The Leeds Teaching Hospitals NHS
NHS Trust

The State of the Art in Multi-Country Cancer RWE ?
ORWIC: Ovarian Real World International Consortium

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The Leeds Teaching Hospitals NHS Trust

http://www.leedsth.nhs.uk/

Hospitals

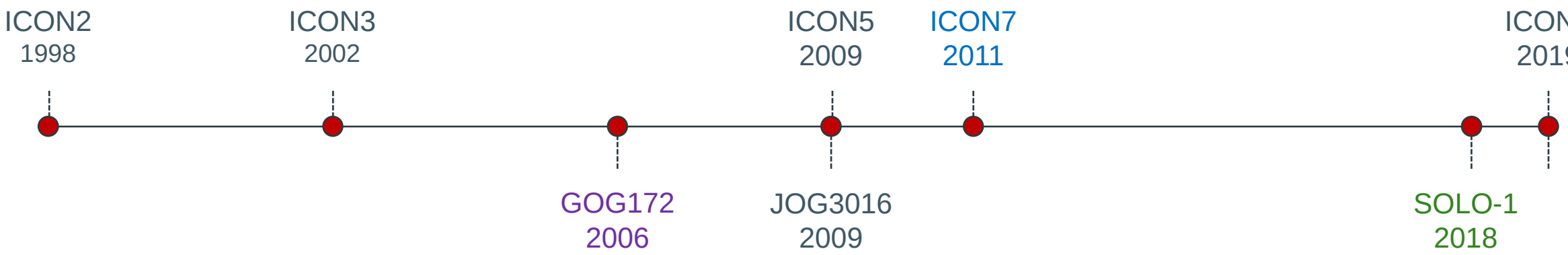
- Leeds General Infirmary
- St' James's University Hospital
- Chapel Allerton Hospital
- Leeds Children's Hospital
- Seacroft Hospital
- Wharfedale Hospital

- The Leeds Teaching Hospitals NHS Trust (LTHT) is one of the largest trusts in the UK
- The trust has **6 sites**, including paediatric centre
- One of the largest **teaching hospitals** in Europe

- Treats **~5% of UK population** with 1,200 inpatient beds together with critical care and day case beds
- **Local district hospital for population of Leeds (~1M)**
- **Specialist cancer services to Yorkshire (~2.7M)**
- **Regional centre for a number of specialist cancer (~5.7M)**

- **Largest provider** of specialist services in UK
- L**argest integrated Cancer Centre** in UK

Clinical trials - the gold standard to define new pathways of care

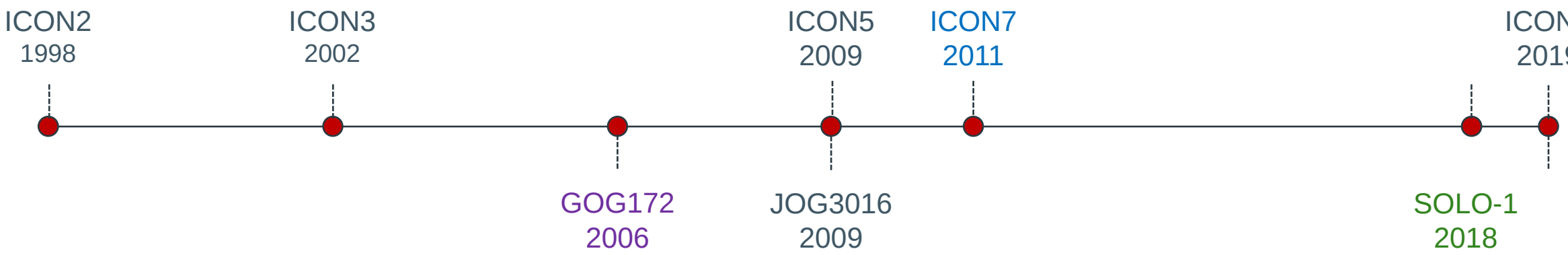


ICON 2	Carboplatin
ICON 3	Carboplatin & Paclitaxel
ICON 5	No improvement from 3-drug combination
JOG3016	Carboplatin & Weekly paclitaxel
ICON 8	Carboplatin & Paclitaxel
GOG172	Intraperitoneal cisplatin & paclitaxel

PRIMA
2019

PAOLA-1
2019

Clinical trials - the gold standard to define new pathways of care

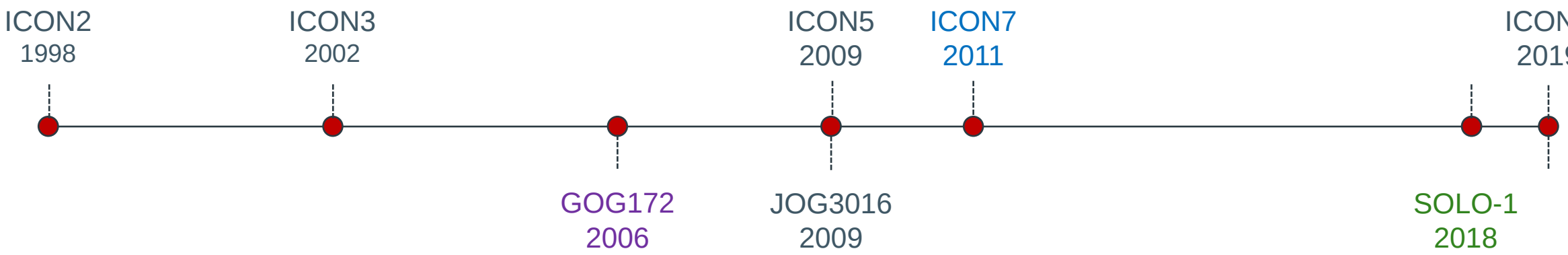


ICON 7	Carboplatin/Paclitaxel & Bevacizumab
SOLO-1	Carboplatin/Paclitaxel plus Olaparib
PRIMA	Carboplatin/Paclitaxel plus Olaparib
PAOLA-1	Carboplatin/Paclitaxel/Bevacizumab & Olaparib

PRIMA
2019

PAOLA-1
2019

Clinical trials - the gold standard to define new pathways of care



Leeds Ovarian cancer cases	~ 5,000
Leeds Trial Recruitment	~ 200 ~ 4% recruitment
Why ?	Elderly, frail, co-morbidity Patient choice Education/deprivation

PRIMA
2019

PAOLA-1
2019

Clinical trials – are they really a gold standard ?

