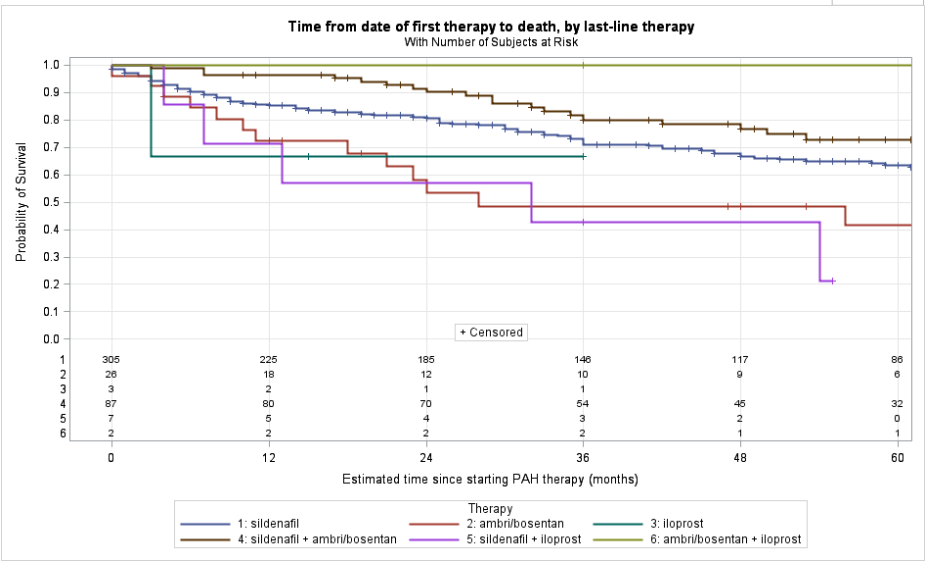
Median age by year of therapy commencement



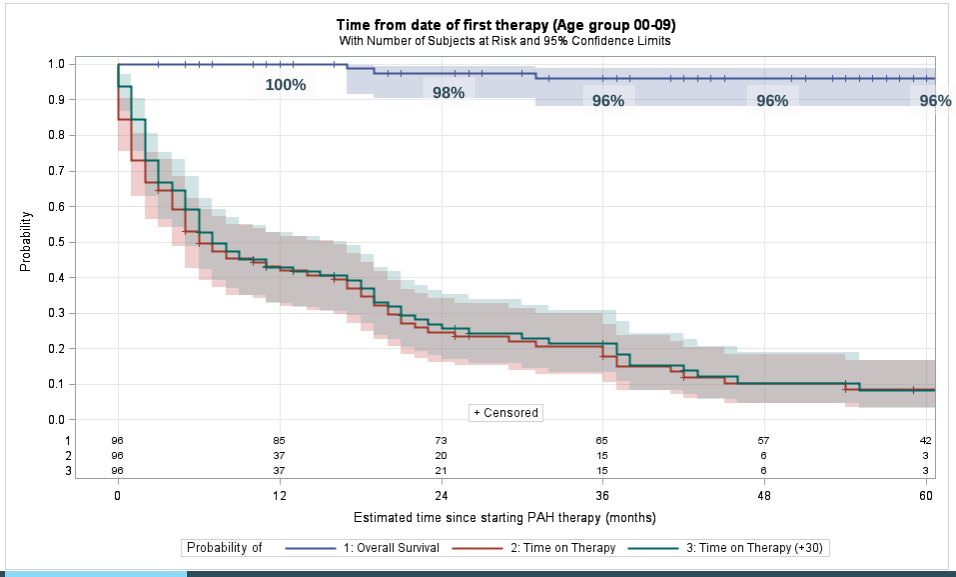
Survival

by last-line therapy

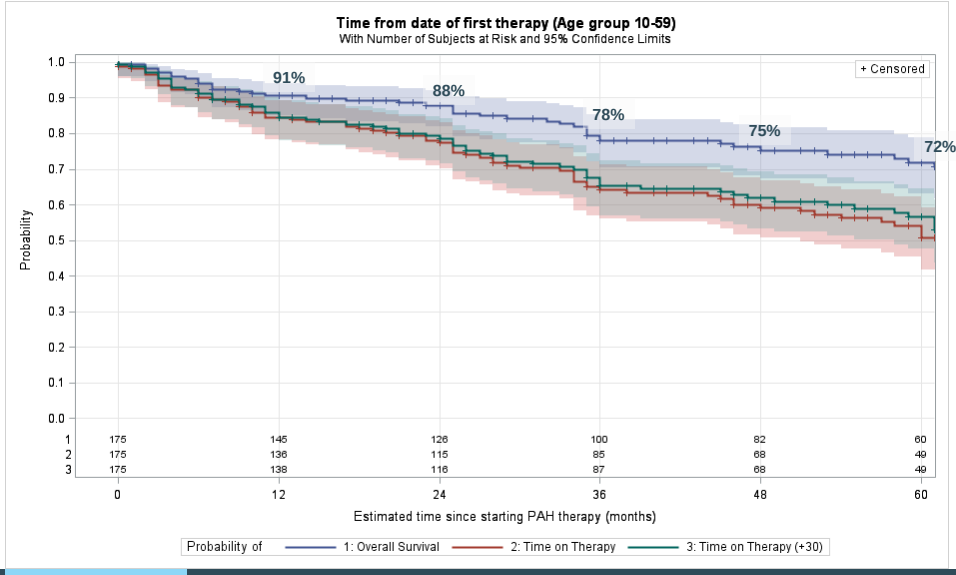
p = 0.0045



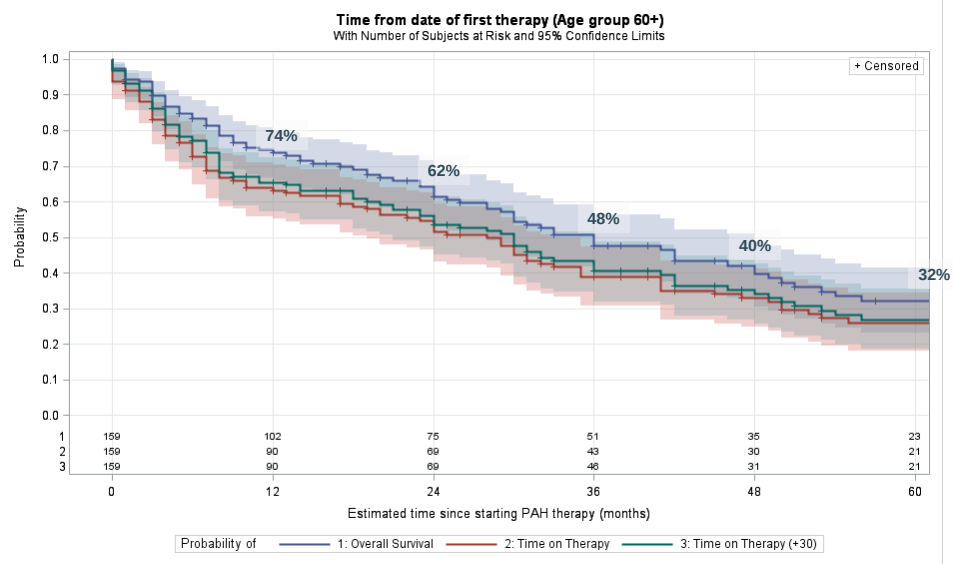
Time on any PAH therapy vs. Overall survival (0-9yo)



Time on any PAH therapy vs. Overall survival (10-59yo)



Time on any PAH therapy vs. Overall survival (60+yo)



Internal location

- Objective fA233314