Serum cytokine levels in breast cancer patients during neoadjuvant treatment with bevacizumab

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Abstract

A high concentration of circulating vascular endothelial growth factor (VEGF) in cancer patients is associated with an aggressive tumor phenotype. Here, serum levels of 27 cytokines and blood cell counts were assayed in breast cancer patients receiving neoadjuvant chemotherapy with or without bevacizumab (Bev) in a randomized cohort of 132 patients with non-metastatic HER2-negative tumors. Cytokine levels were determined prior to treatment and at various time-points. The cytotoxic chemotherapy regimen of fluorouracil, epirubicin, and cyclophosphamide (FEC) had a profound impact on both circulating white blood cells and circulating cytokine levels. At the end of FEC treatment, the global decrease in cytokine levels correlated with the drop in white blood cell counts and was significantly greater in the patients of the Bev arm for cytokines, such as VEGF-A, IL-12, IP-10 and IL-10. Among patients who received Bev, those with pathological complete response (pCR) exhibited significantly lower levels of VEGF-A, IFN-γ, TNF-α and IL-4 than patients without pCR. This effect was not observed in the chemotherapy-only arm. Certain circulating cytokine profiles were found to correlate with different immune cell types at the tumor site in the patients. In the patients from the Bev arm, the serum cytokine levels correlated with higher levels of cytotoxic T cells at the end of the therapy regimen, and were indicative of treatment response. The higher response rate for Bev-treated patients and stronger correlations between serum cytokine levels and infiltrating CD8 T cells merits further investigation.

Introduction

The tumor microenvironment considerably influences tumor progression and clinical outcome.¹ Immune cell infiltration has also been associated with disease progression, estrogen receptor (ER) activity, and genomic complexity in breast cancer patients.² We and others have further demonstrated that immune responses in breast adenocarcinoma and adjacent normal tissue are dependent on patient age and estrogen availability.³ Characterizing the relationship between a tumor and its microenvironment could increase our understanding of various cancers and their pathogenesis.⁴

Analyses of interactions between tumor cells and the immune system may have prognostic value in the assessment of patient survival and treatment response.⁵ However, it remains challenging to accurately measure the extent of immune cell infiltration into a tumor. In addition, immune cells can mediate both pro-tumorigenic and anti-tumorigenic effects.^{6,7}

Factors secreted by stromal, immune, and/or tumor cells may affect the composition of a patient's serum. As such, these factors may represent interesting targets in the detection of cancers or in the monitoring of pathogenesis. Cytokines and chemokines are small molecules (10–30 kDa) which regulate the development, maturation, localization, interactions, activation, and life span of immune cells. Furthermore, cytokines play an essential role in regulating both adaptive and innate immunity. It was recently demonstrated that assays which facilitate a multiplex format and high-throughput analysis of cytokine concentrations in biomaterials, such as those that employ Luminex technology, can help monitor the immune system and provide exceptional insight into disease pathogenesis and immunity. ¹¹

Vascular endothelial growth factor type A (VEGF-A) is a key cytokine produced by both normal cells and tumor cells and it regulates angiogenesis, as well as vascular permeability, by

activating two receptors: VEGFR-1 and VEGFR-2.^{12, 13} Both receptors are present on the plasma membrane of endothelial cells and their expression is regulated by hypoxia.¹⁴

In the serum of cancer patients, including breast cancer patients, a marked increase in VEGF-A and its receptors' levels has been found to be an indicator of poor prognosis. ^{15, 16} Therefore, it has been proposed that targeting of VEGF-driven angiogenesis in combination with standard chemotherapy in a neoadjuvant setting may improve patients' prognosis. ¹⁷ Recently, two trials using Bev: MERiDiAN and GeparQuinto investigated whether plasma level of VEGF-A or SNPs may be predictive biomarkers for Bev efficacy in breast cancer. ^{18, 19} However, the overall benefit of such a combinatorial therapy has been difficult to interpret due to variability in patients' treatment response. ^{18, 20-23} For example, the NSABP B49 trial found that Bev significantly increased overall survival of patient with advanced HER2-non-amplified invasive breast adenocarcinoma. ²⁴ While, the GeparQuinto trial studies reported that for on HER2 negative breast tumors, Bev improved pCR but not disease-free survival. ²⁵⁻²⁷

Consequently, a defined need exists for the identification of markers which can help predict and improve our understanding of patient response to antiangiogenic therapy. It has been observed that antiangiogenic therapy affects the immune system and endothelial cell migration, 12,28 as well as plasma levels of cytokines, including IL-10 and transforming growth factor (TGF)- β . 28,29

In this study, we systematically assessed the levels of 27 cytokines/ chemokines in the serum of breast cancer patients in a randomized phase II neoadjuvant trial using Luminex technology. This trial compared response to treatment with chemotherapy in combination with or without Avastin (bevacizumab (Bev); Neo-Ava; ClinicalTrials.gov: NCT00773695).³⁰ Here, we measured serum cytokine levels at diagnosis, during surgery, and at key time points during each treatment course. These data were analyzed according to clinical parameters such as treatment

type and patient response. In addition, cytokine concentrations were correlated to the counts of circulating white blood cells (WBCs) and cells inferred to be infiltrating immune cells.

Results

Cytokine co-expression during therapy

Serum levels of 27 cytokines were measured in breast cancer patients at four time points during a neoadjuvant clinical trial (chemotherapy with or without Bev).

Initially, a co-expression analysis was performed on the measured cytokines. Correlation heatmaps for Spearman rank correlations were generated to visualize the degree of correlation at each time point (Figure 1). Independent of treatment arm, groups of cytokines were found to be highly correlated in the serum of breast cancer patients at each time point (Figure 1). Co-expression between cytokines may indicate a common role for these cytokines in regulating inflammatory and immune responses.

In the combination treatment arm (e.g. chemotherapy + Bev), the number of significant (Bonferroni corrected) correlations between the 27 cytokines decreased between screening: (n = 160) and 12 weeks (n = 128). Then in the Bev arm, the numbers of significant correlations gradually increased (12 weeks: 128, 25 weeks: 157, 31 weeks: 205). By week 25, 21 out of 27 cytokines were significantly correlated (Figure 1E). At week 31 (6 weeks after therapy), correlations among the 27 cytokines remained high in this arm (Figure 1G). These results indicate that Bev therapy may have profound effects on the immune system and cytokine levels.

In the chemotherapy-only arm, we observed a different behavior of cytokine correlations during treatment: the number of significant inter-correlations (Bonferroni corrected) increased from week 0 to week 12 (Figure 1, A and B; screening (n = 128), 12 weeks (n = 179) and then decreased between 12 (n = 179) and 25 weeks (n = 146). These results further suggest that remodeling of the immune system occurred in response to the cytotoxic effects of FEC therapy within the first 12 weeks of treatment and may be affected by addition of Bev.

Overall, the co-expression analysis of serum cytokine levels suggests that FEC treatment reshaped the immune response by the end of the 12-week treatment regimen. Furthermore, these effects were more prominent in the patient group receiving Bev, as demonstrated by the continuously increased cytokine co-expression up until week 31.

Changes in cytokine levels at two successive time points

To assess changes in cytokine levels according to chemotherapy type, differences between cytokine levels at two successive time points were examined (Figure 2 and Table 1).

Between the initial time point (screening) and 12 weeks after FEC \pm Bev, the levels of most of the cytokines examined decreased in both treatment arms. Most notably, when considering samples from both arms, IL-17A and PDGF-BB concentrations significantly decreased (P = 0.014 and P < 0.001 respectively; Figure 2A and Table 1). Levels of VEGF-A also decreased when considering samples from both arms (P = 0.022, Figure 2A and Table 1), yet this result is driven by the important decrease in VEGF-A in the combination (Bev) arm of treatment. In general, the decrease in cytokine levels after FEC administration may reflect a global loss of circulating leukocytes.

While the levels of most of the cytokines decreased in both treatment arms during the first treatment period (i.e. between 0 and 12 weeks), after treatment with taxane \pm Bev (between 12 and 25 weeks), PDGF-BB and IP-10 levels increased in both arms (P = 0.001 and P < 0.001 respectively; Figure 2B and Table 1). In addition, treatment-arm specific variations in cytokines levels were observed during the second treatment course.

Six weeks after the completion of neoadjuvant treatment (i.e. between weeks 25 and 31), the levels of IL-10 increased in both treatment arms (P = 0.055, Figure 2C and Table 1).

Blood cell counts during treatment

These initial results led us to hypothesize that the global decrease in serum cytokine levels observed at 12 weeks was due to the cytotoxic effects of FEC chemotherapy on immune cells. Hence, we assessed the changes in blood cell counts. Circulating WBCs and neutrophil counts significantly decreased between the initial screening and the end of therapy at 25 weeks (Figure 3, A and B, respectively). In contrast, platelet counts increased between week 0 and week 12, and then decreased between weeks 12 and 25 (Figure 3C). Similar observations were made when the patients were subdivided according to treatment arm or response to treatment (Supplementary Figure 2). To further investigate the relationship between circulating immune cells and serum cytokines, we correlated serum cytokine levels and blood cell counts across all patients within a treatment arm and at a given time point. At the initial screening, no or negative correlations were observed between cytokine levels and blood cell counts (Figure 3D). In contrast, significant positive correlations were observed between WBC and cytokine levels at 12 weeks in both treatment arms (Figure 3E), suggesting that the decrease in both WBC and cytokine levels between 0 and 12 weeks could be interrelated. After 25 weeks of treatment, different patterns of correlations between WBCs and cytokines were observed according to treatment arm, which suggests that a global depletion of WBCs because of FEC administration was followed by further reshaping of the immune response during taxane treatment.

Taken together, these results indicate that FEC chemotherapy drastically decreased the counts of circulating leukocytes in the cohort examined, affecting cytokine levels.

Effect of Bev on serum cytokine levels

We next wanted to test the hypothesis that Bev may induce specific changes in cytokine levels that reshape the immune system. Therefore, we further investigated the effects of Bev on cytokine levels (Table 2).

Administration of Bev was associated with a significant decrease in the levels of VEGF-A at 12 and 31 weeks (P < 0.001 and P = 0.008 respectively; Figure 4A and Table 2). A concomitant significant decrease in IL-12 levels was also observed (week12, P = 0.041, week 25, P = 0.002 and week 31, P = 0.01, Figure 4B and Table 2), suggesting that the decrease in VEGF-A may directly influence the level of IL-12. In addition, levels of IP-10 (CXCL10), a cytokine involved in the chemoattraction of monocytes/macrophages, cytotoxic T cells, natural killer (NK) cells, and dendritic cells, and levels of IL-10, an anti-inflammatory cytokine, both had significantly lower levels at week 25 in the serum of the patients treated with Bev compared to patients without Bev treatment (P = 0.023, Figure 4C; P = 0.028, Figure 4D respectively and Table 2). Lower serum levels of IL-4 and IL-5 were also detected during the treatment course of Bevtreated patients (ANOVA P = 0.013 and P = 0.033 respectively; Supplementary Figure 3 and Table 2).

Overall, these results indicate that combination therapy with Bev, in addition to the obligate decrease in VEGF-A serum levels can have important repercussions on systemic levels of other cytokines, which may be involved in angiogenesis and/or the immune response.

Bev, serum cytokine levels, and pCR

The addition of Bev to neoadjuvant treatment increased the fraction of patients exhibiting pCR from 12% to 26%. 30 In patients with pCR, a number of serum cytokines had lower global levels than those in non-PCR (ANOVA < 0.05, all time points considered together) (Table 3 and Supplementary Figure 4). When stratified by treatment arm the levels of six cytokines (VEGF-A, IL-17A, IFN- γ , TNF- α , IL-4, and IL-5) were globally lower in the serum of Bev-treated patients who responded to treatment (ANOVA < 0.05, Table 3, Figure 5 and Supplementary Figure 5). Moreover, the levels of these cytokines were predictive to response only in the Bev arm. Lower levels of VEGF-A in the serum of Bev-treated patients at week 12 after FEC were

associated with pCR (Figure 5B). Similarly, other cytokines exhibited a decrease in their levels at week 12 after FEC, and these included: IL-17A, an inducer of inflammatory and angiogenic growth factor production;³¹ INF- γ and TNF- α , markers of TH1 activity; and IL-4, a regulator of TH2 activity (Figure 5, D, F, H, and J). Furthermore, lower levels of TNF- α and IL-4 were detected at week 25 after taxane treatment (Figure 5, H and J).

These results indicate that several cytokines had serum levels that were associated with treatment response in the Bev-treated patients. Furthermore, lower levels of VEGF-A, and possibly other related cytokines, at week 12 (after a course of FEC) may predict treatment response in Bev-treated patients.

Effect of Bev on intratumoral immune infiltration and its correlation to circulating cytokine levels

To further investigate the possible mechanisms by which Bev, in combination with chemotherapy, could induce a better patient response by changes in cytokine levels, we assessed whether the observed changes in cytokine levels correlated with immune cell infiltration of tumors. Using expression data³⁰ and the algorithm, CIBERSORT, we inferred the extent of immune cell infiltration in the tumor at the initial screening and at weeks 12 and 25 in both treatment arms (Supplementary Table 3). CIBERSORT is able to predict the relative proportions of 22 types of immune cells by using a set of 547 reference gene expression values obtained from bulk tumor samples.³² We then assessed the correlations between the measured serum levels of the 27 cytokines and the relative immune cell infiltration at each time point with Spearman rank correlation heatmaps (Supplementary Figure 6).

At week 12, specific correlations appeared to differ between the treatment arms. For example, in the chemotherapy arm, a pattern of significant correlations between the cytokines examined and naïve CD4+ T cells as well as B cells naïve and memory was observed, whereas in the Bev

arms, most of the significant correlations identified were associated with the levels of M0 macrophages. On the overall, comparing the average of the significant correlations between the two arms remained insignificant (P = 0.31) at this time point (week 12).

At week 25, however, the correlation heatmaps greatly differed, the average of the significant correlations between the two treatment arms (P < 0.001), indicating that Bev therapy has a profound effect on the immune system and cytokine levels. Most notably only for the Bevtreated patients, increased correlations between several cytokines and CD8+ cytotoxic T cells or T follicular helper cells were observed (Supplementary Figure 6).

Considering the increased positive correlations observed between the cytokines examined and cytotoxic T cells or the negative correlations between cytokines and T follicular helper within the Bev-treated patients, we hypothesized that infiltration of cytotoxic T cells or T follicular helper cells may facilitate the treatment response in the Bev arm. Correspondingly, the Bev-treated patients that exhibited pCR had higher levels of cytotoxic T cells at weeks 12 and 25 at their tumor sites (P = 0.07 and P = 0.06, respectively; Figure 6A). Responders in the Bev arms also exhibited higher levels of T follicular helper cells at 25 weeks, which may also contribute to complete response (Figure 6B). Furthermore, at week 25, responders who received Bev, had their levels of INF- γ in their serum associated with higher infiltration in CD8 cytotoxic T cells as well as serum levels of IL-17A associated to higher infiltration of T follicular helper cells in their tumor (Figure 7).

Discussion

In the present cohort,³⁰ treatment with bevacizumab increased the number of patients with complete response in breast and axillary nodes from 8 patients (12%) to 15 patients (23%).³⁰ Results of the present study suggest that a certain threshold of VEGF-A inhibition in serum is necessary for Bev therapy to be effective in breast cancer (Figure 5B). For other types of cancer, such as small cell lung cancer, low serum levels of VEGF also correlated with better survival.³³ In addition, Hyodo et al. reported that gastrointestinal cancer patients with lower pretreatment plasma levels of VEGF exhibited better response to treatment.³⁴ The results of the present study further suggest that targeted depletion of VEGF-A by Bev influenced the serum levels of other cytokines, and a greater correlation was observed among cytokines in the Bev arm during the treatment course (Figure 1). Interestingly, low levels of TNF- α were also associated with treatment response in the Bev-treated patients. TNF- α induces VEGF-A production and can trigger metastasis through inflammatory pathways.^{35, 36} Further studies are needed to confirm these findings and to investigate a possible correlation.

In Silwal-Pandit et al, we reported the association of hormone receptor status (ER status) to pCR: Of the 132 patients, 23 (17%) achieved pCR. Among the estrogen receptor–positive patients, 11 of 54 (20%) treated with bevacizumab and chemotherapy achieved pCR, while in the arm treated with chemotherapy only 3 of 57 (5%) reached pCR.³⁰. We also recently showed that cytokine levels in the tumor interstitium were associated with breast tumor subtype,³⁷ it is therefore conceivable that ER status may influence the results described here. However, in the present study, there were only few ER negative samples, eight in the chemotherapy only arm and ten in the Bev arm, which did not allow to assess thoroughly the effect of the ER status on cytokine serum levels. The number of ER negative patients achieving pCR in each arm is even lower r and ER status specific analysis underpowered.

The levels of 27 cytokines in serum during neoadjuvant chemotherapy with or without concomitant bevacizumab are reported here. In the assessment of a breast cancer patient cohort randomized for chemotherapy with or without the humanized anti-VEGF monoclonal antibody, Bev, serum levels of VEGF-A were observed to decrease significantly following treatment with Bev. The decrease in circulating levels of VEGF-A was most significant after 12 weeks of FEC therapy and was most prominent in patients, which exhibited good treatment response. Moreover, these effects were sustained for at least six weeks after the therapy ended.

Levels of IL-12 also decreased in the Bev arm at weeks 12 and 25. IL-12 is mainly secreted by activated B cells, macrophages, and other antigen presenting cells of myeloid and lymphoid origin. Subsets of CD49d+ pro-inflammatory leukocytes also produce IL-12 and express both VEGFR1 and VEGFR2. Bev-induced depletion of VEGF-A may directly affect the function and production of such cells causing decreased production of IL-12. IL-12 can act as a suppressor of angiogenic activity of VEGF. In the present study, the patients exhibiting good response in the Bev arm concomitantly exhibited reductions in levels of IL-12, IFN- γ , and VEGF-A. These results suggest that the interaction of VEGF-A with IL-12 and IFN- γ , as well as their effect on IP-10 (CXCL10) should be examined in future studies of resistance to antiangiogenic treatment.

Levels of IL-17A and PDGF-BB were highly correlated in both treatment arms, and these correlations were stronger after the second line of treatment that combined taxane with Bev. IL-17A is a hallmark of Th17 immunoactivity and is a pro-inflammatory cytokine which triggers the release of inflammatory and angiogenic growth factors. 31, 35, 44 PDGF-BB has two subunits and binds to PDGF receptor beta to activate the mTOR/JAK/STAT pathway and initiate cell growth and proliferation. 45, 46 Here, FEC affected the levels of both inflammatory cytokines and growth factors concomitant with significant reductions in blood levels of IL-17A and PDGF-BB. High levels of IL-17A have previously been associated with resistance to anti-

VEGF therapy,⁴⁷ with induction of VEGF-A production³⁵ leading to induction of PDGF-BB, and both molecules synergistically promoting neo-angiogenesis.^{31, 48, 49} In the present study, patients achieving pCR in the Bev arm had significantly lower serum levels of IL-17A at 12 weeks after FEC administration, and these levels remained lower up to 31 weeks after the start of treatment. These results indicate that counteracting the effects of IL-17A during antiangiogenesis therapy may also increase treatment response.

The serum levels of PDGF-BB, IL-17A, and IP-10, which decreased at week 12 (Figure 2A) were increased again at week 25 (Figure 2B, marked with *). IP-10 recruits cytotoxic T cells and NK cells, which express a receptor for IP-10, CXCR3.⁵⁰⁻⁵³ Therefore, the induction of higher levels of IP-10 may account for the observed increase in levels of CD8+ T cells that were found in the Bev-responsive tumors.