- Clinical trials
  - “Perfect” data on an imperfect population

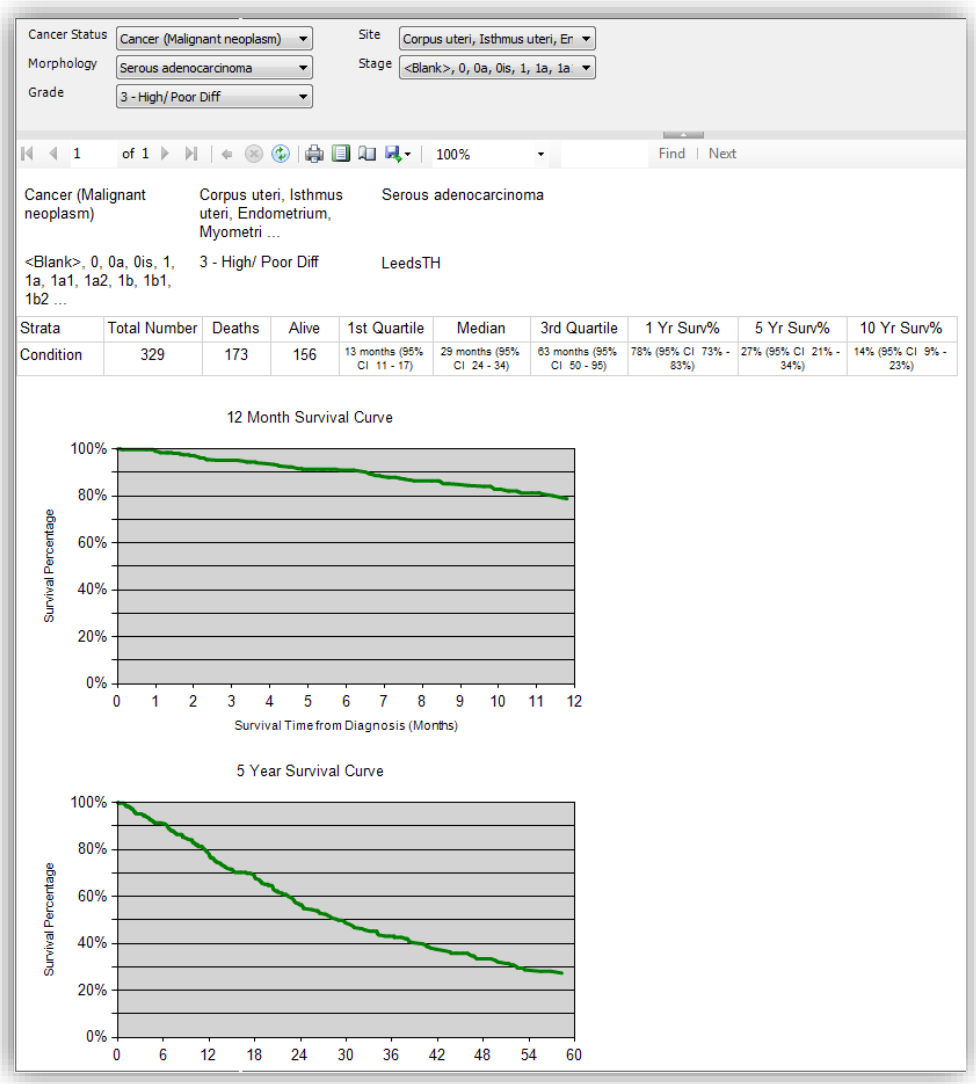
Clinical trials – are they really a gold standard ?

- Clinical trials
  - “Perfect” data on an imperfect population
- Real World Evidence
  - Imperfect data on the perfect population

PPM and Cancer Outcomes – 2003 to today

Instant analysis of uncurated data within clinic
Excellent for counts, overall survival

Strata	Total	Events	Censored	Surv Day30	Surv Day60	Surv Day90	Surv Year1	Surv Year2	Surv Year5
Breast - Breast - Carcinoma in Situ	1218	64	1154	100.00%	100.00%	99.91%	99.05%	97.73%	93.08%
Breast - Breast - Mal.Neoplasm	10621	2488	8133	99.31%	98.86%	98.44%	94.71%	88.61%	72.46%
UGI - Oesophagus - Mal.Neoplasm	2285	1780	505	94.93%	89.21%	83.84%	47.56%	27.88%	13.31%
UGI - Stomach - Mal.Neoplasm	1754	1370	384	92.73%	84.76%	77.68%	45.39%	27.09%	15.44%
LGI - Small Intestine - Mal.Neoplasm	188	104	84	94.68%	89.89%	87.74%	69.72%	53.76%	39.24%
LGI - Colon - Mal.Neoplasm	3819	2276	1543	94.59%	91.16%	88.30%	72.23%	58.28%	34.19%
LGI - Rectum - Mal.Neoplasm	3130	1617	1513	98.27%	95.96%	93.38%	77.49%	61.49%	36.11%
LGI - Rectosigmoid Junction - Mal.Neoplasm	532	325	207	95.85%	92.82%	91.29%	76.07%	58.41%	36.40%
LGI - Anus - Mal.Neoplasm	343	143	200	98.83%	98.83%	97.03%	80.91%	70.17%	53.65%
HPB - Bilary Unspec - Mal.Neoplasm	225	160	65	93.33%	90.67%	86.21%	64.02%	37.92%	20.73%
HPB - Gallbladder - Mal.Neoplasm	180	153	27	91.06%	79.33%	70.95%	33.76%	19.15%	9.11%
HPB - Liver & Bile Duct - Mal.Neoplasm	1131	868	263	90.05%	82.29%	75.56%	47.24%	29.62%	14.85%
HPB - Pancreas - Mal.Neoplasm	1350	1219	131	86.94%	74.97%	66.10%	27.27%	11.47%	4.62%
Lung - Bronchus & Lung - Mal.Neoplasm	10218	8863	1355	88.06%	78.65%	71.61%	33.91%	17.54%	6.90%
Lung - Heart, Mediastinum - Mal.Neoplasm	76	66	10	86.84%	76.32%	68.42%	36.01%	22.78%	5.84%
Lung - Mesothelioma	711	624	87	95.77%	91.21%	85.27%	38.07%	12.29%	2.16%
Lung - Thymus - Mal.Neoplasm	35	18	17	97.14%	97.14%	94.20%	84.74%	77.96%	50.91%
Gynae - Cervix Uteri - Mal.Neoplasm	1124	393	731	99.27%	97.69%	96.25%	84.26%	72.51%	57.73%
Gynae - Corpus Uteri - Mal.Neoplasm	2193	661	1532	99.30%	98.35%	97.06%	88.41%	77.44%	59.77%
Gynae - Ovary - Mal.Neoplasm	1540	859	681	96.56%	93.68%	91.25%	78.35%	62.30%	35.02%
Gynae - Uterus Unspec - Mal.Neoplasm	161	89	72	96.83%	93.59%	90.97%	71.04%	60.16%	37.26%
Gynae - Vagina - Mal.Neoplasm	109	65	44	99.08%	97.23%	95.38%	72.00%	48.25%	36.72%
Gynae - Vulva - Mal.Neoplasm	363	154	209	98.86%	97.11%	95.04%	78.86%	68.96%	52.26%



