TAILORx (Sparano 2018): EAG summary of key points

This document provides the EAG's initial summary of key findings and implications of TAILORx, reported by Sparano et al. 2018.[1] This is based on a brief assessment of the article which has only just reported and may be subject to revision.

Trial design

- Patients with RS 0-10 received endocrine therapy, those with RS 26+ received chemo-endocrine therapy, while those with RS 11-25 were randomised to endocrine or chemo-endocrine therapy
- TAILORx used different RS cut-offs to those currently used (current cut-offs: 0-17, 18-30, 31+)
- Patients were HR+ HER2- LN0, and "met NCCN guidelines for recommendation or consideration of chemotherapy". In the randomised group, 73-74% were clinically low-risk according to modified AOL, so it is likely a similar proportion may have not been eligible for chemotherapy in UK
- Genomic Health funded part of the study and contributed to the manuscript

Key findings

- Across all patients, there was no clinically relevant (or statistically significant) difference between endocrine and chemo-endocrine therapy in patients with RS 11-25
    - Primary endpoint of 9-year invasive disease-free survival (IDFS): 84.3% with chemo, 83.3% without chemo, absolute difference 1.0%, ITT HR 1.08 (0.94 to 1.24), p=0.26 (similar for as-treated analysis). Upper CI was within non-inferiority margin (pre-specified: HR=1.322)
    - Freedom from distant recurrence (DRFI) at 9yr: 95% with chemo, 94.5% without chemo, absolute difference 0.5%, ITT HR 1.10 (0.85 to 1.41), p=0.48 (as-treated analysis similar)
- Prognostic ability: Continuous RS was associated with DRFI (i.e. DRFI increased as RS increased)
- **Exploratory** subgroup analyses were conducted; these did not appear to account for stratification factors and should be treated with caution. These include the following:
- Chemotherapy effect in different **RS subgroups**:
    - No significant interaction between chemotherapy treatment and RS (p=not reported), implying that the HR for chemotherapy did not differ significantly between RS subgroups (within RS 11-25)
    - However, some subgroups (e.g. RS 21-25 for IDFS) did show a significant chemotherapy effect. It is difficult to be certain that there was no effect of chemotherapy in any RS group
    - Chemotherapy effect was not assessed outside RS 11-25 as patients were not randomised.
- Chemotherapy effect when varying other factors:
    - Significant interactions between chemotherapy treatment and **age** on IDFS and RFI but not on DRFI, with patients aged ≤50 years showing a significant effect of chemotherapy
    - No significant interactions between chemotherapy treatment and tumour size, grade, clinical risk, or menopausal status (but trend for greater effect in pre-menopausal patients)
    - Article notes that the greater effect of chemotherapy in younger / premenopausal patients may be partly due to anti-estrogenic effect of chemotherapy-induced menopause
- Chemotherapy effect when varying **RS** and **age/menopausal** status:
    - In women aged ≤50 years with higher RS, chemotherapy had a significant effect (RS 21-25 all outcomes and RS 16-20 some outcomes). The effect of chemotherapy varied significantly between combinations of age and RS group for IDFS (p=0.004) but not for DRFI or RFI. This suggests that for patients ≤50 years, there was some evidence for a difference in chemotherapy effect between RS subgroups, but this was based on exploratory analyses

- Similarly, for pre-menopausal patients, chemotherapy had a significant effect for RS 21-25 (on some outcomes) though this pattern was not consistent across outcomes
- In women older than 50 years, there was little effect of chemotherapy overall, but those with age 51-65 and RS 21-25 had HR for chemo of 1.38 (0.94 to 2.03) for IDFS

Implications

- Across all patients, there was no clinically relevant (or statistically significant) difference between endocrine and chemo-endocrine therapy in patients with RS 11-25. However, exploratory subgroup analyses suggest chemotherapy may have an effect in some subgroups, such as RS 21-25 and possibly RS 16-20, particularly in those aged ≤50 years. Some subgroups had upper CIs above the non-inferiority margin (though numbers were small)
- For patients with RS 11-15, there was no clear effect of chemotherapy in any subgroup shown
- In terms of prediction of differential chemotherapy benefit, there was no significant interaction between chemotherapy treatment and RS, implying that the HR for chemotherapy did not differ significantly between RS subgroups (within RS 11-25). However, subgroup analyses indicated significant effects in some higher RS groups
- 73-74% of randomised patients were clinically low-risk via modified AOL; it is likely a similar proportion may not be eligible for chemotherapy in UK. There was no chemotherapy effect in either low or high clinical risk (mAOL) subgroups, though these were not subgrouped by RS

Detailed summary

Population and treatment arms
The population and treatment arms in TAILORx are shown in Table 1.

Table 1: Population and treatment arms

Population	Arm	RS score	Treatment	N (ITT)	Low clinical risk (mAOL)
HR+ HER2- LN0 Met NCCN guidelines for recommendation or consideration of chemotherapy	A	0-10	ET	1619	78%
	B	11-25	ET	3399	74%
	C	11-25	ET+CT	3312	73%
	D	26+	ET+CT	1389	43%

Main results: No significant effect of chemotherapy overall, for patients with RS 11-25
When comparing patients with RS 11-25 randomised to chemo-endocrine therapy vs. endocrine therapy alone, there was no significant effect in terms of freedom from distant recurrence (DRFI), invasive disease-free survival (IDFS), freedom from distant or loco-regional recurrence (RFI) and overall survival (OS), at 5 years and at 9 years. Results at 9 years are shown in Table 2.