Paclitaxel, the chemotherapy used in the second stage of treatment in this study, has been shown to inhibit mitosis by affecting microtubule dynamics.⁵⁴ The administration of taxane has also been reported to increase T-cell blastogenesis and NK cell cytotoxicity.⁵⁵ Consistent with the present findings, another study recently reported that paclitaxel upregulates IP-10.⁵⁶ Based on these observations, it is possible that higher levels of inflammatory cytokines and greater NK cell invasion as a result of taxane administration may result in greater immune related toxicity/ adverse events.⁵⁵⁻⁵⁷

TH2 related cytokines stimulate antibody production and may also activate eosinophils and inhibit macrophages.⁵⁸ In the current study, the TH2 related cytokines, IL-4 and IL-5, remained at stable levels or were present at lower levels after treatment with taxane in the Bev arm. It has been hypothesized that a TH2 dominant immune response at a tumor site can stop tumor rejection and/or promote factors involved in tumor recurrence.⁵⁹ Consistent with this concept, a decrease in IL-4 and IL-5 levels was observed in the serum of patients achieving pCR.

IFN-γ and TNF-α polarize mesenchyme stromal cells into TH1 type cells.⁶⁰ In addition, IFN-γ enhances IL-12 expression, and vice versa.⁵⁸ Lower levels of IL-12 between weeks 12 and 25 affected IFN-γ production by TH1, and this correlation continued to be observed up to week 31. TH1 cells activate macrophages and phagocytes, and these interactions mediate phagocyte-dependent immune responses.⁶¹ Consequently, it is hypothesized that TH1-mediated immunity leads to tumor rejection.⁵⁹

The results of the present study suggest that cytotoxic therapy radically affects WBC counts, and this facilitates a remodeling of the immune system to enhance treatment response by an increase in cytotoxic T cell infiltration to a tumor site. The current assessment further demonstrates that complex interactions within the immune system may influence the levels of various cytokines. It is important to recognize that the pro-inflammatory agents and growth factors that were examined in this study may be produced by epithelial, endothelial, stromal, and/or hematopoietic cells, as well as by cancers cells. Additional studies are needed to understand the interactions between the cytokines examined, especially regarding the interplay between IL-12 and VEGF-A which was identified in this study.

In the present cohort, the administration of bevacizumab in combination with chemotherapy suppressed levels of VEGF-A as well as levels of functionally related cytokines, particularly IL-12. Furthermore, patients who achieved pCR in the Bev treatment arm had lower serum concentrations of VEGF-A, as well as lower serum concentrations of cytokines previously shown to regulate adaptive immunity, including IFN-γ, TNF-α, IL-4, and IP-10. In contrast, expression data indicated an increase in CD8 T cells at the tumor site.,Here we demonstrate the potential for cytokine level monitoring during treatment to contribute to treatment decisions in breast cancer. These results will require confirmation in a separate cohort of patients in another clinical trial.

Materials and methods

Patient material

Patients with large primary breast tumors (≥ 2.5 cm) (T2–T4) were recruited between November 2008 and July 2012 at Oslo University Hospital or St. Olav's Hospital, Trondheim. The few patients who received hormonal therapy in the trial were excluded from this sub-study. The trial was approved by our institutional protocol review board, the regional ethics committee, the Norwegian Medicines Agency, and carried out in accordance with the Declaration of Helsinki, International Conference on Harmony/Good Clinical practice. The study is registered at http://www.ClinicalTrials.gov/ database with the identifier NCT00773695. Available blood/ serum samples were collected: prior to treatment (screening: SC, week 0), after 4 cycles of FEC regimen (at 12 weeks from the beginning of chemotherapy), after subsequent 4 cycles of taxane therapy (week 25 from start of chemotherapy) and at 6 weeks after the end of chemotherapy (week 31, also corresponding to the time of surgery). WBC, neutrophil, and platelet counts were recorded at the same time points at week 0, 12 and 25.

A block randomization procedure was used, and the randomization was performed by the centralized research support facility at Oslo University Hospital. The randomization list was not known to the personnel responsible for providing information or treatment to the patients. The patients were stratified based on their tumor size $(2.5 \le T \le 5 \text{ cm}, T > 5 \text{ cm})$ and hormone receptor status (positive for estrogen (ER), progesterone, or both), and randomized 1:1 to receive bevacizumab and chemotherapy (combination-therapy arm) or chemotherapy alone (chemotherapy arm). Of the 138 patients treated with chemotherapy, 66 in each group were included in the primary efficacy analysis.³⁰ The findings and results for pCR relative to hormonal status are included in the recent study, and therefore not included here.³⁰

Treatment

A total of 132 breast cancer cases were included in the trial, of these, serum was available for 98 patients. Patients were randomized to treatment with (n = 50) or without Bev (n = 48), Supplementary Table 1. Between 0 and 12 weeks, patients received chemotherapy: 5fluorouracil (FEC; 600 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (600 mg/m²) three times (every third week). Over the next 12 weeks, patients received taxane (100 mg/m² docetaxel every third week or 80 mg/m² paclitaxel weekly). Response to treatment was evaluated at time of surgery based on a histopathological assessment of the remaining tumor. Pathological complete response (pCR), herein defined as complete eradication of all invasive cancer cells in both breast and axillary lymph nodes (at time of surgery), was the primary end point. Patients were then categorized as pathological complete responders (pCR) (n = 20), incomplete responders or non-responders (No-pCR) (n = 78). Of the 20 complete responders, 14 were in the Bev arm. Of the 78 non-responders, 36 were in the Bev arm and 42 in the Chemo arm. Tumor measurement prior to treatment was determined based on magnetic resonance imaging, ultrasound, and mammography, MR measurements were used if available for the patient, and otherwise the largest measurement of either mammography or ultrasound were recorded and used.

Granulocyte colony-stimulating factor (G-CSF; 6 mg/dose) was administered to 33 patients (Supplementary Table 1) suffering from neutropenia during the first 12 weeks of therapy, with by mean 3–4 injections performed over these 12-weeks period. Detailed treatment information, side effects, and response have previously been published.³⁰ Since G-CSF was administered mostly between 0 and 12 weeks, specific changes in cytokine levels induced by G-CSF were monitored at the start and end of the 12-week period (Supplementary Figure 1). No significant changes in cytokine levels were detected between the groups of patients receiving G-CSF.

However, as some patients received G-CSF the results concerning G-CSF are only discussed here.

Cytokine measurements

A total of 27 molecules (Supplementary Table 2), including interleukins, chemokines, growth factors, interferon (IFN), and tumor necrosis factor (TNF), were measured in a 27-plex commercially available cytokine panel from Bio-Rad and were analyzed with the Luminex xMAP 200 platform. The assays included a series of known concentrations to generate standard curves. The results obtained were collected and processed with Bio-Plex Manager 6.0 (Bio-Rad). Supplementary Table 2 lists the log transformed cytokine levels for all of the patients examined at all of the time points assayed.

Inferred infiltrating immune cells

Normalized gene expression data³⁰ was available for 132 patients from the NeoAva trial, of whom 88 patients had also serum cytokine levels. These were used to infer the relative proportions of 22 types of infiltrating immune cells using CIBERSORT, a deconvolution algorithm that uses a set of reference gene expression values (547 genes) to predict 22 immune cell type proportions from bulk tumor sample expression data by using support vector regression.³² To assess the reliability of the deconvolution method, CIBERSORT derives a P-value for each sample. Gene expression datasets were uploaded to the CIBERSORT web portal [http://cibersort.stanford.edu/] and an analysis was performed by using the default signature matrix at 1000 permutations. Output of this CIBERSORT analysis is provided in Supplementary Table 3.

Statistical analysis

Statistical analyses done (after natural log transformations of cytokines levels) were performed with IBM SPSS Statistics 22 or R version 3.3.2. Three-way analysis of variance (ANOVA) was performed with time points, treatment arm, and treatment response as factors to identify cytokines with global significant differences in log cytokine expression levels for any of the factors (the results are repeatedly shown in Table 1–3, respectively, to highlight that only cytokines with global significant differences according to the three-way ANOVA are considered further in post-hoc and sub-group analyses). P-values were adjusted for multiple testing by controlling the false discovery rate (FDR) according to the method of Benjamini-Hochberg.⁶² FDR-corrected p-values less than 0.1 were considered significant.

Following the global three-way ANOVA, individual factors were further analyzed with ANOVA analyses - followed by t-tests for sub-group analyses and for post-hoc two-group comparisons (if appropriate) corrected for multiple testing by Bonferroni - to investigate significant global differences in cytokine levels: (i) between all four time-points (one-way ANOVA; Table 1), (ii) between the two arms of treatment at all four time-points (two-way ANOVA; Table 2), and (iii) according to pCR versus non-pCR for the patients in each arm at four time-points (ANOVA followed by t-test for each time point separately; Table 3).

Spearman rank correlations among the cytokine expression levels were assessed with R and were visualized with the corrplot package version 0.84. Spearman rank correlations between cytokine levels and circulating or infiltrating immune cells were assessed by using R and heatmap (pheatmap package version 1.08) or corrplot packages, respectively.

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Figures legends

Figure 1: Co-expression of 27 cytokines in the serum of breast cancer patients during therapy. Correlation heatmaps assess the strength of correlation between the 27 cytokines measured by the Luminex assay. Correlations are assessed by Spearman rank test, only significant correlations (Bonferroni corrected P < 0.05) are shown. An initial correlation heatmap included cytokine levels is shown for all samples at screening (A, n = 88). Both arms of the randomized control trial are represented: left panel: chemotherapy, right panel: Combination (+ Bev) arm at the different time points of measurement, (A, week zero) pretreatment; (B & C, week 12, n = 41 and 44) after FEC therapy; (D & E, week 25, n = 40 and 40) after taxane; and (F & G, week 31, n = 45 and 45) six weeks after surgery.

Figure 2: Changes in serum cytokine levels between two consecutive time points. Differences in cytokine levels between two successive time points are presented as barplots in both treatment arms, (A) Differences between 0 and 12 weeks, n = 85, (B) between 12 and 25 weeks n = 80, (C) between 25 and 31 weeks, n = 80. Error bars represent \pm 1 standard deviation. * P < 0.05 (FDR adjusted P < 0.1), t-test showing significant differences of cytokine levels between two time points independently of the treatment arm.

Figure 3: Effects of treatments on blood cell counts and correlation with cytokines levels. Comparison of the blood cell counts (10^9 per liter): white blood cells (WBC, A), neutrophils (Neutro, B) and platelets (C), at the different time points of treatment. * indicates t-test P < 0.01 between two successive time points, error bars represent standard deviation. Heatmap showing Spearman rank correlations between cytokine levels and blood cell counts at screening n = 98, (D), 12 weeks, (n = 44, Bev; n = 41, Chemo) (E) and 25 weeks (n = 40, Bev; n = 40, Chemo) (F). All correlations are shown independently of p values. Heatmaps were obtained using the pheatmap R package.

Figure 4: Effect of Bevacizumab on serum cytokines levels. Cytokine serum levels were assessed in the two treatment arms: chemotherapy (blue), chemotherapy + Bev (green), and at four different time points, 0, 12, 25 and 31 weeks. To find the most relevant and significant differences between the two arms, we first tested for global differences using ANOVA (Table 2), and only for the significant values that also showed a significant result in the global three-way ANOVA (FDR-adjusted P < 0.1) (and TNF-alpha) further tested for significant difference at each time point were sought using t-test. For (A) VEGF-A, (B) IL-12, (C) IP-10, and (D) IL-10, we found a global difference between their levels when comparing the two arms (ANOVA P < 0.05) and further identified significant differences at the indicated time points: *P < 0.05, **P < 0.01, ***P < 0.001. Error bars represent ± 1 standard deviation.

Figure 5: Cytokine levels associated with pathological complete response. Cytokine levels were assessed in the patients with pathological complete response in both treatment arms: chemotherapy (left panel) and combination arm (right panel). To find the most relevant and significant differences between responders and non-responders, we first tested for global differences using ANOVA (Table 3) and only for the significant values (ANOVA P < 0.05) that also showed a significant result in the global three-way ANOVA (FDR-adjusted P < 0.1) (and TNF-alpha), we further tested for significant difference at each time point using t-test. (A & B) VEGF-A, (C & D) IFN- γ , (E & F) TNF- α and (G & H) IL4, we found a global difference between responders and non-responders in the combination arm (ANOVA P < 0.05) and further identified significant differences at the indicated time points. * P < 0.05, ** P < 0.01. Error bars represent \pm 1 standard deviation.

Figure 6: Levels of CD8 T and T follicular helper cells according to response and treatment. Levels of infiltrating CD8 T cells and T follicular helper cells were inferred using CIBERSORT and expression levels. In both treatment arms levels of CD8 T cells and T follicular helper are plotted at the different time points (screening, 12 and 25 weeks). The global

levels of CD8 and follicular T cells appeared significantly different only in the combination (+Bev) arm $(ANOVA\ P < 0.001\ in\ both\ cases)$.

Figure 7: Levels of CD8 T cells and T follicular helper cells according in relation to levels of INF- γ and IL-17A. Levels of infiltrating CD8 T cells and T follicular helper cells inferred using CIBERSORT and expression levels were analyzed in regard to the circulating levels of INF- γ and IL-17A respectively. In each treatment arm, we divided patients for having low or high levels of circulating cytokines according to the median level of cytokine and further assessed for differences in infiltrating CD8 T or T follicular helper cells. Only significant Students t-test p-values (P < 0.05) are depicted.

Supplementary Figure legends

Supplementary Figure 1: G-CSF induced changes in serum cytokine levels. Changes in cytokine levels induced by G-CSF between screening (week 0) and week 12. Differences in cytokine levels between these two time points are shown in barplots in the two group of patients which have received G-CSF (n = 33, purple bars) or not (n = 65, gray bars). Error bars represent ± 1 standard deviation.

Supplementary Figure 2: Effects of treatments on blood cell counts. Blood cell counts (10^9 per liter) white blood cells (A), neutrophils (B) and (C) are shown at the different time points for the different groups of patients receiving or not Bev and responding (pathological complete response, pCR) or not to treatment. * indicates t-test P < 0.01, error bars represent \pm 1 standard deviation.

Supplementary Figure 3: Effect of Bevacizumab on global serum cytokines levels. Cytokine serum levels were assessed in the two treatment arms: chemotherapy (blue), chemotherapy + Bev (green), at four different time points, 0, 12, 25 and 31 weeks. For IL4 (A) and IL5 (B) despite no significant difference at each time point, a global difference was observed when comparing all time points using ANOVA (Table 2). Error bars represent ± 1 standard deviation.

Supplementary Figure 4: Cytokines levels associated with response. Cytokines levels were assessed in perspective of pathological complete response in all patients. Response to treatment was evaluated at week 25 by pathological assessment of the remaining tumor; and patients were categorized as pathological complete responders when more than 90% of the tumor was eradicated (pCR), incomplete responders or not responders in the other case (No-pCR). To find the most relevant and significant differences between responders and non-responders, we first

tested for global differences using ANOVA (Table 3) and only for the significant values (ANOVA P < 0.05), that also showed a significant result in the global three-way ANOVA (FDR-adjusted P < 0.1) (and TNF-alpha)), we further tested for significant difference at each time point using t-test. (A) VEGF-A, (B) IL-12, (C) IFN- γ , (D) G-CSF, (E) TNF- α , (F) IL-10, (G) IP-10, (H) IL-17A, (I) IL-4 and (J) IL-5. * P < 0.05, ** P < 0.01. Error bars represent ± 1 standard deviation.

Supplementary Figure 5: Global serum cytokines levels associated with pathological complete response. Cytokine levels were assessed in patients with pathological complete response in both treatment arms: chemotherapy (left panel) and combination arm (right panel). To find the most relevant and significant differences between responders and non-responders, we first tested for global differences using ANOVA (Table 3) and only for the significant values (ANOVA P < 0.05), we further tested for significant difference at each time point using t-test. For IL-5 and IL-17A no significant difference was observed at any time point, but a global difference was observed when comparing all time points using ANOVA. (A & B) IL-5 and (C & D) IL-17A. * P < 0.05, ANOVA. Error bars represent ± 1 standard deviation.

Supplementary Figure 6: Correlations between cytokine levels and infiltrating immune cells. CIBERSORT and expression data were used to infer for the presence of 22 different immune cell types at the tumor sites. Correlation heatmaps depict the significant correlations (FDR-adjusted P < 0.2) between cytokine levels and infiltrating immune cells at screening (n = 88) at 12 weeks (Bev, n = 36 and Chemo, n = 38) and 25 weeks (Bev, n = 33 and Chemo, n = 32).