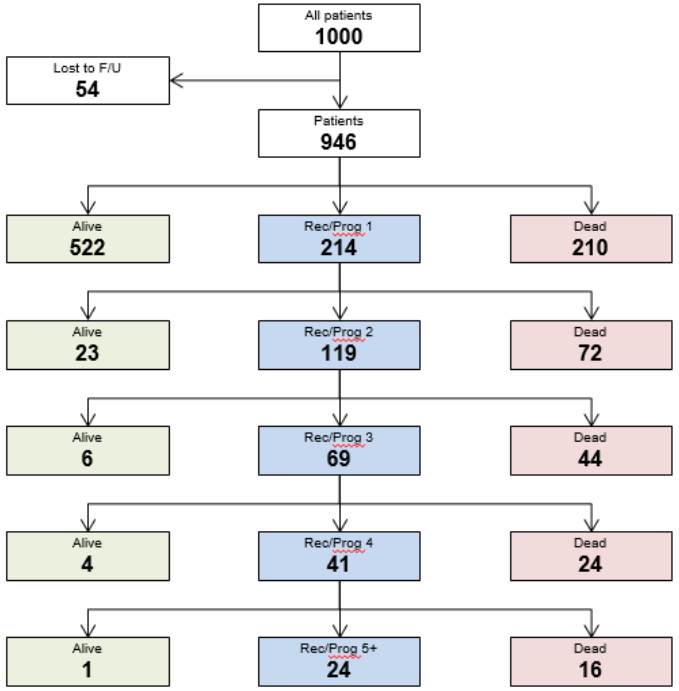
Leeds Real World Evidence – Patterns of Recurrence

- **1000 sequential breast cancer diagnoses**

- **1999 to 2001**
- Leeds only cases – Surgery, ChemoRx, RadioRx

- Case note review and curation
- Define each recurrence until last review or death

- **Assess patterns of recurrence**
- **Describe pathways of care from diagnosis to death**



	mOS months	mPFS months
	-	-
	17.9	8.6
	11.3	6.1
	9.4	5.2
	9.0	4.4

Case Study – Breast cancer & Novartis

- ER/PR +ve, HER2 –ve breast cancer
  - Patient characteristics (e.g. histology, biomarkers, stage)
  - Treatment patterns (lines of chemotherapy, radiotherapy and oncology surgery)
  - Outcomes from diagnosis, recurrence(s) to death

Characteristic n (% of sub-cohort)	Study cohort (N = 196)	Diagnosed metastatic (N = 72)	Progressed metastatic (N = 124)
Age at diagnosis, median (range)	67 years (33-92)	69 years (33-92)	67 years (33-90)
Pre/peri-menopausal[a]	25 (12.8%)	11 (15.3%)	14 (11.3%)
Post-menopausal	167 (85.2%)	60 (83.3%)	107 (86.3%)
Morphology (1° tumour)			
Infiltrating duct carcinoma, NOS[b]	117 (59.7%)	40 (55.6%)	77 (62.1%)
Lobular carcinoma, NOS	29 (14.8%)	11 (15.3%)	18 (14.5%)
Carcinoma, NOS	26 (13.3%)	12 (16.7%)	14 (11.3%)
Other	24 (12.2%)	9 (12.5%)	15 (12.1%)
Non-visceral metastasis[c]	**163 (83.2%)**	**60 (83.3%)**	**103 (83.1%)**
Bone	133 (67.9%)	51 (70.8%)	82 (66.1%)
Lymph nodes	68 (34.7%)	27 (37.5%)	41 (33.1%)
Skin and soft tissue	29 (14.8%)	8 (11.1%)	21 (16.9%)
Visceral (incl. CNS) metastasis	**119 (60.7%)**	**44 (61.1%)**	**75 (60.5%)**
Pulmonary	64 (32.7%)	26 (36.1%)	38 (30.6%)
Liver	56 (28.6%)	24 (33.3%)	32 (25.8%)
Pleura	33 (16.8%)	9 (12.5%)	24 (19.4%)
Peritoneum	10 (5.1%)	<5	<10
CNS	8 (4.1%)	<5	<5

Figure 1. Patients receiving treatment during follow-up, by intent and menopausal status

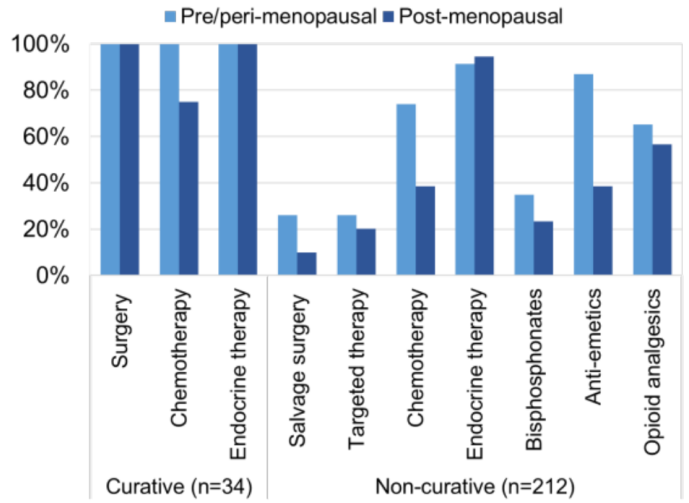
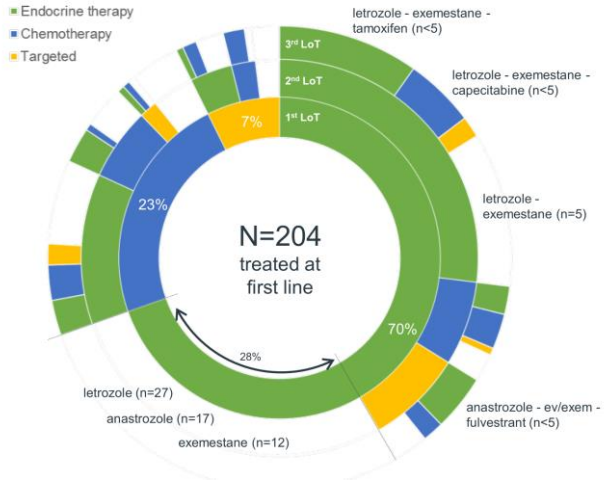
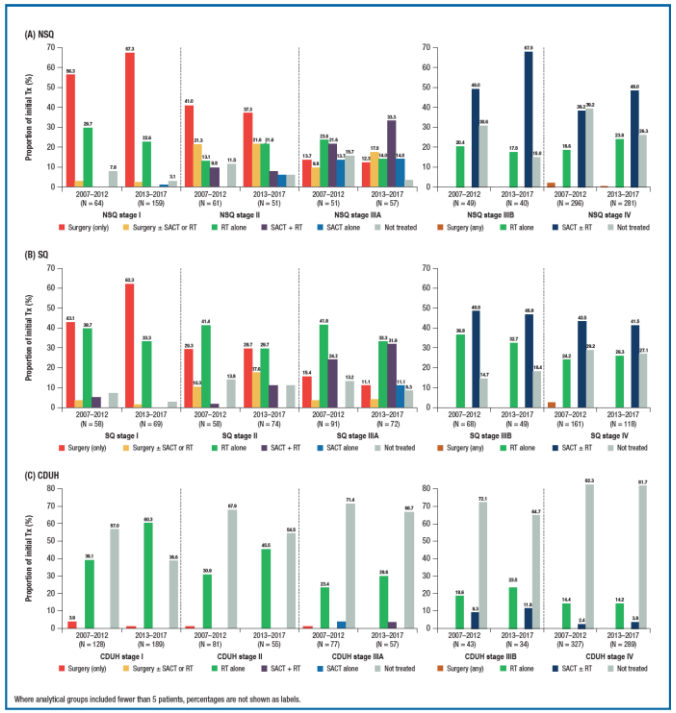