When including all four RS and treatment groups (randomised and non-randomised), there were significant differences in the rates of IDFS, recurrence, and death (P<0.001), driven largely by the higher likelihood of having an event in the cohort with RS 26+ (data not shown in this document).

Table 2: Main results

RS score	9yr (ITT)				9yr (as-treated)
	ET	ET+CT	Abs diff	HR (95% CI), p-value	HR (95% CI), p-value
Freedom from distant recurrence (DRFI) (%)					
0-10	96.8				
11-25	94.5	95.0	0.5%	1.10 (0.85 to 1.41), p=0.48	1.03 (0.80 to 1.33), p=0.81
26+		86.8			
Invasive disease-free survival (IDFS) (%)					
0-10	84.0				
11-25	83.3	84.3	1.0%	1.08 (0.94 to 1.24), p=0.26	1.14 (0.99 to 1.31), p=0.06
26+		75.7			
Freedom from distant or loco-regional recurrence (RFI) (%)					
0-10	95.0				
11-25	92.2	92.9	0.7%	1.11 (0.90 to 1.37), p=0.33	1.12 (0.91 to 1.38), p=0.28
26+		84.8			
Overall survival (OS) (%)					
0-10	93.7				
11-25	93.9	93.8	-0.1%	0.99 (0.79 to 1.22), p=0.89	0.97 (0.78 to 1.21), p=0.78
26+		89.3			

Prognostic ability of RS within the RS 11-25 subgroup
Distant recurrence was associated with RS as a continuous variable between RS 11 and 25 (no other information reported; not stated whether this is across patients receiving any treatment or separately for those receiving endocrine or chemo-endocrine therapy).

Differences in chemotherapy effect within subgroups

Differences in chemotherapy effect by RS subgroup: There was a significant effect of chemotherapy (vs. endocrine therapy alone) in the highest RS group for 9yr IDFS (RS 21-25; Figure 1). There was no significant effect of chemotherapy for DFRI or RFI in any RS subgroup. There may be a non-significant trend for greater chemotherapy effect with greater RS.

However, there were **no** significant interactions between **chemotherapy** treatment and **recurrence score** within the RS 11-25 range. (This was compared between RS 11 to 15 vs. 16 to 20 vs. 21 to 25 subgroups, and also between 11 to 17 vs. 18 to 25 subgroups.) In other words, the effect of chemotherapy (vs. endocrine therapy alone) did not differ significantly between RS subgroups.

These results are only for the RS 11-25 range. Chemotherapy effect could not be assessed for patients outside this range as they were not randomised.

Figure 1: Effect of chemotherapy by RS subgroup (within RS 11-25) (hazard ratios)

DRFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

IDFS (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

RFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

Differences in chemotherapy effect by age: Chemotherapy (vs. endocrine therapy alone) showed a significant effect in patients aged ≤50 years for RFI and IDFS; this was borderline non-significant for DRFI (Figure 2). There **was** a significant interaction between **chemotherapy** treatment and **age** for IDFS (p=0.03) and RFI (p=0.02) but not DRFI (p=0.12).

Figure 2: Effect of chemotherapy by age (within RS 11-25) (hazard ratios)

DRFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

IDFS (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

RFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

Differences in chemotherapy effect by other factors: There were no significant interactions between chemotherapy treatment and the following: tumour size, grade, clinical risk, menopausal status. However, pre-menopausal patients showed a trend towards greater chemotherapy effect than post-menopausal patients (data not shown in this document).

Differences in chemotherapy effect by age and RS subgroup: In women aged ≤50 years, chemotherapy had a significant effect for RS 21-25 for all three outcomes reported (Figure 3); a significant effect for RS 16-20 for IDFS and RFI (but not DRFI), but no significant effect for RS 11-15 on any outcome. Effects for overall survival were stated to be similar (no data reported).

In terms of statistical interactions, the effect of chemotherapy varied significantly between the nine combinations of age and RS group for IDFS (p=0.004) but not for DRFI or RFI (p=not reported). For the age ≤50 group alone, it is not reported whether there was a significant interaction between chemotherapy treatment and RS subgroup.

These results suggest that for the age ≤50 subgroup (which was the only age group showing a significant effect of chemotherapy), there was some evidence for a difference in chemotherapy effect between RS subgroups within the RS 11-25 range, but this was not conclusive. Chemotherapy effect could not be assessed for patients outside the 11-25 range as they were not randomised.

For the age older than 50 subgroup, the majority of patients showed little effect of chemotherapy; however those with age 51-65 and RS 21-25 had HR for chemo of 1.38 (0.94 to 2.03) for IDFS (not statistically significant, but point estimate HR above the non-inferiority margin).

Figure 3: Effect of chemotherapy by age and RS group (within RS 11-25) (hazard ratios)

DRFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

IDFS (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

RFI (9yr, ITT)
Figure removed for copyright but data can be found in Sparano et al. 2018.[1]

Differences in chemotherapy effect by menopausal status and RS subgroup:

Within pre-menopausal patients (who showed a trend towards greater chemotherapy effect than post-menopausal patients), chemotherapy effect was significant for RS 21-25 only (for DRFI and RFI); however for IDFS the chemotherapy effect was greater for RS 16-20 (data not shown within this document).

In terms of statistical interactions, effect of chemotherapy varied significantly over the six combinations of menopausal status and RS category for IDFS (p=0.02) but not for DRFI or RFI (p-not reported).

These results suggest that for the premenopausal subgroup, there was some evidence for a difference in chemotherapy effect between RS subgroups within the RS 11-25 range, but this was not conclusive.

[1] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018. doi: 10.1056/NEJMoa1804710.