Figures and tables

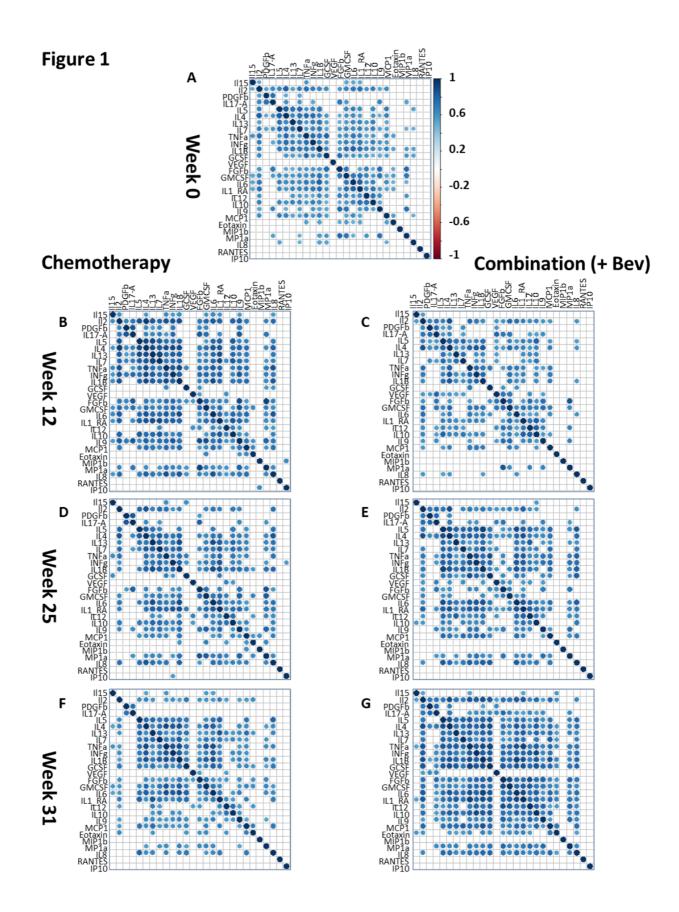


Figure 2

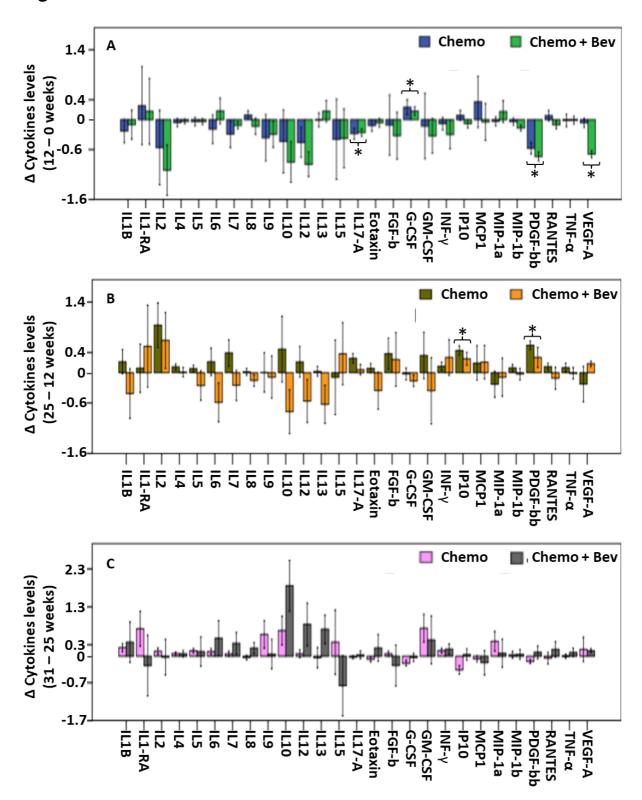


Figure 3

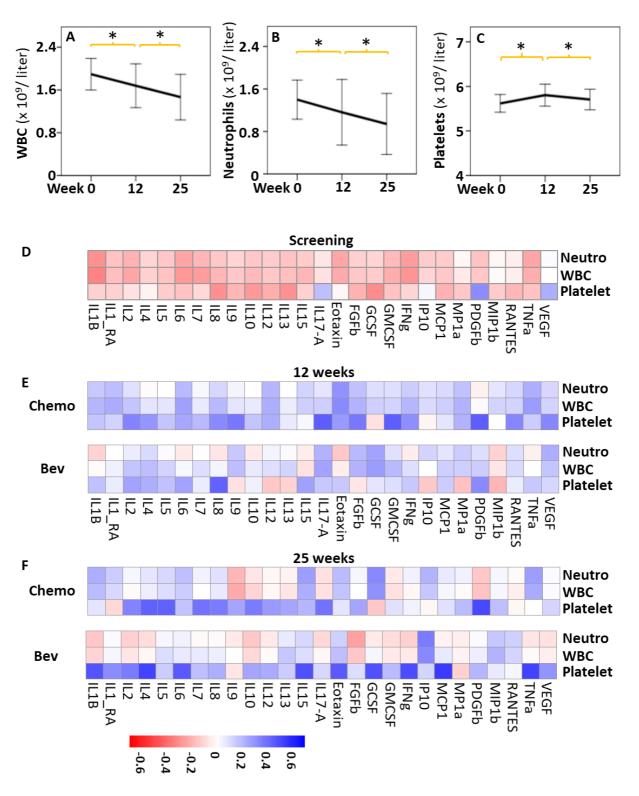


Figure 4

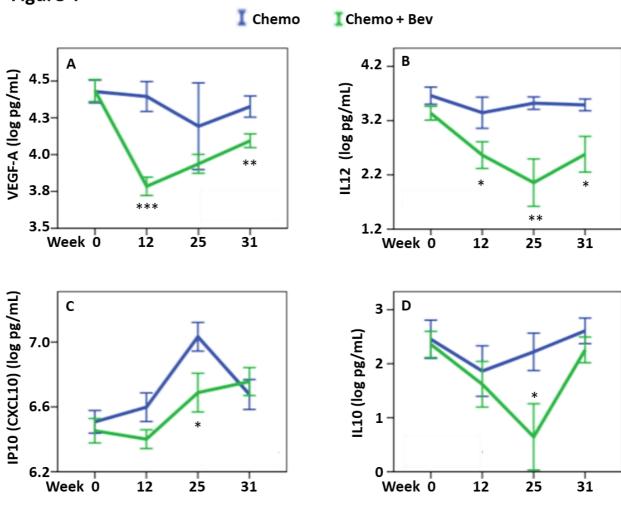
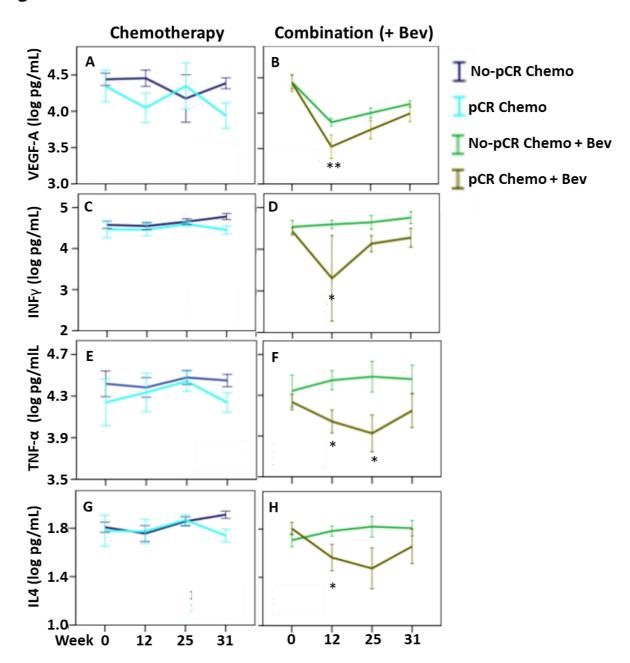
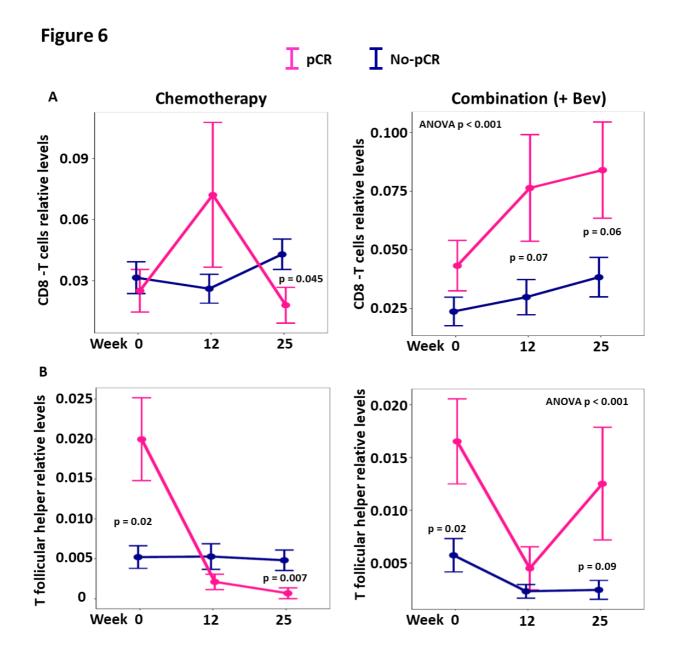


Figure 5





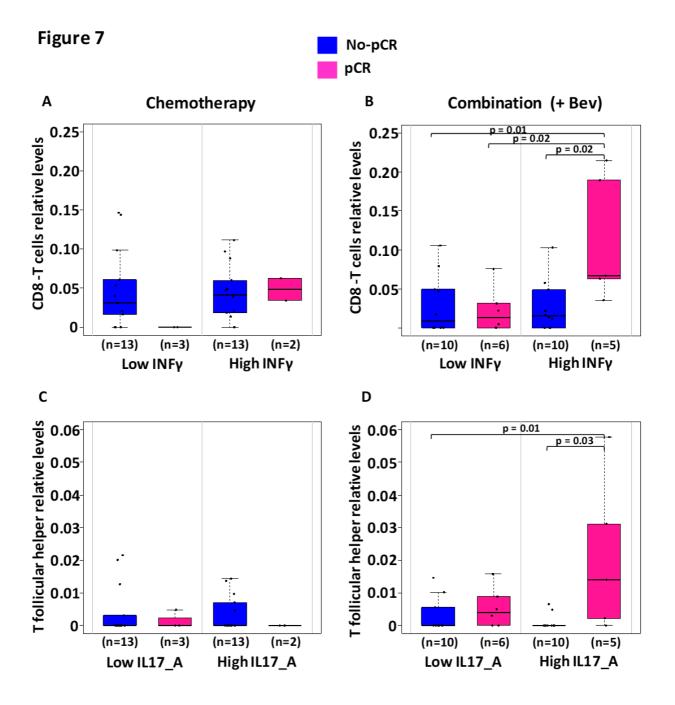


Table 1: One-way ANOVA to compare log cytokine levels between time points of treatment, independent of treatment arm (F-tests).

Cytokines with FDR-adjusted p-value<0.1 in the global three-way ANOVA with time points, treatment arm and treatment response as factors (and TNF-alpha in addition) are highlighted. Only these highlighted cytokines are investigated further in post-hoc tests, if the ANOVA F-test was significant (p<0.05).

Cytokines	ANOVA p-value	Po	st-hoc p-values) *	Global tl	nree-way ANOVA
Cytokines	ANOVA p-value	0 to 12W	12 to 25W	25 to 31W	Raw p-value ^a	FDR-adjusted p-value ^b
IL1B	0,843				0,503	0,679
IL1-RA	0,792				0,539	0,693
IL2	0,115				0,062	0,152
IL4	0,373				0,025	0,075
IL5	0,79				0,013	0,044
IL6	0,856				0,716	0,773
IL7	0,388				0,079	0,178
IL8	0,819				0,487	0,679
IL9	0,722				0,343	0,579
IL10	0,018	0,472	1	0,055	0,006	0,023
IL12 (P70)	0,042	0,16	1	1	<0.001	<0.001
IL13	0,327				0,255	0,492
IL15	0,983				0,955	0,955
IL17-A	0,024	0,014	0,356	1	0,037	0,1
Eotaxin (CCL11)	0,666				0,131	0,272
FGF-basic	0,657				0,485	0,679
G-CSF (CSF3)	0,002	0,014	1	0,299	0,004	0,022
GM-CSF (CSF2)	0,806				0,649	0,762
IFN-gamma	0,207				0,006	0,023
IP10 (CXCL10)	<0.001	1	<0.001	0,598	<0.001	<0.001
MCP-1 (CCL2)	0,451				0,627	0,762
MIP-1a (CCL3)	0,676				0,317	0,571
MIP-lb (CCL4)	0,445				0,706	0,773
PDGF-bb	<0.001	<0.001	0,001	1	<0.001	<0.001
RANTES (CCL5)	0,784				0,931	0,955
TNF-alpha	0,94				0,447	0,679
VEGF-A	0,009	0,022	1	1	0,003	0,02

^{*} Post-hoc t-tests for pairwise comparisons with multiple testing adjusted by Bonferroni; performed only if ANOVA P<0.05 (and if global three-way ANOVA FDR-adjusted p<0.1, or if TNF-alpha). W=week

a Global F-test in three-way ANOVA with treatment (2 levels), timepoint (4 levels) and treatment response (2 levels) as fixed factors

b FDR-adjustment with the method of Benjamini-Hochberg.

Table 2: Table 1: Two-way ANOVA to compare log cytokine levels between the two arms of treatment across all four time-points (F-tests).

Cytokines with FDR-adjusted p-value<0.1 in the global three-way ANOVA with time points, treatment arm and treatment response as factors (and TNF-alpha in addition) are highlighted. Only these highlighted cytokines are investigated further in subgroup analyses, if the ANOVA F-test

was significant (p<0.05).

Cytokines	ANOVA P-value		Sugroup	p-values*	Global three-way ANOVA						
Cytokines	ANOVA F-Value	0W	12W	25W	31W	Raw p-value ^a	FDR-adjusted p-value ^b				
IL1B	0,008					0,503	0,679				
IL1-RA	0,424					0,539	0,693				
IL2	0,241					0,062	0,152				
IL4	0,013	0,86	0,72	0,108	0,131	0,025	0,075				
IL5	0,033	0,85	0,687	0,15	0,179	0,013	0,044				
IL6	0,256					0,716	0,773				
IL7	0,039					0,079	0,178				
IL8	0,625					0,487	0,679				
IL9	0,624					0,343	0,579				
IL10	0,046	0,95	0,487	0,028	0,297	0,006	0,023				
IL12 (P70)	<0.001	0,11	0,041	0,002	0,01	<0.001	<0.001				
IL13	0,009					0,255	0,492				
IL15	0,703					0,955	0,955				
IL17-A	0,113					0,037	0,1				
Eotaxin (CCL11)	0,609					0,131	0,272				
FGF-basic	0,178					0,485	0,679				
G-CSF (CSF3)	0,003	0,6	0,364	0,027	0,255	0,004	0,022				
GM-CSF (CSF2)	0,17					0,649	0,762				
IFN-gamma	0,134					0,006	0,023				
IP10 (CXCL10)	0,042	0,51	0,063	0,023	0,53	<0.001	<0.001				
MCP-1 (CCL2)	0,504					0,627	0,762				
MIP-1a (CCL3)	0,005					0,317	0,571				
MIP-lb (CCL4)	0,265					0,706	0,773				
PDGF-bb	0,781					<0.001	<0.001				
RANTES (CCL5)	0,245					0,931	0,955				
TNF-alpha	0,271					0,447	0,679				
VEGF-A	0,002	0,99	<0.001	0,4	0,008	0,003	0,02				

^{*} Subgroup t-tests for comparisons between treatment arms at each time point; performed only if ANOVA P<0.05 (and if global three-way ANOVA FDR-adjusted p<0.1, or if TNF-alpha). W=week

b FDR-adjustment with the method of Benjamini-Hochberg.

a Global F-test in three-way ANOVA with treatment (2 levels), timepoint (4 levels) and treatment response (2 levels) as fixed factors

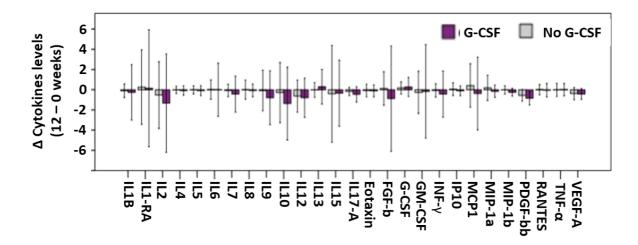
Table 3: ANOVA to compare log cytokine levels between pathological complete response (pCR) groups, for both treatment arms, as well as within each arm separately, across four time-points. Cytokines with FDR-adjusted p-value<0.1 in the global three-way ANOVA with time points, treatment arm and treatment response as factors (and TNF-alpha in addition) are highlighted. Only these highlighted cytokines are investigated further in subgroup and post-hoc tests, if the ANOVA F-test for pCR in both arms was significant (p<0.05).

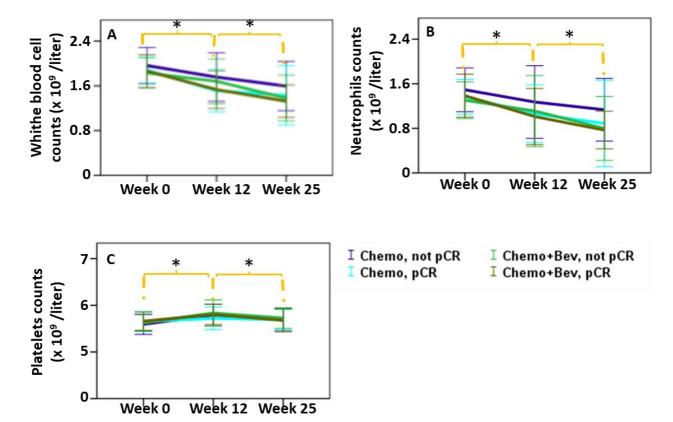
Ostablassa	ANOVA P-value	ANOVA pCR	P	ost-hoc	p-values	s*	ANOVA pCR Combination	Po	ost-hoc _l	o-values	*	Global three way ANOVA		
Cytokines	pCR in both arms	Chemotherapy- only arm	0W	12W	25W	31W	(+Bev) arm	0W	12W	25W	31W	Raw p-value ^a	FDR-adjusted p-value ^b	
IL1B	0,044											0,503	0,679	
IL1-RA	0,077											0,539	0,693	
IL2	0,109											0,062	0,152	
IL4	0,003	0,402					0,021	0,3	0,028	0,053	0,27	0,025	0,075	
IL5	0,001	0,205					0,012	0,6	0,151	0,055	0,14	0,013	0,044	
IL6	0,137											0,716	0,773	
IL7	0,072											0,079	0,178	
IL8	0,136											0,487	0,679	
IL9	0,13											0,343	0,579	
IL10	0,039	0,405					0,31					0,006	0,023	
IL12 (P70)	<0.001	0,202					0,45					<0.001	<0.001	
IL13	0,059											0,255	0,492	
IL15	0,569											0,955	0,955	
IL17-A	0,031	0,539					0,022	0,7	0,067	0,19	0,12	0,037	0,1	
Eotaxin (CCL11)	0,034											0,131	0,272	
FGF-basic	0,093											0,485	0,679	
G-CSF (CSF3)	0,002	0,419					0,12					0,004	0,022	
GM-CSF (CSF2)	0,233											0,649	0,762	
IFN-gamma	<0.001	0,154					0,003	0,6	0,038	0,086	0,08	0,006	0,023	
IP10 (CXCL10)	0,006	0,014	0,1	0,037	0,33	0,6	0,725					<0.001	<0.001	
MCP-1 (CCL2)	0,366											0,627	0,762	
MIP-1a (CCL3)	0,011											0,317	0,571	
MIP-lb (CCL4)	0,127											0,706	0,773	
PDGF-bb	0,529											<0.001	<0.001	
RANTES (CCL5)	0,565											0,931	0,955	
TNF-alpha	0,008	0,289					0,006	0,6	0,027	0,046	0,22	0,447	0,679	
VEGF-A	0,006	0,358	0,7	0,158	0,86	0,033	0,034	0,9	0,015	0,103	0,21	0,003	0,02	

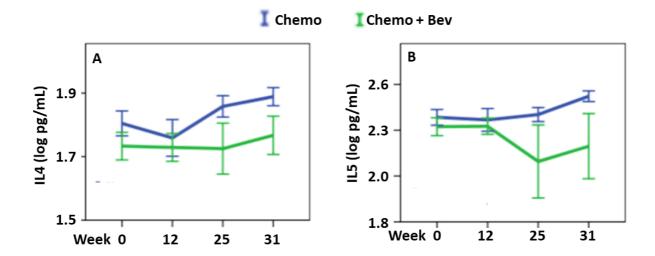
^{*} Post-hoc t-tests for pairwise comparisons with multiple testing adjusted by Bonferroni; performed only if ANOVA P<0.05 (and if global three-way ANOVA FDR-adjusted p<0.1, or if TNF-alpha). W=week

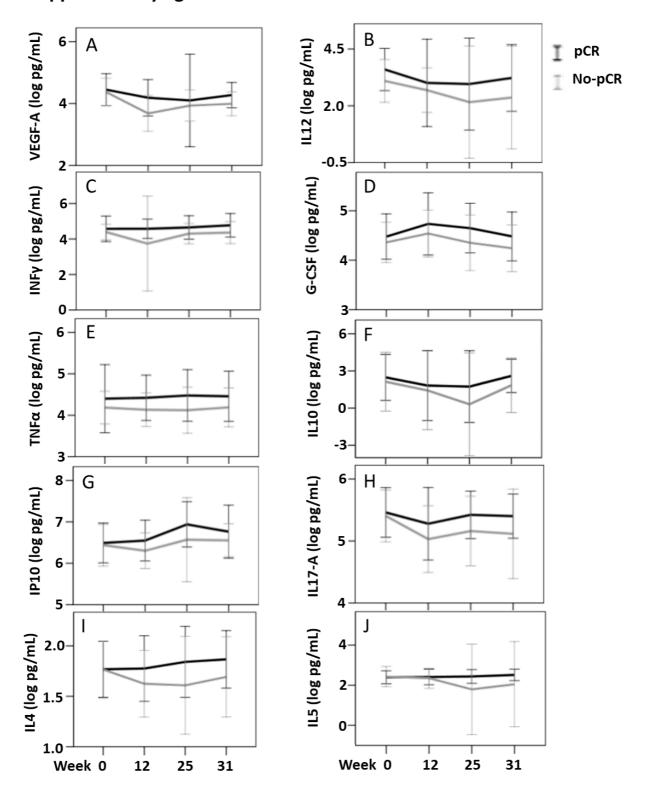
a Global F-test in three-way ANOVA with treatment (2 levels), timepoint (4 levels) and treatment response (2 levels) as fixed factors b FDR-adjustment with the method of Benjamini-Hochberg.