Figure 2. Categories of sequential non-curative treatment received (up to 3 LoT shown). The 7 most common regimen sequences are named and corresponding numbers of patients shown

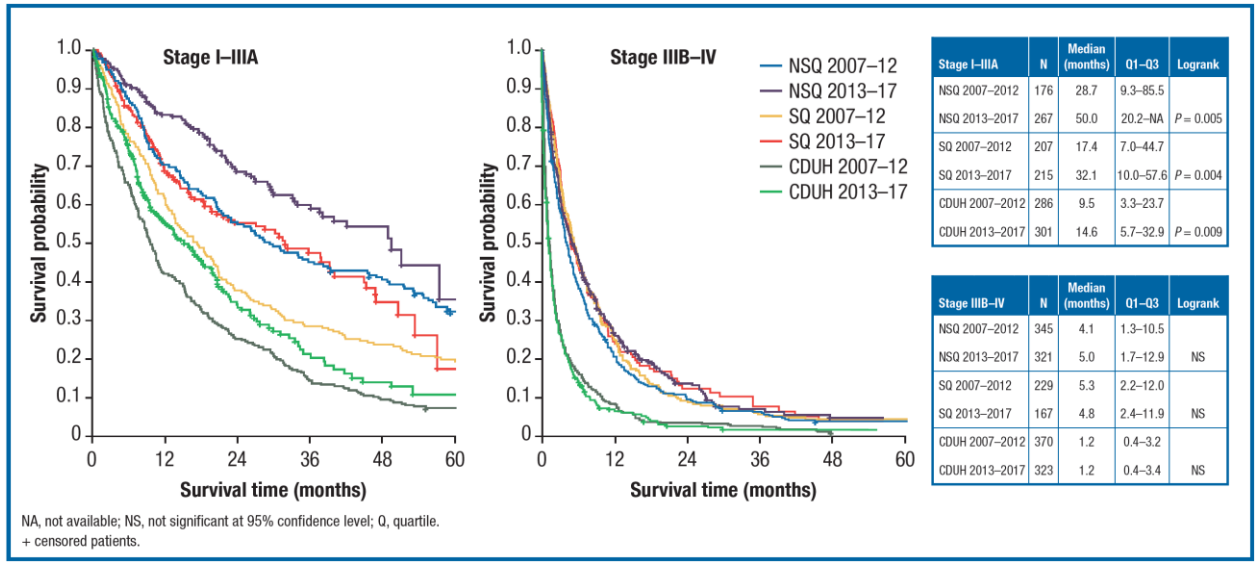


Case Study – Lung Cancer – BMS

- Non-small cell lung cancer
  - Patient characteristics (e.g. histology, biomarkers, stage)
  - Treatment patterns (lines of chemotherapy, and surgery)
  - Outcomes from diagnosis, recurrence(s) to death



9th European Lung Cancer Congress (ELCC)



Stage I–IIIA	N	Median (months)	Q1–Q3	Logrank
NSQ 2007–2012	176	28.7	9.3–85.5	
NSQ 2013–2017	267	50.0	20.2–NA	$P = 0.005$
SQ 2007–2012	207	17.4	7.0–44.7	
SQ 2013–2017	215	32.1	10.0–57.6	$P = 0.004$
CDUH 2007–2012	286	9.5	3.3–23.7	
CDUH 2013–2017	301	14.6	5.7–32.9	$P = 0.009$

Stage IIIB–IV	N	Median (months)	Q1–Q3	Logrank
NSQ 2007–2012	345	4.1	1.3–10.5	
NSQ 2013–2017	321	5.0	1.7–12.9	NS
SQ 2007–2012	229	5.3	2.2–12.0	
SQ 2013–2017	167	4.8	2.4–11.9	NS
CDUH 2007–2012	370	1.2	0.4–3.2	
CDUH 2013–2017	323	1.2	0.4–3.4	NS

NA, not available; NS, not significant at 95% confidence level; Q, quartile.
+ censored patients.

Multi-centre study – Ovarian cancer - ORWIC

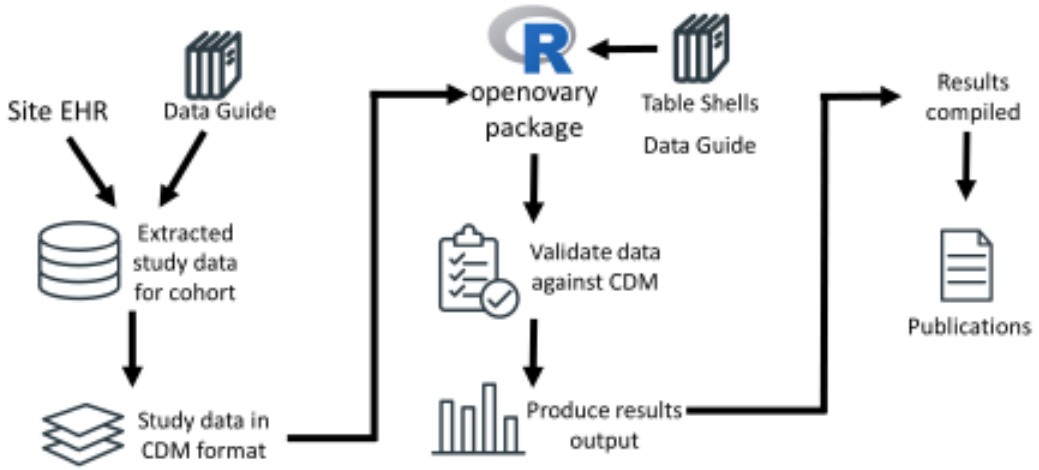
- **Epithelial ovarian cancer**
  - Intermediate frequency cancer
  - Complex treatment pathways, multiple lines of therapy
  - Recent introduction of targeted therapy, variably funded internationally
  - Diverse international standards of care

- **ORWIC**
  - Multi-centre study, multi-nation study
  - Unify disparate models of data capture and curation

  - Respect opt-out but no formal consent
  - Accept sharing patient level data is not possible (GDPR, IG, privacy)
  - Establish common data analysis

Multi-centre study – Ovarian cancer - ORWIC

- Epithelial ovarian cancer
  - Patient characteristics (e.g. histology, biomarkers, stage, breast cancer)
  - Genetic and molecular phenotype (germline, somatic BRCA, HRD)
  - Treatment patterns (surgery, lines of chemotherapy)
  - Outcomes from diagnosis & recurrence(s) to death