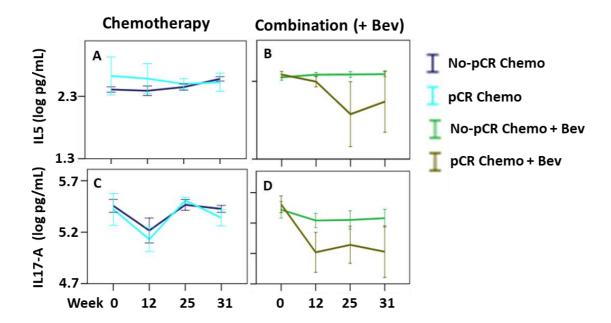
Supplementary figures and supplementary tables

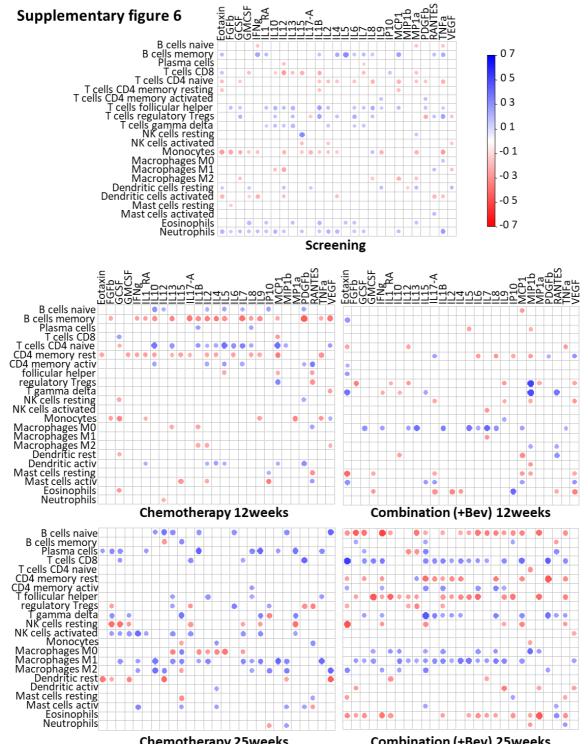












Chemotherapy 25weeks

Combination (+Bev) 25weeks

Supplementary table 1

Number of p	ationts*	Number of	samples in	G-CSF therap		
Number of p	Datients	Treatment	No.	Respons	e cat.***	No. Of patients
Timepoints	No.	arm	140.	pCR	IpCR	No. Of patients
Screening	88	Bev + Chemo	46	13	33	
Screening	00	Chemo	42	6	36	
12 weeks	85	Bev + Chemo	44	11	33	15
12 Weeks	63	Chemo	41	7	34	12
25 weeks	80	Bev + Chemo	40	12	28	4
25 Weeks	80	Chemo	40	5	35	2
21 weeks	90	Be + Chemo	45	13	32	
31 Weeks	31 weeks 90		45	7	38	

^{* 98} patients haveat least one measurement at a given time point

^{**}Number of patients have at least one measurement at a given time point in the Chemo + Bev arm (n=50) and Chemo only (n=48)

^{***} Patients with pathological comlete response (pCR)= 21, incomplete pathological complete response (IpCR)= 77

Supplementary fields is ing transferment insult of 17 sylutions measured in the server of branch array public undergoing republicant elementary, with an of the discussion made

adjustance of the same	a leg state									Lancia					-												
D Time	124		ia .	ы	ut.	14	1.7	14	1.6	120	L/G	L'E	UE	127	40.11		25		ENG LTD	01036	603	004	624	HOOMA	604	104	VBCAL
2 Sweet	1327			1111	2185	1360	134	444	1.00	146	1411	1000	-142	6361	1447	1288	1400	14%			140	SMS	E386	6408	2.00	6380	4224
1 Sunn	0.60			1.000	238	1808	188	101	100	1.70	1,366	1.836	153	6327 6712	1401	1204	2.38E	12%	1.00 1.00	E465	1433 1330	1.100	6407	8401 7380	30.00	1304	1.627 1.627
E Same	040			1881 1884	2180	186	164	124	130	1400	1316	1.161	462	6367	1441	476	4304	1179	140	136	1.107	246	Eace	7,075	30.047	6368	LEC
E Gunt	140			20	1112	1331	158	141	140	1227	140	14%	442	TAIL	1224	6138	1381	131	1.00	646	1400	186	LIT	7278	220	1300	124
7 Supply	0.623			1.124	3,040	1424	140	1.00	150	1.76	1487	1.881	444	6.000	1411	1400	4108	4464	1.000	6827	146	1.134	1,800	6.284	38.713	140.	4107
A Sweet	1.000			1411	2275	1104	183	170	1407	140	1400	5004	442	6444	6170	1404	438	176	4.900	440	1.446	1.790	E.123	6366	30.000	4300	136
6 Guneti	040			1.561	1407	1.04	156	130	1.00	1.600	5.00	0.404	463	E114 E114	124	135	186	130	LOW	608	1.360 -1.608	1444	E 204	6301	20.004	3.00	456
11 0 000	1.79			1414	2112	1104	106	164	178	148	1220	1,404	442	6780	5301	476	1100	180	4376	630	1.081	2780	Eaci	7304	30,354	6.00	1.00
22 Supply	1.000	ALE: I	208	2288	2464	4364	4380	122	1.30	Loss	6386	188	1461	E244	7.241	List	Last	4.00	440	130	1961	2480	6.716	6.167	10.144	47%	1861
II Grand	1.7%			1711	3.167	1767	138	144	1.000	1.30	1461	1.801	448	1117	6.180	LHE	434	147	1.000	14%	140	2286	6.034	6.000	32.764	1884	4120
22. Grande	044			im	3284	1.00	165	1.24	6.766	140	LTD	1.821	444	1211	1276	-6466	144	4464	142	LTH	1.707 1.736	1334	6.004	6.140	25.944	1.80	4760
18 Guneti	1.00			1,704	3304	1104	180	1.00	100	1.700 1.700	146	140	1.07	6304 6371	6341	1360	6.00E	180	1.00	636 676	LTE	148	E 384 E 384	7,101	20.00	636	180
27 0 000	14%			200	3714	1750	163	100	147	1700	1404	3.440	3.384	144	6104	6.00	1407	196	Lac	130	136	220	E.304	7471	3.74	474	1.07
14 Guerin	1.00			5241	3754	1484	1.01	140	1.77	1414	1.00	1.661	-142	E424	470	4174	4.070	16%	4.700	476	146	3,040	E.E34	7.100	10.141	4101	440
22 Guneri	1.146	6166 1	104	1.787	3116	146	1384	170	172	Loss	0.000	3,060	442	6276	CHI	4334	8.100	146	4.60	6.000	148	3.307	6.246	6111	20.473	4374	4198
31. Grande	1.400	1886 1	.276	2001	1704	1.00	141	144	1300	1.010	1.344	7236	-142	E1100	E300	4384	1461	141	LEA	672	LIE	5.027	EACE	7.114	240	cat	6.56
34. Grande	1.386			1441	2112	1354	1374	107	1466	146	1.0%	1.783	444	6764	6211	6.66	1.000	106	140	140	146	228	E.176	7,401	241	434	100
14 Guneri	1.340			1.704 3.254	2201	1790	1106	1.00	146	146	LAN	1.661	442	6144	6361	0.00 0.004	LOI	192	1.00 1.00	64% 620	14% 470	110	E 264	7334	10.484 10.100	CHET	Las
SE Summit	1420			1471	2315	1/00	170	140	1.00	LEB	100	1,404	5.164 3.244	LAST	LIM	4.04	122	1.01	1400	430	LTS	5101 5101	1364	un	22,471	6.000 6.000	4.760
34 Guneri	130			1471	2412	1365	137	101	136	100	Lin	2111	442	6474	6364	4101	1.01	140	478	4.00	1.736	1.414	E 204	6267	23.414	434	140
36 Grande	610	1017	£10	1111	2271	1770	169	1.00	110	146	1.360	1.734	-142	6224	6363	3.7%	4196	130	4.700	East	1400	1.146	6416	6.841	20.004	1441	4186
No Green	1.096			:114	2201	1302	166	1.00	138	1.044	1886	1.760	-142	1461	6.161	170	4386	1370	LEE	640	1420	1.711	E.344	6314	2333	1861	1400
12. Grande	LIB			1714	2355	1865	1460	140	148	LIN	1776	108	442	ELER	6361	4144	4386	1.00	4.960	130	1.061	1.430	626	6401	340	6180	LEX
12 Greek	1,000			1.794	2331	388 338	1.00	100	1.607	140	1301	1,076	1.07	E287 E287	6.86E	6376 5.756	4344	141	1.00m	6401	140 179	106	E364 E434	6281	2000	CHI	1.01
EL Grands	1.181		-	1404	2111	1100	130	140	108	146	100	220	-142	EUM	LIST	4366	1400	1.01	196	646 636	1.000	306	6271	7004	20244	6380	144
II Gunn	0.766			1427	186	176	176	137	106	120	100	1,347	-142	1406	638	1460	1475	165	130	Lin	1.061	1.00	E-014	6179	30,410	1790	4.00
M. Grands	1.040	1311	Hi :	1411	3266	1302	1400	154	1.00	140	1881	1.876	444	1241	6124	4356	1484	1300	1.00	6.001	1.600	1466	6763	6.181	35.146	4376	100
14 Sunnis	1.00			-444	2411	101	164	141	130	1477	146	2286	-642	EARL	6387	6496	1,100	1.00	14%	640	1000	2786	E.886	6.100	2239	6.00	1404
10 Gunde	188			1461	3.754 3.867	1400	176	1.07	1.05	100	146	1.000	446	E1124 E2734	6.887 6.108	CHA	181	168	LANG	6.716 6.088	140	1.440	E.101	6.704 7.474	30.00	C180	4.00
AS Some	1.004			1444	2100	1100	107	1.08	140	100	130	1.861	-142	E714 E411	6306	400	438	160	1.96	6.007	Lini	1,440	E.234	7414	30.044	4334	101
II Green	1.480			2011	37%	140	100	174	140	1460	Lists	100	462	1411	1341	433	4.00	137	176	630	106	1060	1241	7.114	31.170	444	4.01
A Green	048			1.147	1860	LET	176	1.04	4404	4464	1.00	1.341	442	1400	6467	4404	141	4404	146	630	4464	1.345	130	6.794	20,347	1/04	4:30
II. Grande	1.136	100	224	1444	1870	1300	130	1.00	1.00	1.907	2.686	1343	442	6.140	6.187	4384	4.04	136	1.00	6.716	172	2111	6360	6404	31,004	4388	141
AE Green	1.00			1861	2714	100	170	140	144	140	1121	5401	2381	E4E	6310	cm	UM	100	LTD	Len	140	5400	1.101	6.880	35.707	CAL.	1861
AT Green	1.601			1441	2111	1.01	138	1.00	148	Lin	1.761	5000	442	LIII	1407	CHAR	4.0%	130	140	636	106	5065	E-204	EHI:	200	644	476
AA Guneti AA Guneti	1.2%			3311	120	1300	176	160	100	1.000	1366	1201	442	6001	CH	6388 6886	4.07	136	144	140	140	1,686 3,006	E E E E	7414	30.704	4307	1701
E Comm	1.18			3334	1411	176	176	1.04	176	140	136	1224	LIIT	E284	7417	4370	1460	140	tas	440	EGS	228	0.000	7.00	20.00	7,124	121
E Green	0.7%			1,800	2201	183	127	438	1707	176	140	Litti	442	1241	140	186	146	130	130	640	1420	1470	EHI	7384	246	176	174
Ci Sannin	1.888			1.186	3200	1466	149	1.00	440	1.386	1446	1.8%	444	6400	8.880	0.404	480	4.004	4.700	640	1.141	1401	6.000	6401	2.40	4368	680
II. Greek	0400			2287	21117	3388	1100	136	140	1.700	6.2%	1,100	-142	EASE	1414	4384	4.04	176	149	120	1.107	4.63	E 864	7,486	36461	4387	4796
II. Gund	1.086			:444	2114	:ar	1100	1.01	1.00	1411	1.760	1.410	-142	EMIL	6.040	4155	4384	154	LED	696	1.280	1.0%	EHIT	7471	3134	CHI	1401
EE South	1,040			1.00	1200	1200	176	4.74	1.00	Lon	1411	1.364	463	1411	CHA	680	5.00 \$101	4404	160	£300	140	1410	6.123	7,477	20.007	174	Last
E7 Gunn	136			1.711	3.00	1811	136	163	14%	146	101	1.444	442	ELTI.	4744	14%	4188	108	430	440	1200	1.146	E444	6473	244	6188	4.00
th Sund	4464			1414	120	1400	178	101	4,202	0.000	046	6765	442	1212	4384	-6404	14%	4404	175	640	1040	1.346	6466	1441	33473	1286	107
D South	4464			1441	186	4404	138	187	6.607	140	1361	4.62	442	1487	1.886	-6404	130	4404	168	606	4362	1.866	6307	am	25,116	174	LET
40 Gunn	1.441			1411	2100	1862	1300	1.00	130	146	1401	LTES	1.16	1411	6100	cme	4760	140	1.00	450	1007	212	LIN	7441	20201	CIU.	6.00
41 Gund	1.081			1.147	1400	1186	1879	4.04	1.00	1.904	1.660	1.304	-142	1411	CIM	1124	176	146	146	4.000	146	1.800	6.063	6464	30.144	1/14	446
EL Commit	1.00			1766	3.076	1888	1107	140	186	1.704	1.004	1.661	463	6.071 6.027	4.704	170	C188	154	190	£427	1.7% 1.6%	1.643	E-201	6471	20.000	1207	127
41. Sumb	1.444			1467	346	3.034	160	130	146	1.704	1444	1,386	5.384	6406	6186	4394	100	106	1.00	430	106	210	140	7.141	30,040	6.04	4700
AT Sweet	1.00			1411	2311	1100	130	1.04	1.00	140	140	106	444	1881	6.000	1.762	4.04	1.7%	TEN	1873	1401	1.661	6.147	6371	35.134	4387	1108
AL Sweet	0.765	1000	461	LHT	3114	3100	148	1.08	1407	1.007	1.004	1.367	-142	1464	1141	4476	4108	1.04	4.786	680	1421	1222	EAST	7461	240	4384	1461
47 Sund	1.387			:411	3.00	1100	1394	141	1300	1.041	1407	1,400	442	6208	5204	4381	1400	176	4.780	600	1.7%	140	E.220	6414	31,004	448	4160
A Comm	186		-	2411	3485	146	1.776	1.70	149	LTD	1144	5888	-142	LEIT	Lift	4308	1860	1.07	176	6.004	138	1227	6.004	7111	35344	4.88	487
All Counts TL Counts	0.387			:10	3380	120	170	104	1.00	1.007	E401	1.100	1.800	E204 E244	£185	C100	4307	100	1.000 1.000	43D	1.607 1.660	1444	6.0E3	7,500 6,604	3000	6304 6804	4.00 4.00
The Green	0.403			1417	3282	1800	100	140	130	1400	1071	1411	444	6347	6784	1754	140	166	140	6.266	LEE	4.60	E 141	683	30.041	6385	141
71. Gund	040			1.104	244	1/86	146	1.75	Lan	4464	1.7%	0.866	442	EAGE	6444	6800	4.08	1.04	146	636	1.001	286	LAST	6.710	20.141	1.790	4470
71. Grande	1.136	1866 1	087	ian .	2111	2711	148	140	180	1.061	Lon	1.607	-142	ш	6784	4381	4384	136	1.00	6.05	1.766	1.721	E.167	6.784	2.114	4188	4386
7E Grant	0.880			1414	2777	100	188	1107	1401	1.001	1.664	1,147	-142	E380	6884	1.860	1.60	100	LETE	640	1400	1.773	1470	7,081	20.144	1417	4100
TE Greek	1.104			1201	2188	1766	138	101	100	1.060	1.761	1.861	-142	1114	1411	1801	4197	1.07	Line	640	147	2124	7.144	670	224	4381	1.00
77 Sunnis	1.00			1200	2100	1207	186	146	1.00	140	1.107	1.00	4.62	E400	7,570 5,746	424	1387	170	1876	676 676	146	1.444	636	7,027	30.400	7,865 6,187	4.01
AG Guerri	1.100			1.714	3117	1365	129	154	146	100	1.441	5.365	442	8410	Last	4301	1.04	169	190	6300	146	1.446	1400	6401	3044	4368	444
AL Count	1.861			1444	3400	3346	1100	1.70	14%	100	1400	2422	444	8.808	6.776	4300	4.04	1400	140	6.000	142	1117	6.000	6294	30.141	6380	4104
All Green	1411			1971	1700	7111	188	127	1.00	1.000	1417	2386	-142	LIN	6261	4274	4.0%	130	LTE	610	1001	2136	E141	6.880	2019	6,800	470
AL Commit	136			1.758 3.088	310	1318	1.00	136	130	1404	1.73	1.894	1.60	1211	1144	141	4.04	140	LWE	E40	1400	1.641	E340 E340	6400	39.100 31.140	6376	4.04
AL Comm	0.00		.123 .087	1441	210	1007	100	140	100	1436	170	170	448	E284	6861	1201	430	126	1.00	6.700 6.600	140	1.8%	E.160 E.754	7361	30,000	4381	101
AT COMM	1.000			1.707	207	1107	1707	146	100	140	100	2426	442	1411	4761	6.00	476	167	LOE	120	1.160	2117	E327	7,141	30.460	6377	161
AA Gund	1.000			1.880	2186	1304	100	161	140	176	Liti	50%	442	E411	6268	100	4364	187	130	6.945	Like	1.361	6.084	7404	30,717	CHE	1406
Ab Grande	046			:414	2121	176	1490	148	140	1.600	1401	5800	442	E441	420	170	4388	129	4.00	1.78	146	1.444	6434	640	31,000	1861	4300
40 Gunnh	1.000		-	1.850	2251	384	130	1.26	1107	186	1444	1.044	-142	1241	E304	1327	12%	1.08	140	678	FEE	1.783	E.141	680	2540	LEF	1224
40 Gunde	136			1.798 3.008	3382	1360	104	140	1407	140	1.444	1.761	462	E414	6.86E	186	2.00E	150	1.00 1.00	600 600	1.760 1.227	1.461	E.751 E.201	7,000	3344	CON	4.964
41 Sum	13%			1401	140	1187	166	120	149	146	13%	LTM	153	1427	1300	180	1.04	140	100	Lac	188	146	6.001	6404	31247	an	100
41. Gunn	1.7%			1.764	2154	130	10	161	13%	140	136	3:084	442	E147	E186	6386	147	176	LOSE	1300	136	140	LAG	7,800	30.047	CHAIL	4380
46 Gunn	1.106	1246 2	261	1,800	2302	180	1326	1.04	1.00	1.136	1360	1.027	4.62	1411	6814	6480	1484	1.0%	140	672	148	210	LIK	7487	38,710	4364	4.04
4F Summ	0.106			:414	3304	140	1470	154	14%	161	100	1.003	442	E244	1107	100	4381	176	4.775	6307	130	-1.602	LIE	6.161	30.341	6276	1104
44 Sumb	170			3,508	1204	3888	186	130	148	140	100	5433	3480	EAST	LIME	420	4.708	144	Lan	440	112	218	E344	7,276	30,000	4.700	484
1 Hand	0.880			3,080 1,177	3.76L 3.124	1274	185	1.00	146	140	1.067 1.066	1.861	462	EAST SACE	1.444	1300	438	1.04	430	6727 6400	138	1,100	1381	6361	10.000	1766	4.00
E House	0.400			:441	2101	1816	136	130	170	146	1.344	3.2%	442	EAST	440	4361	4386	137	4.777	670	148	1.465	6760	7411	3124	6387	474
6 Danie	140	1200 3	401	1414	3.61	3386	140	140	106	1.00	430	1.636	448	E161	100	1,670	450	130	4.004	168	1.704	1477	0.161	6.834	20.001	4317	6380
7 Haren	1.046		141	7131	1870	1404	188	147	1867	1400	1.001	1400	-142	1861	120	1144	484	148	LEA	6.766	14%	1.8%	1473	1411	2000	MI	4.758
A Harris	-1.608			1111	520	-6.604	4404	190	41104	4464	4164	0.404	-1.62	3041	3.834	-6404	176	4404	140	E750	-1802	0.686	1414	1,340	2244	188	154
10 Hands	1477			120	755	188	138	1.00E	170	1477	130	1111	1407	E217	0.10E	6888	1800	172	1.00	4.00 4.00	1361	346	7.386 E467	7.00T 6.001	31,004	4101	121
11 13 mm	0.890			180	2447	1886	186	154	187	140	1.2%	1.801	153	1401	137A	166	100	1.01	190	120	140	173	LACT	E484	30.324	1464	161
3 3 40	140			3384	1204	1.07	100	1.00	1.00	LTG	1.001	2400	140	1384	CHE	4147	186	100	Leg	640	188	1107	6.000	6471	220	4464	122
13. 23 menh	146	E.136 1	383	3341	2111	133	146	439	166	1.000	tin	3473	3460	LETT	1.744	cat	1300	141	Line	14%	1.146	240	6.273	644	2.01	6486	444
11 11 mm	1400	E086 1	:14	3,000	2189	1818	1.00	1,000	Len	140	112	2.361	2,800	EAGL	1111	1221	130	Line	1.80	6.616	1476	2407	1407	7411	30301	4764	1.07
M Hann	1.383			1.767	3186	1804	1104	1.04	1807	140	1607	1.400	-142	1444	1860	1741	100	170	1,075	636	1.704	1.441	E.383	6344	30.761	6364	1760
If Hand	14%			1,204	2386	1386	188	101	100	1.000	140	1476	128	E400	6.300 6.870	1,07	4.004 4.006	1.79	130 130	T.086 6.016	140	1477	E 860	EARL	10.000	1801	1275
14 House	140			2000	1287	1386	102	1.00	120	1.20	E286	0.000 0.000	1.616	EHH	6116	1404	Last	1.00	LEV	640	1406	240	E.765	1461	20.404	4117	446
11 13	1.00			1414	210	130	158	141	1.778	4464	140	1471	442	E424	6.000	CATA	180	1.00	100	640	100	2.736	E.III	6316	35.604	6386	4.004
10 23 made	04%		Lea	1284	2411	1870	1.00	130	4868	178	Hill	1,275	442	1001	1714	380	test	4464	170	120	1.034	LIB	6.766	1.111	20,007	144	1.00
11 13 mm	1.046			1411	230	1180	1400	140	1800	130	Little	1.444	-142	1411	EH	1.104	4.0%	176	1.704	434	1136	1466	0.140	E.141	18,404	6.66	1.01
M Hand	135			1400	1812	1108	100	147	1.07	LIN	LIF	140	462	E101	5465 5464	6.10E	6.75E	101	4.000 4.000	£400 T-010	1000	2.00	E.85	6.00E	240	686	2.34 2.44
24 33 400	04%			1,286	2112	1704	160	120	100	4464	140	1.384	462	1401	E261	1806	4300	101	4.70	640	1414	100	6.753	1414	220	141	174
27 23-000	0.863			1.00	3200	188	167	100	1.00	176	136	1.400	462	1401	6267	186	478	101	436	£700	1.046	3,084	140	540	2070	6306	4100
March Hard	148			2241	3461	340	1166	1.2%	170	140	Lati	2.0%	442	6306	6467	can	1400	146	LTE	636	136	2.286	127	6471	240	446	165
10 III medi	1.861	1481	471	2414	3.184	1274	155	1407	144	1477	1460	3286	444	E.108	1111	4386	4479	10%	Lea	630	1.400	2111	1411	6346	3843	4476	1479
li li mi	1.186			1484	2111	1404	1.0%	1/04	1.09	LTH	176	LEG	-142	IAI:	1414	4104	186	180	1.2%	6478	146	3,806	E444	E.141	18,854	484	4.000
E Sant	1.866			140	2289	189	155	176	1.466	1404	146	1.761	462	EAG	CHI	22% 248	270 8160	180	470	T36	LTS	5.045 5.465	E401	7,110	200	484	100
H Hann	1361			140	2312	164	103	1.98	148	140	140	5.600	153	1411	6.700	688	130	176	470	6.TH	130	2372	E404	6.001	2.71	6380	Lur
H Hann	140			1464	3.186	144	107	140	145	LID	136	140	463	5344	1411	1401	1114	148	4.7%		130	140	E.300	6261	10.404	4741	1407
			_	_		_																					