- **Common data model agreed**
- Data curated by each centre to CDM

- Single analytic script defined (R package)
- Parallel analysis of data by each site

- Output of analysis combined

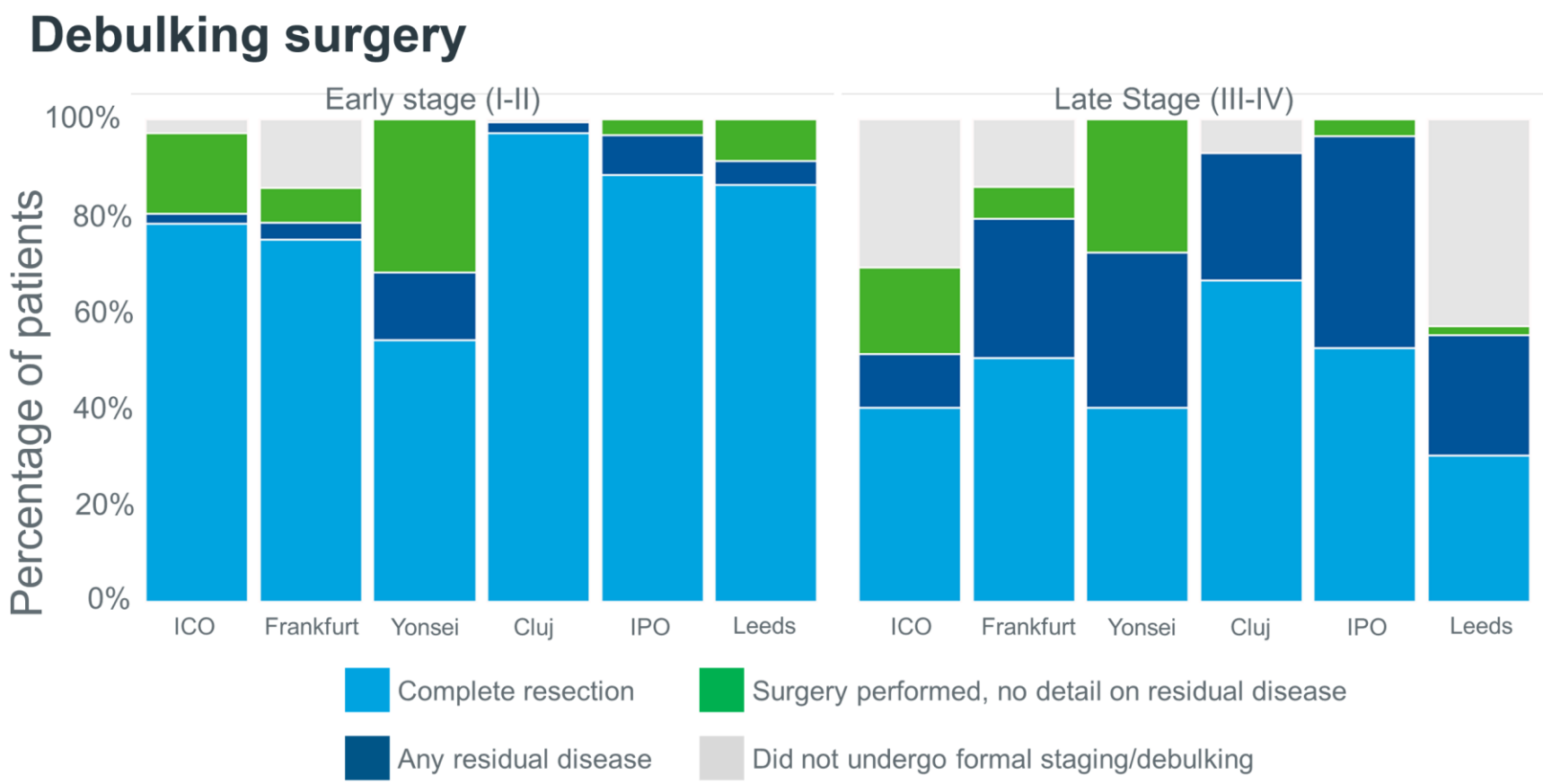
Multi-centre study – Ovarian cancer – ORWIC