H Bank 130 F Bank 130	1786 5.146 1400 5.245	1407	701	13%	150	141	188	14%	146	1407	136	1131 1154	E104 E144	4384	1334 1334	130	140	125	1.044	118	EAST EAST	6347 6339		COT LOS
14 13 mm 148	1711 1.884 1.101 1.814	1.04	2365	18%	170	105	120	140	100	1.600	16	LEF	1361 1361	176	444	178	4.361 4.00	430 128	100	5544	E.127 E.624	E284 E813	32.764	CHIC CHIC
11 Hammi 138	1.100 5.787	170	238	1304	1100	107	1.08	106	136	508	444	EAGE	680	CHE	4190	147	180	670	140	3.166	LIN	626	10.404	122 1224
11. Til medi 0.481	468 468	1.187 3.284	21117	1460	135	130	100	3.0% 0.00	0.047	0.600	163	1414	17M	-0.000 -0.000	4390	4404	100	Lar	1.140	1.114	LITE	E400	10.140	101 136
H 13 and 1000 H 13 and 040	1341 1301 1344 1307	2.00	27H 22H	1707	1860	100	100	130	1.100 1.760	Little	448	E.180 E.080	6281	6100	127	1.07	190	430 430	1366	5.124	EAST EAST	6401 6484	20.424	CHT CHE
17 13 and 1366 14 13 and 1308	1327 1327 6701 3341	3301 1790	1410	180	196	1.02	170	1.00	1427 4361	1300	99	6.27% 6.867	6467 6360	101	100	130	130	64E	140	5376 1466	E386 E384	6044 6404	35344	CHA LAST
10 13 mm 1.00 10 13 mm 1.00	7.00 1.004	2381	3346	1.00	188	1.70	180	1.00	1.027 1.386	5427 5756	144	EAST EASC	4411	488	6.760 6.860	1.00	4.700 4.700	640	140	1.460 5.800	140	7.861		110F 14EA 110E 14FE
E Danie 185	176 1477 188 146	120	238E	1804	136	187	140	100	108	170	468	E34E E43E	1371 1376	170 430	438A 438A	122	1.00 1.700	E 065	140	1756 5884	E.507 E.500	73%	244	1100 E700 1175 £100
11 Hand 178	1436 1464 1436 1486	1800	252	140	195	1.00	180	176	140	238	444	LIII	0.24E	6365	488	144	14%	LIE	100	1494	E256	670	20,404	CHE LIST
H Hann SAF	480 480	1,004	140	130	1327	137	0.30 1.30	ATE	130	2400	16	6000 6400	6281 6354	4464	170	180	140	£00	-4.60k	170	tan tan	6128	3.00	100 100 170 120
17 Danie 1400	136 366	140	200	134	137	1.70	176	100	148	3.236 1.886	444	E124 E474	5365 5366	630E	474	146	102	646	100	1,866	1414	6.106 6.700	2.00	1300 1386
6 Hamb 13% 6 Hamb 13%	140 5.05	1464	3382	1380	1465	100	144	140	100	1.465	163	6.280	6144	6385	4384	179	4.500	6.003	143	146	E484 E488	6346	3270	1107
61 Hamb 1388	1776 3481 1476 3484	1460	3,800	1384	152	127	100	1700	140	1.00	15	E30E	CH	430E	4.981 4.952	14%	1.0%	6.007 6.007	100	5.086	1111	6.100 6.179	30.004	1100 1100 1101 1100
6. Hand 140 6. Hand 140	1.000 1.000	144	288	188	150 170	1.776	186	146	1.00	3.126 3.836	100	LIM	1.708 1.118	470 430	440	136	186	670 670	146	53% 53%	ESTE.	6764		1700 4380 1800 1700
E Danie Lie	100 5.00 110 5.00	1256 1466	3351 3351	133	101	1.05	140	1.00 1.07	1.766 1.766	1.000 1.000	46	1481 1138	E.123. E.160	146	4.0E	130	T-000	640	1.00 1.70	146	E.27E	636		130F 430E
44 Harris 1398 44 Harris 278	0.00 0.007 0.00 0.000	1860	2484	160	100	170	108	1766 1666	130	1286 1786	1.800	EJEL EJEL	LASC LEST	190	4.00	101	4.700 4.700	64% 67%	1007	3.304 3.476	140	E.100		COM 1874
71. Hands 0.007 71. Hands 1.000	1780 5460 1460 1.767	180	228	188	134	140	146	188	170 170	1.0%	163	E114 E144	C184	4100	4.00 4.70	196	LOS LOS	6400 6400	1.00	5346 5346	E361 E404	6060 6071		1964 1767 1366 1766
11. House 1327	E136 1040	1884	7111	1386	130	160	146	178	170	1.764	1394	un	6407	638.	488	148	170	840	1.761	1.861	6.080	6408	2344	1701 1771
16 Harris 1000	1200 1,700	181	338	1386	130	155	1707	4464	1.66	1404	10	1361	2711	181	4.700 4.700	130	170 102	120	1400	5000	7.00	6010	234	130 140 130 140
77 Hand 1688	128 288	1471	1122	1384	136	140	150	140	147	0444	468	E404 E387	E180 E112	1300	\$190 4390	134	440	638	140	100	670 6407	6360	30441	130 1314 138 1707
76 Hands 0.755 40 Hands 1.755	138 380 108 370	1207	2100	1107	130	140	130	100	140	1.100	1466	E761 E264	E301	4334	180	138	THE	EAS:	14%	5781 5788	E.E38 E.708	EHE.	2.01	CHE 136 CHE 186
44 13 mm 0.475 44 13 mm 1.476	128 0381 186 1281	1,830 3,004	1860 3866	1400	130	100	170	1.7%	1.100 1.701	1.864 3.667	163	1347 1344	1861	1400 6171	474E	180	1.60	LEE LTE	172 172	1.000 3400	E 804	EASE EASE	38,771	131 131 134 134
44 13 mm 1.363 44 13 mm 1.464	1805 1:000 1704 1:711	1400	241	174	194	176	170	140	1.765 1.800	1.420 3.621	1331	E.IEE	LIST.	4387 4308	4.04	14%	162	630	130	2.886 2.227	6.000 6.004	6334	20,421	147 181 181
M 11 mm 1.2%	1344 5.771 1341 5464	1211	2121	1360	194	141	168	1400	140	3.10E	161	E241 E471	1487 1460	1.01 4.00	4.10A 4.10D	132	1,00	64%	14%	1.447 3.146	E.IE	cm cm	10.404	1271 1277 1221 1461
AF 13 mm 1.08	176 4.60 106 5.60	530	3334	104	196	164	120	130	145	3.140 1.401	463	LIST	1818 1383	1471	4.00	139	1.000 1.000	100	146	146	E.101 E.404	640	240	CH 18%
46 13 mm 1360 41 13 mm 1340	100 140 400 400	1477	3760 3407	188	164	140	130	1300	140	27%	463	E121 E281	E.IIE E.IIE	139	161	100	1477	600 676	140	1044	E.IDE EAST	6386	3339	1011 1014 1704 1101
46 House 1327	1000 1800	1417	2386	1311	134	140	140	1307	146	LIN	444	E284	1383	1700	438	138	190	LASE	1439	140	E401	6414	SIR	GPL 1467
41 Tiland 048 41 Tiland 136	100 240	1201	7154	120	122	1.00	130	1.107	146	1000	10	1401 1314	1,916 1,711	-6.000 C.110	122	141	LEE	100	1407	550	1,876 E.160	67H	31.334	101 174 136 174
46 Danie 486 47 Danie 410	486 486	1381	1800	1807	164	1.00	144	1.001	1.00	1.00	ģ	1341	6381 6366	181	100	140	200	ESE:	1407	1384 4868	E.874	LIE	38,400	138 178 138 138
14 Direct 147	466 186	1,000	201	1808	120	140	108	178	140	3.880 1.636	Ė	E711 E244	1461	6765 8367	160	1.04	Local	470	1.000	110	E384 E307	6410		1761 1761
5 25 mm 1,327 5 25 mm 248	1428 1.341 -4.658 3.414	1400	2207	138	106	176	14%	140	1.000	1,100	46	E414	1401	430F	4.00	1.07	1.00 1.00	1886 8750	1.007	1.000	E.20E E.20E	676		1800 1.00A 1801 1.007
1 Hamb 1375 4 Hamb 148	140 110	333	7111	16%	154	1.00	198	140	14%	3.367	46	6.114 0.410	1347 1371	C244	4.758 4.658	103	1.00	100	1400	540	6.700 6.674	7381	240	1276 1276 1796 1280
7 Hamb 1380 A Hamb 1380	176 546 180 546	1450	2111	1300	122	155	170	146	1377 1375	1,884	46	E134	E304 6404	1207	101	136	4.900 4.900	£100 1260	100	1.480	E380 E380	6361	10.400	COST COM
6 Hond LIE 10 Hond 146	148 146 178 146	1811	3236	188	134	1.06	170	136	146	1.666	448	EAST EAST	E361	188	433	124	1.30 1.00	170	140	1.607	EAST	6339	20498	CHE 476
13 House 1460	600: 5000	276	3306	186	160	1.04	178	Lati	146	1.101 1.101	1.65	6007 6348	176	1200	48%	100	Lato	T461	176	1277	E407	638	35.401	1380 44FA
11 House 1338	146 386	1401	3411	1400	1.03	1.00	130	12%	1407	1340	444	E.286	CHIL	4155	101	1.30	140	Tess	100	5386	6.160	6171	224	CHET CHIE
11 Hand 1477	E 201	3361	3275 5264	1861	176	1.00	100	136	140	5481	140	EAGL	134E	6224	LINE	1400	140 138	1766	1366	588	E384 E314	6401	10407	CHEC CARE
3 Hand 133	1701 3461 1341 3441	20	3334	138	160	152	1.0%	126	140	1.620 1.620	1340	E180 E241	234 234	127	6.000 6.07E	186	190	1756 £767	1475	182	E-860 E-064	6400	20.184	CHC CHF CHF 1765
50 35 med 2.708 51 35 med 2.381	1765 3.001	1714	2786	1116	186	100	150	Len Len	LIE	1466 1466	440	E140 E410	6187 6188	688 688	1274	144	170 180	130 640	140	5.680	EARL EARL	CHI.		130 E31
15 10 mm 5428 14 10 mm 1.128	100 100	140	2002	1307	186	124	130	170	146	140	464	1427	6366 6388	170.	455	100	4.00 4.00	110	120	140	EAST	EAST.		1887
11 10 and 1100 11 10 and 140	146 546 4464 5564	138	3347	1301	160	146	166	1404	148	1.00	46	LIE	1404	0.000 0.000	107	135	1.00	1780a 4770d	1430	1.46E	E.124 E.301	620		106 106
14 Hamb 136 17 Hamb 247	1766 5.866 1.286 5.865	1401	3185	130	198	176	140	100	1.78E	1.480 1.890	46	LIST	1341 1344	LIST	6.600 6.676	131	450	T.065 4.065	140	140	6.000 1.400	6404	20,000	CHE CHE
14 Hamb 546	110 100	1791	220	136	130	147	130	12%	179	1766	46	E361	SACE CACE	174	476	1.00	190	646 630	148	4.60	6.546 6.045	63%	33.160	188 189 186 181
10 House Little	1427 1446	1871	2176	134	100	140	108	1.00	136	1000	444	6297	4294	6388	6400	1.01	LEE	126	149	1047	LIII	7.569	25467	130 130
11 10 mm 1.120 11 10 mm 1.00	1401 1540	1964	3341	1312	170	107	176	110	146	148	16	EAST.	E181	270 270	170 170	120	1.00 1.00	185	130	1000 1007	6.004 6.763	7,000	3020	1700 1300 1700 1307
H Hand 1786 H Hand 1187	E011 1.361 E134 1.360	233	122	18%	129	124	132	1.30s 1.0G	136	1.00	188	EASE	LIST	2354 2374	276 286	170	Lac	130 640	136	5345	EAST EAST	7,007 7,002	20.040	CHE LON
H Hamb SHS	146 140 114 1470	140	2110	122	1100	166	140	175	1400	1427	136	8.201 8.470	1862	1367 2382	Lat	140	102	138 668	100	1.441 1.146	1401 E314	7,004	244	031 438 031 144
17 31 and 136 14 31 and 136	1721 5384 1124 5381	120	3800	138	15E	1.70	180	1478 1470	LAD LAD	5.000 5.000	į	E340 E304	8361 8330	1386	4.00 4.00	178	170 100	126	132	5.0% 5.2%	ESH EAH	6334	38,804	C101 -6404 C18E - 6400
10 10 mm 1.176 11 10 mm 1.178	146 136 138 146	2214 2214	3400 3486	1300	184	1475	195	146	100	1.725 1.726	163	EASO EASE	CHI	2170 2807	4744	100	1.00	T1081 £709	140	5381 1495	EATI EATI	6401		1312 1326 1386 1386
H H-mm 125	1383 3460 1094 3461	1401	2181	130	100	160	172 14%	170	1886 4386	100	4.60	LIN	COL	1871. 4393.	4366 4366	100	1.000 1.400	£.000	1.76s 1.044	146	6.0% 6.000	7,560 6,661	274	121 127
17 House 1386	1861 1.120 1861 1.000	1817	3766	101	161	100	176	140	Lati	230	46	LIFE	LIM	618F	400	132	176	1467	100	100	E.385 1.860	646	3139	CENT CARE
E Hann 146	688 ERE	1200	2381	1201	184	172	170	LOT	610	136	133	LAST	7,884	E (10)	136	470	4.00	640 130	140	1381 1481	1761 1761	7344	33.454	1967 CNL
	140 100	-0.00		1200	100	144	100	100	1340	146	444	E204 E204	1384	6138	4394	1.00	439	6775	1.18	146	LITE	7,101	22,014	1386 1300
D House 12%	136 549 136 133	1477	2101				9.105		140		444		6766	4700	£195	120	190	640	140	5.000	E484	6366		1704
13 31 amh 236 14 31 amh 1375 15 31 amh 1338 16 31 amh 1338	1341 1334 1481 1507 1784 1538	1480 3388	2388	130	182	164	1.00	1.961	1300	1.277	444	1244				200	100				6.073	7464	246	1276 1276
12 March 0784 13 March 1775 14 March 1786 15 March 1786 15 March 1786 16 March 1786 16 March 1786	1341 1.734 1.461 3.507 2.741 1.341 1.771 1.461 1.461 1.561	1,880 3,084 1,777 1,807	3383 3393 3393	137 181 121 137	185 185 185 185	161 163 138	106 108 119	136 138 176	148	1.077 1.665	163	1307	E200	430	474	101 101	140	107	147	5316 5346	EAST	6.700 6.700	200 200 200	1276 1276 1286 1280 1281 1281
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1 Horse 17th	1341 1524 1524 1524 1524 1524 1524 1524 15	100 100 100 100 100 100 100 100 100 100	100 100 100 100 100 100 100 100 100 100	139 148 149 149 149 149 149 149 149 149 149 149	185 185 195 198 199 109 109 108 198 198 198 197 197	121 169 189 181 171 180 180 180 180 180 180 180	100 100 110 110 100 100 100 100 100 100	136 137 137 137 130 130 130 484 131 140 140	148 148 156 148 149 148 148 148 148 148 149	1.00 1.40 1.40 1.70 1.00 1.00 1.00 1.00 1.00 1.00 1.0	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	COST COST COST COST COST COST COST COST	6300 6300 6301 6302 6302 6303 6303 6307 6302 6303 6303 6303	4365 1765 1265 4365 4366 4366 4366 4366 4366 4366 43	271 227 238 238 230 230 230 231 231 231 231 231 231	136 125 127 127 111 442 142 142 144 146 146	1.01 1.02 1.02 1.02 1.03 1.04 1.04 1.04 1.04 1.04 1.04 1.04 1.04	140 140 140 140 170 140 140 140 140 140	147 135 145 146 146 146 146 146 146 146 146	5.150 5.160 5.460 5.260 5.260 5.160 5.160 5.160 5.160 5.160	C127 C115 C216 C216 C216 C216 C216 C216 C216 C216	6.361 6.360 6.139 6.147 6.141 7.001 6.144 6.171 6.771 6.760 6.460	2.46 2.46 2.46 2.19 2.41 2.41 2.41 2.41 2.42 2.42 2.42 2.43 2.43 2.44 2.45 2.45 2.45 2.45 2.45 2.45 2.45	200 400 100 100 100 100 100 100 100 100 1
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The column	61 33 mm 0.73 143 1330 1384 1381 1387 1300 1388 1483 4864 1388 1.75	1 -4-KE 0-00 C441 1441 1441 1461 1561 1562 1562 1562 1572 1441 1571 15621 1573 1462
T. C. 19. 18. 18. 18. 18. 18. 18. 18. 18. 18. 18	44 Numb 075 1307 1407 1401 1404 1404 1405 1306 1306 1405 4804 1475 0407 44 Numb 0400 1415 1307 1401 1504 1408 1408 1407 1408 4804 1715 1408	7 448 UTS 188 188 188 478 482 180 178 180 178 180 170 180 170 180 170 180 180 180 180 180 180 180 180 180 18
1	66 House 246 186 2407 186 2501 186 182 162 162 465 118 246	
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		4 -480 840 8110 4104 4770 100 1758 4840 1250 110 8840 8841 1110 4104 4104
	16 House 148 800 148 148 148 170 148 148 148 148 140 100 140 140	
	9 House 1179 1842 1844 1844 1845 1846 1850 1850 1870 1870 1870 1870 1870 1870 1870 187	
	11 House 04% 1407 1407 1504 1500 1601 1500 1505 1505 1505 1505 1505	
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64 France 1346 1446 1577 1579 1346 1346 1347 1479 1470 1486 1346 1346 1346 1346 1346 1346 1346 134	41 House 164 1547 1446 1559 1450 1450 1470 1470 1470 1470 1480 1680 1687 1487 1597	
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68 Trans Life D. 15 D.	46 Trans 136 160 136 140 316 136 136 136 136 136 136 136 136 136	4 -4-00 CH CH CH CH 100 TON 100 CH 100 CH LOS CH
	46 H and 136 146 156 156 146 156 136 136 136 136 146 146 156 156 156 156	4 4-45 CH CH CH 520 CH CH 520