Table 1: Patient characteristics at diagnosis

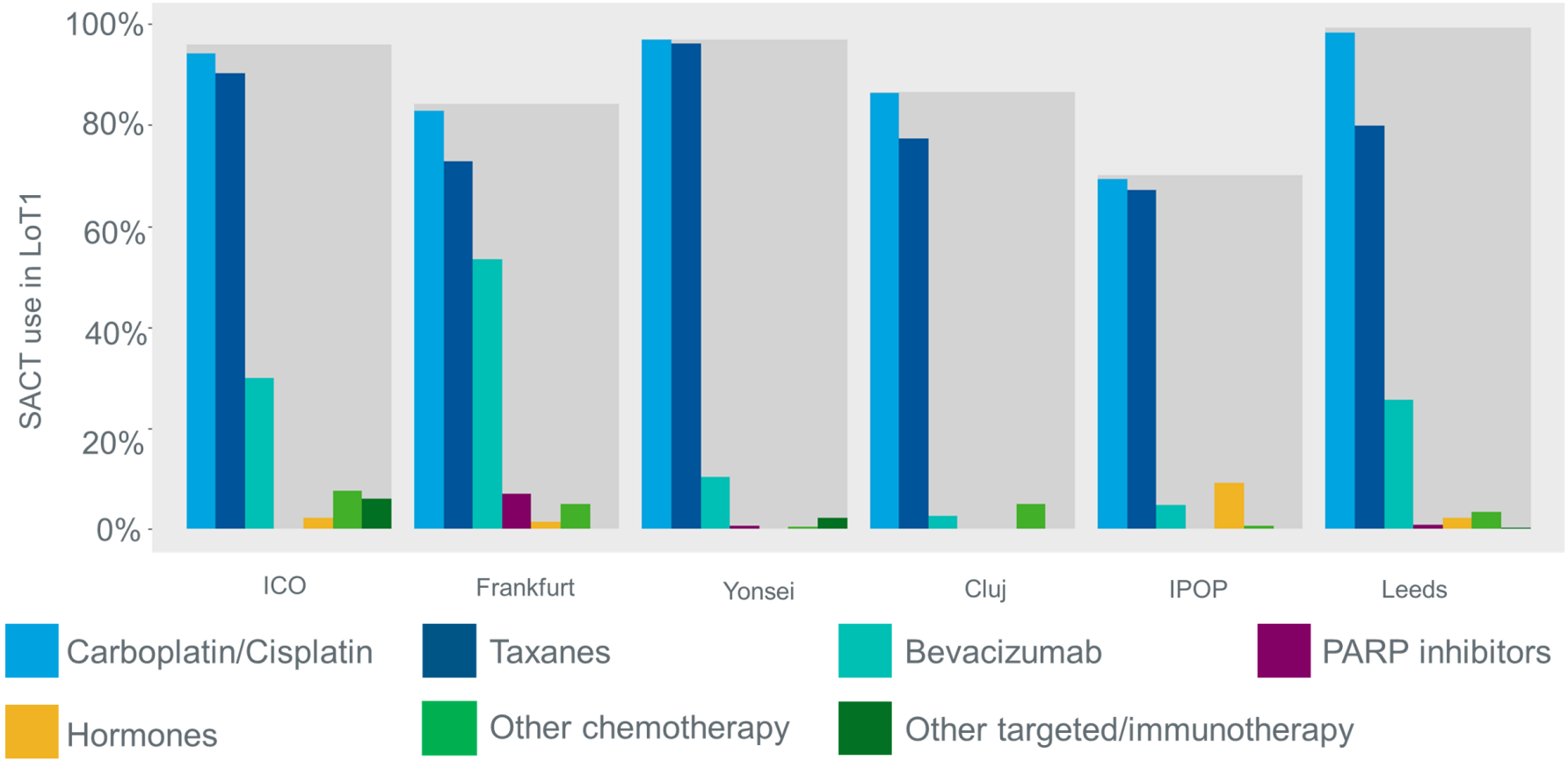
Overall Study Cohort		ICO	Frankfurt	Yonsei	Cluj	IPOP	Leeds
		696	140	851	446	268	515
Age Group	<45	45 (6.5%)	17 (12.1%)	166 (20.4%)	81 (18.2%)	12 (4.5%)	20 (3.9%)
	45-59	174 (25.0%)	54 (38.6%)	440 (54.1%)	209 (46.9%)	75 (28.1%)	125 (24.3%)
	60-74	329 (47.3%)	51 (36.4%)	217 (26.7%)	139 (31.2%)	114 (42.7%)	235 (45.6%)
	75+	148 (21.3%)	18 (12.9%)	28 (3.4%)	17 (3.8%)	67 (25.1%)	135 (26.2%)
FIGO stage at diagnosis	I	73 (12.5%)	21 (15.0%)	232 (27.3%)	101 (22.7%)	39 (14.6%)	56 (10.9%)
	II	27 (4.6%)	8 (5.7%)	68 (8.0%)	37 (8.3%)	18 (6.7%)	25 (4.9%)
	III	323 (55.2%)	72 (51.4%)	279 (32.8%)	259 (58.1%)	106 (39.7%)	293 (56.9%)
	IV	162 (27.7%)	35 (25.0%)	211 (24.8%)	49 (11.0%)	94 (35.2%)	140 (27.2%)
	Missing/Unknown	111 (15.9%)	4 (2.9%)	61 (7.5%)		11 (4.1%)	<6

2,916 patients

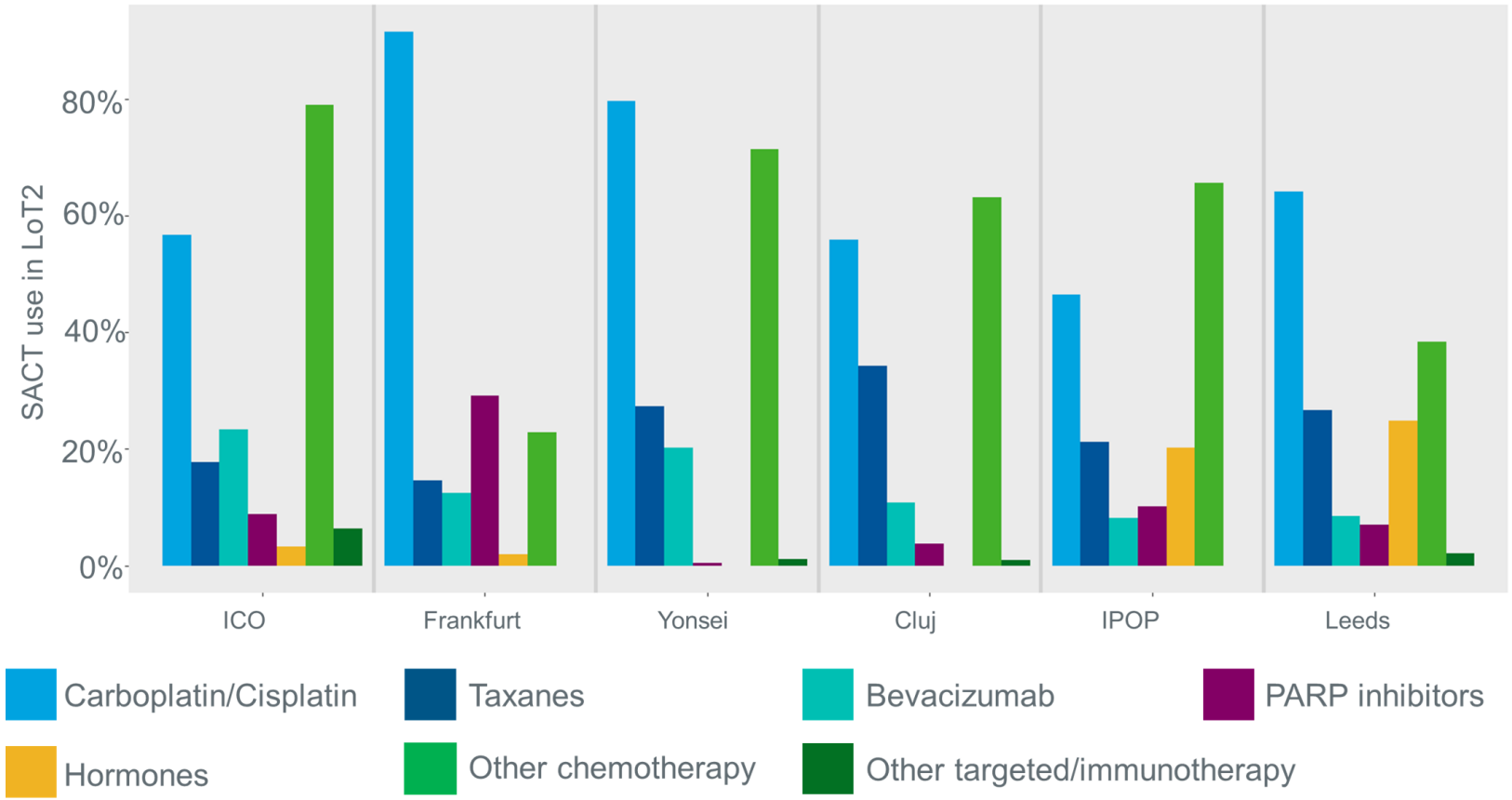
Multi-centre study – Ovarian cancer – ORWIC