Supplementary table 3

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ID Time B.cells.naive B.cells.memory Plasma.cells T.cells.CD8
T.cells.CD4.naive T.cells.CD4.memory.resting T.cells.CD4.memory.activated
T.cells.follicular.helper T.cells.regulatory..Tregs. T.cells.gamma.delta
NK.cells.resting NK.cells.activated Monocytes Macrophages.M0 Macrophages.M1
Macrophages.M2 Dendritic.cells.resting Dendritic.cells.activated
Mast.cells.resting Mast.cells.activated Eosinophils Neutrophils
1 12week 0.015575342 0 0.10849816 0.016567504 0.05466253 0.097745403
0.004901416 0 0 0 0.005190278 0 0 0.130306998 0.03337372 0.064527371 0 0
0.055887986 0 0 0
2 12week 0 0.03192461 0.059279622 0.037718245 0.037459943 0 0.026331769
0.027000588 0 0.025086505 0.007502399 0 0 0.372170546 0.022573851
0.15716725 0 0 0 0.049887415 0 0
3 12week 0.005938979 0 0.095366223 0.001793445 0.067723992 0.086833621
0.011480721 0 0 0 0.015716542 0 0 0.117219581 0.019893868 0.070275102 0 0
0.045099442 0 0 0
4 12week 0.032888341 0 0.122276011 0.030791163 0.07213028 0.028356676
0.027119794 0 0 0 0.007130448 0 0.033568233 0.078720548 0.040362558
0.017677012 0 0 0.027359341 0 0 0
5 12week 0.006574197 0 0.158638663 0.010720579 0.05768052 0 4.00E-04 0
0.009478802 0.00436741 0 0.008495245 0 0.158177956 0.014319015 0.125031214
0 5.00E-04 0 0.014031192 0 0
6 12week 0 0 0.091683593 0.061921403 0.047507151 0.136739423 0 0 0 0
0.03542823 0.006386283 0.002389799 0.006434666 0.046414655 0 0 0.010556438
0 0 0
7 12week 0.009227643 0 0.08495157 0.052258052 0.10070034 0.093677743 0
0.003777598 0 0 0.02305868 0.014032899 0.012996475 0.065810464 0.001514677
0.071999552 0 0 0.012212259 0 0 0.039341461
9 12week 0.012311289 0 0.011336009 0.014218127 0.010481103 0.017970209
0.032767324 0 0 0 0 0 0 0.34950236 0.015515397 0.110307096 0 0 0.032442572
0.002988787 0 0
10 12week 0.020300539 0 0.026693843 0.012153038 0.012130227 0.023714487
0.052865401 0 0 0 0.007527064 0 0.001935591 0.214521587 0.026539025
0.139493269 0 0 0 0.164767833 0 0.021534896
11 12week 0.019030666 0 0.191021134 0 0.089898798 0 0.002783759 0
0.001180102 0 0.006305245 0 0 0.054916204 0.024952316 0.052968228 0 0
0.056842603 0 9.00E-04 0
12 12week 0 0.007244918 0.129346697 0.050841615 0.00411588 0.053224435 0 0
0 0 0 0.044669657 0.073254722 0.071995807 0.018536296 0.084393289 0 0 0
0.102270167 0 0
13 12week 1.00E-04 6.00E-04 0.025261549 0 0.105581314 0.021025681
0.004227483 0.004201634 0 0 0.014660907 0.003995388 0 0.197847351
0.005929693 0.117332784 0 0 0.026148221 0 0 0.004122923
14 12week 0.033091669 0 0.071268188 0.039068662 0.057929045 0.018174078
0.032584605 0 0 0 0.002314249 0.001391054 0.00283477 0.102742635
0.067637569 0.074921453 0 0 0.190993895 0 0 0
15 12week 0.013295201 0.003629017 0.020065675 0 0.050906514 0.033094807 0
0.005403001 0.018771435 0 0.006025883 0.036763279 0.016506705 0.054797831
0.018122785 0.093571342 5.00E-04 0 0.087796601 0 0.00615341 0
16 12week 0.009049755 0 0.167958747 0.013934355 0.016739843 0.082707288
0.06183714 0 0 0.014054257 0 0 0.022328365 0 0.027700024 0.128311957 0 0
0.054104818 0 0 0
18 12week 0.01206139 0 0.059059662 0 0.049037879 0.052058948 0 0.012418637
0.016607678 0 0 0.005110515 0.006293585 0.050429038 0.019042037 0.058988199
0 0 0.118107191 0 0 0
20 12week 0.009788651 0.001221378 0.007073351 0 0.006574556 0.050655048 0
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0.003875328 0.016753632 0 1.00E-04 0.010358982 0 0.292257929 0.022914978
0.083911695 0 0 0 0.001240367 0 0
22 12week 0.00586033 0 0.145423422 0.047795371 0.051876359 0.168117122
0.003407429 0 0 0 0 0.008108978 0.008935118 0.017077049 0 0.102241016 0
0.004946819 0.022071342 9.00E-04 0 0
24 12week 0.01208007 0.002661967 0.017736132 0 0.030259065 0.039111986 0
0.012667834 0.014369384 8.00E-04 0 0.042972197 0 0.110559868 0.011752609
0.085112542 0 0 0.114512752 0 0 0
25 12week 0.010157997 0 0.116924442 0 0.048601119 0 0.004382152 0.015732854
0 0.026431675 0 0.001230068 0 0.083623899 0.007378296 0.153890617 0 6.00E-
04 0.03774396 0 0 0
26 12week 0.004855683 0 0.149538017 0.050476124 0.1293102 0.085196422
0.021533784 0 0 0 0 0.006424856 9.00E-04 0.068780993 0.009705975
0.083957432 0 0 0.012544074 0.006113828 0 0
27 12week 0 0.107067299 0.059359982 0.16738988 0.057181096 0 0.258874837 0
0 0.114932638 0 0 0 0.091111208 0.066651123 0.091086484 0 0 0.022018339 0 0
28 12week 0 0 0.092759867 0.349064707 0.09095624 0 0.029395581 0 0
0.087389298 0 0.014883133 0 0.067595001 0.0294306 0.099988748 0.00540304 0
0 0.020891631 0.008294984 0
29 12week 0.004091359 0 0.097280883 0 0.05151988 0.059001916 0.006346101 0
0.00429861 0.045026321 0.01604412 0 0 0.027172839 0.013162924 0.105847217 0
0 0.06877859 0 0.002592125 0
30 12week 0.005097537 0 0.038365972 0 0.035915389 0.021921641 0.004678831
0.005752404 0.00418942 0.001681994 0.016798494 0 0 0.305287731 0
0.061637029 0 0 0.001895707 0.00746391 0 0
31 12week 0 0.059571596 0.081432207 0.135633945 0.034237171 0.034624387
0.0081932 0 0.006989014 0 0 0.028852 0 0.046801133 0.0553387 0.094128226 0
0 0.050401611 0 0 0.010784321
32 12week 0.012175221 0 0.108788684 0.04350211 0.089959862 0.020055685 0 0
0.022796947 0 0.007648867 0 0.005732455 0.093313728 0.009363303 0.055936413
0 0 0.035537664 0 0 0
33 12week 0 0.017191324 0.165725958 0.174094532 0 0.055273533 0.005773011
0.004433182 0 0.013989761 0 0.036698995 0 0 0.014495696 0.292675337 0 0
0.021856835 0.006468587 0 0.002530762
34 12week 0 0.023708558 0.075598073 0.059791642 0.05836012 0.085261411 0 0
0 0 0 0.014639302 0.033090824 0.037594968 0.005369907 0.121613353 0 3.00E-
04 0.102090053 0 0 0
35 12week 0.013446569 0 0.072613447 0 0.068882246 0.032629371 0.01272672 0
0.013802265 0 0.021718011 0 0 0.119761645 0.002427764 0.08177398 0 0
0.026201268 0 0 0
36 12week 0.010907827 0 0.062607472 0 0.048985196 0 0 0.007504081
0.008484428 0.019679519 0 0.025616761 0 0.110860204 0.016020633 0.172219661
0 0 0.05916829 0 0 9.00E-04
37 12week 0.049334191 0 0.097797143 0.145081523 0 0.034486475 0.137852296
0.042704615 0 0 0 0 0 0.199617853 0.056318849 0.13984945 0 0 0 0.003452694
0 0
38 12week 0.004707105 0 0.08806886 0 0.03197312 0.013377273 0.001307435
0.005959633 0.004782695 0 0.011205767 0.007416352 0 0.143907322 0.016056221
0.105113332 0 0 0.026045303 0 0.003496926 0
39 12week 0.010484967 0 0.025198734 0 0.018260344 0.049895837 0 0
0.007221616 0 0.006056557 0.011740403 0 0.214514499 0.014485413 0.050481044
0 0 0.041900228 0 0.002034466 0
40 12week 0 0.091795137 0.150381458 0.073603956 0.089494381 0 0.013623822 0
0 0 0.002608829 0 0.018698075 0.09626925 0.022530755 0.038652179 0 0 0
0.006423272 0 0
```

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41 12week 0.013741577 0.005606832 0.036805702 0.021106555 0.048144183 0
0.002824155 0 0.012406101 0.025418227 0 0.010302238 0 0.1708375 0.006778711
0.167754587 0 0.018448836 0.025322279 0 0.003071835 0
42 12week 0 0.015761818 0.130943794 0.150186269 0.010874097 0.01027022
0.077551445 0 0 0.087818529 0 3.00E-04 0 0.157212437 0.030861855
0.346692555 0 0 0.006355569 0.025290793 0 0.001630895
43 12week 0.010640206 0 0.046999304 0.008725902 0.032679094 0.017753285
0.039299878 0 0 0 0.013563271 0 0 0.478274457 0.013354846 0.019444784 0 0
0.01100465 0 0 0
92 12week 0.005087472 0 0.059642727 0 0.062031965 0.067609869 0 0
0.009238531 0 0.02937515 0.010504136 0 0.090288061 0.005835029 0.047801707
0 0 0.008941139 0 0 0
93 12week 0.011697787 0 0.083925815 0 0.019820911 0.019849445 0.004845053
0.009762199 0.007169621 0.008748794 0.008297215 0 0 0.259285166 0.009751946
0.128833013 0 0 0 0.004424604 0 0
94 12week 0.016727341 0 0.067219404 0.103556124 0.049920266 0.035722207
0.040975701 0 0 0 0.014546917 0 0 0.169691574 0.027033039 0.045922014 0 0
0.041932423 0 0 0
95 12week 0.051097696 0 0.055362228 0.139712323 0.01231884 0 0.095583744 0
0 0.035197485 0 0 0.011706923 0.108514675 0.061384103 0.063918848 0 0
0.046496077 0 0 0
96 12week 0.019718042 0 0.032600826 0.003749098 0.084643514 0 0.03875951 0
0.008016635 0.023798236 0.011421765 0 0 0.253310224 0.00674275 0.060127922
0 0 0.007597107 0.00333848 0 0
97 12week 0.052238493 0 0.084207314 0 0.002646509 0.082999773 0.023811652
0.008308395 0 0 0.076572186 0 0.003843097 0.033876011 0.040964171
0.06260104 0 0 0.024699741 0 0 0
44 12week 0 0 0.186541898 0.075832055 0.043647158 0.059920974 0 0 0 0
0.009470257 0.011622642 0.001934742 0.039933555 0.027513227 0.027533733 0 0
0.008646448 0 0 0
45 12week 0.009625164 0 0.108413675 0.013260484 0.079503579 0 0 0.009596351
0 0.009537775 0 0.014327539 0 0.044578513 0.01822524 0.081890789 0 0
0.138505218 0 0 0
46 12week 0 0 0.206711791 0 0.027773811 0.065816322 0 0 0 0 0.006098697
0.003426707 0 0.045892731 0.013492819 0.038521248 0 0 0.0083729 0 0 0
47 12week 0 0.068260638 0.079838758 0.132724909 0.074152857 0 0.001930086 0
0.002434549 0 0 0.018069596 0 0.086427882 0.052178198 0.090304189 0 0
0.028023467 0 0 0
48 12week 0 0 0.11201338 0.032373523 0.001 0.042040084 0 0 0.012697955 0 0
0.017443739 0 0.095854721 0.0099357 0.070818373 0 0 0.044985833 0.011296442
0 0
49 12week 0.001993775 0.010345565 0.005319167 0.092501665 0 0.038621763 0
0.009009944 0 0 0 0.021561263 9.00E-04 0.186697077 0.013518634 0.233453508
0 0 0.007731279 0 0 0
51 12week 0 0 0.137141779 0.061443152 0.007733132 0.015917719 0.006715262 0
0 0 0 0.009279171 0.002618881 0.136306636 0.01885015 0.039777028 0 0
0.052143646 0.001591091 0 0
52 12week 0 0.006504788 0.014593107 0.07339949 0 0 0.004329333 0.00418164 0
0.061067013 0 4.00E-04 0 0.374719654 0.023028741 0.372914227 0 0
0.002793714 0.003711038 0 0
53 12week 0 0.014563208 0.065272838 0 0.030844405 0.057211466 0 0.004835173
0.004968813 0.004529118 0.005365479 0 0 0.126885962 0.018325237 0.116302136
0 0 0.062256811 0 0 0
54 12week 0.023361946 0 0.060687635 0 0.05306127 0.064339886 0 0.004779383
1.00E-04 0 0.007196239 0.00722792 0 0.137945182 0.053813362 0.096656718 0 0
0.061286847 0 0 0
```

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55 12week 0.014364888 0 0.154064007 0.004300546 0.020624936 0.03353608
0.009732432 0 0.008419953 0.00982195 0.00165813 0 0 0.170601608 0.025104476
0.109152468 0 0 0.010080118 0 0 0
56 12week 0.003734197 0 0.129852714 0.014462955 0.013558648 0.0475228 0
0.02795221 0.001810791 0 0 0.006154149 0 0.096547241 0.018821666
0.056080842 0 0 0.022286781 0 0 0
57 12week 0.031504226 0 0.121047103 0.053385485 0.052881254 0.160907533
0.001746298 0 0 0 0 0.024605937 0.016640739 0.02905986 0.032502389
0.027201194 0.001975007 0 0.012413905 0 0 0
58 12week 0.005903999 0.004809256 0.05024633 0 0.026009838 0.029315521 0 0
0.010204838 0.036679901 0 0.010867991 0 0.232639763 0.010429359 0.093637751
0 0 0.025386699 0.003321263 0 6.00E-04
59 12week 0.035279426 0 0.047108589 0 0.0264877 0.019362755 4.00E-04
0.018624146 0.00435068 0 0.008086908 0.001478887 0 0.208986348 0.025295596
0.079033108 0 0 0.034700511 0 0 0
60 12week 0.008606711 0 0.082565266 0.170072336 0.095686109 0 0.026090998 0
0.020789651 0.139782681 0 0.016714534 0 0.156657779 0.024895252 0.111495187
0 0 0.002200023 0.01528478 0 0
61 12week 0.050486802 0 0.163310789 0.022116622 0.064812544 0.132555799
0.009469225 0 0 0 0 0.011247585 0 0.052736912 0.047412378 0.077208858 0 0
0.038834789 0.005399707 0 0
62 12week 0.009012584 0 0.249487259 0.037487482 0.088680468 0 0.011067903 0
0.005206517 0.007881811 0 0.001 0 0.061729452 0.01471947 0.042981849 0 0
0.030791595 0 0 0
64 12week 0 0.078647385 0.024585551 0.26624037 0 0 0.039228151 0.012989489
0.002611881 0.098174302 0 0.043286348 0 0.095439819 0.04173116 0.287011133
0 0 0.007194149 0 0 0
65 12week 0 0 0.151238434 0.090352587 0 0.076160158 0 0.001074054 0 0 0
0.062418502 0.010077116 0.003057144 0.02389427 0.052769589 0 0 0.046359157
0.019740372 0 0.011397958
66 12week 0.009643952 0 0.078694689 0 0.037619673 0 0.00154369 0.005386737
0.005517812 0 4.00E-04 0.003005482 0 0.212066755 0.021285455 0.077903867 0
0 0.01066103 0.003681087 0.00587486 0
67 12week 0.016137367 0 0.232625296 0.029887587 0.075100161 0 0.004084446 0
0.008432783 0.011822482 0 0.009802614 0 0.073276777 0.043935969 0.034755981
0 0 0 0.017790229 0 0
68 12week 0.022550714 2.00E-04 0.066840588 8.00E-04 0.049009381 0 0
0.004854612 0.029515581 0.046798584 0 0 0 0.134588417 0.022742469
0.112387782 0.002468547 0 0.026112213 0 0 0
69 12week 0 0.058129811 0.08709983 0.0983767 0.132797386 0 0.019259278 0 0
0.050596563 0 0.034488962 0 0.101300253 0.045171299 0.287493932 0 0 0
0.019378788 0 0
70 12week 0.012162696 0 0.256580939 0 0.067850848 0 0.003235183 0.006203823
8.00E-04 0 0.017729713 0.001160995 0 0.024387709 0.015029423 0.042942244 0
0 0.014005861 0 0 0
72 12week 0.028196804 0 0.075199812 0 0.045861678 0.097316949 0.003332316 0
0 0 0.02006155 0 0 0.181860221 0.035281418 0.098864808 0 0 0.033202378 0 0
74 12week 0.01064626 0 0.21354798 0.014730006 0.05201414 0 0 0 0.006137476
0.020517534 0 0.023911386 0 0.081179866 0.025219609 0.075313392 0 0
0.005454122 0.019994518 0 0.012457424
75 12week 0.009693418 0 0.01672109 0 0.011792559 0.046362763 0.00990402
0.003809873 0.006930826 0 0.024973241 0 0 0.292133549 0.018554495
0.098262831 0 0 0.005637654 0.002338908 0 0
76 12week 0.011648719 0 0.045337324 0 0.061587031 0 0.004563816 0
0.005262727 0.019230132 0.013562648 0 0 0.245659853 0.030748426 0.115467258
```