Multi-centre study – Ovarian cancer – ORWIC – First-line therapy



Multi-centre study – Ovarian cancer – ORWIC – Second line therapy



Multi-centre study – Ovarian cancer – ORWIC

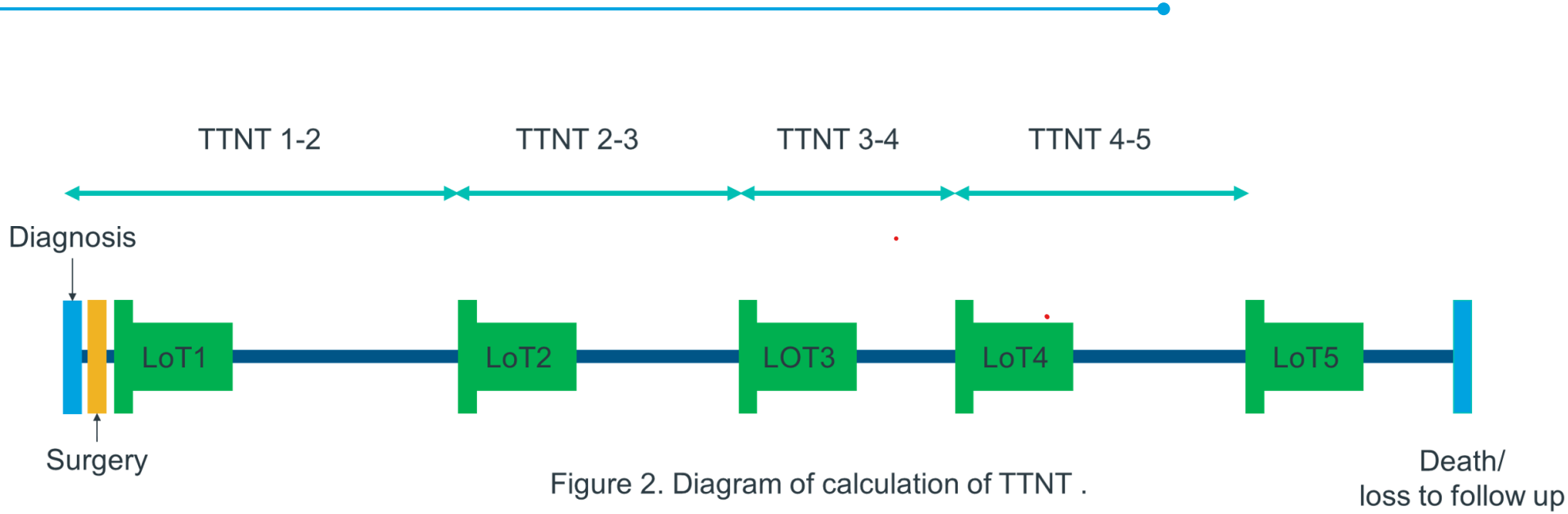
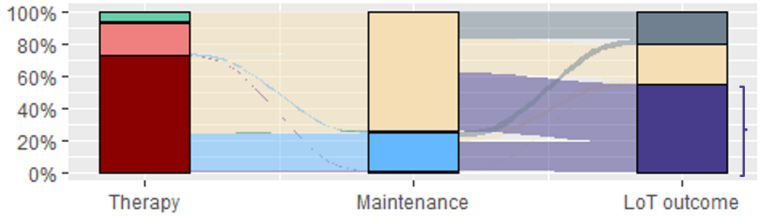


Figure 2. Diagram of calculation of TTNT .

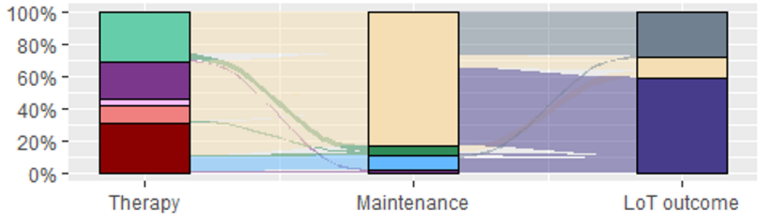
Multi-centre study – Ovarian cancer – ORWIC

1st line therapy (LOT1) – 509 patients

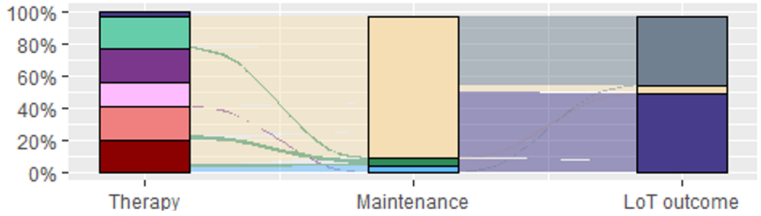


Received next line therapy

2nd line therapy (LOT2) – 282 patients



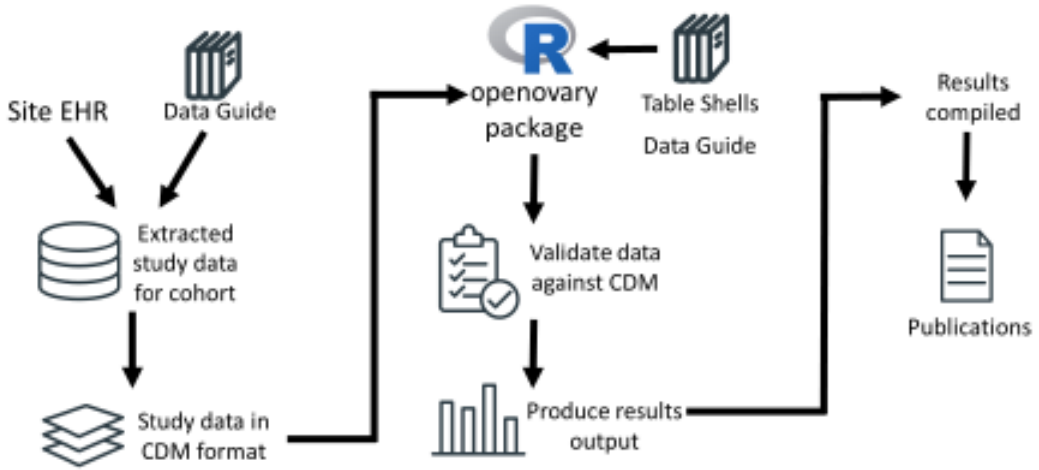
3rd line therapy (LOT3) – 168 patients



- Platinum combination
- Platinum single agent
- Taxane single agent
- Hormone monotherapy
- Trial / Other
- No maintenance
- Bevacizumab
- PARP inhibitor
- Died
- Alive, no progression
- Progression, further Rx

Multi-centre study – Ovarian cancer - ORWIC

- Epithelial ovarian cancer
  - Patient characteristics (e.g. histology, biomarkers, stage)
  - Treatment patterns (lines of chemotherapy, and surgery)
  - Outcomes from diagnosis, recurrence(s) to death



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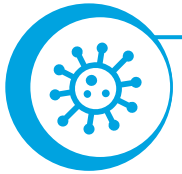
How could we improve ?

RWE – the data-model



We need to agree a common language for Real World Evidence

We need to agree key definitions

- Date of diagnosis ?
- Progression or Time to Next Treatment ?