```
0 0 0 0.014912597 0 0
77 12week 0.014880147 0 0.06118217 0.018860734 0.06320139 0.004210304
0.00741538 0 0.010203318 0 0.011037275 0 0 0.270031539 0.042799072
0.091111393 0 0 0.027300374 0 0 0
78 12week 0.012775621 0 0.056071768 0 0.026211028 0.087312921 0 0
0.01064111 0 0.018007384 0.016228783 0 0.021608486 6.00E-04 0.029034171 0 0
0.105678699 0 0 0
79 12week 0.019221671 0 0.01940576 0 0.131053891 0 0 0.00803335 0.036155131
0 0.002264736 0.024121809 0.010377595 0.0308451 0 0.099511641 0 0.003400933
0.054004675 0 0 0
80 12week 0 0 0.014640082 0.075906846 0 0 0.02624172 0.00357198 0 0
0.006390358 0 0.019254311 0.310853416 0.020232987 0.080184411 0 0
0.018613442 0 0 0.027135573
81 12week 0.006147814 0.002232234 0.032774714 0 0.056021858 0 0 0.003896034
0.012515946\ 0.048350364\ 0\ 0.044535405\ 0\ 0.220923007\ 0.021483224\ 0.137489839
0 0 0 0.042626637 0.01156232 0
82 12week 0.007210641 7.00E-04 0.034000882 0 0.063100718 0 0 0.007605491
0.007190074 0.004148101 0 0.019263581 0 0.105242801 0.004362099 0.195945668
0 0 0.055195686 0 0 0
83 12week 0.019269908 0 0.070801756 0 0.072356737 0.071826674 0 0.00253806
0.006159443 0 0.030742312 0.006993709 0.008246344 0.050095082 0.018018673
0.059403034 0 0 0.018964109 0 0.003819251 0
84 12week 0.02253368 0 0.10300895 0.088031749 0.116650788 0.071532891
0.01840717 0 0 0.028355835 0 0 0 0.056200637 0.049453702 0.233807073 0 0
0.011960151 0.008948759 0 0
85 12week 0 0.018614205 0.03723953 0.108192281 0 0.089860149 0.076765689 0
0 0 0 0 0 0.340304655 0.031579912 0.195807583 0 0 0 0.01351018 0 0
87 12week 0.040480511 0 0.097266706 0.023847864 0.069557452 0 0.049635572 0
0.015740586 0.020688835 0 0 0 0.143256219 0.03389493 0.172333145 0 0
0.08049066 0 0 0
88 12week 0.043197151 0 0.029271921 0.128991124 0.114298451 0 0.178837049
0.008674458 0.001010464 0.069108588 0 0 0 0.1968884 0.113382017 0.023298962
0 0 0.028982803 0 0 0
89 12week 0.014382092 0 0.021604976 0 0.013165484 0.070636835 0 0.005701871
0.014032206 0 0.029210871 0.001041212 0 0.144952377 0.002745258 0.061948111
0 0 0.01758938 0 0.003313123 0
90 12week 0.016469887 0 0.037583858 0 0.037482355 0.007634414 0.0045673
0.007250628 0 0.034128846 0 0 0 0.223963504 0.023201396 0.070785712 0 0
0.03130378 0 0 0
1 25week 0.006821112 0 0.068229566 0 0.086234963 0.045945707 9.00E-04
0.006531278 0.006578157 0 0.02067453 0.008622676 0 0.030074588 0.040327378
0.053669317 0.016812713 0 0.053635428 0 0.003671041 0
2 25week 0.002064045 0.021024523 0.025392024 0.035290111 0.038328584 0
0.010205857 0.057694581 0 0.039330901 0 0.025169719 0 0.139295981
0.030559318 0.138480299 0 0 0 0.012114149 0.001306094 0
3 25week 0 0.045674499 0.101814305 0.070634258 0.092054947 0.083094008
0.004949769 0 0 0 0 0.015706111 0 0.078684757 0.021406076 0.075703272 0 0
0.017864512 0 0 0
4 25week 0.002779373 0 0.05442713 0.016606112 0.069904782 0.139053036
0.018656812 0 0 0 0.037793971 0 0.002707276 0.062118406 0.017257492
0.03677335 0.002833376 0 0.002789952 1.00E-04 0.008646356 0
5 25week 0 0.016361538 0.009527629 0.021412001 0 0.046470924 0.015047261 0
0 0 0.017940728 0.02844642 0.02156267 0 0.037015319 0.277868809 0 0
0.05268204 0 0 0
7 25week 0.037400712 0 0.05342227 0 0.025055409 0.034121142 0 0.020069247 0
0 0.007367561 0.016179659 0 0.125105266 0.010393224 0.135094007 0 0
```

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0.022022146 0 0.004482792 0
8 25week 0.014240074 0 0.043567993 0.063044287 0.016976859 0.093243907
0.007368733 0.003033444 0 0 0.069025327 0.011580569 0.013446942 0.005744615
0.01713427 0.117594887 0 0 0.069560584 0 0.006303203 0
9 25week 0.006163885 0.004248948 0.007884574 0 0.020584713 0.013628955 0
0.008737295 0.008138638 0.028921112 0 0.013949183 0 0.264589679 0.006140455
0.244452952 0 0 0 0.026609913 0 0
11 25week 0.018983037 0 0.069230675 0.022613416 0.03311861 0.145640332 0
0.005039996 0 0 0.007350172 0.014258263 0.007551698 0.106450033 0.014240951
0.124604464 0 0 0.022415468 0 7.00E-04 0
12 25week 0.025129174 0 0.133976956 0 0.048762831 0.035050326 0 0.013813603
0.006208934 0.019388029 0.014510126 0 0 0.04473864 0.012803719 0.120160306
0 0 0.054077561 0 0 0
13 25week 0.021745085 0 0.067166599 0.031767431 0.077067099 0 0 0.031054263
0 0.033039603 0 0.019878444 0.012564001 0 0 0.161956839 0 0.013542361 0
0.075298693 0.006478059 0
14 25week 0 0 0.164637773 0.039466926 0.03195315 0.003630039 8.00E-04
0.01441319 0 0 0.00548339 0.004093987 0.037651376 0 0.024718339 0.138185149
0 0 0.027203857 0 0 0
15 25week 0.039718986 0 0.084123365 0.01750844 0.032662685 0.039703201
0.009687233 0 0 0 0.022133151 0 0 0.174329105 0.022410004 0.039673348 0 0
0.014491534 0 0 0
16 25week 0.008016788 0 0.125797532 0.03084821 0.052978344 0.126597671
0.008712517 0 0 0 0.025685752 0 0.02393836 0.012404079 6.00E-04 0.054352544
0 0.002719057 0.004335585 0 0.00505598 0
17 25week 0.032725161 0 0.021007445 0 0.030158512 0 0.051928033 0.005643033
0 0.012612164 0.015651341 0 0 0.328028262 0.017249952 0.045296341 0 0 0
0.02325123 0.004458032 0
18 25week 0.006762765 0 0.154037639 0 0.071778025 0.039729755 0 0.0126963
0.004540639 0 0.003111213 0.022112414 0.010187088 0.008369612 0.013246672
0.058544888 3.00E-04 0 0.067654573 0 0 0
19 25week 0.009516326 0 0.036788682 0.016166144 0.057081723 0.129998801 0 0
0 0 0.022451831 0.010851907 0 0.078028353 0.016750283 0.055544069 0 0
0.011607081 0 0 0
23 25week 0.024419721 0 0.013717319 0.139028953 0 0.013594508 0.06719234 0
0 0 0 0.047669683 0.023971574 0.038922317 0.054374108 0.219578656 0 0
0.005050046 0.013154835 0 0
26 25week 7.00E-04 0 0.137371703 0.038118504 0.022204813 0.141947246 0 0 0
0 0 0.038329867 0.012193829 0.019878239 0.009787964 0.052610735 0 0 0
0.025494952 0.001125815 0
29 25week 0.016471189 0 0.092057638 0.0756458 0.04898885 0.067393212 0
0.015809245 0.003007654 0 0.028533139 0 0 0.07114549 0.007002425
0.037395972 0 0 0.031735468 0 0.007042312 0
31 25week 0.009482679 0 0.185968922 0 0.061259233 0.038778973 0 0
0.019551503 0 0.035268149 0.008697978 0 0.037562411 0.003360275 0.072538099
0 0 0.012729345 0 0 0
32 25week 0.068055518 0 0.09757193 0.018769017 0 0.064835907 0 0.021525165
0.012227769 0 0 0.025463999 0 0.066369533 0.041975471 0.05309363 0 0
0.012480096 0 0.003449662 0
34 25week 0.010680582 0 0.070130697 0 0.045731628 0.122660738 0.003914214 0
0 0 0.030493633 0.012050253 0.00583346 0.10072715 0.008860024 0.054466691 0
0 0.036436718 0 0.001389032 0
35 25week 0.005740432 0 0.209170878 0 0.073017458 0.052323961 0 0 0
0.015389754 0 0.018668201 0.004145601 0.014124278 0.00463322 0.009119378 0
0 0.022478404 0 6.00E-04 0
36 25week 0.010077215 0 0.057717857 0 0.026443959 0.218104634 0 0 0 0
```

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0.026579196 0.010897571 0 0.017800779 0.001715344 0.099962466 0 0 0
0.015929861 0.007080156 0
37 25week 0.058001551 0 0.113742689 0.111608006 0 0.116556239 0.074286561
0.004549114 0 0 0 0.035031823 0.01468154 0.027971296 0.01513676 0.127087688
0 0 0.003544661 0 0 0
38 25week 0.014845048 0 0.053126209 0 0.023392071 0.123220228 0 0 0 0
0.04144376 0.017685689 0 0.107941393 0.010077833 0.064764356 0 0 0
0.018580818 0.007054882 0
39 25week 0.006970118 0 0.016030521 0.057757071 0 0.065301815 4.00E-04 0 0
0 0 0.032539473 0 0.195826718 0.027946794 0.047231102 0 0 0.048982061 0 0 0
41 25week 0.020284886 0.010027916 0.06475542 0.016239479 0.058283708 0
0.023845919 0.010896315 0.015900215 0.022854509 0 0.008821012 0 0.180298877
0.040658151 0.139252592 0 0 0.014940703 0 0.002190264 0
43 25week 0.037127006 0 0.029858759 0.046699508 0.110050422 0.101242348 0 0
0 0 0 0 0 0.041382754 0.104993438 0.076001939 0 0 0.013977457 0 0.008867953
91 25week 0.007782848 0.022473618 0.061186018 0.049479722 0.130970569
0.080668818 0.009995958 0 0 0 0 0 0.086168058 0.007612412 0.062673824 0 0
0.014746528 0 0 0
92 25week 0.006676984 0 0.079835163 0.062744886 0.06597598 0.161385031 0 0
0 0 0.002316031 0.004258459 0.022417104 0 9.00E-04 0.049481923 0 0.00480016
0.00562392 0.00494982 0 0
93 25week 0.01118439 0 0.077950505 0.049318488 0.078887058 0.114824284
0.007755195 0 0 0.006627981 0 0 3.00E-04 0.041900316 0.0211591 0.08158732 0
0 0.014772741 0 0 0
94 25week 0.007805079 0 0.058737863 0.079054457 0.039035955 0.102756126
0.004581811 0 0 0 0 0.034285491 0.018222571 9.00E-04 0.008401512
0.083524675 0 0.002166044 0 0.053953885 0.008070494 0
96 25week 0.005072324 0 0.102505236 0.021940547 0.060340171 0.122500838
6.00E-04 0 0 0 0.019568924 0 0 0.051420769 8.00E-04 0.111026853 0 1.00E-04
0.020876157 0.007078309 0 0
97 25week 0.026850399 0 0.02633632 0.066839784 0.034017893 0.019214537
0.066871339 0 0 0 0 0.012025393 5.00E-04 0.187103093 0.007509632
0.101086463 0 0 0.006115477 0 0 0
98 25week 0.005470473 0 0.01621839 0.013517196 0.072345073 0.096787115
0.006188738 0 0 0 0.013960627 0 0 0.192048004 0.00957984 0.058482321 0 0 0
0.012189774 0.007503124 0
44 25week 0.003988803 0.006780839 0.043456582 0.005227371 0.088684076
0.116904747 0 0 0 0 0.020836684 0 0 0.059173714 0.005563064 0.099350838 0 0
0.015507197 0 0 0
45 25week 0.012422588 0 0.109479746 0 0.033479645 0.15201151 0 0.010212892
0 0 0 0.031902005 0 0.027876887 0.020974005 0.077433974 0.005058598 0
0.013647301 0.008397239 0.002044235 0
46 25week 0.002142582 0.010915504 0.027423118 0.053402923 0.011610995
0.110294564 0.017483143 0 0.012315435 0 0.030269005 0 0 0.099838355
0.005356879 0.078801986 0 5.00E-04 0.024293736 0 0 0
48 25week 0 0 0.108141713 0.039789025 0.030037372 0.103722746 0 0 0 0
0.017848913 0.009525776 0.018015452 3.00E-04 0.045573418 0 0 0.004892388 0
0 0
49 25week 0.001650654 0.005826523 0.00475491 0.098680082 0 0.032162775 0 0
0 0 0 0.025826588 0.002887699 0.164409933 0.016809021 0.25625252 0 0
0.008529523 0 0 0
50 25week 0.00794946 0 0.046609923 0 0.116877648 0.167442928 0 0.002211661
0 0 0.024970167 0 0.025795667 0.006829217 0.013650109 0.045329896 5.00E-04
0 0.014100181 0 0.007477546 0
```

51 25week 0.010595558 0 0.142628946 0 0.012620408 0.109184477 0 0

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0.005274276 0 0.003188477 0 0 0.05072826 0 0.096863294 0 0 0.054635227 0 0
0.012394931
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0.006418609 0 0.027751221 0.004363657 0.025265062 0 0 0.056581204 0
0.007219637 0.035051522 0 0.002405155 0
54 25week 0.028892336 0 0.077612034 0.143466853 0.050241619 0.045974774
0.02425653 0 0 0 0 0.020169692 0.011907539 0.123375985 0.037981174
0.088089083 0 0 0.049087291 0 0 0
55 25week 0.027929637 0 0.131873998 0.047296311 0.061267663 0 0.014281698 0
6.00E-04 0 0.01150013 0 0 0.185842079 0.024399132 0.063404339 0 0
0.004353452 0.003315914 0 0
56 25week 0.003398794 0 0.082747715 0.031099724 0.017575722 0.025016961
5.00E-04 0 0 0.001215898 0 0.00607831 0 0.331818477 0.012056554 0.038722874
0 0 0.003972134 0.006096249 0 0
57 25week 0.017914732 0 0.173287696 0.105636747 0.031060149 0.088497327
0.004040833 0 0 0 0 0.087680214 0.02449405 0.001855574 0.019807199
0.019524525 0.001976419 0 0 0.02245616 0.005717058 0
58 25week 0.019157748 0 0.113375798 0.013748984 0.071737535 0.119377049
0.003924771 0 0 0 0.015730451 0.026872235 0 0.142274432 0.013018059
0.079097094 0 0 0.009696056 0.009029207 0 0
59 25week 0.006947834 0 0.102471552 0 0.033226168 0.03359217 0 0.00311481 0
0 0.006196715 0.005228022 0 0.163462546 0.006226027 0.078224533 0 0
0.017743239 0 0.002836586 0
60 25week 0.009440628 0 0.187804162 0.189569363 0.116716005 0 0.015340539 0
0 0.04354224 0 0.016841715 0 0.090805252 0.036597633 0.052583815 0 0
0.011182074 0.003251873 0 0
61 25week 0.012585209 0 0.171329267 0.108031409 0.092457505 0.084841091 0 0
0 0 0 0.054198344 0.028985827 0.007460728 0.021575105 0.03336411
0.004675013 0 0 0.033181539 0.011381483 0
62 25week 0.004372016 0 0.13576459 0 0.087450798 0.094283885 0 0.004799613
0 0 0 0.062274814 0.019434787 0.014877193 0.01257364 0.011188299 3.00E-04 0
0 0.013994412 0.005418956 0
63 25week 0.031028809 0 0.07794265 0.020793099 0.028215727 0.034993006
0.089583665 0 0 0 0.007708451 0 0 0.310263921 0.026457979 0.136587955 0 0
0.001479078 0.026264411 0 0.005150233
64 25week 0 0.017048096 0.030809923 0.214445019 0 0 0.001469175 0.013969248
0.003288022 0.07655265 0 0.031282689 0 0.035619167 0.001216386 0.381729323
0 0.00210164 0.001466607 0 0 0
65 25week 0.020904353 0 0.111904093 0.059788421 0.0040148 0.122131157
0.005489744 0.00974362 0 0 0 0.05759454 0.015782913 0.022728398 0.026090712
0.064770079 0.00366796 0 0.042711796 0.01384057 0 0
66 25week 0.018027662 0 0.091405066 0 0.033276835 0.006161565 0.007202378
0.0146836 0.004176239 0 0.011879951 0.005669263 0 0.231938579 0.028303037
0.092907748 0 0 0 0.020280285 0 0
67 25week 0.015800134 0 0.126932085 0.102780037 0.034966092 0.009357992
0.131373898 0 0 0 0 0 0.006656823 0.184990184 0.051006358 0.094810871 0 0
0.010921212 0 0 0
68 25week 0.006480101 0 0.201786255 0.089263987 0.03818432 0.06823373
0.003201839 0 0 0 0 0.015085101 0.031770731 0 0.014219299 0.08563661 0
0.001004784 0.043403522 0 0 0
69 25week 0 0.049156597 0.097302781 0.092836859 0.026220074 0 0.074268063 0
0 0.020777545 0 0 0.009665037 0.348277821 0.028973303 0.232525598 0 0 0
0.034083767 0 0
70 25week 0 0 0.219120127 0.012283176 0.001 0.012630417 0 0.004826405 0 0 0
0.023676361 0.006412868 0 0.003690363 0.075151461 0 0 0 0.085956867 0
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0.008871599

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0.001294487 0.006072529 0
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0 0 0 0.015707252 0.024643557 0.015717535 0.010915235 0.057154561 0
0.003041733 0 0.015594358 0.010424442 0
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0.002956807 0 0 0 0 0.020604958 0 0.059639556 0.001332578 0.092164623 0
0.001143906 0.004305452 0.006399248 0.004689366 0
74 25week 0 0.053774914 0.227649546 0.097148212 0.048304988 0.017274135 0 0
0 0.014641802 0 0.078612872 0 0.103326752 0.029877532 0.085740135 0 0 0
0.044201025 0 0
75 25week 0 0.015833327 0.019161948 0 0.030591745 0.03119654 0 0.008467575
0 0.013211563 0 0.023678208 0 0.218868016 0.006789491 0.144698772 0 0 0
0.067202772 0.003035582 0
76 25week 0 0.013612636 0.073424487 0.146189466 0 0.043618052 0.003284521 0
0 0 0 0.045845465 0 0.078334084 0.008003375 0.159002474 0 0 0 0.046321308 0
77 25week 0 7.00E-04 0.074780559 0.061138112 0.008162619 0 0.002287696
0.007022932 0 0.023388127 0 0.039179961 0.007150812 0.493768326 0.028222002
0.009284451 0 0 0 0.034717663 0.004706371 0
79 25week 0.025089978 0 0.048339807 0.041431587 0.043933172 0.001910783
0.001196988 0 0.006953689 0 0.013847082 0.015165118 0 0.140378038
0.011680056 0.090281098 0 0 0.001984 0.005118253 0.004559269 0
80 25week 0.00641281 0 0.037964791 0.014477906 0.054988855 0.188965169 0 0
0 0 0 0.03201199 0.014417862 0.022481803 3.00E-04 0.118773612 0 2.00E-04
0.008714618 0 0 0
81 25week 0.025656875 0 0.013679767 0.034417947 0 0.142816287 0 0 0 0
0.063107133 0.072280948 0.035097875 0.027949626 0.122587378 0 0 0
0.073317219 0.003056505 0
82 25week 0.017298665 0 0.180732364 0.026603393 0.084678205 0 0 0
0.005860176 0.053968531 0 0.052322082 0.022209947 0.018888681 0.020085713
0.107513865 0 0 0 0.053648775 0.007516008 0
83 25week 0.018360429 0 0.06919118 0 0.082691752 0.050791662 0.005880532
0.01377459 0 0.045996351 0 0.066768365 0.012928101 0.022351792 0.024066655
0.095317015 0 0 0 0.022641756 0.002249801 0
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0.002400315 0 0 0 0.031658548 0 9.00E-04 0.046246831 0.013712551
0.035461105 0 0 0 0.025589193 0 0
87 25week 0.023896264 0 0.135590292 0.075184653 0.027685047 0.126321588 0 0
0 0 0 0.01803752 0.018923295 0 8.00E-04 0.043994254 0 0.002172742 0
0.00419555 0 0
88 25week 0.065406394 0 0.103076336 5.00E-04 0.057936977 0 0.003016904 0
0.028104583 0 0 0.004249126 0 0.175702955 0.038666946 0.085355745 0 0
0.023808626 0 3.00E-04 0
89 25week 0.015996524 0 0.039203512 0 0 0.046704169 0 0.020964969
0.011845853 0 0.004525604 0.009009974 0 0.240233024 0.018120796 0.078702272
0 0 0 0.012800258 0.007553571 0
90 25week 0 0.011136864 0.022771022 0.046545181 0.025386906 0.11950295 0
0.002022163 0 0 0 0.113532058 0.004584228 0.009718105 0.011949015
0.044501382 0 0 0 0.106860375 0.001222278 0
1 0week 0.018109301 0 0.117642186 0.012921631 0.073419763 0.086716934
0.005362714 0 0.002932845 0.001141831 0 0 0.016607528 0.102985261
0.042251604 0.079697311 0 0 0.030747513 0 0 0
2 Oweek 0.007365339 0.009303903 0.022246244 0 0.031508875 0.012189594
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0.001845318 0.02923097 0.006160834 0.027340576 0 0 0 0.25186706 0.016885785

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0.07774598 0 0 0.005924299 0 0 0
3 Oweek 0.050502355 0 0.125837759 0.032526731 0.048268525 0.044838152
0.006052058 0.003336688 0 0 0.004625998 0 0.009385004 0.038801236
0.037824767 0.046989049 0 0 0.047965552 0 0 0
4 Oweek 0.027677232 0 0.103221617 0.061966112 0.104978259 0.11666183
0.007050812 0 0.005455723 0.01844632 0 0 0 0.105277178 0.054879901
0.019131524 0 0 0.022070946 0 0 0
5 Oweek 0.01240067 0 0.154262709 0 0.054125725 0 0 1.00E-04 0.016887389 0 0
0.017213524 0 0.12050677 0.020891063 0.078077251 0 0 0 0.015142418 0 0
6 Oweek 0.002445856 0 0.126474059 0 0.066610489 0.088824965 0 0 0 0
0.004422334 0.005593526 0 0.034888702 0.012908343 0.033784239 0.004235356 0
0.03659324 0 0 0
7 Oweek 0.042785672 0 0.070760621 0 0.070304057 0.070917601 0.005990092 0 0
0 0.020076909 0 0.011674621 0.085493582 0.007735397 0.079545612 0 0
0.032116396 0 0 0
8 Oweek 0 6.00E-04 0.040991577 0.052747534 0 0 0.080618953 0.033543522
0.004912278 0 0.029925542 0 0 0.284789177 0.06057181 0.100155268 0 0 0
0.023828237 0 0
9 Oweek 0.013289217 0 0.074493631 0 0.042413901 0.043004598 0.006558656 0
0.010390318 0 0.011801536 0 0 0.209890966 0.033596439 0.083378118 0 0
0.024081164 0 0 0
10 Oweek 0 0.072461832 0.025046723 0.008377211 0.076808441 0.06413802
0.031651602 0 0 0 0.021497717 0 0 0.227310382 0.014874524 0.279529753 0 0 0
0.087580258 0 0
11 Oweek 0.02764634 0 0.117091396 0.057953498 0.067133486 0.134530084
0.011838786 0 0 0 0.004615747 0 0 0.053558376 0.042806302 0.10239526 0 0
0.001026149 0 0 0
12 Oweek 0.007966121 0 0.115067557 0.031571044 0.081656522 0.100114354
0.006520148 0 0.003530966 0.002804513 0 0 0.004194675 0.066940996
0.036644211 0.069257926 0 0 0.071528233 0 0 0
13 Oweek 0.027016998 0 0.014057486 0 0.033350777 0.021007903 0 0.00397041
0.008286628 0 0.016530232 0 0 0.268342184 0.013591236 0.076572181 0 0
0.003027839 0 0 0
14 Oweek 0.024601103 0 0.034474965 0.01346033 0.03672533 0 0.009688619
0.012672368 0.02529556 0.027358599 0 0.024085147 0 0.127289381 0.03166444
0.07719948 0 0 0.165360676 0.009073685 0 0
15 Oweek 0.006436591 0 0.168052956 0.034709537 0.02696318 0 0.007583607
0.005994646 0 0 0 0.021670178 0 0.048022875 0.026138637 0.053310611 0 0
0.019119253 0 0 0.004136178
16 Oweek 0.020287163 0 0.147926753 0 0.047879744 0.079048013 0 0
0.004900434 0 0 0.00546376 0 0.08988148 0.046334906 0.067515331 0 0
0.016025158 0 0 0
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0.002128364 0.016290042 0.009512166 0 0 0.376340491 0.028799154 0.043011585
0 0 0 0.031555493 0 0
18 Oweek 0.036696233 0 0.116143464 0 0.099577273 0.021687997 0 0.001549676
0.011042546 0 0.003947868 0 0.001011034 0.051755817 0.053536177 0.042502752
0 0 0.045429809 0 0 0
19 Oweek 0.056624811 0 0.186343335 0 0.066057338 0 0.027477315 0.018329543
0.006151349 0.01875697 0.002307637 0 0.007243518 0.03021361 0.005326808
0.054521323 0 0.007828199 0.03194081 0 9.00E-04 0
20 Oweek 0.012703786 0 0.032420741 0 0.025431811 0.03421117 0.001717694
0.006767913 0.006889881 0 0.007383295 0 0 0.265688326 0.011953158
0.067882144 0 0 0 0.011820154 0.002766104 0
21 Oweek 0.060025032 0 0.114093986 0.056343397 0.101254339 0 0.139359214 0
0 0.008444249 0.006277619 0 0.001718339 0.095086209 0.060845937 0.122167677
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0 0 0.012544698 0 0 0
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0 0.012658077 0 0.007342858 0 0 0.049622677 0.073465082 0.071282719 0 0
0.009367663 0.007167018 0 0
23 Oweek 0.00527113 0 0.087651352 0.007819356 0.028292483 0.042723159
0.023921741 0 0 0 8.00E-04 9.00E-04 0 0.246786565 0.05912538 0.092685376 0
0 0 0.014662642 0 0
24 Oweek 0.001139749 0.003293749 0.042311327 0.035078997 0 0 0 0.010178173
0.015099886 0 0 0.003973542 0 0.188391254 0.031850258 0.065436426 0 0
0.061861693 0.02219372 0 0
25 Oweek 0.011344157 0 0.134869864 0 0.045040202 0.006852366 0.003067822 0
0.007197375 0.006180689 0.005164199 0 0 0.161371512 0.009830395 0.098892742
0 0 0.004432164 0 0 0
26 Oweek 0 0 0.024728126 0.02203972 0.016893431 0 0.005936585 0 1.00E-04
0.014317464 0 0 0 0.430392099 0.031548837 0.073168629 0 0 0 0.007640479 0 0
27 Oweek 0.07556307 0 0.094569918 0.140743882 0.024134571 0 0.188885271 0 0
0.03827661 0.007496191 0 0 0.104332998 0.099549413 0.070439433 0 0
0.002374589 3.00E-04 0 0
28 Oweek 0 0 0.049847175 0.094824026 0.030670044 0 0.142914788 0.02189972 0
0.029870581 0 0.013481939 0 0.099461216 0.075736491 0.083774044 0
0.024033271 0.015785861 0 0 0
29 Oweek 0.015250139 0 0.058177052 0 0.00277624 0.015399542 0 0.029413813 0
0 0.009939941 0 0 0.214861316 0.013074824 0.069544891 0 0 0.023424718
0.019643319 0 0
30 Oweek 0.045601412 0 0.058783326 0.043324588 0.080935769 0 0.045579332 0
0 0 0 0.001 0 0.122063843 0.056387793 0.054987744 0.001498852 0 0
0.060591512 0 0
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0.004376904 0.022911404 0 0.008525989 0.001246172 0 0.154771296 0.053219382
0.096628443 0 0 0.034115033 0 3.00E-04 0
32 Oweek 0.009669961 0 0.189528823 0 0.084225296 0.014962723 0.007763772
0.002609316 0.008010273 0 0.019427559 0 0 0.034767751 0.047443987
0.048649799 0 0 0.039452083 0 0 0
33 Oweek 0 0.014025947 0.101234975 0.06676314 0.010658539 0.007468822
0.132578241 0 0 0 0.034266063 0 0.025638786 0.267090054 0.049026516
0.042109089 0 0.050182126 0 0.050731873 0 0
34 Oweek 0.036218185 0 0.057570094 0 0.038868056 0.047360432 0.00127799
0.007929684 0.016272538 0 0.008931288 0.01312754 0.01257024 0.061811618
0.030588887 0.084709162 0 0 0.084645909 0 0 0
35 Oweek 0.007724482 0 0.110879368 0 0.021607579 0.023245745 0.003646158
0.007336734 0.00918272 0 0.002406805 0.015590452 0 0.179586847 0.019933012
0.126982699 0 0 0.002101688 0 0.00425538 0
36 Oweek 0.010660914 0 0.038523905 0 0.042833765 0.020720749 0 0
0.011839706 0 0 0.020867305 0 0.241807888 0.011071075 0.071069184 0 0 0
0.033266005 0 0
37 Oweek 0.023159104 0 0.050785363 0.076074262 0 0.018481405 0.100610698
0.022796285 0.001468376 0 0.014644645 0 0 0.165386037 0.112892733
0.06828917 0 0 0.003412955 0 0 0
38 Oweek 0.062323973 0 0.132972106 0.038390548 0.020959474 0.058560762
0.103673336 0 0 0 0 0 0.006395619 0.056852732 0.042296145 0.077006205 0 0
0.025447152 0 0 0
39 Oweek 0.0074056 0.003839357 0.037037658 0 0.035860522 0.084136288 0
0.008245096 0.009712097 0 0.020617616 0.008160053 0 0.129490347 0.009267242
0.072962048 0 0 0.027676766 0 0.001390549 0
40 Oweek 0 0.04930259 0.127412449 0.126767532 0 0.011526556 0.013949171
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0.040787456 0.006778617 0 0 0.038395902 0.004887023 0.086926432 0.057743173

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0.057069656 0 0 0.007707363 0 0 0
41 Oweek 0.01155533 0 0.120993058 0.024079206 0.044165578 0.033548161
0.002269068 0 0.019818038 0.009192262 0 0 0 0.123458578 0.040938862
0.090518572 0 0.012602413 0.010760735 0 0.004014586 0
42 Oweek 0.028644449 0 0.024979082 0.006010484 0.002410155 0 0.127612216
0.04089012 0.014692527 0.02356397 0 0.015885667 0 0.123227045 0.101401882
0.090829921 0 0 0 0.047826884 0 0.003868278
43 Oweek 0.003945302 0 0.0168544 0 0.024848304 0.051583493 0.003832187
0.002409553 0.003969918 0 0.015485909 0 0 0.250677188 0.002465664
0.050845746 0 0 0.015621882 0 0 0
91 Oweek 0 0.020663535 0.038751674 0 0.032184588 0.070005364 0 0
0.013873123 0 0.026269512 0.016298339 0 0.13643542 0.013713052 0.066435862
0 0 0.021685396 0 1.00E-04 0
92 Oweek 0.026104599 0 0.08203605 0 0.01490438 0.033045216 0 0.059159663
0.006249842 0.0062693 0 0.019408183 0 0.038543705 0.007214668 0.074279346 0
0 0.070825134 0 0 0.015109813
93 Oweek 0 0 0.045233449 0.042960238 0 0.009646726 0.053261823 0.001680037
0 0 0 0.018755235 0 0.203152298 0.039956277 0.091845874 0 0 0.004991433 0 0
94 Oweek 0.026168575 0 0.074743822 0 0.058225571 0.031580147 0.004195741 0
0.015971335 0 0.006549694 0 0 0.159154462 0.020771735 0.073614544 0 0
0.035332291 0 0 0
95 Oweek 0.066525025 0 0.133130561 0.132717141 0.001748136 0 0.111384804 0
0 0.031027916 0 0.02900015 0 0.039708891 0.078309925 0.044118078 0 0
0.041016061 0 0 0
96 Oweek 0.046395004 0 0.116599518 0.023991072 0.016833816 0.015988578
0.019753014 0.006742583 0 8.00E-04 0 0.003263082 0 0.101033531 0.011431157
0.052362839 0 0 0.0469838 0 0 2.00E-04
97 Oweek 0.065035554 0 0.085606132 0 0.036244632 0.022249338 0.057563496
0.016362685 0 0 0.053379389 0 0 0.056336929 0.023048188 0.058886053 0 0
0.02166786 0 0 0
98 Oweek 0.072043083 0 0.185837318 0.064933477 0.040416536 0 0.10281646 0
0.007963951 0.006465346 0.01015694 0 0 0.129706315 0.056296252 0.070984676
0 0 5.00E-04 0.002194367 0 0
44 Oweek 0.070321794 0 0.07849052 0.015912669 0.159607638 0.101948444
0.043506182 0 0 0 0.022174637 0 0.004531553 0.108444835 0.029863101
0.044007757 0 0 0.010667292 0 0 0
45 Oweek 0 0.015252249 0.071409284 0.048100814 0.089591587 0.061981977
0.013486262 0 0 0 0 0 0.013963888 0.037573827 0.03582577 0.065368738
0.004182335 0 0.165130508 0.007718185 0 0
46 Oweek 0.054833067 0 0.113644514 0.191889299 0.045065811 0 0.026639783 0
0.020232901 0.002094146 0 0.003828587 0.007925248 0.08490899 0.056028142
0.094173944 0 0 0.015045764 0 0 0
47 Oweek 0.040388541 0 0.088322458 0.108134241 0.028386596 0 0.13991755
0.004476539 0 0.012632379 0 0.003311708 0 0.185569291 0.096774891
0.068857485 0 0 0.002920578 0 0 0
48 Oweek 0.008406241 0 0.091465935 0 0.076698854 0.040692685 9.00E-04 0
0.003055037 0 0.023379193 0 0 0.078916762 0.009909404 0.08465106 0 0
0.016586659 0 0 0
49 Oweek 0.010488333 0 0.052432932 0 0.026484689 0.013376051 0.007207659
0.01005948 0.016422503 0.008626705 0.006344505 0 0 0.229005498 0.015636925
0.071570661 0 0 0 0.01116854 8.00E-04 0
50 Oweek 0.039626314 0 0.119254485 0.048856047 0 0 0.154015477 0.019402091
0 0.013757986 0.003668991 0 0 0.183450259 0.067748113 0.092222472 0 0
0.013255408 0 0 0
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51 Oweek 0.005189046 0 0.093274319 0.008050596 0.039393021 0.065868199

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0.003470325 0 0 0 0.01170013 0 0 0.207546318 0.016755351 0.059046664 0 0
0.012897865 0 0 0
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0.02461454 0.013272929 0.040968509 0.020459638 0 0 0.307810352 0.031601978
0.056215711 0 0 0 0.033032143 0 0
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0.073629049 0 0 0 0.027529352 0 0
54 Oweek 0.016099399 0 0.03679397 0.005984675 0.022276916 0.007851257 0
0.031667524 0.005323559 0.003596706 9.00E-04 0 0 0.229397511 0.029106843
0.126951927 0 0 0.01801467 0 0 0.007260078
55 Oweek 0.036306578 0.032745398 0.165554109 0.065414592 0.039256272
0.035313857 0.010202623 0 0 0 0.009145487 0 0 0.1337035 0.025327546
0.080551945 0 0 0 0.011158195 0 0.004384012
56 Oweek 0.012737444 0 0.0566312 0 0.032267507 0.034807558 0 0.025020031
0.008632545 0 0.017220268 0 0 0.192701198 0.021626952 0.035337163 0 0
0.015507887 0 0.002327655 0
57 Oweek 0.034296436 0 0.10933239 0.065017652 0.087185759 0.054400723
0.007813109 0 0 0 0 0 0 0.067324935 0.049114998 0.055607944 0.00100608 0 0
0.013537263 0 0
58 Oweek 0.004988494 0.008699116 0.060010726 0 0.058782453 0.028884073
0.006860777 0 0.022043392 0 0.011346927 0 0 0.114330476 0.008427948
0.129311889 0 0 0.024660972 0 0 0.015895295
59 Oweek 0.030213675 0 0.071920428 0 0.038526308 0.065642365 0 0.009374819
0.020882875 0 0.038924783 0 0.00509604 0.072880581 0.03204338 0.064646366
0.00142863 0 0.026949585 0 0 0.002959906
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0.029537221 0.086219995 0 0 0 0.239027807 0.043625766 0.120278278 0 0
0.014221247 0 0 0
61 Oweek 0.04598438 0 0.167650744 0.045567722 0.101158827 0.069714482
0.006820463 0 0 0.009124412 0 0 0.022770868 0.021428904 0.056063789
0.064218057 0.00963474 0 0.029910579 0 0 0
62 Oweek 0.077701966 0 0.118521839 0.033395565 0.123238926 0 0 0.01458223
0.014646813 0.041581744 0 0.008010992 0.011361976 0.11843311 0.052245104
0.077413969 0 0 0.017635423 0 0 0
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0.028737011 0 0 0 0.025771647 0 0.006182294 0.256826826 0.008324622
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0 0.019038114 0 0.052075429 0 0.023357931 0.067945553 0.041381506 0
0.015453587 0 0.00230009 0 0
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66 Oweek 0.012807447 0 0.104567896 0.006422051 0 0 0 0.025589759
0.025030586 0 0.007188243 0 0 0.16589958 0.015516916 0.042579397 0 0 0
0.020916737 0 0.004931887
67 Oweek 0.033921384 0 0.216020018 0.131447732 0.032338992 0 0.047285873
0.001540719 0.004504788 0.018346198 0 0.006010013 0 0.064618815 0.048826638
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0.001194813 0.002843301 0 0.01947625 0 0 0.362303027 0.012906172
0.134071821 0 0 0.018031348 0 0 0
69 Oweek 0.025511708 0 0.171787352 0.017995816 0.030640652 0 0.038146882
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0.056631587 0 0 0 0.056828182 9.00E-04 2.00E-04
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0.012133407 0 0.00877125 0 0 0.133214439 0.032316134 0.084169804 0 0
0.023824622 0 0 0.005017956
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0.001906131 0.032289162 0 0 0.018521533 0 0 0.009413341 0.08270574
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0.047768685 0.01701001 0 0 0 0.125804226 0.068187001 0.080395204 0 0 0
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0 0 0.028633159 0 0 0
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0.033296547 0 0 0.015338762 0.011656955 0 0.192874576 0.048019133
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0.070933939 0.080608583 0.00312735 0 0.055691373 0 0 0
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0.016405087 0 0.009637366 0 0.267206392 0.025727886 0.056340689 0 0 0
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0.015803786 0 0.005131633 0.001895159 0 0.133793469 0.006540902 0.127032556
0 0 0.032252447 0 0.00186817 0
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0.012058033 0.012253883 0.012614063 0 0.002674259 0 0.211610433 0.025332876
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0.013952836 0.022234516 0.025125641 0 0 0.25425077 0.001479852 0.052649347
0 0 0 0.039439291 0.001757333 0
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0.071804697 0.013344231 0 0.009821291 0 0 0 0 0.227021822 0.044490652
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87 Oweek 0.068572866 0 0.065534812 0 0.032408136 0 0.062011221 0.012514689
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88 Oweek 0.034589889 0 0.053897762 0 0.036803706 0 0.009865204 0.018907443
0.014432232 0.011885713 0.005458291 0 0 0.252605509 0.02440706 0.072403261
0 0 0 0.012002958 0 0.004507806
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0.018241561 0 0.022986136 0 0 0.146692576 0.029916185 0.064629292 0 0

0.004551017 0 0.001 0 90 Oweek 0.026464128 0 0.058667573 0.063999217 0.071409173 0.026536955 0.012472156 0 0.019394493 0.0144311 0 0 0 0.131407902 0.127762636 0.059537155 0.017653611 0 0 0.031617779 0 0