We need a common data model

RWE – the data-model

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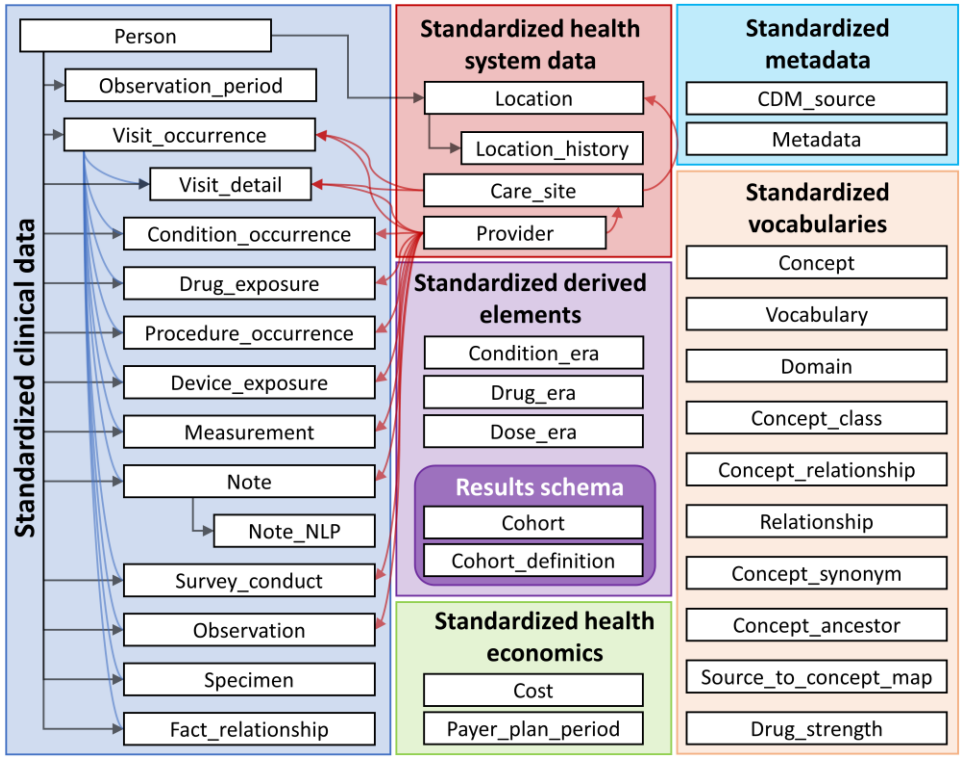
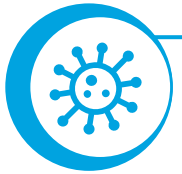
We need a common data model

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS



Observational Medical Outcomes Partnership OMOP

RWE – Data Curation and plain text



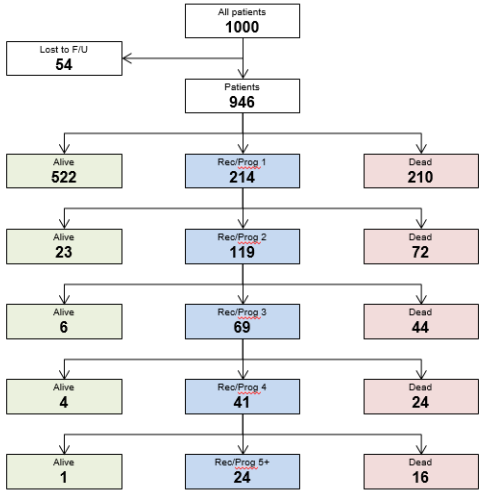
- 85% of EHR data is plain text
  ‘Impossible’ to analyse at scale

- Coded data will never replace plain text in EPRs
  Cannot capture the nuance of a clinical interaction

- Clinicians should not be forced to adapt to technology
  Technology should adapt to clinicians

Problem: We need Next Generation Informatics

RWE – Data Curation and plain text



mOS months	mPFS months	mTTP months
-	-	39.9
17.9	8.6	8
11.3	6.1	6
9.4	5.2	5
9.0	4.4	5

- 85% of EHR data is plain text
  ‘Impossible’ to analyse at scale
- Coded data will never replace plain text in EPRs
  Cannot capture the nuance of a clinical interaction
- Clinicians should not be forced to adapt to technology
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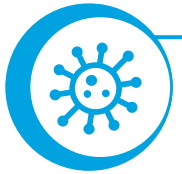
Problem: We need Next Generation Informatics

Solution: AI/ML, Natural Language Processing

Linguamatics
an IQVIA company

CogStack

RWE – Privacy and IG, Rules and Regulations



- Consent or permission ?
  - UK - individual opt-out
  - Explicit permission – global or study-specific

- **Sharing data between centres is challenging**
- **Sharing data between countries is very complex**

RWE – Privacy and IG, Rules and Regulations

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- **Sharing data between centres is challenging**
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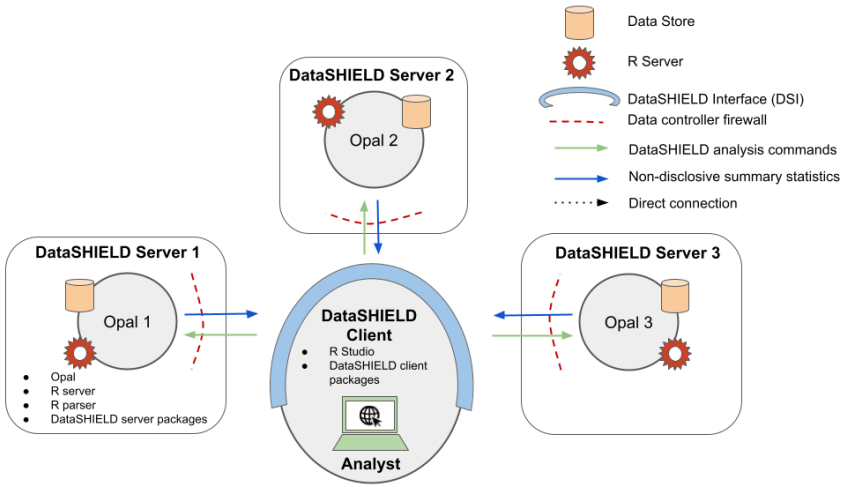
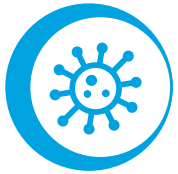
- Do NOT bring the data to the analysis
- **Bring the analysis to the data**
- **FEDERATED ANALYSIS**

DataSHIELD
Secure Bioscience Collaboration



RWE – Extended datasets

ORWIC – State of the Art ?



- **I hope not**

- Shared ambition to use every patient's experience to help others
- Patient, public and carer – support and active involvement

- Application of AI and ML to curation including NLP
- Common Data Model – OMOP
- Federated analytics
- Extend data to digital imaging and pathology, molecular/genetic, PROMs

Thankyou !

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